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RESEARCH ARTICLE

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Alcohol cue reactivity in the brain: Age-related differences in the role of social processes in addiction in male drinkers

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Abstract

Social attunement (SA)—the tendency to harmonize behavior with the social environment—has been proposed to drive the escalation of alcohol use in adolescence, while reducing use in adulthood. Little is known about how heightened social sensitivity in adolescence may interact with neural alcohol cue reactivity—a marker of alcohol use disorder—and its relationship to alcohol use severity over time. The aims of this study were to test whether (1) adolescents and adults differ in social alcohol cue reactivity in the nucleus accumbens, anterior cingulate cortex, and right medial prefrontal cortex (mPFC), and (2) age moderates the relationship between social alcohol cue reactivity and social attunement, measures of drinking at baseline, and changes in drinking over time. A sample of male adolescents (16–18 years) and adults (29–35 years) completed an fMRI social alcohol cue-exposure task at baseline and an online follow-up two to three years later. No main effects of age or drinking measures were observed in social alcohol cue reactivity. However, age significantly moderated associations of social alcohol cue reactivity in the mPFC and additional regions from exploratory whole-brain analyses with SA, with a positive association in adolescents and negative association in adults. Significant age interactions emerged only for SA in predicting drinking over time. Adolescents with higher SA scores escalated drinking, while adults with higher SA scores reduced drinking. These findings warrant further research on SA as a risk and protective factor and suggest that social processes influence cue reactivity differentially in male adolescents and adults.

KEYWORDS
adolescence, cue reactivity, fMRI, social processes

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1 | INTRODUCTION

Heavy alcohol use typically emerges in early-to-mid adolescence and rates of alcohol use disorder (AUD) peak in late adolescence to young adulthood (Johnston et al., 2018; Lee et al., 2018). Heavy adolescent alcohol use may have a negative impact on brain development (Cservenka & Brumback, 2017; De Goede et al., 2021), and early-onset AUD is associated with worse long-term outcomes (Hingson et al., 2006). However, as most adolescents naturally recover from AUD without formal treatment and do not transition to long-term abuse (Chassin et al., 2004), adolescence may also be a period of resilience. Neurobiological changes during the transition from adolescence to adulthood may play a critical role in both the emergence and desistance of harmful alcohol use.

AUD is characterized by a lack of control over heavy alcohol use despite the negative effects of continued use on daily functioning and overall health (American Psychiatric Association, 2013a). Alcohol cue reactivity—one's neurophysiological responsivity to alcohol-related stimuli—is traditionally considered a strong neurobiological markers for the development and maintenance of AUDs (Zeng et al., 2021). Repeated pairings of alcohol-related cues with the rewarding effects of alcohol are thought to result in heightened alcohol cue reactivity in the salience and reward system of the brain (Robinson & Berridge, 1993). Indeed, heightened alcohol cue reactivity has been robustly observed in heavy to dependent drinkers in regions of the mesocorticolimbic circuit—the key dopamine pathway involved in attentional and reward processes—with consistent associations with alcohol craving, use severity, treatment success, and relapse rates (Cofresí et al., 2019; Schacht et al., 2013; Zeng et al., 2021). In heavy to dependent drinkers, the nucleus accumbens (NAcc)— the primary target of dopaminergic neurons in the ventral tegmental area (Wise, 2002)—shows the most robust activations to alcohol compared to non-alcohol cues (Schacht et al., 2013). Activity in the ventral striatum (VS), composed by the NAcc and olfactory tubercle, has most frequently been found to positively correlate with drinking measures such as severity of dependence, amount of alcohol use, craving, and loss of control (Schacht et al., 2013). However, AUD patients and heavy drinkers did not show heightened alcohol cue reactivity in the NAcc and VS compared to controls in two meta-analyses (Schacht et al., 2013; Zeng et al., 2021). Some evidence suggests that even light and social drinkers show heightened cue-reactivity in the NAcc and VS (Seo et al., 2011; Vollstädt-Klein et al., 2010), which may make differences between heavy and dependent drinkers more difficult to detect. In addition, as drinking transitions from goal directed to compulsive, some evidence points toward alcohol cue reactivity shifting toward the more dorsal regions of the striatum (Cofresí et al., 2019; Vollstädt-Klein et al., 2010). The anterior cingulate cortex (ACC) and medial prefrontal cortex (mPFC) have direct projections to these striatal regions and show heightened alcohol cue-related activity in AUD patients compared to controls in a recent voxel-wise meta-analysis (Zeng et al., 2021).

Neurocognitive models of adolescence suggest that enhanced reward processing combined with delayed maturation of cortical areas involved in executive control increases adolescents' risk for addiction (Conrod & Nikolaou, 2016), but heightened responsiveness to social stimuli might also play an important role. Adolescents are hypersensitive to both positive and negative social stimuli at the behavioral and neural level (Chein et al., 2011; Foulkes & Blakemore, 2016). Also, peer alcohol use and social drinking motives are one of the strongest predictors of heavy drinking during adolescence (Chassin et al., 2009; Huang et al., 2014; Larsen et al., 2010). It has recently been proposed that the seemingly paradoxical nature of adolescence as a period of both risk and resilience reflects developmentally normative changes in the salience of social information (Cousijn et al., 2018). In the social plasticity hypothesis, Cousijn et al. (2018) propose that aside from neural development and plasticity, social attunement—the tendency to harmonize behavior with the social environment—drives the escalation of alcohol use when the act of drinking, especially heavy drinking, is socially valuable in adolescence, but also explains the rates of natural recovery in emerging adulthood when heavy drinking is no longer as socially valuable.

Despite the general importance of social processes in trajectories of adolescent versus adult alcohol use, little is known about how heightened social sensitivity in adolescence may interact with alcohol cue reactivity and its relationship to alcohol use severity over time. Moreover, direct comparisons between adolescents and adults are missing. Only one study has investigated the role of social context in neural alcohol cue reactivity (Groefsema et al., 2020). In male young adult drinkers, social compared to non-alcohol cues elicited more activation in the bilateral superior temporal sulcus and inferior parietal lobe, but this activity was not related to actual drinking behavior. Therefore, the *first aim* of this neuroimaging study was to examine whether adolescents and adults differ in their neural response to social versus non-social alcohol cues. The NAcc, ACC, and right mPFC were chosen as regions of interest (ROIs) given their robust engagement in alcohol cue reactivity (Schacht et al., 2013; Zeng et al., 2021). We expected higher social alcohol cue reactivity in these regions in adolescents compared to adults based on evidence of adolescents' heightened social sensitivity (Chassin et al., 2009;

Significance

Alcohol cue reactivity measures the responsivity of the reward networks in the brain and is associated with alcohol-related problems. This study examined whether adolescents and adults differ in alcohol cue reactivity in social contexts. Adolescents with stronger tendencies to change their behavior to their social environment have higher social alcohol cue reactivity and are also more likely to escalate their drinking over time, whereas the opposite is observed in adults. It is important to examine how social processes may modulate brain mechanisms of alcohol use in adolescents versus adults.

Foulkes & Blakemore, 2016; Huang et al., 2014; Larsen et al., 2010). Given the novelty of the age comparison and inclusion of social factors, we also used an exploratory whole-brain approach to identify other regions that respond differentially in adolescents and adults. The *second aim* was to examine whether age moderates the relationship between social alcohol cue reactivity and measures of drinking severity (i.e., recent alcohol consumption, severity of use-related problems, and craving) as well as social attunement. We expected social attunement and drinking severity to be more strongly associated with social alcohol cue reactivity in adolescents compared to adults (Cousijn et al., 2018). The *third aim* was to examine whether social alcohol cue reactivity, social attunement, and drinking severity at baseline predicted changes in drinking at two- to three-year follow-up and whether age moderates these effects. We expected the social measures (i.e., social alcohol cue reactivity and social attunement) to predict escalation of use in adolescents but not in adults, with higher social alcohol cue reactivity and higher social attunement predicting larger increases in use for adolescents at follow-up (Cousijn et al., 2018).

