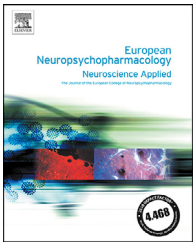
European Neuropsychopharmacology (2019) 29, 1476–1485



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Nucleus accumbens connectivity at rest is associated with alcohol consumption in young male adults

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Received 17 July 2019; received in revised form 21 October 2019; accepted 29 October 2019

KEYWORDS
Alcohol use;
Adolescents;
Resting-state functional connectivity;
Nucleus accumbens;
Lateral prefrontal cortex

Abstract
Alcohol consumption during adolescence might impede normal brain development, while more excessive drinking during this period poses a risk for developing alcohol use disorder. Here it was tested whether nucleus accumbens (NAcc) resting-state functional connectivity could be associated with lifetime drinking behavior in young adults, and whether it could predict their alcohol consumption during a one-year follow-up period. The current investigation was part of the bicentric *Learning and Alcohol Dependence* (LeAD) population-based prospective cohort study. One hundred and eighty-four 18-year-old male social drinking volunteers without a lifetime diagnosis of psychotic, bipolar, or alcohol use disorder were recruited from the general population. Seed-based resting-state functional connectivity was calculated for the bilateral NAcc in

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https://doi.org/10.1016/j.euroneuro.2019.10.008

each participant. Across the group, the association between NAcc functional connectivity and lifetime alcohol consumption was assessed ($p < .05$, whole-brain FWE-corrected). Individual connectivity values were then extracted from regions that demonstrated a significant association to predict drinking behavior during a one-year follow-up period ($n = 143$), correcting for lifetime alcohol consumption. Weaker connectivity between the left NAcc and bilateral dorsolateral prefrontal cortex, inferior frontal gyrus, left caudate nucleus, left putamen, and left insula was associated with greater lifetime alcohol consumption, as well as with greater alcohol consumption during the one-year follow-up period. Our findings underscore the relevance of fronto-striatal connectivity to the field of alcohol research. Impaired prefrontal cognitive control might mediate excessive drinking behavior and may prove a promising biomarker for risk of future alcohol (ab)use.

1. Introduction

Alcohol is the most frequently used psychoactive substance worldwide (Gowing et al., 2015). Although its negative consequences are widely acknowledged, the use of alcohol is socially accepted across many cultures, even in adolescence. It is this developmental stage in particular that is characterized by marked changes in motivated behavior, during which an increased focus on rewarding outcomes is generally demonstrated (van Duijvenvoorde et al., 2016). Such reward-driven behavior, together with the presence of associated personality traits was shown to be a risk factor for early alcohol use (Nees et al., 2012). At the same time, frontal control areas are not yet fully developed, which is thought to underlie reduced behavioral control (Mills et al., 2014). Consequently, this brain developmental mismatch may lead to risky behavior, such as exploration of recreational, but intoxicating substances, including alcohol, which might ultimately endanger one's health in the case of substance abuse. However, most alcohol-consuming adolescents do not develop a sustained *alcohol use disorder* (AUD), although several variables, such as the starting age of alcohol use, a (steadily increasing) drinking load, and the number of binge episodes during adolescence are clear risk factors for developing AUD (Feldstein Ewing et al., 2014).

As the brain still undergoes significant structural (Gogtay et al., 2004) and functional (Grayson and Fair, 2017) maturation throughout adolescence and into early adulthood, it might be particularly vulnerable to the toxic effects of alcohol. Previous research has indeed demonstrated that excessive alcohol use is associated with structural brain changes in adolescents: areas identified to be most susceptible to such changes are the cerebellum and prefrontal cortex, which are relevant to behavioral fine-tuning and mediation of higher-order cognitive control, as well as regions of the limbic and mesolimbic system, which are involved in motivation, emotion, learning, and reward processes (Cservenka and Brumback, 2017; Feldstein Ewing et al., 2014). Specifically, accelerated gray matter volume decreases (Heikkinen et al., 2017), attenuated white matter volume increases (Squeglia and Gray, 2016), and smaller overall brain volume (Squeglia et al., 2014) and cortical thinning have been reported in (heavy) drinking adolescents (Cservenka and Brumback, 2017; Silveri et al., 2016).

On the other hand, reduced top-down modulation of subcortical structures by prefrontal areas has been linked to increased substance use (Silveri et al., 2016; van Duijvenvoorde et al., 2016), and to alcohol use in specific (Goldstein and Volkow, 2011), as well as to the pathogenesis of substance use disorders, including AUD (Park et al., 2010). For example, in healthy adolescents and young adults it was shown that weaker functional connectivity between the amygdala and orbitofrontal cortex was associated with recent alcohol use, while it could predict future alcohol consumption during a two-year follow-up period as well: Although lesser integration of fronto-limbic circuits may initially have been caused by previous alcohol intake, the prospective results illustrate the potential of using connectivity measures to better understand and predict future alcohol use (Peters et al., 2017).

