Addictive Behaviors Reports 21 (2025) 100585

Contents lists available at ScienceDirect

Addictive Behaviors Reports

journal homepage: www.elsevier.com/locate/abrep

Influence of binge drinking on the resting state functional connectivity of university Students: A follow-up study

Samuel Suárez-Suárez [a], Fernando Cadaveira [b,c], Alfonso Barrós-Loscertales [d], José Manuel Pérez-García [e], Socorro Rodríguez Holguín [b,c], Javier Blanco-Ramos [e,f], Sonia Doallo [b,c,*]

[a] Department of Health Sciences, University of Burgos 09001 Burgos, Spain
[b] Departamento de Psicoloxía Clínica e Psicobioloxía, Facultade de Psicoloxía, Universidade de Santiago de Compostela, Santiago de Compostela, Spain
[c] Instituto de Psicoloxía (IPsiUS), Universidade de Santiago de Compostela, Spain
[d] Departamento de Psicología Básica, ClínicaSpain y Psicobiología, Universitat Jaume I, Castelló de la Plana, Spain
[e] Department of Educational Psychology and Psychobiology, Faculty of Education, Universidad Internacional de La Rioja, Logroño, Spain
[f] Fundación Pública Andaluza para la Investigación Biosanitaria en Andalucía Oriental, FIBAO, Spain

ARTICLE INFO

Keywords:
Binge drinking
Resting-state
Functional magnetic resonance imaging
Functional connectivity
Adolescence

ABSTRACT

Binge Drinking (BD) is characterized by consuming large amounts of alcohol on one occasion, posing risks to brain function. Nonetheless, it remains the most prevalent consumption pattern among students. Cross-sectional studies have explored the relationship between BD and anomalies in resting-state functional connectivity (RS-FC), but the medium/long-term consequences of BD on RS-FC during developmental periods remain relatively unexplored. In this two-year follow-up study, the impact of sustained BD on RS-FC was investigated in 44 college students (16 binge-drinkers) via two fMRI sessions at ages 18–19 and 20–21. Using a seed-to-voxel approach, RS-FC differences were examined in nodes of the main brain functional networks vulnerable to alcohol misuse, according to previous studies. Group differences in RS-FC were observed in four of the explored brain regions. Binge drinkers, compared to the control group, exhibited, at the second assessment, decreased connectivity between the right SFG (executive control network) and right precentral gyrus, the ACC (salience network) and right postcentral gyrus, and the left amygdala (emotional network) and medial frontal gyrus/dorsal ACC. Conversely, binge drinkers showed increased connectivity between the right Nacc (reward network) and four clusters comprising bilateral middle frontal gyrus (MFG), right middle cingulate cortex, and right MFG extending to SFG. Maintaining a BD pattern during critical neurodevelopmental years impacts RS-FC, indicating mid-to-long-term alterations in functional brain organization. This study provides new insights into the neurotoxic effects of adolescent alcohol misuse, emphasizing the need for longitudinal studies addressing the lasting consequences on brain functional connectivity.

1. Introduction

Alcohol consumption is a significant social and health issue among youth and adolescents in most Western countries, associated with numerous adverse outcomes such as increased risk of violence, injuries, accidents, and mental health issues (Rehm & Shield, 2013; Welsh et al., 2017; World Health Organization, 2018).

Among the different hazardous consumption patterns present in youth, binge drinking (BD) is the most prevalent, with around 35 % of students between 15 and 25 years of age practicing BD in Europe (ESPAD, 2020) and 30 % of participants between 18 and 25 in the USA (SAMHSA, 2023) in the previous 30 days. This consumption pattern characterized by the intake of great amounts of alcohol on a single occasion, followed by withdrawal periods, is usually defined as the consumption of 70 g (male) or 50 g (female) of alcohol within an approximately 2-h period (NIAAA, 2004). Previous research suggests

* Corresponding author at: Dpto. de Psicoloxía Clínica e Psicobioloxía, Facultade de Psicoloxía, Universidade de Santiago de Compostela.
E-mail addresses: ssuarez@ubu.es (S. Suárez-Suárez), fernando.cadaveira@usc.es (F. Cadaveira), barros@psb.uji.es (A. Barrós-Loscertales), josemanuel.perezgarcia@unir.net (J.M. Pérez-García), rodriguez.holguin@usc.es (S.R. Holguín), javier.blanco.ramos@gmail.com (J. Blanco-Ramos), sonia.doallo@usc.es (S. Doallo).

https://doi.org/10.1016/j.abrep.2025.100585
Received 3 May 2024; Received in revised form 20 December 2024; Accepted 8 January 2025
Available online 10 January 2025

that maintaining a pattern of acute and intermittent alcohol use during adolescence and emerging adulthood has particularly deleterious effects on the brain (Hiller-Sturmhöfel & Spear, 2018; Jacobus & Tapert, 2013). As such, BD has been related to structural and functional abnormalities (Almeida-Antunes et al., 2021; Carbia et al., 2018; Lees et al., 2019; Pérez-García et al., 2022), and it is considered a risk factor for developing alcohol use disorders (AUD) (Addolorato et al., 2018; Bonomo et al., 2004). Moreover, the highest rates of BD occur between the ages of 18 and 25 (SAMSHA, 2019), when different brain structures and their connectivity are still under maturation (Cao et al., 2014; Luna et al., 2015), leading to a heightened vulnerability to the neurotoxic effects of alcohol (Bava & Tapert, 2010; Squeglia & Gray, 2016).

