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Ventral Striatal Resting-State Functional Connectivity in Adolescents is Associated with Earlier Onset of Binge Drinking

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Abstract

Background: Earlier engagement in heavy drinking during adolescence is a risk factor for the development of alcohol use disorders later in life. Longitudinal studies in adolescents have linked brain structure and task-evoked function to future alcohol use; however, less is known about how intrinsic network-level interactions relate to future substance use during this developmental period.

Methods: In this prospective longitudinal study, resting-state functional connectivity of the ventral striatum, risky decision making, and sensation seeking were measured in 73 adolescents at baseline. Participants were between the ages of 14 and 15 and had no substantial history of substance use upon study entry. Follow-up interviews were conducted approximately every 3 months to assess the initiation of binge drinking (≥ 5 or ≥ 4 drinks per occasion for males or females, respectively).

Results: Adolescents who began binge drinking sooner, exhibited greater connectivity of the ventral striatum to the left precuneus, left angular gyrus, and the left superior frontal gyrus. Greater connectivity of the ventral striatum to the right insula/putamen was associated with longer duration to the onset of binge drinking. Resting-state functional connectivity in these regions was not associated with baseline assessments of risky decision making or sensation seeking.

Conclusions: Findings provide novel information about potential risk factors for early initiation of heavy alcohol use. Interventions that target relevant resting-state networks may enhance prevention efforts to decrease adolescent substance use by prolonging onset to heavier levels of alcohol consumption.

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Contributors

BJN and AMM were responsible for study concept and design. AMM analyzed the data and AMM and NS drafted the manuscript. All authors critically reviewed content and approved the final version for publication.

Declaration of Competing Interest

No conflict declared.

Keywords

binge drinking; alcohol; ventral striatum; resting-state functional connectivity; adolescence; longitudinal

1. Introduction

Alcohol use during adolescence is associated with numerous adverse short- and long-term outcomes. For example, adolescents who binge drink are more likely to report poor school performance, engage in risky behaviors, such as drunk driving or other substance use, and be involved in serious accidents (Miller et al., 2007; Patte et al., 2017). Furthermore, earlier age of first intoxication is associated with increased risk of developing an alcohol use disorder in adulthood (Newton-Howes et al., 2019). Therefore, identifying differences in neurobiology that predict adolescent binge drinking could be helpful for identifying individuals at risk for negative outcomes and the development of tailored prevention efforts (O'Halloran et al., 2017).

Prospective studies suggest that the neurobiology of the ventral striatum (VS), a brain region implicated in reward processing and guiding motivated behavior (Salamone and Correa, 2012), is related to future alcohol use in adolescence. In particular, while engaged in a decision making task involving risk and reward, adolescents exhibiting greater VS activation and who made more risky choices began binge drinking sooner (Morales et al., 2018). Another study found that greater VS volume in adolescence was associated with greater alcohol use 2 years later, an effect that was mediated by greater self-reported levels of sensation seeking (Morales et al., 2019). However, the VS does not work in isolation, and examining individual differences in the connections of the VS to other brain regions provide may novel information about risk factors for alcohol use. Consistent with this hypothesis, one study showed that less fractional anisotropy (an index of white-matter microstructure) in pathways connecting the VS to prefrontal and subcortical areas was associated with the initiation of binge drinking (Morales et al., 2020).

Examining resting-state functional connectivity (RSFC) of the VS extends prior research assessing structural connectivity, as the strength of functional connections are impacted by complex interactions of various factors such as neurochemistry (Nagano-Saito et al., 2017; Schrantee et al., 2016) and neuroanatomy (Betzel et al., 2014). RSFC measures temporal correlations between oscillations in spontaneous blood-oxygen-level-dependent (BOLD) signal. This technique can identify brain regions that work together on related neural processes and which are organized into intrinsic networks in the absence of outside stimulation (Fox and Greicius, 2010). Throughout development from childhood to adulthood, RSFC undergoes widespread linear and nonlinear changes (Betzel et al., 2014; Fareri et al., 2015; van Duijvenvoorde et al., 2019). However, not all individuals develop at the same rate, and studies in adults suggest that individual differences in RSFC may help explain risk and resilience for developing substance use disorders (Ersche et al., 2020).