2 | METHODS AND MATERIALS

2.1 | Participants

A total of 56 male adolescents (16–18 years) and 56 male adults (29–35 years) were recruited via social media and flyers. Targeted recruitment was aimed at alcohol use frequency to create a similar distribution of low to heavy drinkers within each age group. Age groups were closely matched on alcohol use (in standard units) in the previous month and the severity of alcohol use-related problems measured by the Alcohol Use Disorder Identification Test (AUDIT; Saunders et al., 1993). This study was part of larger neuroimaging project that included an olfactory cue-reactivity task. Due to potentially confounding effects of sex and cigarette use on olfactory function (Ajmani et al., 2017; Sorokowski et al., 2019), women and daily cigarette smokers were excluded during screening. If participants reported daily use during the test session, they were retained in the sample. Further exclusion criteria included impaired olfactory function, dislike of beer, past-month drug use besides alcohol, history of mental illness, current use of psychotropic medication, and any MRI contraindication. During their lab visit, participants were screened for current alcohol intoxication using a breathalyzer ($n=0$) and recent drug use besides alcohol using a rapid urine test, resulting in six participants being excluded (cannabis $n=4$, benzodiazepine and cocaine $n=1$, cocaine and XTC $n=1$). Two additional participants were excluded because they fell asleep during the social alcohol cue-exposure task. No participants exceeded the motion threshold of >3 mm maximum framewise displacement (calculated with fMRIprep in preprocessing steps) for exclusion. The final baseline sample consisted of 51 adolescents and 53 adults of which 38 adolescents (75%) and 47 adults (89%) completed the online follow-up ($M=30$ months and $SD=3.2$ months). Participants were all contacted to complete the follow-up on the same day via email. The ethics committee of the University of Amsterdam Faculty of Social and Behavioral Sciences (2018-DP-8730) approved all protocols, and all participants gave voluntary informed consent before baseline and follow-up testing. Participants received 35 euro for completing the baseline session and a 10 euro voucher for completing the follow-up survey. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

2.2 | Social alcohol cue-exposure task

The social alcohol cue-exposure (SACE) task was adapted from Groefsema et al. (Groefsema et al., 2020). Participants were shown non-social beer (NB), social beer (SB), non-social soda (NS), and social soda (SS) images. The social images depicted two or more interacting young adult men and/or women drinking either beer or soda. The non-social images depicted beer or soda on a table. The beer and soda images were closely matched on composition within the social and non-social categories. The task was structured into four epochs (Figure 1) that each contained four blocks with a six second fixation cross between each block. Each block contained five four-second stimuli from the same condition. In total, 80 stimuli were presented during the eight-minute task in a fixed order. Participants were instructed to imagine themselves in the situation presented in each image. No response was required and an eye-tracker was used to monitor wakefulness. Current craving for beer and soda was rated before and after the task on visual analogue scales ranging from *not at all* (0) to *very much* (100).

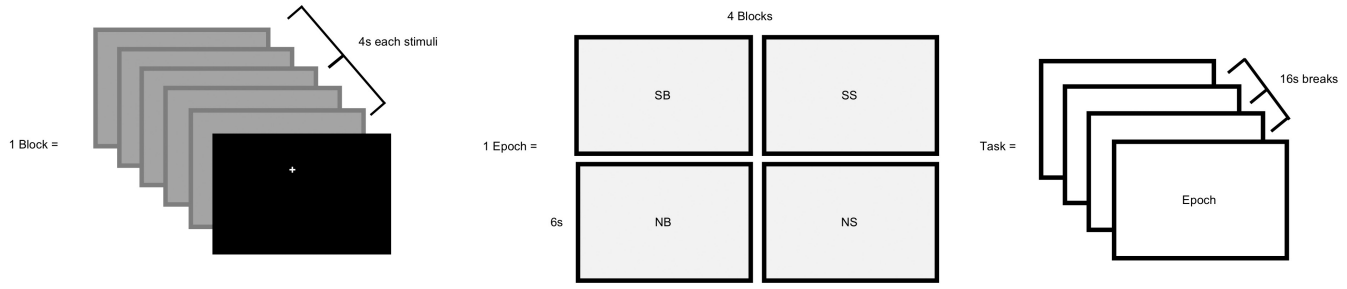

FIGURE 1 Schematic overview of Social Alcohol Cue Exposure (SACE) paradigm.

2.3 | Questionnaire assessments

The 14-item social attunement questionnaire (SAQ; Kroon et al., n.d.) was administered at baseline to assess the extent to which individuals harmonize oneself and one's behavior with their social environment. Participants responded with a Likert scale from 1 = *strongly disagree* to 7 = *strongly agree*.

The Mini International Neuropsychiatric Interview (MINI; Sheehan et al., 1998) was administered to assess AUD symptoms at baseline (interview) and follow-up (online). Recent alcohol consumption (total standard drinks) was assessed over the past 14 days with the timeline follow back (TLFB; Martin-Willett et al., 2020) at baseline and follow-up. An additional substance use history questionnaire assessed age of first drink, first binge, and first drunk episode, number of past-year binge-drinking episodes, average number of drinking days per month, lifetime illicit substance use, lifetime cannabis use at baseline, lifetime history of cigarette use (yes/no), and days of cigarette use in the past year. Self-reported motives for alcohol use (social, coping, enhancement, and conformity) were assessed with the 20-item Drinking Motives Questionnaire-revised (DMQ-r; Cooper, 1994) at baseline and follow-up. The DSM5 self-rated level 1 cross-cutting symptom checklist (DSM5-CCSM; American Psychiatric Association, 2013b) was administered to assess mental well-being across disorders in the previous six months at baseline and follow-up.

2.4 | Neuroimaging data collection and preprocessing

Anatomical and functional MRI scans were collected at baseline using a 3T Philips Achieva MRI scanner with a 32-channel SENSE head coil. For registration purposes, an anatomical T1 scan was acquired (TR/TE = 8.5/3.8 ms, FOV = 188 × 240 × 220 mm^3, voxel size = 1 × 1 × 1 mm^3, flip angle = 8°). Blood-oxygen-level-dependent signal was measured with a T2* gradient-echo planar imaging sequence during the SACE task (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°). The *fMRIprep* pipeline was used for data preprocessing (see Supporting Information for details of the settings). The data were skull-stripped, spatially smoothed, motion corrected using ICA-AROMA (non-aggressive), and high pass filtered (100 s; in FSL first level model).

2.5 | Data analysis

2.5.1 | Behavioral data

Task-induced beer craving was calculated by subtracting pre-task from the post-task craving. Change in recent alcohol consumption (TLFB) and alcohol use problem severity (AUD symptoms) was calculated by subtracting baseline from follow-up scores. Age differences in these scores, alcohol and substance use history variables, and drinking motives were examined with independent samples t-tests or Mann–Whitney U-tests when the assumption of normality was violated. A Chi square test was conducted to examine differences age differences in lifetime cigarette use. A repeated measures analysis of variance was conducted to examine whether beer craving increased from pre- to post-task, and whether this effect differed by age group. Differences in baseline sample characteristics between participants who did and did not drop out at follow-up were examined with Welch's *t*-tests. All behavioral and ROI analyses were conducted in JASP v0.15 (Team, 2022).

2.5.2 | fMRI data

Subject-level analyses were performed with FMRI Expert Analysis Tool (FEAT), part of FMRIB Software Library version 6.0 (Woolrich et al., 2009). Functional images were entered into a general linear model with a regressor for each condition (SB, SS, NB, and NS). Regressors were convolved with a Double-Gamma hemodynamic response function. The interaction contrast [(SB > SS) > (NB > NS)] was calculated per subject to examine the interaction between social context and drink type. This contrast isolates activity to social beer pictures (versus social soda pictures) compared to non-social alcohol pictures (versus non-social soda pictures).

2.5.3 | ROI analyses

Mean activity in the NAcc, dACC, and right mPFC was extracted for the [(SB > SS) > (NB > NS)] contrast. In line with a recent meta-analysis (Zeng et al., 2021), spherical masks (10 mm diameter) were created based on the MNI coordinates of the voxels with the highest activation for AUD patients compared to healthy controls in the right mPFC (MNI: 12, 62, 0) and dACC (MNI: 0, 2, 34). For the NAcc, binarized lateral masks were created with a high-resolution probabilistic subcortical atlas (Pauli et al., 2018) with a threshold of 0.3 for voxel inclusion.