Amid the plethora of changes that take place during brain development, the reorganization and increasing efficiency of large-scale intrinsic functional networks (IFNs) supports the age-related improvement observed in different cognitive abilities and self-regulation processes (Stevens, 2016). Whole-brain functional magnetic resonance imaging in resting-state (rs-fMRI) is a relevant technique to assess functional connectivity (FC) (i.e., the statistical relationship among two or more neurophysiological events, (Friston, 2011) between regions comprised in these IFNs. This kind of analysis, based on the time series of spontaneous fluctuations in the blood-oxygen-level-dependent (BOLD) activity, has consistently identified several IFNs (Biswal et al., 1995; Raichle, 2011; Thomas Yeo et al., 2011) and has allowed to relate the presence of impairments in FC with multiple pathological conditions including AUD (Dupuy & Chanraud, 2016; Sutherland et al., 2012).

However, the potential abnormalities in rs-fMRI FC associated with BD are still not yet well characterized, with only a handful of articles exploring this relationship (Arienzo et al., 2019; Crane et al., 2018; Herman et al., 2018; Morris et al., 2016; Sousa et al., 2019; Tong et al., 2021). Furthermore, the possibility of studying longitudinal effects of BD behaviors opens the door to understand the dysregulation of neurofunctional networks by repeated cycles of intoxication and withdrawal that are suggested to contribute to the development of AUD in neurobiological models of addiction (e.g., Koob & Volkow, 2016). Particularly, preliminary evidence indicates that this progression from recreational to pathological consumption patterns may result from the dysregulation of frontal, striatal and limbic circuitry (Everitt & Robbins, 2016; Zilverstand et al., 2018). For instance, prior studies with clinical populations across AUD severity levels have reported abnormal FC between and within nodes of the executive control (ECN) and attentional (ATN) networks (Galandra et al., 2019; Müller-Oehring et al., 2015; Y. Wang et al., 2018; Weiland et al., 2014; Zhu et al., 2015), the default mode network (DMN) (Chanraud et al., 2011; Müller-Oehring et al., 2015; Zhu et al., 2015, 2017), the salience network (SAN) (Galandra et al., 2019; Müller-Oehring et al., 2015; Zhu et al., 2015, 2017), the reward network (RWN) (Camchong et al., 2013; Müller-Oehring et al., 2015; J. Wang et al., 2016) and the emotion network (EMN) (Zhu et al., 2017).

Although still emerging, studies with BD samples reported anomalies within most of the explored IFNs without a clear pattern in the direction of the BD effect on the FC. Both increased (Sousa et al., 2019) and decreased (Arienzo et al., 2019; Morris et al., 2016) FC has been observed in brain areas related to the ECN (i.e., middle and inferior frontal gyrus) and the control of motor responses (e.g., subthalamic nucleus). Also, compared to controls, young binge drinkers (BDs) showed an increased FC in frontal and subcortical areas closely related to salience detection (anterior cingulate cortex [ACC]) and reward processing (caudate, nucleus accumbens [Nacc] and orbitofrontal cortex [OFC]) (Arienzo et al., 2019). On the other hand, decreased intra-network FC of the ATN has been observed between the right supramarginal gyrus, frontal regions and insular cortex (Herman et al., 2018). In this same direction, Crane and colleagues (Crane et al., 2018) reported decreased FC between the amygdala, an essential component of the EMN, and OFC in young BDs. Finally, the only longitudinal rs-fMRI FC study on BD published to date, to our knowledge, reported decreased connectivity between DMN and ventral attention network across a 2-year follow-up through network-level analysis (Tong et al., 2021).

It is important to note that the available evidence suggests that some impairments associated with BD during youth would only arise after maintaining this consumption pattern in the mid to long-term. For instance, impairments in the FC of the DMN have only been described by studies with a longitudinal approach (Correas et al., 2016; Tong et al., 2021). Thus, considering the scarcity of longitudinal studies, we deemed it crucial to explore changes in rs-fMRI FC related with maintaining a BD pattern during emerging adulthood.

Here, we investigate the FC of young BDs during a 2-year period using a seed-to-voxel FC method by examining a set of critical nodes of relevant IFNs — following the approach proposed by Muller-Oehring et al. (2018, 2015) — in which alcohol misuse-related anomalies have been described (i.e. DMN, ECN, SAN, ATN, EMN and RWN). Like previous longitudinal studies in the field (Correas et al., 2016; Tong et al., 2021) we expect to see differences emerge between groups at the end of the 2-year follow-up period. More specifically, we hypothesized that the patterns of FC in BDs and controls would differ during the follow-up period in a seed-dependent way, revealing distinctive neurobiological alcohol-related changes in each seed. Based on previous evidence, we expected that BDs, compared to controls, would show in the 2nd vs 1st assessment: i) decreased FC in the superior parietal lobule (SPL; (Herman et al., 2018) as a node of the ATN and the amygdala (Crane et al., 2018) as part of the EMN; ii) increased FC in the Nacc and the ACC (Arienzo et al., 2019) as nodes of the RWN and the SAN, respectively; and iii) we will explore abnormalities in the FC of the superior frontal gyrus (SFG) and posterior cingulate cortex (PCC) associated respectively with the ECN and DMN.