To date, the nucleus accumbens (NAcc), implicated in incentive motivation and reward processing (Hikida et al., 2016), has been underrepresented in developmental research, especially with respect to substance use during adolescence. Nucleus accumbens function has repeatedly been implicated in the development and maintenance of AUD (Claus et al., 2011; Garbusow et al., 2016), as well as connectivity between the NAcc and prefrontal areas (Forbes et al., 2014; Park et al., 2010). Although NAcc connectivity has been studied in patients and in substance-naïve young adults with a family history of AUD (Camchong et al., 2014; Cservenka et al., 2014; Squeglia et al., 2015), no study has looked at its association with alcohol consumption during adolescence so far.

Here we tested whether lifetime drinking behavior is associated with NAcc resting-state functional connectivity (RSFC), and whether NAcc connectivity predicts the use of alcohol during a one-year follow up period. Given the importance of prefrontal-striatal connectivity for cognitive control, we hypothesized that weaker NAcc connectivity to the prefrontal cortex would be associated with higher lifetime drinking behavior, as well as with more alcohol consumption during the year after scanning.

2. Experimental procedures

2.1. Participants

For the current study, 199 healthy 18-year-old male adolescents were recruited by mail via local resident registration offices in Berlin ($n = 92$) and Dresden ($n = 107$) as part of a large-scale bi-

centric study (LeAD; www.lead-studie.de; clinical trial number NCT01744834). Inclusion criteria were: (1) right-handedness; (2) sufficient comprehension of German; (3) at least two drinking occasions during the three months before inclusion, thereby ensuring inclusion of social drinking behavior in the study sample; (4) normal or corrected-to-normal vision. Exclusion criteria were: (1) present or past severe head trauma or central nervous dysfunction; (2) use of illicit drugs in the past three months, cannabis use during the past ten days, use of medication affecting the central nervous system, and alcohol intake in the past 24 h; (3) lifetime diagnosis of bipolar disorder, psychotic disorders, or substance use disorder (except nicotine); (4) acute diagnosis of major depression, generalized anxiety disorder, obsessive-compulsive disorder, posttraumatic stress disorder, hypomania, or borderline personality disorder, diagnosed by the interviewer-administered computer-based Composite International Diagnostic Interview (CIDI) (Jacobi et al., 2013; Lachner et al., 1998; Wittchen et al., 1998); (5) color vision deficiency. The Medical Ethics Committees of Charité – Universitätsmedizin Berlin and Technische Universität Dresden approved the study, and all participants provided written informed consent. Participants received a monetary compensation of 10€/hour for study participation.

2.2. Assessment of drinking behavior

At baseline, participants were interviewed using the CIDI (Jacobi et al., 2013; Lachner et al., 1998; Wittchen et al., 1998), which includes comprehensive questions on lifetime and current alcohol use. During the one-year follow up, participants underwent a CIDI-interview by phone to enquire their current and past-year alcohol consumption.

To estimate lifetime drinking behavior until the baseline measurement, a drink score (Nebe et al., 2017) was calculated based on the following CIDI information: (1) timespan since first drink (i.e., drinking a whole alcoholic beverage), (2) timespan since first time being drunk, (3) timespan since first binge-drinking episode, (4) number of lifetime binge-drinking episodes, (5) average lifetime alcohol consumption per binge (grams of alcohol), (6) average alcohol consumption per drinking occasion in the past year (grams of alcohol), (7) average alcohol consumption per day in the past year (grams of alcohol per day). Binge drinking was defined as the consumption of at least five drinks ($\geq$60 g of alcohol) on one occasion. Next, values for each variable were *z*-standardized (with zero mean) across participants, and missing values were set to zero, so that these would not influence the drink score. At the end, all *z*-transformed values were summed up to get the lifetime drink score per participant.

Similarly, a drink score for a one-year follow up period after the scan session (FU drink score) was calculated for those who still participated in the study ($n = 143$). For this score, all timespan and lifetime variables were excluded and replaced by (1) the number of binge-drinking episodes (past year), and (2) the average alcohol consumption per binge (past year), together with (3) the average alcohol consumption per drinking occasion (past year) and (4) the average alcohol consumption per day (past year). Values were then *z*-standardized, missing values set to zero, and summed to calculate the FU drink score per participant.