To address aim one, independent sample t-tests were conducted to compare mean social alcohol cue reactivity between adolescents and adults for each ROI. To address aim two, a multiple regression analysis was conducted for each ROI to examine the association of social cue-reactivity with social attunement, recent alcohol consumption, AUD symptoms, and task-induced craving at baseline as well as moderated regression analyses with age as the moderator in these associations. To address aim three, multiple regression models were computed with recent alcohol consumption and AUD symptom difference scores as the dependent variables separately with age and social alcohol cue reactivity in the ROIs as the predictors. Social attunement, task-induced craving, and their two- and three-way interactions with age and social alcohol cue reactivity were added as additional predictors. Bootstrapped (5000 samples) coefficients and confidence intervals are reported. Holm–Bonferroni corrections were applied to control for multiple comparisons using a family-wise approach for

each ROI (Holm, 1979). Only results that survive this correction are reported.

2.5.4 | Whole brain analyses

Exploratory whole-brain voxel-wise analyses were conducted with FEAT FLAME 1 mixed effects analyses for the contrast reflecting social alcohol cue reactivity [(SB > SS) > (NB > NS)]. To address aim one, an unpaired two-group difference analysis was conducted to compare the mean social alcohol cue reactivity of the adolescents and adults. To address aim two, higher-level regression models were calculated to examine the association between social alcohol cue reactivity and social attunement, recent alcohol consumption, AUD symptoms, and task-induced craving at baseline. Next, a higher-level interaction contrast was computed for each predictor to compare the slopes of these associations between adolescents and adults. Using a similar approach for aim three, recent alcohol consumption and AUD symptom difference scores were used in the simple regression and moderated regression analyses. Predictors were mean-centered and added to the models as separate regressors per age group for each analysis. Automatic outlier de-weighting was applied in FSL. Cluster-wise multiple comparison correction was applied at Z-threshold of 2.3 and a cluster-*p* significance threshold of .05. Mean peak activity for significant clusters was extracted and visualized for interpretation of the interaction effects.

3 | RESULTS

3.1 | Sample characteristics

Adolescents and adults were well-matched on all alcohol-related measures except that adolescents consumed significantly more drinks per use episode compared to adults ($Mdn_{adol} = 6.0$, $Mdn_{adult} = 4.6$; $W = 1700.5$, $p = .02$; Table 1). While lifetime cigarette

TABLE 1 Sample characteristics.

	Adolescents			Adults		
	Median	MAD	Range	Median	MAD	Range
Age	17	1	16 to 18	31	1	29 to 35
Alcohol use measures						
AUD symptom count	2	1	0 to 9	1	1	0 to 8
Days of use (month)	5	3	0 to 25	8	4	0 to 30
# Drinks in past 2 weeks (standard units)	19	17	0 to 134	24	17	0 to 198
Drinks per use episode (standard units)*	4	2	1 to 25	3	1	1 to 15
Age at first drink	15	1	11 to 17	14	1	10 to 20
Age at first binge	16	1	13 to 18	16	1	13 to 23
Age at first drunk	16	1	13 to 17	15.5	0.5	13 to 24
Past-year binge drinking (episodes)	25	20	0 to 180	12	12	0 to 200
Craving (beer)**						
Pre-task	23	6	3 to 46	21	9	0 to 44
Post-task	27	6	2 to 50	25	8	0 to 42
Drinking motives						
Social	17	3	7 to 25	13	4	6 to 24
Conformity	6	1	5 to 18	6	1	5 to 16
Enhancement	15	3	5 to 22	12	3	6 to 23
Coping	6	1	5 to 19	6	1	5 to 15
Lifetime illicit substance use (episodes)*	0	0	0 to 300	6	0	0 to 278
Lifetime cannabis use (episodes)	6	6	0 to 120	5	5	0 to 1000
DSM 5 Cross Cutting Symptoms (count)*	10	4	1 to 40	6	2	1 to 23

Note: Differences based on independent samples *t*-tests or Mann–Whitney U-tests when the normality assumption was violated.
Abbreviation: MAD, median absolute deviation.
*Significant group difference $p < .05$; **Significant increase from pre- to post-task $p < .05$.

use did not differ between the age groups (X^2 (1, $N = 100$) = 3.001, $p = .08$), adolescents reported more days of cigarette use in the past year ($Mdn_{adol} = 30.0$) compared to adults ($Mdn_{adult} = 0.5$, $W = 953.0$, $p = .005$). Compared to adults, adolescents also reported more mental health symptoms ($Mdn_{adol} = 12.1$, $Mdn_{adult} = 8.6$, $W = 1695.5$, $p = .03$) and fewer lifetime use episodes of illicit substances ($Mdn_{adol} = 6.0$, $Mdn_{adult} = 4.6$; $W = 1700.5$, $p = .02$).

From baseline to follow-up, adolescents reported an escalation of recent alcohol consumption ($Mdn_{adol} = 9.0$ standard drinks) and AUD symptoms ($M_{adol} = 0.8$ symptoms), while adults reported a reduction in consumption ($Mdn_{adult} = -6.9$ standard drinks; $W = 1306.5$, $p < .001$) and symptoms ($M_{adult} = -0.4$ symptoms; $W = 1214.5$, $p = .003$). More adolescents dropped out (25%) compared to adults (11%). Drop-outs compared to non-drop-outs reported significantly more AUD symptoms ($t(21.7) = 2.47$, $p = .02$) and higher enhancement motives ($t(25.3) = 2.61$, $p = .015$), but did not differ on any other sample characteristic measure at baseline (Table 2). Regardless of age, participants reported a significant increase in craving from pre- to post-task ($M_{pre} = 20.39$, $M_{post} = 24.16$, $F(1,101) = 45.05$, $p < .001$).

3.2 | ROI analyses

3.2.1 | Main effect of age group

Adolescents did not show higher social alcohol cue reactivity in the right mPFC, lateralized NAcc, and dACC compared to adults. In the exploratory whole-brain analysis, adults showed higher social alcohol cue reactivity compared to adolescents in the parahippocampal gyrus, inferior temporal gyrus, temporal fusiform cortex, and lateral occipital cortex (Figure 2a; Table 3).

3.2.2 | Main effects of drinking measures and social attunement

In the full sample, ROI (Table 4) and whole-brain social alcohol cue reactivity did not significantly relate to recent alcohol consumption, AUD symptoms, task-induced craving, or social attunement at baseline. Furthermore, ROI and whole-brain social alcohol cue reactivity

TABLE 2 Baseline characteristics of follow-up responders and non-responders.

	Completed ($N = 85$)			Drop outs ($N = 19$)		
	Median	MAD	Range	Median	MAD	Range
Alcohol use measures						
AUD symptom count	1	1	0 to 8	3	2	0 to 9
Days of use (month)	6	4	0 to 30	5	3.5	1 to 20
# Drinks in past 2 weeks (standard units)	21	17.1	0 to 198	19	17	0 to 112
Drinks per use episode (standard units)*	4	2	1 to 25	5	3	1 to 16
Age at first drink	14	1	10 to 20	14	1	11 to 17
Age at first binge	16	1	13 to 23	15	1	14 to 19
Age at first drunk	16	1	13 to 21	15	1	14 to 24
Past-year binge drinking (episodes)	20.5	18.5	0 to 200	40	34	0 to 180
Craving (beer)						
Pre-task	21	8	0 to 46	28	3	5 to 36
Post-task	25	7.5	0 to 50	27	6	2 to 40
Drinking motives						
Social	16	4	6 to 25	17	2	11 to 24
Conformity	6	1	5 to 18	5	0	5 to 12
Enhancement	13	3	5 to 21	17	4	8 to 23
Coping	6	1	5 to 19	6	1	5 to 15
Lifetime illicit substance use (episodes)*	0	0	0 to 278	2	2	0 to 300
Lifetime cannabis use (episodes)	5	5	0 to 600	7	7	0 to 1000
DSM 5 Cross Cutting Symptoms (count)*	8	3	1 to 40	11	6	2 to 32

Note: Welch's *t*-test conducted to compare baseline characteristics of participants who completed the follow-up survey versus those that dropped out.
Abbreviation: AUD, alcohol use disorder.
*Significant group difference $p < .05$.