2. Materials and methods

2.1. Participants

A sample of university students was assessed at two different timepoints when they were at their first (18–19 years old) and third (20–21 years old) academic years.

Within the framework of a broader research project 85 volunteers were initially selected to underwent MRI assessment from a pool of 2998 first-year students from the University of Santiago de Compostela (USC, Spain). Participants were selected based on their willingness to participate and the responses to a classroom questionnaire that assessed alcohol and substance consumption, including the adapted versions of different standardized questionnaires such as the Alcohol Use Disorders Identification Test (AUDIT) (Saunders et al., 1993; Varela et al., 2005), among others. Participants then completed a semi-structured interview and several standardized questionnaires (see supp. material for more details regarding sample selection procedure and references to previous results) to ensure they met selection criteria (see Table 1). This study was approved by the Bioethics Committee of the USC.

According to the NIAAA's definition of BD (NIAAA, 2004), we classified as BDs those participants who drank 3 70 g (male) or 3 50 g (female) of alcohol in one drinking occasion (i.e., BD episode) at least six times for the last six months. Participants who did not reach this alcohol consumption threshold were classified as controls (CN). All participants fulfilled the group classification criteria at both evaluations.

Out of 85 subjects, 55 participated in both neuroimaging assessments and 44 (16 BDs) maintained a stable consumption pattern for the duration of the study. After the exclusion from the analysis of two participants due to technical problems during image acquisition and seven participants due to excessive head movement, the final sample included 35 right-handed participants, with 14 BDs (7 females) and 21 CN (10 females) (see Table 2).

Table 1
Selection criteria established in the study.

Inclusion Critera	Exclusion Criteria
Control group (CN): Alcohol consumption < 6 BD episodes [1] over the last 6 months and cannabis consumption < 12 units over the last 3 months	Chronic medical conditions that could affect neurocognitive functioning (diabetes, hypothyroidism, liver diseases, etc.)
	History of neurological disorders or brain injury
Binge drinkers (BDs): Alcohol consumption ≥ 6 BD episodes over the last 6 months and cannabis consumption < 12 units over the last 3 months	Personal history of DSM-IV-TR Axis I and/or II diagnosed disorders (including SUD), or a score above 90th percentil in the Global Severity Index (GSI) or in two or more symptoms dimensions of the SCL-90-R
	Family history of major psychopathological disorders in first-degree relatives
	Family history of first-degree alcoholism or other SUD
	AUDIT score > 20 at the start of the study
	Use of psychoactive medications and/or use of illegal drugs (except occasional consumption of cannabis) in the last 6 months
	Non-corrected sensory deficits and MRI contraindications

[1] BD episode: consumption of ≥ 5 (female) or ≥ 7 (male) Spanish standard drinks (10 g of alcohol) on one occasion; AUDIT, Alcohol Use Disorders Identification Test; SUD, substance use disorder; SCL-90-R, Symptom Checklist-90-Revised.

Table 2
Demographic and substance use characteristics of the final sample (mean ± SD).

	First evaluation		Second evaluation	
	Controls	BDs	Controls	BDs
N (females)	21 (10)	14 (7)	21 (10)	14 (7)
Age	18.59 (±0.31)	18.55 (±0.31)	20.56 (±0.32)	20.57 (±0.3)
Caucasian (%)	100	100	100	100
Mean time (months) between first and second evaluation	—	—	24.3 (±2.86)	23.5 (±3.13)
Average framewise displacement (mm)	0.13 (±0.05)	0.13 (±0.04)	0.13 (±0.05)	0.15 (±0.06)
Tobacco consumption (n > 2 cigarettes per day)	0	1	0	2
Cannabis consumption in the last 30 days (n > 1 unit and < 4 units)[c]	0	1	0	2
Age of onset on drinking	16.5 (±0.94)	15.5 (±0.85)**	—	—
Average # drinks per drinking occasion	1.73 (±1.40)	7.1 (±2.66)***	1.86 (±1.28)	8.27 (±3.01)***
Number of BD episodes [a], past 6 months	0.57 (±1.40)	21.5 (±10.33)***	0.62 (±1.32)	29 (±18.86)***
Total AUDIT score [b]	1.57 (±1.94)	9.46 (±3.82)***	1.76 (±1.92)	9.71 (±4.44)***

Age of onset measured as the self-reported age of the first full drink.
** $p < 0.01$.
*** $p < 0.001$.
[a] BD episode: consumption of ≥ 5 (female) or ≥ 7 (male) Spanish standard drinks (10 g of alcohol) on one occasion.
[b] Missing scores for the second (participant 1) and the sixth and seventh items (participant 2) of the AUDIT at baseline were replaced by the correspondent group mean in each specific item.
[c] Cannabis consumption was an exclusion criterion when it exceeded the > 1 unit/week threshold (see supp. Material).