2.3. Demographics and psychometrics

Socioeconomic status (SES) was computed as the sum of *z*-transformed self-ratings of social status, household income and inverse personal debt scores (Schmidt et al., 2006). Nicotine dependence was assessed with the Fagerström Test for Cigarette Dependence (FTCD; Fagerström, 2012; Heatherton et al., 1991), verbal intelligence with the MWT-B (Mehrfachwahl-Wortschatz-Intelligenztest; Lehrl et al., 1995), Impulsivity with the short version of the Barrat Impulsiveness Scale (BIS-15; Patton et al., 1995), and self-reported substance abuse-related personality traits with the Substance Use Risk Profile Scale (SURPS; Woicik et al., 2009). The SURPS comprises four subscales: anxiety sensitivity, hopelessness, sensation seeking, and impulsivity. Anxiety and depressive symptoms during the past week were assessed with the Hospital Anxiety and Depression Scale (HADS; Zigmond and Snaith, 1983).

2.4. MRI data acquisition

Imaging data were acquired on 3T Siemens Magnetom Tim Trio MRI scanners (Siemens Medical Solutions, Erlangen, Germany), with a 12-channel receiver head coil. One-hundred-forty-eight T_2^*-weighted gradient-echo echo-planar imaging resting-state volumes were acquired with the following scan parameters: TR = 2410 ms, TE = 25 ms, 80° flip angle, 42 axial slices with a 1 mm slice gap, 2 mm slice thickness, FOV = 192 × 192 mm^2, with a 3 × 3 mm^2 in-plane resolution, duration = 6 min. Participants were instructed to lie still with their eyes closed and let their minds wander without focusing on a specific thought.

A high-resolution T1-weighted structural scan was acquired for registration purposes using a magnetization-prepared rapid gradient-echo (MPRAGE) sequence with the following scan parameters: TR = 1900 ms, TE = 2.52 ms, 9° flip angle, 192 sagittal slices, 1 mm slice thickness, FOV = 256 × 256 mm^2, with a 1 × 1 mm^2 in-plane resolution. All T1-weighted images were screened for clinically relevant findings by a neuroradiologist prior to analysis.

2.5. Imaging preprocessing

Imaging data were first screened to exclude participants with corrupted data, serious acquisition artifacts, or excessive head movement (i.e., mean frame-wise displacement >0.5 mm). Preprocessing of resting-state data included motion correction, slice-timing correction, non-brain removal, 6 mm FWHM spatial smoothing, all done using FSL (FMRIB Software Library v5.0). Next, data were denoised using Independent-Component-Analysis-based artifact removal (ICA-AROMA; Pruim et al., 2015b), a data-driven approach to remove motion- and physiological noise-related signal sources, and a highpass filter of 0.008 Hz was applied. Resting-state volumes were co-registered to the T1 image using boundary-based registration (BBR; Greve and Fischl, 2009), including a fieldmap to consider distortions due to local field inhomogeneity. Non-linear normalization of the T1 image to the 2 mm MNI standard space template (Montreal Neurological Institute, Quebec, Canada) was done using Advanced Normalization Tools (ANTs; Avants et al., 2011). Lastly, resting-state data were normalized to MNI standard space, applying the registration matrices and warp images from the two previous registration steps, and then resampled into 3 mm isotropic voxels.

2.6. Imaging analysis

To examine NAcc functional connectivity, a seed-based connectivity analysis was employed. Binary seed masks of the left and right NAcc were defined using the Harvard-Oxford Subcortical Probability Atlas, only including voxels with a probability higher than 50%, which allowed sufficient coverage of the accumbens while minimizing the risk of partial volume effects with surrounding structures. All participants demonstrated robust signal intensities within the bilateral masks, suggesting that the NAcc was not affected by MR susceptibility artifacts. As a control, additional seed masks were

created for the left and right primary visual cortex (V1) using the Juelich Histological Atlas, only including voxels with a probability higher than 90%. Applying these masks (see Supplemental Fig. 1), the first Eigen time series was extracted from the preprocessed resting-state data, for the left and right seeds separately. To obtain functional connectivity maps, the time series of each participant's left and right seed (as subtle laterality effects might exist) was regressed separately against every other voxel's time series using the general linear model (GLM) with FSL's command line tool *fsl_glm*. Time series extracted from masks of the deep white matter and CSF were included as nuisance variables.

The individual z-transformed whole-brain NAcc and V1 connectivity maps were fed into a higher-level GLM, for the left and right seeds separately, using the lifetime drink score (baseline) as regressor of interest and scan site as dummy (i.e., coded binary) variable. The resulting *t*-statistical maps, describing the association between connectivity and the drink score, then underwent Threshold-Free Cluster Enhancement (TFCE; Smith and Nichols, 2009), using the default parameter settings ($H = 2$, $E = 0.5$, $C = 6$), and significance testing was carried out with permutation testing (10,000 iterations) using the in-house developed *TFCE_mediation* software (Lett et al., 2017). In the latter step, a null distribution of random results was generated against which the true findings were tested, which resulted in whole-brain voxelwise statistical images that are family-wise error corrected for multiple comparisons, thresholded at $p < .05$. To rule out that grey matter volume would drive potential connectivity effects, the analysis was repeated with a voxelwise grey matter volume covariate. To this end, FSL's command line tool *feat_gm_prepare* was used to produce a voxelwise confound regressor: first, structural scans are grey matter segmented using FAST (fMRI's Automated Segmentation Tool, Zhang; et al., 2001); second, the previously generated ANTs warp files were applied to the grey matter maps, concatenated across participants, and demeaned.