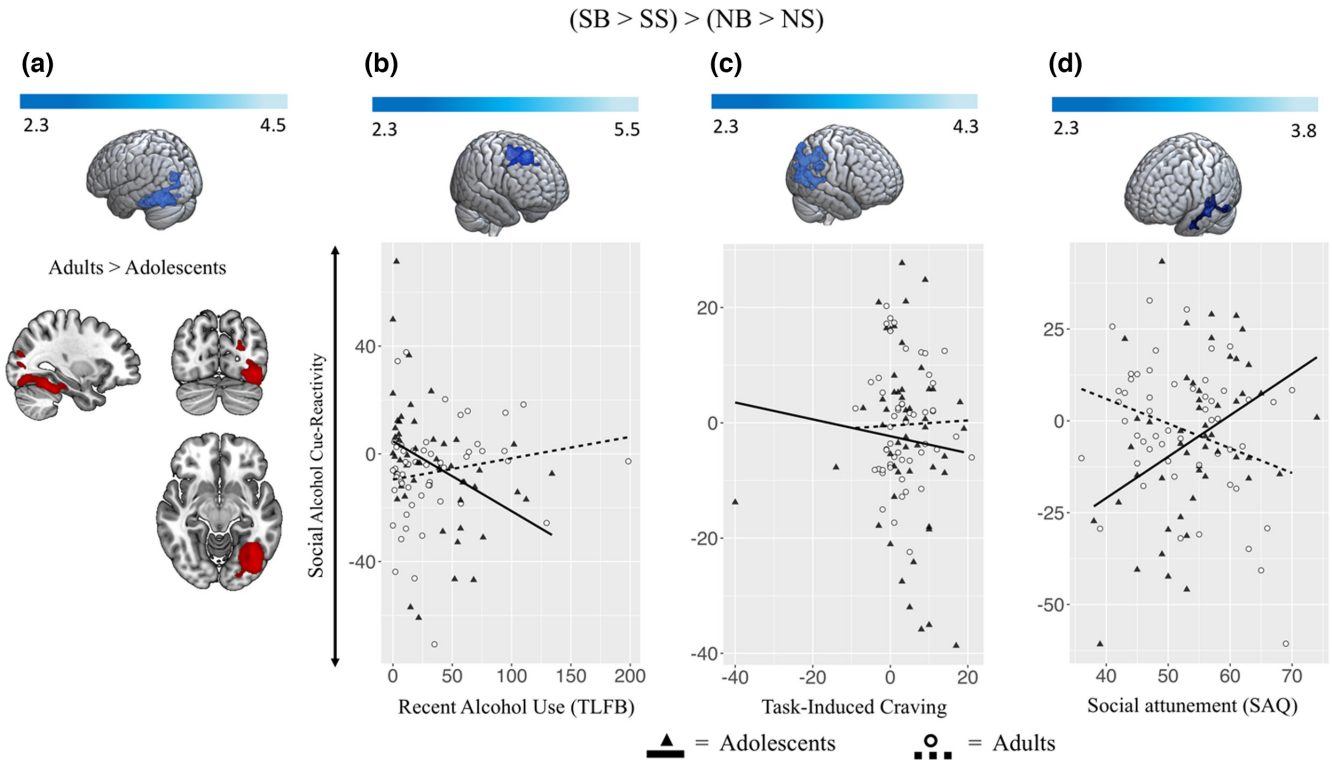

FIGURE 2 Results of whole brain exploratory analyses of the moderating role of age in social alcohol cue reactivity and its association drinking measures and social attunement (Z threshold = 2.3, $p < .05$). Cluster information in Table 3. (Panel a) Main effect of group in social alcohol cue reactivity; (Panel b) significant interaction between age and recent alcohol use; (Panel c) significant interaction between age and task-induced craving; (Panel d) significant interaction between age and social attunement tendencies; (Panel b–d) data points represent mean parameter estimate for social alcohol cue reactivity contrast (SB > SS) > (NB > NS) per participant in significant cluster of voxels. Values above zero on the y-axis indicate higher activity to social compared to non-social alcohol cues. Values below zero on the y-axis indicate higher activity to non-social alcohol cues compared to social alcohol cues.

did not significantly predict changes in either alcohol consumption or AUD symptoms (Table 5).

3.2.3 | Interaction effects of age and drinking measures

Age significantly moderated the associations between social attunement (SAQ) and social alcohol cue reactivity in the right mPFC, but not in the NAcc of dACC (Table 6). As expected, adolescents exhibited a positive association between social alcohol cue reactivity and social attunement in the mPFC, while adults exhibited a negative association ($\beta = -1.21$, CI[−2.05, −0.3] $t(103) = -3.12$, $p = .002$; Figure 3). A post hoc sensitivity analysis, adding social and conformity drinking motives to the model, showed that the interaction remained significant, suggesting this effect was not guided by social drinking or conformity behavior ($\beta = -1.23$, CI[−2.1, −0.3], $t(103) = -3.02$, $p = .003$). Age did not significantly moderate the associations between ROI social cue-reactivity and recent alcohol consumption, AUD symptoms, or task-induced craving.

In whole-brain exploratory analyses, significant age interactions emerged for recent alcohol consumption, task-induced craving, and social attunement (Table 3). Adolescents who consumed more alcohol and had higher craving showed relatively higher non-social alcohol cue reactivity in the superior frontal gyrus, middle frontal gyrus, and frontal pole (Figure 2b) and clusters in the occipital and parietal regions, respectively (Figure 2c). The opposite was observed in adults, with those reporting more alcohol consumption and higher craving showing relatively higher social alcohol cues-reactivity. In contrast, adolescents reporting higher social attunement showed stronger social alcohol cue reactivity in the middle temporal gyrus (MTG) and inferior temporal gyrus (ITG), while the reverse pattern was observed in adults (Figure 2d). These results remained significant when excluding outliers (±3SD of the mean). The recent alcohol consumption and social attunement effects did not hold when using a stricter Z-threshold of 3.1.

Significant age interactions emerged only for social attunement in predicting changes in recent alcohol consumption and AUD symptoms (Table 7). Adolescents with higher social attunement scores escalated drinking, while adults with higher social attunement scores reduced drinking ($\beta = -2.7$, CI[−4.25, −1.6], $t(103) = -3.41$, $p = .001$; Figure 4a). This effect remained significant even when including baseline AUD symptoms, and social and conformity drinking motives ($\beta = -0.18$, CI[−3.1, −0.7], $t(103) = -3.41$, p = .003), and when excluding outliers (±3SD of the mean). In parallel, adolescents with higher social attunement reported an increase in AUD symptoms, while adults with higher

TABLE 3 Significant clusters of whole-brain exploratory analyses.

	Cluster size (voxels)	Brain region	Hemisphere	MNI coordinates			Zmax
				x	*y*	*z*	
Comparison of mean activity							
Adults > Adolescents							
	3134	Parahippocampal Gyrus, inferior Temporal Gyrus, Temporal Fusiform Cortex, Lateral Occipital Cortex[a]	L	−38	−44	−24	4.37
Adolescents > Adults		–	–	–	–	–	–
Age X Covariate Interactions							
Adult > Adolescents							
TLFB total drinks	1246	Superior frontal gyrus, Middle frontal gyrus, Frontal pole	–	–	–	–	–
Task-induced craving	3262	Lateral Occipital Cortex, Planum Temporale, Temporal Occipital Fusiform Cortex, Superior Parietal Lobule, Angular Gyrus, Lingual Gyrus, Intracalcerine Cortex *	R	36	−68	10	4.4
SAQ		–	–	–	–	–	–
AUD symptoms		–	–	–	–	–	–
Change in TLFB		–	–	–	–	–	–
Adolescents > Adults							
TLFB total drinks		–	–	–	–	–	–
Task-induced craving		–	–	–	–	–	–
SAQ	1344	Inferior Temporal Gyrus, Middle Temporal Gyrus	L	−58	−54	−14	3.76
MINI AUD symptoms		–	–	–	–	–	–
Change in MINI			–	–	–	–	–
Change in TLFB		–	–	–	–	–	–

Note: Whole brain exploratory analyses results. Cluster threshold $Z = 2.3$, $p < .05$; TLFB timeline followback 14 days.