2.2. Imaging data acquisition

MRI scans were collected with a 3 T Achieva Philips body scanner (Philips Medical Systems, Best, NL) equipped with a 32-channel SENSE head coil (located at the University Hospital Complex of Santiago de Compostela) using a T2*-weighted echo-planar imaging sequence with the following acquisition parameters: TR/TE = 3000/30 ms, flip angle = 87°, FOV = 230 × 230 mm, voxel size = 3 mm^3, 45 axial slices and 200 volumes (10 min), preceded by 4 "dummy" functional volumes to allow for signal-equilibration effects. Participants were instructed to lie quietly with their eyes fixed on a central fixation cross and not to think about anything. High-resolution anatomical T1-weighted images were acquired using a 3D turbo field-echo sequence with the following parameters: TR/TE = 7.7/3.4 ms, flip angle = 8°, FOV = 240 mm, voxel size = 0.8 mm^3, 200 transverse slices (7 min).

2.3. Image processing and RS-FC analysis

Imaging data were processed using Statistical Parametric Mapping (SPM12; https://www.fil.ion.ucl.ac.uk/spm/software/spm12/) implemented in Matlab (version 2018a, The Mathworks, Inc., Natick, MA). The first 5 functional volumes were discarded to avoid brain signal related to the instruction screen presented at the beginning of the recording. Functional images were then corrected for slice timing and realigned and unwrapped. The anatomical T1 images were coregistered to the realigned mean functional image, and then images were transformed into standard MNI space using anatomical segmentation-based normalization parameters. The resulting functional images were spatially smoothed using a 7-mm FWHM Gaussian kernel.

Additional preprocessing steps to reduce spurious BOLD variances and RS-FC analysis were carried out using the CONN Functional Connectivity Toolbox v20 (Whitfield-Gabrieli & Nieto-Castanon, 2012). A Principal Component Analysis (PCA) was applied to white matter and CSF masks to estimate potential sources of spurious variance following the anatomical component-based noise correction method (aCompCor; Behzadi et al., 2007). The identified PCAs in each mask were then regressed from the BOLD time series, in addition to the six-movement parameters. First-order temporal derivatives and quadratic effects of the motion-related parameters were also included in the regression (see Supp. Material for further description regarding movement correction methods).

Functional connectivity analysis was performed using a seed-to-voxel approach in a set of ROIs previously defined as core nodes of some of the main functional networks (i.e., DMN, ECN, SAN, ATN, EMN and RWN), following a similar approach to Müller-Oehring et al. (2015, 2018). Six Seed regions were selected for five networks from the automated anatomical labelling (AAL; Tzourio-Mazoyer et al., 2002) template as follows: PCC for the DMN, SFG for the ECN, ACC for the SAN, SPL for the ATN and the amygdala for the EMN. For the RWN, bilateral ROIs were created for the Nacc based on the anatomical coordinates defined by previous studies (Neto et al., 2008; see Müller-Oehring et al., 2015, 2018) (see Supp. Material for further description of seed definition).

The mean BOLD time courses were computed across all voxels over each seed region. For each participant, seed-to-voxel analyses were performed by calculating Pearson's bivariate correlation coefficients between the time series of each ROI and that of all other voxels in the brain. After applying a Fisher Z transformation, first-level correlation maps were created for all volunteers. Then, individual seed-to-voxel maps were entered into a second-level random-effects analysis with sex as a covariate.

2.4. Statistical analysis

Demographic and consumption variables were submitted to pairwise comparisons in either of the assessments between the groups (BDs vs.

controls) using Student's t-tests or chi-squared tests when appropriate. Moreover, 2x2 mixed-model ANOVAs were employed to test potential differences between groups for each alcohol-related measure across evaluations. Values associated with each assessment (score in time 1 and time 2) were submitted as the within-subjects factor "time" and group (BDs, CN) was submitted as the between-subjects factor. All analyses were done with SPSS software (version 26).

To test for group differences across the two assessments (initial and follow-up) in RS-FC, between-group contrast analyses for each ROI were performed with time (within-subject) and group (between-subject) as factors of interest. All analyses were set with a combined peak-and-extent threshold with a voxelwise level of $p < 0.001$ (uncorrected) and a cluster extent threshold of $p < 0.05$, corrected for family-wise error (FWE). Additionally, false discovery rate (FDR) correction for multiple comparisons was applied to control for the number of ROIs (see Supp. Material for details).

Finally, Spearman's rho correlation analyses were performed for the whole sample to assess the relationship between the percent of change in FC (from baseline to follow-up; for a description of this measure see Supp. Material) —in those ROIs that showed significant between-group differences in the FC longitudinal analysis— and the intensity of alcohol consumption habits at follow-up.

Additional exploratory analyses examining the impact of BD as a function of biological sex can be found in the Supplementary Material.

3. Results

3.1. Sample characteristics

There were no significant differences between groups in sex, age, time between evaluations or the amount of movement (framewise displacement) (see Table 2).