In adolescents, greater RSFC between the VS and dorsolateral prefrontal cortex (i.e. superior and middle frontal gyri, dlPFC) has been linked to greater risk-taking (DeWitt et al., 2014)

and earlier substance use (Lee and Telzer, 2016; Weissman et al., 2015), suggesting that greater segregation between these regions at rest is associated with better cognitive control over reward-related behavior. Here, we extend this work with a prospective study focused on determining how individual differences in VS RSFC were associated with temporal variation in the onset of binge drinking in 14- to 15-year-old adolescents without substantial exposure to alcohol or drugs. We hypothesized that greater RSFC between the VS and the dlPFC would be associated with earlier initiation of binge drinking. Furthermore, we hypothesized that greater VS-dlPFC RSFC would be linked to greater risky decision making and sensation seeking at baseline.

2. Materials and methods

2.1. Participant characteristics

Participants were part of an ongoing study of adolescent neurodevelopment (Cservenka et al., 2015; Cservenka and Nagel, 2012; Jones et al., 2016), approved by the Oregon Health & Science University (OHSU) Institutional Review Board. Parents provided written consent and children provided assent. Participants from the overarching study were included in this project if they were between 14 and 15 years old at baseline and they emerged to binge-level alcohol use by the time of data analysis (n = 76, 3 were excluded due poor resting-state quality). Exclusionary criteria at baseline for this project and the overarching parent study included: left handedness [Edinburgh Handedness Inventory (Oldfield, 1971)], DSM-IV criteria for a psychiatric diagnosis (Lucas et al., 2001), serious medical problems, significant head trauma, intellectual or learning disabilities, psychotic illness in a biological parent, prenatal exposure to drugs or alcohol, MRI contraindications, or pregnancy. Furthermore, participants were excluded from study entry if they reported consuming > 10 lifetime alcoholic drinks, > 2 alcoholic drinks on any one occasion, > 10 lifetime uses of marijuana, > 4 lifetime uses of cigarettes, or any other drug use [Customary Drinking and Drug Use Record (Brown et al., 1998)].

2.2. Baseline visit

At baseline, the Hollingshead Index of Social Position was used to assess socioeconomic status based on the education and occupation of the parent who earn the higher income (Hollingshead, 1957). Scores range from 11 to 77 with lower scores indicating higher socioeconomic status. Intellectual functioning was assessed using the two-subtest form of the Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999) and sensation seeking was measured using the Impulsive Sensation Seeking Scale of the Zuckerman-Kuhlman Personality Questionnaire (Zuckerman et al., 1993). To measure risky decision making, a modified version of the Wheel of Fortune (WOF) Task (Cservenka and Nagel, 2012; Ernst et al., 2004) was administered. The WOF task was conducted during functional magnetic resonance imaging (fMRI); however, since fMRI findings were presented in prior publication (Morales et al., 2018), here, we focus only on the association between task performance and RSFC. During the WOF task, participants chose between higher or lower risk/reward options (e.g. 10% probability of winning $7 versus 90% probability of winning $1). Participants were instructed to choose the option they thought would win them the greatest amount of money, as they would receive a portion of their total earnings. The

primary outcome measure was the total number of higher risk/reward selections made across 52 trials.

2.3. Follow-up assessments

After completion of baseline procedures, phone interviews were conducted approximately every 3 months to assess changes in substance use using the 90-day Timeline Followback (Sobell et al., 1996). We calculated the number of months between baseline and the initiation of binge drinking (≥ 5 drinks per occasion for males and ≥ 4 drinks per occasion for females). Participants are part of an ongoing study and will be followed through age 21.