To see if NAcc functional connectivity can predict future drinking behavior, individual mean connectivity values were extracted from a sphere of 6 mm radius around the peak voxels of clusters that showed a significant association with the lifetime drink score at baseline (means were not weighted for the effect strength), which were then entered as independent variables in an ANOVA, using IBM SPSS Statistics for Windows, version 20 (IBM Corp., Armonk, N.Y., USA). The FU drink score was added as dependent variable, and lifetime drink score, given its strong correlation with FU drinking behavior, and site as covariates. The significance level for this analysis was set at $p < .05$.

2.7. Procedure

To rule out alcohol or drug use (except for nicotine, which was allowed without restriction) at the day of scanning, an alcohol breath test and drug urine test were administered upon arrival of participants. As the resting-state acquisition was part of a larger behavioral and neuroimaging study, all participants completed a battery of learning tasks outside and inside the MRI scanner. Within the scanner, two learning tasks (PIT: Garbusow et al., 2016; Two-Step: Sebold et al., 2017) were followed by the acquisition of two structural scans (i.e., FLAIR and T1), allowing for a task-free gap of approximately 10 min, after which the resting-state scan was acquired as the last scan in the scanning protocol. Subsequently, participants were taken out of the scanner, debriefed, and paid for their participation.

3. Results

Seed masks, as well as voxelwise uncorrected (*t*) and corrected (TFCE *p*) statistical maps of our analyses are available on NeuroVault.org (Gorgolewski et al., 2015) via this link: https://identifiers.org/neurovault.collection:3020.

After excluding participants for excessive head movement ($n = 2$), acquisition artifacts and/or corrupted or missing files ($n = 5$), incidental findings in the T1 structural image ($n = 4$), or a positive urine drug test ($n = 4$), the final sample comprised 184 participants (Berlin: $n = 84$; Dresden: $n = 100$). Importantly, framewise displacement (FD) across participants was low (mean=0.081; SD=0.052; range=0.02-0.36), while no association was found between FD and drink score ($r_{184} = 0$, $p = .995$). Thirty-four participants indicated in the exit interview that they experienced short periods of drowsiness during the eyes-closed resting-state scan, but they did not differ from the fully awake participants ($n = 140$; 10 participants did not provide feedback) on the drink score ($p = .181$), or on any of the functional connectivity effects reported later on (all p's $> .2$).

3.1. Demographic, drinking, and psychometric variables

Demographic, drinking, and psychometric variables are listed in Table 1. Both the lifetime and the follow-up drink score were normally distributed across the sample and were strongly correlated in our sample, $r(184) = 0.894$, $p < .001$. Only two participants could be considered outliers on both the lifetime and follow-up drink score (i.e., >3 standard deviations from the mean).

Our sample comprised 18 ex- and 33 current smokers, of which most indicated very low to low nicotine dependence and consumption (see Table 1). Current smokers reported more lifetime alcohol consumption ($M = 2.48$, $SD = 5.24$) than non-smokers ($M = -0.54$, $SD = 4.4$), $t(182) = -3.45$, $p = .001$, which did not change when including ex-smokers. A similar difference was found for the follow-up drink score ($p = .003$).

Over half of the sample indicated to have used cannabis once or more, although the majority reported not to be a frequent user (see Table 1). As for nicotine, more lifetime alcohol consumption was found for participants who had used cannabis ($M = 0.91$, $SD = 4.29$) than those who did not ($M = -1.63$, $SD = 4.98$), $t(182) = -3.64$, $p < .001$, as well as for the follow-up drink score ($p < .001$).

Only few participants in our sample ever used other illicit drugs than cannabis: amphetamine ($n = 7$), ecstasy ($n = 7$), LSD ($n = 2$), cocaine ($n = 1$), inhalants ($n = 2$), and/or mushrooms ($n = 4$).

Associations of both the lifetime and follow-up drink score were found with the MWT-B ($r(184) = -0.175$, $p = .018$, and $r(143) = -0.178$, $p = .034$, respectively), BIS-15 ($r(181) = 0.257$, $p < .001$, and $r(141) = 0.267$, $p = .001$, respectively), SURPS sensation seeking ($r(182) = 0.15$, $p = .043$, and $r(142) = 0.21$, $p = .012$, respectively), and SURPS impulsivity ($r(182) = 0.231$, $p = .002$, and $r(142) = 0.223$, $p = .008$, respectively).