As expected, BDs reported a significantly greater degree of alcohol use than CN (see Table 2). More specifically, BDs reported significantly earlier alcohol onset ($t = 2.94$; $p = 0.007$), and a significant main effect of group was found in both assessments for: i) number of drinks per drinking occasion ($F_{1, 33} = 85.05$, $p < 0.001$); ii) number of BD episodes in the past 6 months ($F_{1, 33} = 113.45$, $p < 0.001$); and iii) total AUDIT score ($F_{1, 33} = 65.4$, $p < 0.001$). A main effect of time was found for the number of drinks per drinking occasion ($F_{1, 33} = 4.28$, $p = 0.046$) as both groups slightly increased the mean number of drinks per drinking episode in the follow-up compared with the baseline (see Table 2).

3.2. Functional connectivity

Functional connectivity analysis for the whole sample revealed, for both fMRI assessments, the expected resting-state networks closely resembling what was found in previous studies (Müller-Oehring et al., 2018, 2015; see supplementary Figs. 2 and 3).

The maintenance of the BD pattern revealed group-by-time significant differences at a voxelwise level of $p_{unc} < 0.001$ and FWE-corrected cluster-extent threshold of $p < 0.05$ in four of the six explored networks (i.e., SAN, EMN, ECN, and RWN; see Table 3). BDs showed a pattern of decreased (ECN, SAN, EMN) and increased (RWN) brain connectivity compared with controls in the longitudinal analysis (2nd assessment compared to 1st one). Specifically, decreased connectivity was observed between i) the right SFG, as a node of the ECN, and the right precentral gyrus (BA 6); ii) the ACC, as the seed of the SAN, and the right postcentral gyrus (BA 3); and iii) the left amygdala, as a critical node of the EMN, and the medial frontal gyrus (mFG) extending to the dorsal ACC (dACC; BA 32, 9; see Table 3, Fig. 1). On the other hand, BDs demonstrated greater FC relative to controls in the 2nd vs 1st fMRI assessment between the right Nacc (RWN) and four independent clusters, including the middle frontal gyrus (MFG) (BA 8, 9) bilaterally, the right middle cingulate cortex (MCC) and the right MFG extending to the SFG (BA 6) (see Table 3, Fig. 2).

3.3. Correlation analysis

Spearman's rho correlations revealed significant relationships between the percent of change in FC across assessments and different alcohol consumption measures reported at the follow-up. Regarding alcohol consumption, the number of BD episodes correlated with the FC of the ACC (rho = -0.409, p = 0.015) and with the FC of the left amygdala (rho = 0.375, p = 0.026). The average number of drinks per drinking episode correlated with the FC of the ACC (rho = -0.345, p = 0.043), the left amygdala (rho = 0.369, p = 0.029) and with the FC between the right Nacc and the MCC (rho = -0.397, p = 0.018). Finally, total AUDIT scores followed a similar pattern, showing a significant correlation with the FC of the ACC (rho = -0.390, p = 0.021) and the left amygdala (rho = 0.373, p = 0.027) (see Supp. Material figures S3a and b).

4. Discussion

Longitudinal results show the effect of maintaining a BD pattern for at least two years on the FC in four out of six investigated regions. There were decreases in FC in BDs compared to controls between the right SFG and the precentral gyrus (ECN), between the left amygdala and the medial frontal gyrus/dACC (EMN), and between the ACC and the postcentral gyrus (SAN). On the other hand, increases in FC were observed between the Nacc and the PCC and middle frontal gyrus (RWN).

First, the decreased FC observed in BD (vs controls) between the SFG and the precentral gyrus supports, partially, our hypothesis based on the findings of BD (Arienzo et al., 2019) and AUD studies (Galandra et al., 2019; Müller-Oehring et al., 2015; Weiland et al., 2014). This

Table 3
Functional connectivity differences between groups 2nd vs 1st assessment.

Network/ROI	Region	Side	P_{FWE}	k	x	y	Z	T
SAN/ACC	Postcentral gyrus (BA 3)	R	0.0058	232	46	−24	64	5.66
CN > BDs								
EMN/Amygdala L	Medial frontal gyrus/ dACC (BA 32, 9)	R		319	10	34	36	4.86
CN > BDs			0.0007					
ECN/SFG R	Precentral gyrus (BA 6)	R	0.0060	232	44	−4	62	5.16
CN > BDs								
RWN/NAcc R	MFG (BA 8, 9)	R	0.0020	269	34	26	36	5.25
BDs > CN	MCC (BA 31)	R	0.0305	159	12	−36	38	4.82
	MFG (BA 8, 9)	L	0.0012	293	−36	28	48	4.77
	MFG/SFG (BA 6)	R	0.0122	194	28	−4	52	4.33

Note. BA: Brodmann Area; CN, control group; BDs, binge drinkers.
L, left; R, right; SAN, salience network; EMN, emotion network; ECN, executive control network; RWN, reward network; dACC, dorsal anterior cingulate cortex; MCC, middle cingulate cortex; MFG, middle frontal gyrus; Nacc, nucleus accumbens; SFG, superior frontal gyrus.
All results are significant at voxelwise level of $p_{unc} < 0.001$ a FWE-corrected cluster-extent threshold of $p < 0.05$ and survived FDR correction for multiple comparisons (q = 0.05) to control for the number of explored ROIs (see Supp. Material for further detail).