2.4. Image acquisition

Scanning occurred at OHSU's Advanced Imaging Research Center on a 3.0 Tesla Siemens Magnetom Tim Trio. Anatomical, high-resolution T1-weighted MPRAGE structural scans were collected in the sagittal plane (TR = 2300 ms, TE = 3.58 ms, inversion time = 900 ms, flip angle = 10°, voxel size = 1×1×1.1 mm). Functional T2* weighted gradient echo-planar images to assess RSFC were collected axially, parallel to the anterior–posterior commissure line in 2 runs (TR = 2500 ms, TE = 30 ms, flip angle = 90°, voxel size = 3.75×3.75×3.8 mm, total acquisition time = 8:34 or 10:34 minutes). During resting-state scans, participants kept their eyes open and focused on a white fixation cross that appeared on a black background.

2.4. Image processing

Structural and functional images were visually inspected for artifacts. FreeSurfer (v6.0.0, Dale et al., 1999) was used to segment the structural image and to create masks of the gray matter, white matter, ventricles, and the whole brain. Preprocessing of the functional images was conducted using Analysis of Functional NeuroImages (v19.0.26, Cox, 1996) and included removal of the first 3 volumes that were collected before the scanner achieved a steady state, despiking, and slice time correction. Spatial transformations to account for head motion, to align the functional image to the structural image, and for nonlinear registration of the structural image to Montreal Neurological Institute (MNI) space were applied to the functional images in a single step to mitigate interpolation error. Images were scaled to have a mean of 100 and smoothed using a 4-mm Gaussian kernel. To account for head motion, data were processed with Automatic Removal of Motion Artifacts (Pruim et al., 2015), which uses independent component analysis to identify and remove signal associated with artifacts. Furthermore, any participants with average framewise displacement greater than 0.3 were excluded from the analysis (n = 3) and mean framewise displacement was included as a covariate in group-level statistical analysis. Finally, linear regression was used to apply a high-pass filter and to remove signal correlated with timecourses extracted from white matter, ventricular, and whole brain masks.

Seed-based RSFC was used to test *a priori* hypothesis about the importance of VS connectivity in the initiation of binge drinking. The Oxford-GSK-Imanova structural striatal atlas (Tziortzi et al., 2014) was used to create a seed mask of VS in MNI space. Since the ventral aspects of the brain are susceptible to dropout, an automated procedure was used to create subject-specific VS masks excluding any voxels with significant dropout (Peer et al., 2016). At every voxel within the gray matter, the correlation between the timecourse

in that voxel and the average timecourse within the VS was calculated. The resulting maps underwent Fisher's r to z transformation to improve normality.

2.5. Group-level statistical analyses

Bivariate correlations and independent samples t-tests were used to assess associations between demographic variables and duration to onset of binge drinking. To characterize VS RSFC across the whole brain, we conducted a one-sample t-test (cluster forming threshold of $p < 0.01$, cluster-level significance of $p < 0.05$, two-sided, cluster size > 551 voxels). Linear regression was conducted to examine the association between months until the initiation of binge drinking and voxel-wise assessment of VS RSFC, controlling for age, sex, and mean framewise displacement. Voxel-wise group-level analyses used a cluster forming threshold of $p < 0.01$ and results were corrected for multiple comparisons using *nonparametric* permutation analysis (3dttest++ -Clustsim) to determine the cluster size necessary to achieve a cluster-level significance of $p < 0.05$, two-sided (cluster size > 521 voxels). Recent work demonstrates that compared with parametric analyses, nonparametric methods provide adequate control over the rate of false positives at a variety of cluster-forming thresholds including $p < 0.01$ (Cox et al., 2017; Eklund et al., 2016). Average RSFC was extracted from significant clusters and correlated with risky decision making and sensation seeking using age, sex, and mean framewise displacement as covariates (threshold for significance $p < 0.0125$, reflecting Bonferroni correction for the 4 clusters examined).