Abbreviation: AUD, alcohol use disorder; SAQ, social attunement questionnaire.

[a]A portion of the cluster survives at the stricter cluster threshold $Z = 3.1$, $p < .05$.

social attunement reported a decrease ($\beta = -0.13$, CI[−0.21, −0.05], $t(103) = -3.41$, $p = .003$; Figure 4b). This effect remained significant even when including baseline alcohol consumption and social and conformity drinking motives ($\beta = -0.12$, CI[−0.21, −0.05], $t(103) = -3.41$, p = .003). Social alcohol cue reactivity in the ROIs and task-induced craving did not predict changes in recent alcohol consumption or AUD symptoms. Whole brain analyses revealed no age-related differences in the associations between social alcohol cue reactivity and changes in alcohol consumption and AUD symptoms.

4 | DISCUSSION

The aim of this prospective study was to investigate the moderating role of age in *social* alcohol cue reactivity and its relationship with addiction markers in a sample of adolescent and adult drinkers. As hypothesized, age moderated the associations of social alcohol cue reactivity with recent alcohol consumption, craving, and social attunement. Furthermore, while stronger social attunement tendencies predicted the escalation of use and AUD symptoms in adolescents, they predicted a reduction of use and symptoms in adults. These findings highlight the importance of social attunement tendencies as both a risk and protective factor for alcohol use across development, as well as the added value of investigating alcohol cue reactivity in social versus non-social contexts in order to better understand the neural mechanisms of alcohol use problems in adolescents and adults.

In contrast to meta-analytic results of studies on general alcohol cue reactivity in heavy drinkers and AUD patients (Schacht et al., 2013; Zeng et al., 2021), we did not observe associations between alcohol use measures and social alcohol cue reactivity in the right mPFC, NAcc, or dACC. Social alcohol cue reactivity in the mPFC, however, was positively associated with social attunement in adolescents and negatively associated in adults. The same effects

TABLE 4 Simple regression results for baseline associations with ROI activity.

Model					
mPFC	***β***	***SE (B)***	**95%CI**	***t***	***p***
TLFB	−0.02	0.04	−0.10 to 0.06	−0.36	.72
MINI	−0.47	0.71	−1.83 to 0.93	−0.61	.54
Craving	−0.03	0.03	−0.09 to 0.03	−1.10	.28
SAQ	0.00	0.22	−0.44 to 0.45	0.01	.99
rNAcc	***β***	***SE (B)***	**95%CI**	***t***	***p***
TLFB	0.01	0.03	−0.06 to 0.07	0.37	.71
MINI	−1.07	0.71	−2.57 to 0.24	−1.68	.10
Craving	0.00	0.03	−0.06 to 0.06	0.08	.94
SAQ	−0.26	0.18	−0.64 to 0.07	−1.60	.11
LNAcc	***β***	***SE (B)***	**95%CI**	***t***	***p***
TLFB	0.03	0.03	−0.03 to 0.09	0.74	.46
MINI	−0.65	0.57	−1.69 to 0.55	−1.02	.31
Craving	−0.02	0.02	−0.07 to 0.02	−0.97	.34
SAQ	−0.12	0.18	−0.51 to 0.21	−0.79	.43
dACC	***β***	***SE (B)***	**95%CI**	***t***	***p***
TLFB	−0.04	0.09	−0.21 to 0.14	−0.40	.69
MINI	−0.74	1.53	−3.67 to 2.41	−0.46	.65
Craving	−0.03	0.04	−0.11 to 0.06	−0.59	.56
SAQ	0.02	0.53	−0.94 to 1.15	0.03	.98

Note: TLFB: Alcohol use in past two weeks (standard drinks); MINI = AUD Symptom Severity.

Abbreviations: dACC, dorsal anterior cingulate cortex; LNAcc, left nucleus accumbens; mPFC, medial prefrontal cortex; rNAcc, right nucleus accumbens; SAQ, social attunement questionnaire.

TABLE 5 Simple regressions predicting change in drinking at follow-up.

Model					
TLFB difference score	***β***	***SE (B)***	**95%CI**	***t***	***p***
Social alcohol cue reactivity					
mPFC	0.05	0.19	−0.35 to 0.40	0.24	.81
rNAcc	−0.48	0.33	−1.19 to 0.1	−1.73	.09
lNAcc	−0.24	0.26	−0.78 to 0.25	−0.82	.42
dACC	−0.07	0.16	−0.38 to 0.24	−0.57	.57
MINI	−1.35	3.57	−8.07 to 6.06	−0.64	.52
Craving	0.06	0.05	−0.02 to 0.17	0.99	.33
SAQ	0.23	0.48	−0.74 to 1.14	0.51	.61
MINI difference score	***β***	***SE (B)***	**95%CI**	***t***	***p***
Social alcohol cue reactivity					
mPFC	0.00	0.01	−0.02 to 0.03	0.12	.91
rNAcc	0.01	0.01	−0.01 to 0.04	0.74	.46
lNAcc	0.02	0.01	0 to 0.05	1.50	.14
dACC	0.00	0.01	−0.01 to 0.01	−0.40	.69
TLFB	0.01	0.01	0 to 0.02	1.03	.31
Craving	0.00	0.00	0 to 0.01	0.50	.62
SAQ	0.04	0.02	0 to .09	1.78	.08

Note: TLFB: Alcohol use in past two weeks (standard drinks); MINI = AUD Symptom Severity; Craving: Task-induced craving.

Abbreviations: dACC, dorsal anterior cingulate cortex; LNAcc, left nucleus accumbens; mPFC, medial prefrontal cortex; rNAcc, right nucleus accumbens; SAQ, social attunement questionnaire.

TABLE 6 Moderated regression results for ROI.

Model						
mPFC	***β***	***SE* (*B*)**	**95%CI**	***t***	***p***	***F*-test**
Intercept	−3.71	2.46	−8.55 to 1.13	−1.72	.09	$F(3,100) = .53$, $R^2 = .02$, $p = .663$
TLFB	−0.07	0.07	−0.19 to 0.08	−1.03	.31	
Age	1.77	3.06	−3.97 to 7.90	0.64	.53	
Age*TLFB	0.09	0.08	−0.08 to 0.22	1.03	.31	
mPFC						
Intercept	−3.48	2.52	8.39 to 1.56	−1.59	.12	$F(3,100) = .27$, $R^2 = .008$, $p = .85$
MINI	−0.66	1.13	2.81 to 1.68	−0.64	.53	
Age	1.57	3.17	4.32 to 7.84	0.55	.59	
Age*MINI	0.50	1.49	2.59–3.24	0.36	.72	
mPFC						
Intercept	−3.81	2.47	8.46 to 1.08	−1.79	.08	$F(3,100) = 2.29$, $R^2 = .06$, $p = .083$
Craving	0.03	0.05	0.07 to 0.11	0.82	.42	
Age	1.49	3.01	4.35 to 7.41	0.52	.61	
Age*Craving	−0.11	0.05	0.22 to −0.01	−2.31	.02	
mPFC						
Intercept	−4.42	2.41	8.87 to 0.69	−2.06	.04	$F(3,100) = 3.39$, $R^2 = .09$, $p = .021$
SAQ	0.71	0.37	0.07 to 1.41	2.41	.02	
Age	2.18	2.98	3.73 to 7.80	0.71	.48	
Age*SAQ	−1.21	0.44	2.04 to 0.31	−3.12	.002	
rNAcc						
Intercept	−2.22	2.17	6.91 to 1.62	−1.24	.22	$F(3,100) = 1.23$, $R^2 = .04$, $p = .303$
TLFB	−0.05	0.07	0.21 to 0.08	−0.85	.40	
Age	3.41	2.69	1.78 to 8.82	1.29	.20	
Age*TLFB	0.11	0.08	0.04 to 0.27	1.39	.17	
rNAcc						
Intercept	−1.66	2.01	6.03 to 1.89	−0.94	.35	$F(3,100) = 2.44$, $R^2 = .07$, $p = .069$
MINI	−2.21	1.16	4.24 to 0.39	−2.36	.02	
Age	2.84	2.52	1.91 to 8.06	1.11	.27	
Age*MINI	2.39	1.35	0.49 to 4.83	1.79	.08	
rNAcc						
Intercept	−2.35	2.16	6.87–1.49	−1.30	.20	$F(3,100) = 1.29$, $R^2 = .008$, $p = .28$
Craving	0.03	0.04	0.06 to 0.11	1.15	.25	
Age	3.47	2.67	2.00 to 8.55	1.29	.20	
Age*Craving	−0.06	0.06	0.18 to 0.04	−1.47	.15	
rNAcc						
Intercept	−2.22	2.11	6.59–1.78	−1.21	.23	$F(3,100) = 1.78$, $R^2 = .02$, $p = .155$
SAQ	0.01	0.30	0.68 to 0.50	−0.03	.98	
Age	2.99	2.59	2.17 to 7.92	1.14	.26	
Age*SAQ	−0.43	0.37	1.10 to 0.35	−1.24	.22	