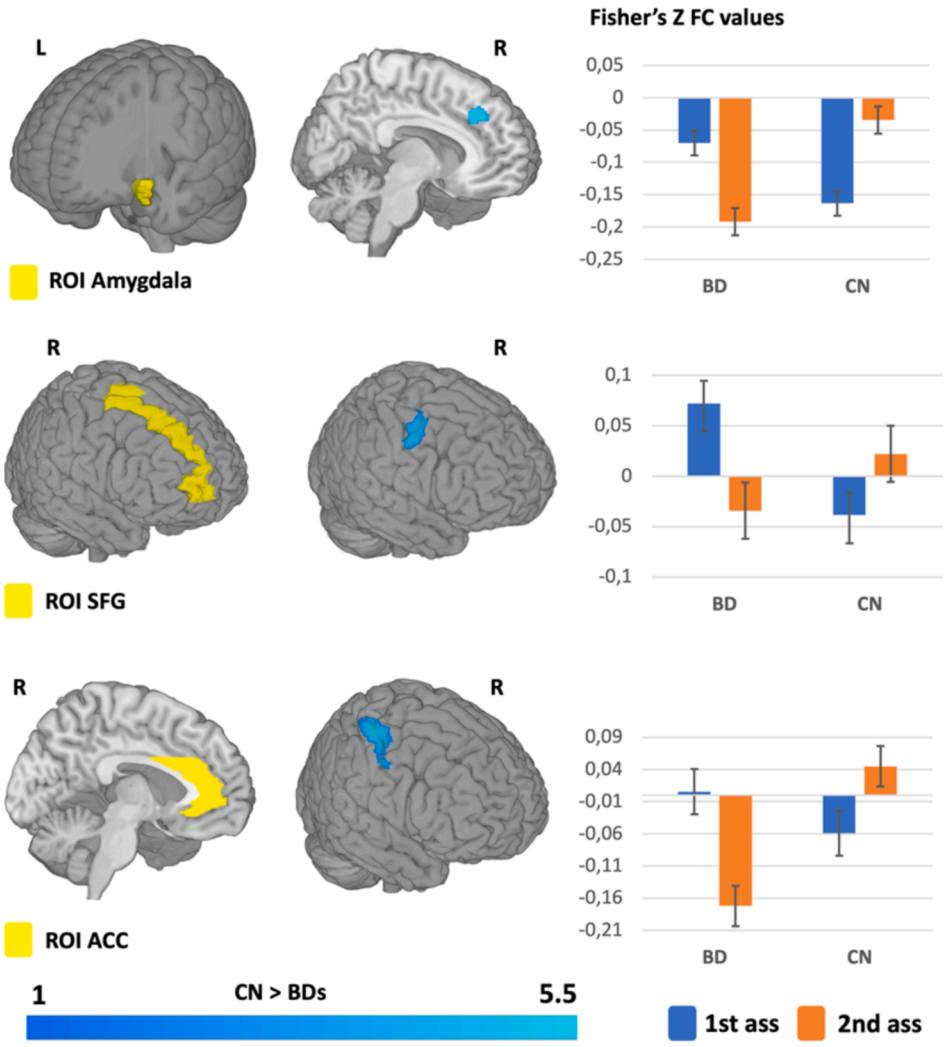

Fig. 1. Seed-to-voxel FC maps for the longitudinal analysis. Binge drinkers (BDs) in comparison with controls (CN) showed decreased FC between i) the left amygdala and the medial frontal gyrus/dACC (BA 32, 9); ii) the rigth superior frontal gyrus (SFG) and the precentral gyrus (BA 6); iii) the ACC and the postcentral gyrus (BA 3). Results are shown corrected for multiple comparisons with a combined peak and cluster threshold (peak $p < 0.001$ and cluster $p_{FWE\ corrected} < 0.05$). Color bar represents t-values. MNI coordinates can be found in Table 3. L, left; R right.

connectivity pattern seems to reflect reduced FC among brain areas previously identified as part of the ECN, a network that has been recently highlighted for its negative association between FC and past month's BD (Lesnewich et al., 2022). Our results also align partially with some of the previous reports from cross-sectional studies in the BD population (e.g., Arienzo et al., 2019; Morris et al., 2016; Herman et al., 2018) and may be related to the executive dysfunction associated with mid and long-term alcohol misuse (Goldstein & Volkow, 2011; Zilverstand et al., 2018).

Moreover, the decreased FC of the amygdala with the mFG/dACC is in line with reported FC anomalies of this region with frontal areas in studies focused on BD (Crane et al., 2018), adolescents with moderate consumption of alcohol (Peters et al., 2015), social drinkers (Hu et al., 2018) and AUD patients (Müller-Oehring et al., 2015; Wade et al., 2017; Zhu et al., 2017). The amygdala-prefrontal connectivity is considered key for implementing adequate emotion-regulation responses (Kim et al., 2011; Ochsner et al., 2012), and disruption of this front-limbic circuitry has been linked to addiction vulnerability (Koob & Volkow, 2016). Thus, our results highlight how the maintenance of a BD pattern can lead to a dysfunction of this critical neural circuitry.