3. Results

3.1. Participant characteristics

Thirty-nine of the participants were female and 34 were male. On average, adolescents were 15.07 (SD = 0.59) years old, had IQ scores of 111.66 (SD = 9.50), scored 27.63 (SD = 13.25) on the Hollingshead Index of Social Position, and began binge drinking 29.63 (SD = 19.46) months after baseline assessments. Duration to onset of binge drinking from baseline was not related to any demographic variables ($p > 0.05$). On average, participants chose the higher risk/reward option on the WOF task 63.10 (SD = 24.95) percent of the time and scored 45.06 (SD = 18.90) on the Zuckerman Sensation Seeking Scale (n = 72). As previously reported in a subset of this sample (n = 47, Morales et al., 2018), duration to onset of binge drinking was negatively associated with risky selections on the WOF task when controlling for age and sex; however, the association was not statistically significant (n = 72, $r = -0.23$, $p = 0.054$). Similarly, the association between duration to onset of binge drinking and sensation seeking was not statistically significant when controlling for age and sex (n = 72, $r = -0.23$, $p = 0.056$). Consistent with the exclusion criteria, at baseline, participants reported 0.07 (SD = 0.35) times of cigarette use, 0.29 (SD = 0.91) times of alcohol use, and 0.55 (SD = 1.6) times of marijuana use in their lifetime.

3.2. Ventral striatal RSFC

On average, the VS showed widespread RSFC with cortical and subcortical regions ($p < 0.05$ corrected, Figure 1). Positive connectivity was detected primarily in the frontal cortex and subcortical regions. Regions exhibiting significant positive connectivity included the medial and lateral orbitofrontal gyrus, anterior and middle cingulate, anterior insula,

caudate, putamen, thalamus, and cerebellum. Brain regions within the occipital, parietal and temporal cortex primarily exhibited negative connectivity to the VS.

3.3. Associations between ventral striatal RSFC and the onset of binge drinking

When controlling for baseline age, sex, and mean framewise displacement, participants who began drinking sooner had greater VS RSFC to the left precunus, left angular gyrus, and the left superior frontal gyrus. Earlier onset of binge drinking was also associated with less connectivity of the VS to the right insula/putamen ($p < 0.05$ corrected, Figure 2, Table 1). There were no associations between VS RSFC in clusters significantly associated with the onset of binge drinking and risky selections on the WOF task or sensation seeking, after correction for multiple comparisons (p's > 0.0125, Supplemental Table 1).

4. DISCUSSION

Consistent with our hypothesis and prior research (Weissman et al., 2015), these findings suggest that greater RSFC between the VS and dlPFC is associated with earlier initiation of binge drinking, as evidenced by the significant finding in the left superior frontal gyrus. Weismann and colleagues found a similar effect in the right superior frontal gyrus, but more research is needed to determine if the laterality difference is attributable to methodological differences between the studies, such as the assessment of RSFC in adolescents with more exposure to alcohol and drugs (including current substance use disorders). Additionally, this study provides novel evidence suggesting that VS RSFC to the precuneus, angular gyrus, and insula/putamen may represent pre-existing risk factors for future alcohol use.

Our findings in the superior frontal gyrus, angular gyrus, and precuneus overlap with spatial maps of the default mode network (DMN) observed in prior studies (Gordon et al., 2016). The DMN is a set of functionally connected brain regions that display decreased activation during external goal-oriented tasks, and greater activation during internal mental processes (Fan et al., 2021). Studies examining the development of the DMN have demonstrated that between childhood and adulthood, there is transition towards greater RSFC within the DMN and less RSFC between DMN and brain regions in other networks (Fair et al., 2008; Fair et al., 2007; Fan et al., 2021; Sherman et al., 2014). Based on these studies, our findings of greater VS RSFC to the superior frontal gyrus, precuenus, and angular gyrus in those who begin binge drinking sooner could represent a delay in maturation of DMN. Research to uncover the mechanisms that underlie developmental changes in VS-DMN connectivity may explore the role of dopamine, as the VS receives dopaminergic projections from the ventral tegmental area and changes in dopamine signaling alter DMN connectivity (Schrantee et al., 2016). Since aberrant patterns of DMN connectivity have been observed across various substance use disorders, including alcohol (Zhang and Volkow, 2019), longitudinal studies are needed to determine how DMN connectivity changes as substance use progresses. Lastly, examining how RSFC relates to task-related activation may produce novel insights (Tavor et al., 2016), as our findings are consistent with a prior study demonstrating that adolescents with a family history of alcoholism have greater task-related VS-precuneus connectivity during incentive anticipation (Weiland et al., 2013).