Last, seven participants had one first-degree relative with (a history of) alcohol use disorder, and one participant reported two first-degree relatives. This was, however, too

Table 1 Demographics, and descriptive statistics of measures of substance use and psychometric measures from the participants included in the analyses sample ($n = 184$).

	n	Min	Max	Mean	SD
Descriptive statistics of sample					
Age	184	18.07	18.85	18.38	0.19
Years in school	183	10	14.50	11.62	0.90
Socioeconomic status (SES)	171	−5.45	2.31	−0.08	1.29
Measures of alcohol consumption (CIDI items)					
Lifetime drink score	184	−9.28	19.95	0.00	4.70
Age of first drink	184	9	17.92	14.28	1.40
Age of first time drunk	177	10	18.33	15.75	1.19
Age of first binge-drinking episode	134	14	18.22	16.51	0.83
Number of binge-drinking episodes	176	0	150	14.96	25.22
Alcohol consumption per binge-drinking episode (g)	184	0	450	93.82	66.37
Estimated alcohol consumption in past year (g/day)	184	0.64	112.50	11.71	12.90
Alcohol consumption in past year (g/drinking occasion)	184	18	225	70.04	41.78
FU drink score	143	−9.47	15.51	0.00	4.99
Number of binge-drinking episodes past year	143	0	104	10.74	20.23
Alcohol consumption per binge-drinking episode past year (g)	143	0	805	110.40	97.16
Estimated alcohol consumption in past year (g/day)	143	0	66	11.01	10.44
Alcohol consumption in past year (g/drinking occasion)	143	0	253	60.94	41.41
Nicotine use					
Current smoker	33	-	-	-	-
Frequency per day (<10/10-20/20-30)	29/3/1				
Ex-smoker	18	-	-	-	-
FTCD dependence (very low/low/strong/very strong)	27/4/1/1	-	-	-	-
FTCD sum	33	0	8	0.19	0.88
Cannabis use					
Past year	106	-	-	-	-
Lifetime	118	-	-	-	-
Frequency total lifetime (< 10/10-60/>60)	70/33/15	-	-	-	-
Psychometrics					
MWT-B	184	87	124	98.08	5.18
BIS-15	181	17	45	30.13	5.25
SURPS anxiety sensitivity	184	5	17	10.58	2.29
SURPS hopelessness	184	7	23	11.87	2.80
SURPS sensation seeking	184	7	23	16.59	3.11
SURPS impulsivity	182	5	17	9.90	1.95
HADS anxiety	184	0	11	2.58	2.45
HADS depression	184	0	9	1.68	1.83

Socioeconomic status (SES): computed as the sum of z-transformed social status, household income, and inverse personal debt scores (Schmidt et al., 2006); FTCD - Fagerström Test for Cigarette Dependence (Fagerström, 2012; Heatherton et al., 1991); MWT-B - Mehrfachwahl-Wortschatz-Intelligenztest (test for verbal intelligence; Lehrl et al., 1995); BIS-15 - Barrat Impulsiveness Scale (Patton et al., 1995); SURPS - substance use risk prolife scale (Woicik et al., 2009); HADS - Hospital Anxiety and Depression Scale (Zigmond and Snaith, 1983).

small a subsample to be able to test for effects of family history.

3.2. Overall nucleus accumbens resting-state functional connectivity

Across the entire sample, the left and right NAcc demonstrated RSFC with a set of subcortical and cortical regions, including the caudate nucleus, thalamus, ventral tegmental area, amygdala, hippocampus, cerebellum, temporal poles, posterior cingulate cortex, precuneus, lateral parietal cortex, lateral orbitofrontal cortex, and ventromedial prefrontal cortex (Fig. 1).

3.3. Association between NAcc resting-state functional connectivity and lifetime drinking

Lifetime alcohol consumption, as reflected by the lifetime drink score, was associated with functional connectivity between the left NAcc and a cluster (1003 voxels) spanning the left dorsolateral prefrontal cortex (DLPFC), left inferior frontal gyrus (IFG), left caudate nucleus, left putamen, and left insula, and a cluster (526 voxels) spanning the right