Conversely, the reduced FC observed in the ACC is contrary to our hypothesis of an increment in the FC of this region in BDs (Arienzo et al., 2019). Despite the unexpected direction of the anomalies, the relationship between hazardous alcohol consumption patterns and lower ACC FC with fronto-parietal regions is well documented (Müller-Oehring et al., 2015; Zakiniaeiz et al., 2017). More specifically, the post-central gyrus (BA 3) has been identified as part of the sensory-motor network (Damoiseaux et al., 2006), and its interaction with the ACC −as a node of the salience network- could be critical for integrating interoceptive information and contribute to conscious awareness of internal states (Chen et al., 2021; Critchley et al., 2004; Khalsa et al., 2009). In the context of our study, this could mean that prolonged BD habits make it harder to manage interoceptive responses to salient stimuli (i.e. alcohol-related cues), similar to the heightened awareness of craving in patients with AUD (Volkow et al., 2019; Volkow & Morales, 2015).

On the other hand, the increased brain connectivity observed at the Nacc is in line with our hypothesis and with prior findings that showed abnormalities in reward-related areas both in BDs and AUD patients (e.g., Arienzo et al., 2019; Müller-Oehring et al., 2015). This increased FC in appetitive-driven regions with frontal executive regions (i.e., MFG and SFG) may subserve the missregulation of expectancies and appetitive responses towards alcohol-related stimuli, previously reported in BDs (Ames et al., 2014; Brumback et al., 2015). Interestingly, the opposite pattern (reduced FC) has been suggested to help the maintenance of abstinence in AUD (Camchong et al., 2013). Otherwise,

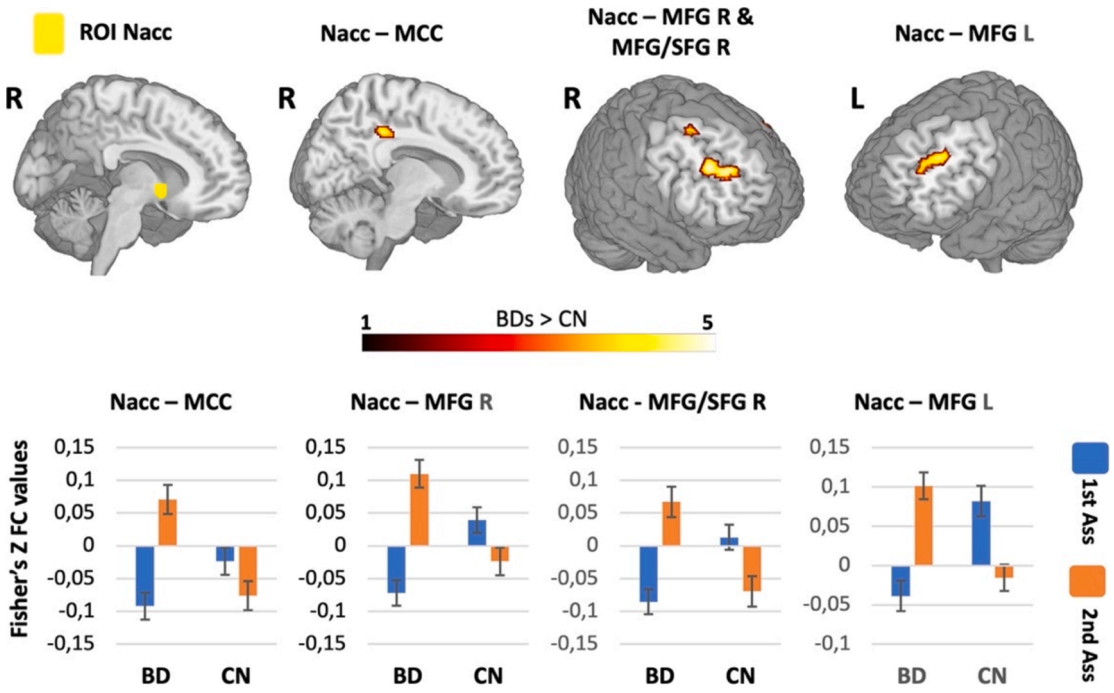

Fig. 2. Seed-to-voxel FC maps for the longitudinal analysis. Binge drinkers (BDs) in comparison with controls (CN) showed increased FC between the nucleus accumbens (Nacc) and i) the middle-posterior cingulate cortex (BA 31); ii) the right middle frontal gyrus (MFG, BA 8, 9) and the right middle-superior frontal gyrus (BA 6); iii) the left MFG (BA 8, 9). Results are shown corrected for multiple comparisons with a combined peak and cluster threshold (peak $p < 0.001$ and cluster $p_{FWE\ corrected} < 0.05$). Color bar represents t-values. MNI coordinates can be found in Table 3.

although our analysis does not allow us to confirm this interpretation of the results, the connectivity with the MCC could favour autobiographical memory processes (Boccia et al., 2019; Rolls, 2019) and be related to reward choice in gain-loss contexts (Zeng et al., 2023), pointing towards an imbalanced relationship between the reward and the default mode network. Therefore, BD-related enhanced FC of the Nacc with the prefrontal cortex and MCC may be interpreted as an initial imbalance that ultimately could lead to disproportionate guidance of drug craving over behavioral control (Everitt & Robbins, 2016; Koob & Volkow, 2016).