Research examining developmental changes in VS-insula RSFC suggest that connectivity to the insula decreases between childhood and adolescence (Fareri et al., 2015; Porter et al., 2015), suggesting that accelerated reduction in VS-insula RSFC connectivity is risk factor for earlier initiation of binge drinking. A study in 18 year-olds found that less VS-insula RSFC was associated with greater lifetime alcohol use and greater alcohol use, measured using a composite score, at a 1 year follow-up assessment (Veer et al., 2019). Together these findings suggest that less VS-insula RSFC is risk factor for not only the initiation of binge drinking, but also increases risk for greater alcohol use during the transition from adolescence into young adulthood.

Although our findings provide novel evidence that differences in VS RSFC are associated with the initiation of binge drinking, prior prospective studies examining different indices of RSFC and alcohol use have produced mixed results. Two studies used a hypothesis-driven approach to examine the association between RSFC and future alcohol use in samples with heterogeneous ages and levels of alcohol use at baseline. Research focused on the RSFC between the VS and hippocampus did not demonstrate an association between RSFC at baseline (ages 12–22) and frequency of alcohol use one year later (Huntley et al., 2020). Another study demonstrated that lower RSFC between the amygdala and orbitofrontal cortex at baseline (ages 12–27) was associated with greater lifetime, and recent, alcohol use two years later (Peters et al., 2017). Using a data driven approach, one study found evidence for greater global RSFC at age 14 in participants who went on to engage in high drinking compared to low drinking at age 19 (Cheng et al., 2019). These studies focused on examining alcohol use after a fixed time interval; however, our findings highlight how RSFC may relate to temporal variation in escalation of alcohol use. Longer longitudinal studies are needed to determine whether RSFC is associated with temporal variation in the onset of sustained levels of heavy drinking including the development of alcohol use disorders.

Some limitations should be considered when interpreting these research findings. While this study employed a seed-based approach to assess RSFC based on *a priori* hypotheses, there are many approaches for analyzing resting-state data, and distinct approaches may produce divergent results, as they tap into different characteristics of resting-state networks. Future research might glean additional information about risk factors for early initiation of binge drinking by examining resting-state networks using different approaches (e.g. independent component analysis, graph theory).

Our study did not find an association between earlier initiation of binge drinking and VS-middle frontal gyrus RSFC or correlations with risk-taking and sensation seeking, as hypothesized based on prior studies (DeWitt et al., 2014; Lee and Telzer, 2016). Large-scale prospective longitudinal studies with varied assessments of behavior, personality, and cognition are needed to determine the mechanisms by which variation in RSFC promotes early initiation of binge drinking and to allow for the examination of sex differences. Although most of the participants in this study were alcohol and drug naïve (n = 54), more research is needed to determine if the low-levels of substance use observed at baseline can impact neurobiology and behavior. Lastly, on average, participants in this study had high IQs and socioeconomic status, this sampling bias may impact the generalizability of these findings to other populations (LeWinn et al., 2017).

5. Conclusions

Overall, these findings provide novel evidence suggesting RSFC of the VS is a biomarker for early initiation of binge drinking. Developing a better understanding of both the genetic and environmental factors that influence the development of resting-state networks may be useful for identifying adolescents at risk for heavy alcohol use. Furthermore, interventions that can modulate the implicated neural circuitry may be effective at curbing early engagement in heavy alcohol use.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Resting state functional connectivity (RSFC) may be a risk factor for alcohol use
- Examined ventral striatal RSFC in adolescents before initiation of binge drinking
- Less ventral striatal RSFC to insula was associated with earlier binge drinking
- Greater ventral striatal-default mode network RSFC linked to earlier binge drinking