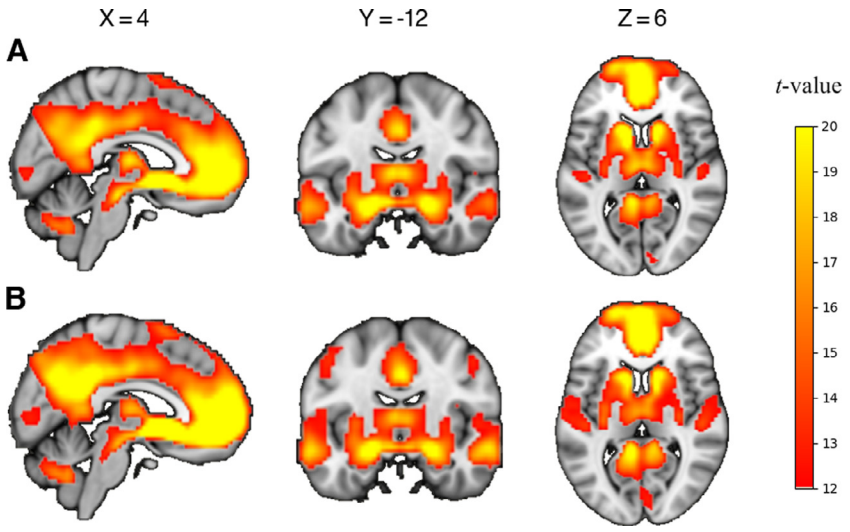

Fig. 1 Average left (panel A) and right (panel B) nucleus accumbens resting-state functional connectivity across the sample. Whole-brain NAcc connectivity patterns (uncorrected, but arbitrarily thresholded at $t > 12$) in red-to-yellow overlaid on the MNI standard brain. Brains are displayed in neurological convention (i.e., left hemisphere is on the left side of the image). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

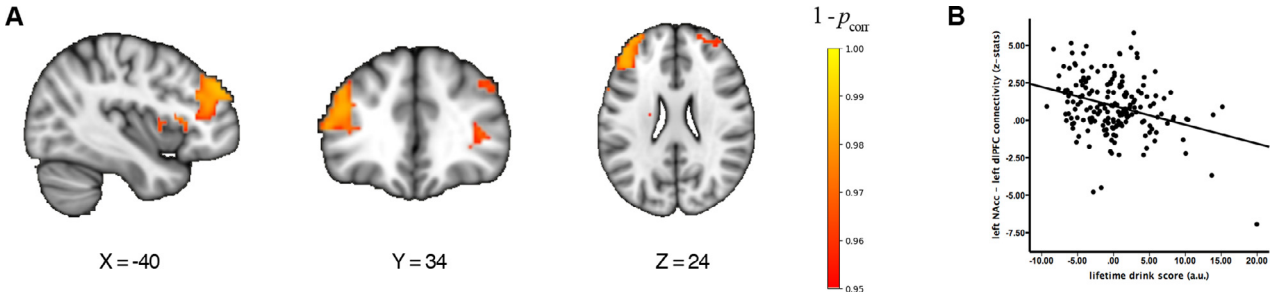

Fig. 2 Association between nucleus accumbens resting-state functional connectivity and lifetime drinking behavior. Panel A: Whole-brain TFCE-corrected associations ($p_{corr} < .05$) in red-to-yellow overlaid on the MNI standard brain. Brains are displayed in neurological convention (i.e., left hemisphere is on the left side of the image). The color bar values are $1 - p_{corr}$. Panel B: Example scatter plot of the association with the lifetime drink score (in arbitrary units), shown for the mean connectivity values (z-stats) from a sphere of 6 mm radius centered around the peak voxel of the cluster demonstrating the strongest association: the left dorsolateral prefrontal cortex (means were not weighted for the effect strength). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

DLPFC and right IFG (all $p_{corr} < .05$; see Fig. 2). Specifically, weaker left NAcc connectivity with the abovementioned areas was associated with greater lifetime alcohol consumption.

Importantly, adding covariates for grey matter volume, or for recent or lifetime cannabis use did not affect the results. In addition, rerunning the analysis without the two drink score outliers gave virtually identical results, which indicates that these outliers did not drive the association. Adding a dummy variable for current or lifetime smoking, however, did remove the whole-brain corrected association with the lifetime drink score, likely because of high collinearity between the drink score and smoking status. This was corroborated in a further – exploratory – whole-brain analysis, which revealed a similar pattern of weaker NAcc connectivity in (ex-)smokers compared to non-smokers ($p_{corr} < .05$), which also disappeared when adding the lifetime drink score as covariate.

The right NAcc demonstrated the same pattern of functional connectivity with the bilateral DLPFC and right IFG associated with lifetime alcohol consumption as the left NAcc, albeit only at a lenient uncorrected threshold ($p < .001$).

An exploratory stepwise multiple linear regression was performed to test whether a specific subset of the drinking variables that were used to calculate the lifetime drink score had driven our results. To this end, individual connectivity values (z-scores) with the left DLPFC, which demonstrated the strongest association with the lifetime drink score, were extracted and entered as dependent variable in the regression model. A significant regression equation was found, $F(1, 182) = 22.44$, $p < .001$, with an R^2 of 0.11. Participants' predicted left NAcc functional connectivity with the left DLPFC could best be explained by a single variable: "Average alcohol consumption per day in the past year", $B = -0.62$, $t = -4.74$, $p < .001$. Nevertheless, all drinking variables but "Age of first drink"

and "Age of first binge-drinking episode" were significantly associated with the left DLPFC connectivity values, most notably "Alcohol consumption per binge-drinking episode in grams" ($r = -0.296$, $p < .001$) and "Alcohol consumption per occasion in past year" ($r = -0.295$, $p < .001$).