TABLE 6 (Continued)

Model						
LNAcc	***β***	***SE* (*B*)**	**95%CI**	***t***	***p***	***F*-test**
Intercept	−0.64	1.82	4.37 to 2.74	−0.36	.72	$F(3,100) = .26$, $R^2 = .01$, $p = .855$
TLFB	0.01	0.06	0.10 to 0.12	0.14	.89	
Age	0.65	2.52	4.32 to 5.52	0.23	.82	
Age*TLFB	0.03	0.07	0.10 to 0.17	0.42	.67	
LNAcc						
Intercept	−0.26	0.12	4.24–3.01	−0.22	.83	$F(3,100) = .52$, $R^2 = .02$, $p = .672$
MINI	−1.08	0.05	2.59 to 0.80	−1.20	.23	
Age	0.20	−0.14	4.38–5.55	0.12	.90	
Age*MINI	0.84	−0.09	1.45 to 3.17	0.71	.48	
LNAcc						
Intercept	−0.62	1.76	4.33–2.70	−0.37	.71	$F(3,100) = .75$, $R^2 = .02$, $p = .522$
Craving	0.01	0.03	0.07 to 0.06	0.10	.92	
Age	0.41	2.45	4.28 to 5.35	0.15	.88	
Age*Craving	−0.05	0.04	0.13 to 0.04	−1.14	.26	
LNAcc						
Intercept	−0.78	1.82	4.55 to 2.63	−0.46	.65	$F(3,100) = 1.01$, $R^2 = .03$, $p = .353$
SAQ	0.18	0.26	0.34 to 0.68	0.72	.47	
Age	0.42	2.49	4.27 to 5.39	0.19	.85	
Age*SAQ	−0.52	0.36	1.29 to 0.15	−1.62	.11	
dACC						
Intercept	−6.61	4.29	15.63–1.05	−1.47	.14	$F(3,100) = 0.23$, $R^2 = .01$, $p = .875$
TLFB	−0.06	0.11	0.31 to 0.12	−0.44	.66	
Age	4.46	6.42	8.47 to 16.73	0.70	.49	
Age*TLFB	0.03	0.18	0.30 to 0.40	0.23	.82	
dACC						
Intercept	−6.28	4.29	15.46 to 1.48	−1.41	.16	$F(3,100) = 0.21$, $R^2 = .01$, $p = .889$
MINI	−0.73	2.16	5.77–2.99	−0.36	.72	
Age	4.12	6.35	8.65 to 16.36	0.64	.53	
Age*MINI	0.41	3.26	5.53 to 7.44	0.13	.90	
dACC						
Intercept	−6.32	4.26	15.46 to 1.19	−1.42	.16	$F(3,100) = 0.26$, $R^2 = .01$, $p = .856$
Craving	−0.03	0.07	0.16 to 0.10	−0.49	.62	
Age	4.35	6.16	8.12–15.91	0.64	.53	
Age*Craving	0.02	0.09	0.16 to 0.21	0.16	.87	
dACC						
Intercept	−6.41	4.17	15.8 to 0.74	−1.47	.14	$F(3,100) = 0.17$, $R^2 = .01$, $p = .916$
SAQ	0.14	0.80	1.52 to 1.66	0.20	.84	
Age	4.33	6.06	7.22 to 16.48	0.70	.49	
Age*SAQ	−0.20	1.10	2.04 to 2.28	−0.17	.87	

Note: TLFB: Alcohol use in past two weeks (standard drinks); MINI = AUD Symptom Severity; Craving: Task-induced craving.

Abbreviations: dACC, dorsal anterior cingulate cortex; LNAcc, left nucleus accumbens; mPFC, medial prefrontal cortex; rNAcc, right nucleus accumbens; SAQ, social attunement questionnaire.

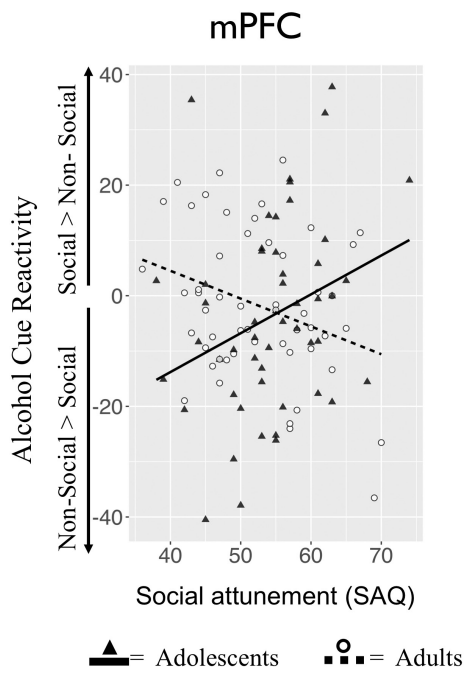

FIGURE 3 Significant interaction between age and social attunement tendencies in social alcohol compared to non-social alcohol cue reactivity in the right mPFC in moderated regression analysis. Statistics in Table 6. Data points represent the mean parameter estimates for the social alcohol cue activity contrast (SB > SS) > (NB > NS) in the mPFC for each participant. Values above zero on the y-axis indicate higher activity to social compared to non-social alcohol cues. Values below zero on the y-axis indicate higher activity to non-social alcohol cues compared to social alcohol cues.

were seen in the ITG and MTG—regions involved in face perception and recognition (Haxby et al., 2000)—suggesting basic sensory processing of the social alcohol stimuli may differ based on social attunement tendencies in a developmentally sensitive way. However, these clusters did not survive a stricter multiple comparison threshold ($Z = 3.1$) and should be interpreted with caution until replicated. While social alcohol cue reactivity was not a significant predictor of change in use over time, social attunement did predict escalation of use and problems in adolescents and reduction of use and problems in adults. Taken together, these findings support the social plasticity theory of adolescent risk and resilience to addiction (Cousijn et al., 2018), which argues that developmentally normative heightened sensitivity to social rewards during adolescence contributes to heavy alcohol use in adolescents when it is a socially normative behavior. When heavy drinking becomes less socially valuable in adulthood, individuals with higher social attunement are more likely to reduce their use to align with their social environment. Longitudinal studies that capture the full transition from adolescence to adulthood are needed to examine whether high social attunement first puts an adolescent at risk for alcohol problems, while becoming a protective factor in the same individual in adulthood. Importantly, research investigating developmental trajectories of social attunement is also critical. Preliminarily, social attunement appeared stable over two to three years, with a post hoc exploratory analysis revealing a strong correlation between SAQ scores at baseline and follow-up ($\rho = 0.618$, $p < .001$).