Our results may also be interpreted in terms of how factors such as BD influence developmental changes in the brain's functional organization (Menon, 2013). Previous studies have suggested that while motivational systems mature earlier, the spatial structure of FC changes during late adolescence particularly affects medial (e.g., ACC), lateral frontal (e.g., SFG) and parietal regions as well as its connectivity with subcortical structures such as the amygdala and hippocampus (Pujol et al., 2021; Stevens, 2016). This pattern of changes is hypothesized to explain the higher levels of impulsivity and sensation-seeking observed in adolescents (Stevens, 2016; van Duijvenvoorde et al., 2016), making them more vulnerable to risky-behaviors such as BD. By analyzing the differences between BDs and controls in our longitudinal study allowed us to map the changes in the FC of maturing brain areas. In this sense, any differences noted between groups in the longitudinal analysis could be influenced by the effects of BD on neurodevelopmental processes. For instance, previous studies have shown that FC between the amygdala and mPFC is age-dependent, with emerging adults showing stronger FC than adolescents (Gabard-Durnam et al., 2014). Hence, the diminished FC pattern observed in the BD group for the amygdala, ACC, and SFG may reflect the impact of alcohol on the ongoing developmental changes in these structures beyond the short-term neurotoxic effects of alcohol on brain organization.

Despite its strengths, our research has some limitations that must be noted. First, the strict exclusion criteria and the high mobility of university students in their third academic year (mobility programs between universities), added to the usual dropout of longitudinal designs, resulted in limited sample size, forcing us to be cautious about interpreting the findings, and signaling that our study would need validation from future larger longitudinal cohort studies. Second, the absence of prior-to-alcohol onset fMRI measures makes it difficult to distinguish which differences are due to an alteration of developmental processes and which are linked to more direct alcohol neurotoxic effects. Lastly, the exploratory character of this study has left some potentially relevant hypotheses untested that should be addressed by future studies, such as the effect of sex on the long-term interactions between BD and FC.

In conclusion, our results provide new evidence about the impact of maintaining a BD pattern during a key timeframe for brain development (i.e., 18–21 years of age). While previous studies have shown that BD can be related to a significantly different FC in some IFNs, the longitudinal nature of the present study allows us to support two critical points: i) some differences would arise after mid-to-long-term maintenance of the consumption pattern, and ii) the neurotoxic effects of alcohol while the brain is still developing could lead to a significantly different functional organization of the brain. Regarding the first point, although it could seem like a logical conclusion, the scarcity of longitudinal designs with neuroimaging measures is still a problem in fully understanding the additive neurotoxic effects that BD could have in the long-term.

Lastly, future studies should explore the imbalance produced by the alcohol consumption pattern in maturing brain areas to explain the previously reported increased vulnerability of BDs to develop an AUD. Also, it remains to be seen if these changes could impact FC in such a way that potentially hinders the typical adult brain organization even after abandoning BD habits.

5. Ethics

This study was approved by the Bioethics Committee of the USC and all participants gave written inform consent at the beginning of each of the scanning sessions.

6. Contributors

F.C., S.R.H., and S.D. designed the study. S.S.-S., J.M.P.-G. and J.B.-R. participated in the data collection. S.R.H. and S.D. were responsible for sample selection. S.S.-S., A.B.-L., and S.D. analyzed and interpreted the data. S.S.-S. wrote the article. All authors reviewed the final version of the manuscript and approved it for publication.

CRediT authorship contribution statement

Samuel Suárez-Suárez: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **Fernando Cadaveira:** Writing – review & editing, Validation, Supervision, Project administration, Funding acquisition, Conceptualization. **Alfonso Barrós-Loscertales:** Writing – review & editing, Software, Methodology, Investigation, Formal analysis. **José Manuel Pérez-García:** Investigation, Data curation. **Socorro Rodríguez Holguín:** Project administration, Data curation, Conceptualization. **Javier Blanco-Ramos:** Investigation, Data curation. **Sonia Doallo:** Writing – review & editing, Supervision, Methodology, Investigation, Data curation, Conceptualization.

Funding

This work was supported by grants from the Spanish Ministerio de Sanidad, Servicios Sociales e Igualdad, Plan Nacional sobre Drogas (PNSD 2015/034) Ministerio de Economía y Competitividad (PSI2015-70525-P) co-funded for European Regional Development Fund, Grant PID2020-113487RB-I00 funded by MCIN/AEI/https://doi.org/10.13039/501100011033 and Xunta de Galicia (GRC ED431C 2021/08). SSS was supported by a postdoctoral fellowship from the Universidade de Santiago de Compostela co-funded with European Funds (Margarita Salas 2022–2024).

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.abrep.2025.100585.

Data availability

Data will be made available on request.

The MRI and behavioral data supporting the conclusions of this article have been deposited at Open Science Framework repository (https://osf.io/ez5dt/?view_only = 46f1c06a0d064f6c95dbb31278d3cb3a).

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