3.4. Association between NAcc resting-state functional connectivity and psychometric variables

While the psychometric data were associated with the lifetime and follow-up drink score, no such association was found between the psychometric data and the NAcc connectivity associated with the drinking scores.

3.5. Association between NAcc resting-state functional connectivity and future drinking

Not only was weaker left NAcc functional connectivity with the left DLPFC, left IFG and left insula associated with lifetime alcohol consumption, it also predicted higher alcohol consumption during the one-year follow up period (left DLPFC: $F(1, 139) = 6.457$, $p = .012$, $\eta^2 = 0.044$; left IFG: $F(1, 139) = 5.722$, $p = .018$, $\eta^2 = 0.04$; left insula: $F(1, 139) = 4.112$, p=.044, $\eta^2 = 0.029$. Importantly, this prediction was over and above what could be explained by lifetime drinking score, which was added as covariate in the analysis. No association was found for the caudate nucleus or putamen.

3.6. Association between V1 resting-state functional connectivity and lifetime drinking

The analysis of the control seeds in the left and right primary visual cortex (V1) did not reveal an association between the lifetime drinking score and connectivity with the lateral PFC, also not at the lenient uncorrected threshold of $p < .001$.

4. Discussion

The aim of the current study was to examine whether nucleus accumbens resting-state functional connectivity is linked to previous lifetime drinking behavior in young, healthy adults and whether it can prospectively predict drinking during a one-year follow up period. Both the left and right NAcc demonstrated a connectivity pattern that was expected based on the studies that have been reported before (Camchong et al., 2014; Cauda et al., 2011; Forbes et al., 2014; Park et al., 2010). In accordance with our a priori hypothesis, we found weaker functional connectivity between the left NAcc and bilateral DLPFC and bilateral IFG, extending into the left dorsal anterior insula, when alcohol consumption in the past was greater. However, a follow-up analysis showed that the drinking load in the past year had the largest predictive power. Moreover, functional connectivity with these regions predicted drinking behavior during a one-year follow up period with lower connectivity being associated with more alcohol use, although with modest variance explained. Analysis of the control seeds in the primary visual cortex did not demonstrate an association with alcohol consumption in the lateral PFC. The current study is the first large-scale study that shows a connection between weaker RSFC of the NAcc with prefrontal control regions, most notably the DLPFC, and higher alcohol consumption among young male adult social drinkers.

The DLPFC and IFG are known to be involved in a variety of higher order executive functions, such as cognitive control, including interference monitoring, choice selection, and response inhibition (Goldstein and Volkow, 2011; Levy and Wagner, 2011). Furthermore, the DLPFC is a key region for goal-directed decision-making and self-regulation with respect to the valuation of reward stimuli (Dixon and Christoff, 2012; Levy and Wagner, 2011), while the IFG is implicated in response inhibition and risk aversion (Christopoulos et al., 2009). Indeed, disruptions in IFG functioning may lead to riskier decision making and less inhibitory control (Christopoulos et al., 2009; Goldstein and Volkow, 2011; Levy and Wagner, 2011), whereas disruptions in DLPFC functioning are thought to contribute to compulsive behavior, including drug intake, through poorer decision-making and therefore less flexible responding (Fecteau et al., 2010; Goldstein and Volkow, 2011). Moreover, lateral prefrontal and subcortical, reward-related regions were more disconnected in highly impulsive individuals (Davis et al., 2013). Not surprisingly, both the IFG and DLPFC have emerged as brain regions that are key to substance use disorders: For example, alcohol induced disturbance of IFG function was found to be associated with reduced inhibitory control and higher alcohol self-administration (Gan et al., 2014), while IFG structure and function could classify binge drinking at age 14 (Whelan et al., 2014). In addition, altered connectivity between the DLPFC and striatal reward regions, in particular the ventral striatum, has been related to impairments in reinforcement learning and stronger craving in alcohol-dependent patients (Forbes et al., 2014; Park et al., 2010). Our results thus suggest weaker top-down modulation of the NAcc by the prefrontal cortex, and therefore less control over drinking behavior (Deserno et al., 2015). Similarly, a prospective study demonstrated less integration of regions within a fronto-parietal cognitive control network to be related to escalation of the alcohol intake per drinking occasion in young adults (Worhunsky et al., 2016).