Additional age-related differences emerged in exploratory clusters spanning the frontal, occipital, and parietal cortices in the association between social alcohol cue reactivity and recent alcohol consumption and craving—traditional markers of drinking severity. In contrast to our hypotheses, higher craving and higher consumption were associated with relatively higher *non-social* alcohol cue reactivity in adolescents and relatively higher *social* alcohol cue reactivity in adults in regions known to respond to alcohol cues in AUD patients including the superior frontal gyrus, angular gyrus, lingual gyrus, and superior parietal lobule (Zeng et al., 2021). An important caveat is that the differential association between superior and middle frontal gyrus and frontal pole activity and alcohol consumption (TLFB) did not survive a stricter multiple comparison threshold ($Z = 3.1$), which has become standard in the field to avoid false positives. As such, we interpret them with caution. However, the differential associations with craving between adolescents and adults in the angular and lingual gyrus, and occipital and parietal cortical regions do survive this more robust correction. Associations between non-social alcohol cue reactivity in these regions and drinking measures in the adolescent group show that non-social cue-reactivity likely plays a role in adolescent drinking and is in line with previous studies of at-risk and heavy drinking adolescents (Brumback et al., 2015; Nguyen-Louie et al., 2018). These findings also highlight that adding social context to alcohol cue reactivity may have added value in understanding the neural mechanisms of heavy and problematic drinking in adults, which has typically been considered more associated with coping and enhancement motives (Merrill & Read, 2010; Windle & Windle, 2015).

In the only previous study to use the SACE paradigm, Groefsema et al. (Groefsema et al., 2020) did not find increased activation in reward-related regions. Instead they observed social alcohol cue reactivity in the superior temporal sulcus (STS) and inferior parietal lobule (IPL), regions that have previously been linked to craving and social cognition (Chase et al., 2011; Olson et al., 2007). Minor differences in the task design (active vs. passive) and sample populations (young adults 18–25 versus adolescents 16–18 and adults 30–35) may explain why we did not observe activity in the same regions. However, combining the results of both studies, the findings highlight the importance of expanding focus outside of standard addiction-related ROIs, especially in the adolescent context given the lack of adolescent samples included in recent meta-analyses (Schacht et al., 2013; Zeng et al., 2021). Furthermore, Groefsema et al. did not observe associations between social cue-reactivity in the STS and IPL and actual drinking behavior in a laboratory-based social setting. In the current study, associations between brain activity and drinking behavior were only observed when social attunement tendencies and age were taken into account, indicating future studies aimed at connecting social alcohol cue reactivity to ad libitum social drinking should account for individual differences in social attunement tendencies and age.

TABLE 7 Moderated regressions predicting change in alcohol use quantity at follow-up.

Model						
TLFB difference score	***β***	***SE* (*B*)**	**95%CI**	***t***	***p***	***F*-test**
Intercept	13.53	4.99	5.39–25.32	2.64	.01	$F(3,81) = 5.30$, $R^2 = .16$, $p = .002$
Craving	0.04	0.09	−0.10 to 0.23	0.45	.65	
Age	−25.96	6.63	−40.28 to −14.23	−3.78	<.001	
Age*Craving	−0.05	0.09	−0.24 to 0.13	−0.36	.72	
	β	***SE* (*B*)**	**95%CI**	***t***	***p***	***F*-test**
Intercept	12.24	4.70	5.65–25.49	2.69	.01	$F(3,81) = 9.85$, $R^2 = .27$, $p < .001$
SAQ	1.50	0.44	0.59–2.31	2.48	.02	
Age	−26.32	6.40	−42.38 to −16.48	−4.23	<.001	
Age*SAQ	−2.74	0.65	−4.12 to −1.54	−3.41	.001	
	β	***SE* (*B*)**	**95%CI**	***t***	***p***	***F*-test**
Intercept	14.11	5.10	6.19–26.65	2.87	.01	$F(3,81) = 5.33$, $R^2 = .17$, $p = .002$
mPFC	0.13	0.23	−0.28 to 0.60	0.53	.60	
Age	−26.22	6.68	−42.4 to −15.49	−3.96	<.001	
Age*mPFC	−0.15	0.40	−1.03 to 0.57	−0.37	.71	
	β	***SE* (*B*)**	**95%CI**	***t***	***p***	***F*-test**
Intercept	14.07	4.84	6.09–25.99	2.96	.004	$F(3,81) = 7.35$, $R^2 = .21$, $p < .001$
rNAcc	−0.75	0.41	−1.71 to −0.03	−2.30	.02	
Age	−26.39	6.41	−41.41 to −15.63	−4.09	<.001	
Age*rNAcc	0.84	0.54	−0.14 to 2.07	1.61	.11	
	β	***SE* (*B*)**	**95%CI**	***t***	***p***	***F*-test**
Intercept	14.10	4.95	6.20–26.66	2.89	.01	$F(3,81) = 5.65$, $R^2 = .17$, $p = .001$
lNAcc	−0.37	0.34	−1.08 to 0.26	−1.03	.31	
Age	−26.03	6.60	−42.25 to −15.31	−3.99	<.001	
Age*lNAcc	0.30	0.47	−0.62 to 1.26	0.56	.58	
	β	***SE* (*B*)**	**95%CI**	***t***	***p***	***F*-test**
Intercept	13.41	4.81	5.72–25.70	2.74	.01	$F(3,81) = 5.89$, $R^2 = .18$, $p = .001$
dACC	−0.15	0.15	−0.42 to 0.18	−0.91	.37	
Age	−26.07	6.28	−41.53 to −16.41	−3.96	<.001	
Age*dACC	0.28	0.28	−0.30 to 0.81	1.30	.20	
	β	***SE* (*B*)**	**95%CI**	***t***	***p***	***F*-test**
Intercept	13.70	5.57	5.38–27.52	2.81	.01	$F(6,78) = 6.33$, $R^2 = .33$, $p < .001$
Age	−28.06	7.12	−47.85 to −18.19	−4.01	<.001	
SAQ	1.64	0.45	0.86–2.64	2.78	.01	
MINI	−0.39	3.50	−7.04 to 6.84	−0.22	.83	
DMQR_Social	−3.39	1.24	−1.71 to 1.01	−2.30	.02	
DMQR_Conformity	−0.18	0.68	−6.96 to −1.60	−0.28	.78	
Age*SAQ	−2.44	0.60	−3.83 to −1.43	−3.11	.003	

Note: TLFB: Alcohol use in past two weeks (standard drinks); MINI = AUD Symptom Severity; Craving: Task-induced craving.

Abbreviations: dACC, dorsal anterior cingulate cortex; LNAcc, left nucleus accumbens; mPFC, medial prefrontal cortex; rNAcc, right nucleus accumbens; SAQ, social attunement questionnaire.

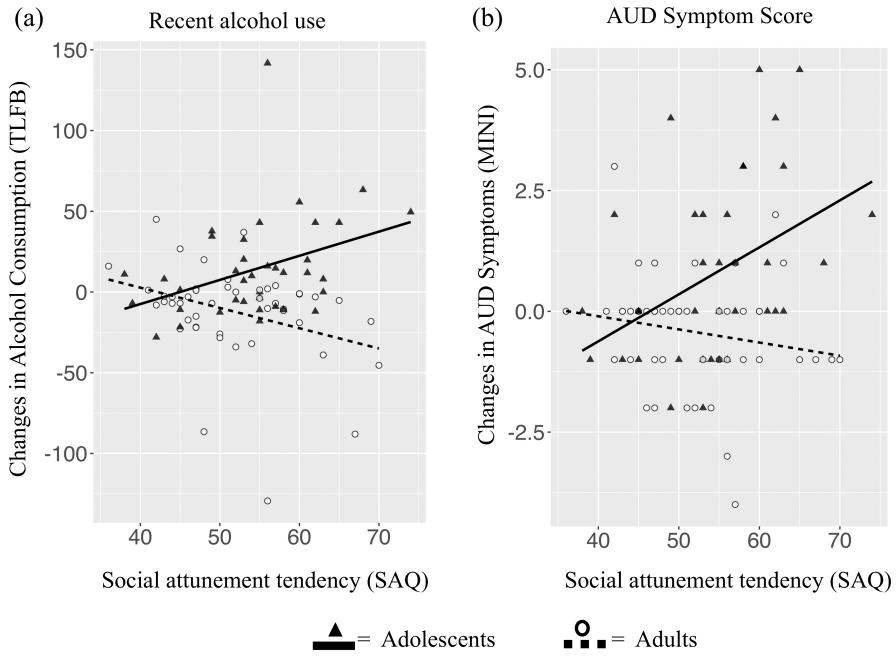

FIGURE 4 Results of moderated regression analyses examining the association between social attunement tendencies (SAQ) and changes in drinking at the two to three-year follow-up. Statistics in Tables 7 and 8; (Panel a) Significant interaction between social attunement tendencies and age on change in recent alcohol use as measured by a timeline follow back (TLFB) questionnaire. (Panel b) Significant interaction between social attunement tendencies and age on change in number of AUD symptoms.

The use of a prospective design and the inclusion of closely matched samples of adolescent and adult drinkers are clear strengths of this study. However, a few limitations need to be addressed. Firstly, only male drinkers were included because of sex differences in olfactory function relevant to another task in this project. Given the evidence for sex and gender differences in the development of alcohol use problems (Kuhn, 2015) and sensitivity to social and peer influence (Dir et al., 2017), a critical next step is replicating and extending this work in a sample with male and female adolescent and adult drinkers. Additionally, the cue reactivity paradigm only included beer images. While all participants reported both drinking and liking beer during the screening process, beer was not necessarily the preferred drink of every participant, which may have reduced cue-elicited craving. Furthermore, age differences in alcohol preferences could have potentially confounded the age-related effects observed. Future studies should consider using personally relevant alcohol stimuli to account for this. Additionally, studies should measure cue-elicited craving in response to social compared to non-social alcohol cues on a behavioral level. Secondly, human research on age differences in AUD-related processes is fundamentally confounded by differences in cumulative alcohol exposure between adults and adolescents. While this is a limitation, the moderating effects of age revealing opposite effects in adolescents compared to adults are unlikely to be driven solely by increased alcohol exposure in the adult group. Thirdly, adolescents were more likely to drop out of the follow-up and had more severe alcohol use problems and mental health issues at baseline. This may have influenced our findings. However, even with more severe groups dropping out, we retained enough variation in alcohol use in the sample to detect an association between social attunement and changes in alcohol use and problems. Finally, current co-users of illicit drugs were excluded from the sample in order to isolate alcohol effects specifically. However, polysubstance use is associated with different phenotypes than single substance use, such as more mental health symptoms and lower educational performance (Crane et al., 2021). The role of social attunement and social cue reactivity in alcohol use may differ in these individuals and future research with larger and more heterogeneous samples is crucial to examine this possibility.

In conclusion, this study provides evidence that social compared to non-social alcohol cue reactivity in the brain is differentially associated with drinking measures in adolescents compared to adults. Furthermore, social attunement is associated with higher social alcohol cue-related activity in the right mPFC in adolescence and lower activity in adulthood and predicts escalation and de-escalation of alcohol use over time in adolescents and adults, respectively. Besides furthering our understanding of how social processes interact with neural mechanisms of AUD, these findings lend support for the social plasticity theory of adolescent risk and resilience to addiction and warrant further research on social attunement as a risk and protective factor.

TABLE 8 Moderated regressions predicting change in alcohol use disorder symptoms at follow-up.

Model						
MINI Difference Score	***β***	**SE (B)**	**95%CI**	***t***	***p***	***F*-test**
Intercept	0.78	0.31	0.22 to 1.46	3.02	.003	$F(3,81)=4.36$, $R^2=.14$, $p=.007$
Craving	2.271e−4	0.01	−0.01 to 0.01	0.08	.94	
Age	−1.23	0.36	−1.94 to −0.54	−3.53	<.001	
Age*Craving	0.00	0.01	−0.02 to 0.01	−0.26	.79	
	β	***SE (B)***	**95%CI**	***t***	***p***	***F*-test**
Intercept	0.67	0.28	0.19 to 1.27	2.89	.01	$F(3,81)=8.65$, $R2^{=}.24$, $p<.001$
SAQ	0.10	0.03	0.04 to 0.17	3.19	.002	
Age	−1.14	0.33	−1.84 to −0.53	−3.60	<.001	
Age*SAQ	−0.12	0.04	−0.21 to −0.05	−3.05	.003	
	β	***SE (B)***	**95%CI**	***t***	***p***	***F*-test**
Intercept	0.80	0.31	0.22 to 1.44	3.16	.00	$F(3,81)=4.54$, $R^2=.14$, $p=.005$
mPFC	0.01	0.01	−0.02 to 0.04	0.63	.53	
Age	−1.21	0.36	−1.94 to −0.53	−3.59	<.001	
Age*mPFC	−0.02	0.02	−0.06 to 0.03	−0.73	.47	
	β	***SE (B)***	**95%CI**	***t***	***p***	***F*-test**
Intercept	0.79	0.31	0.25 to 1.45	3.17	.002	$F(3,81)=4.76$, $R^2=.15$, $p=.004$
rNAcc	0.01	0.02	−0.02 to 0.05	0.58	.57	
Age	−1.25	0.35	−1.95 to −0.59	−3.69	<.001	
Age*rNAcc	0.01	0.02	−0.04 to 0.06	0.35	.73	
	β	***SE (B)***	**95%CI**	***t***	***p***	***F*-test**
Intercept	0.80	0.30	0.24 to 1.42	3.19	.002	$F(3,81)=5.34$, $R^2=.17$, $p=.002$
lNAcc	0.02	0.02	−0.02 to 0.06	1.35	.18	
Age	−1.23	0.35	−1.91 to −0.55	−3.66	<.001	
Age*lNAcc	−0.01	0.03	−0.05 to 0.04	−0.22	.83	
	β	***SE (B)***	**95%CI**	***t***	***p***	***F*-test**
Intercept	0.77	0.31	0.25 to 1.44	3.09	.003	$F(3,81)=4.42$, $R^2=.14$, $p=.006$
dACC	0.00	0.01	−0.02 to 0.02	−0.24	.82	
Age	−1.22	0.35	−1.97 to −0.59	−3.59	<.001	
Age*dACC	0.01	0.01	−0.02 to 0.03	0.48	.63	
	β	***SE (B)***	**95%CI**	***t***	***p***	***F*-test**
Intercept	0.68	0.27	0.19 to 1.24	2.75	.01	$F(6,78)=4.62$, $R^2=.26$, $p<.001$
Age	−1.12	0.34	−1.86 to −0.51	−3.25	.002	
SAQ	0.10	0.03	0.04 to 0.17	2.98	.004	
TLFB	0.01	0.01	0 to 0.02	1.06	.29	
DMQR_Social	0.01	0.04	−0.06 to 0.11	0.29	.77	
DMQR_Conformity	0.03	0.08	−0.08 to 0.23	0.29	.77	
Age*SAQ	−0.13	0.04	−0.21 to −0.05	−3.06	.003	

Note: TLFB: Alcohol use in past two weeks (standard drinks); MINI=AUD Symptom Severity; Craving: Task-induced craving.

Abbreviations: dACC, dorsal anterior cingulate cortex; DMQR, drinking motives questionnaire; LNAcc, left nucleus accumbens; mPFC, medial prefrontal cortex; rNAcc, right nucleus accumbens; SAQ, social attunement questionnaire.

AUTHOR CONTRIBUTIONS

LK: formal analysis, methodology, visualization, writing – original draft, writing – review and editing; GM: conceptualization, methodology, investigation, project administration, resources, software, writing – review and editing; EK: writing – review and editing; IW: conceptualization, funding acquisition, writing – review and editing; HL: conceptualization, funding acquisition, writing – review and editing; JC: conceptualization, funding acquisition, methodology, project administration, supervision, writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare none.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

DECLARATION OF TRANSPARENCY

The authors, reviewers and editors affirm that in accordance to the policies set by the *Journal of Neuroscience Research*, this manuscript presents an accurate and transparent account of the study being reported and that all critical details describing the methods and results are present.

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SUPPORTING INFORMATION

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

Supporting information S1.

Data S1. Transparent Science Questionnaire for Authors

Data S2. Social Attunement Questionnaire

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