An important limitation is the correlational nature of our results. As such, we cannot distinguish cause and effect: More drinking could lead to weaker connectivity, be a result thereof, or the two might even interact. Nevertheless, drinking behavior during a one-year follow-up period was predicted by connectivity strength in our study, even when controlling for lifetime drinking, while prior research in alcohol naïve youth with a positive family history of alcohol abuse revealed comparable alterations in NAcc connectivity, both anatomically (Squeglia et al., 2015) and functionally (Camchong et al., 2014). This suggests that weaker connectivity might be a vulnerability factor for increased substance use, rather than a consequence thereof. Similarly, in substance naïve adolescents, lower gray matter volume and less activity in frontal brain regions were found to be risk factors for future transition into alcohol use (O'Halloran et al., 2017). On the other hand, it

was demonstrated that alcohol exposure during development resulted in weaker fronto-striatal connectivity in mice (Broadwater et al., 2017), while frontal lobe volume abnormalities were found to be both a pre-existing risk factor for and a consequence of human adolescent alcohol use (Silveri et al., 2016). The latter study particularly supports the notion of a dynamic interaction between alcohol use and changes in brain connectivity over time. However, longitudinal studies with an inclusion age before the first alcoholic drink are clearly needed to better characterize neural development in relation to alcohol use, together with longer follow-up periods with frequent assessments to be able to capture the transition of leisurely drinking into pathological alcohol use.

Although drinking outliers, grey matter volume, or cannabis use did not affect our results, current and lifetime smoking, perhaps not surprisingly, demonstrated considerable shared variance with drinking behavior in explaining accumbens connectivity. As such, it is difficult to disentangle whether nicotine use is in fact driving our results. However, given the low nicotine consumption and dependence reported by the majority of the smokers in our sample it is rather unlikely that nicotine dependence drives our results.

Importantly, German alcohol laws are fairly liberal, allowing consumption of undistilled alcoholic beverages (e.g., beer and wine) as of age 16, or under custodial supervision even as early as age 14. In many other countries, however, drinking any alcohol-containing beverage under age 18 is illegal. As such, the association of drinking behavior with accumbens connectivity found in the current study may not generalize to samples from other countries, where rule breaking would play a confounding role in assessing such a relation.

Only males were included in the current study. As such, the results found here might not be generalizable to female adolescents.

No physiological data were acquired during scanning to control for cardiac- and respiratory-induced noise, which could have influenced our results. However, we used a data-driven approach to remove motion- and physiological noise-related signal sources instead, of which the efficacy has been established in functional MRI data (Pruim et al., 2015a).

A careful note should be made regarding the correlational nature of the connectivity analysis. Whether reduced lateral PFC connectivity with the NAcc is indeed related to less top-down regulation in more heavy drinkers could be assessed more directly in future studies using tasks that tap into modulation of striatal responses to rewarding stimuli, combined with effective connectivity methods to test for assumptions of directionality.

Last, effects of heavy drinking or alcohol dependence have not been reported exclusively for the NAcc and its connections with the lateral PFC. By limiting our hypotheses and analyses to NAcc circuitry we may thus have missed other functional connectivity associations with drinking behavior. Relatedly, other seed regions than the NAcc may demonstrate connectivity with the lateral PFC dependent on lifetime drinking as well, which would challenge the specificity of the NAcc for the effect found in this study. However, an additional connectivity analysis using a seed in the primary visual cortex, which connectivity pattern is distinct from the NAcc, did not reveal such an association with lifetime drinking.

In conclusion, our findings underscore the relevance of fronto-striatal connectivity to the field of alcohol research, not only suggesting a neural pathway mediating drinking behavior, but also offering a potential marker for future alcohol (ab)use.

Role of the funding source

This work was supported by the German Research Foundation (Deutsche Forschungsgemeinschaft; DFG): HE2597/13-1 and HE2597/13-2 [to AH], FR3572/1-1 [to EF], SM 80/7-1, SM 80/7-2, and SFB 940/2 [to MNS], WA1539/7-1 [to HW]. The DFG had no further role in study design, in the collection, analysis and interpretation of data, in the writing of the report, and in the decision to submit the paper for publication.

Contributors

MG, MS, AH, MNS, and HW designed the study; MG, SN, RF, SKP, and MS acquired the data; IMV and PJ analyzed the data and drafted the manuscript; SR and EF provided valuable input regarding interpretation of the data. All authors critically reviewed content and approved the final version for publication.

Conflict of interest

All authors report not to have biomedical financial interests or potential conflicts of interest.

Acknowledgments

We thank the Learning and Alcohol Dependence study teams in Berlin and Dresden for behavioral and neuroimaging data acquisition, and Claudia Haegele, Katharina Scholz, and Anna-Maria Walter for collection of the follow-up data in Berlin.

Supplementary material

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.euroneuro.2019.10.008.

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