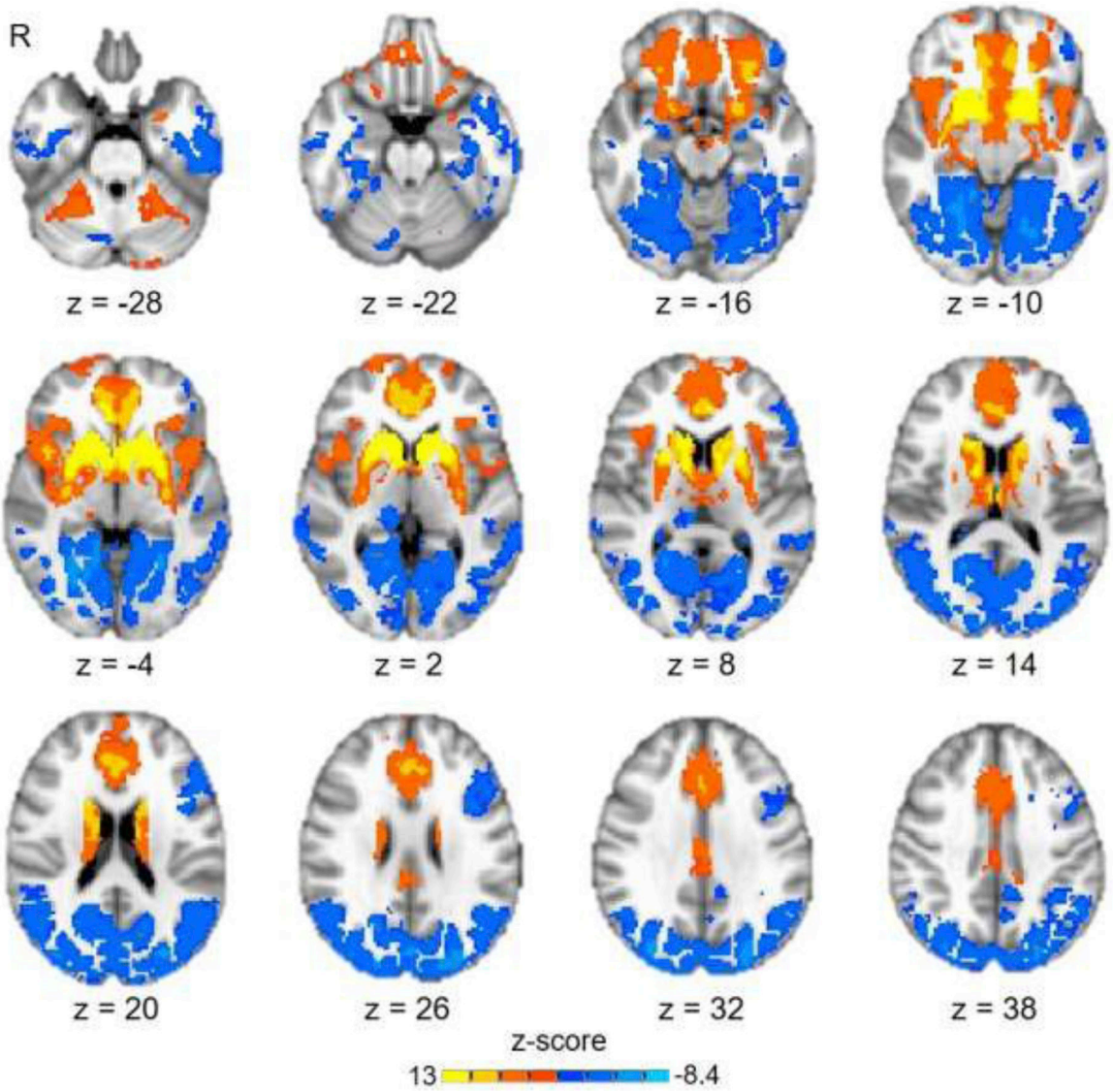

Figure 1. Ventral striatal resting-state functional connectivity.

Whole-brain, voxel-wise statistical maps show connectivity of the ventral striatum to the rest of the brain (cluster-forming threshold $p < 0.01$, cluster-level corrected for multiple comparisons $p < 0.05$). Warm colors indicate positive connectivity with the ventral striatum, while cool colors represent the degree of autocorrelation.

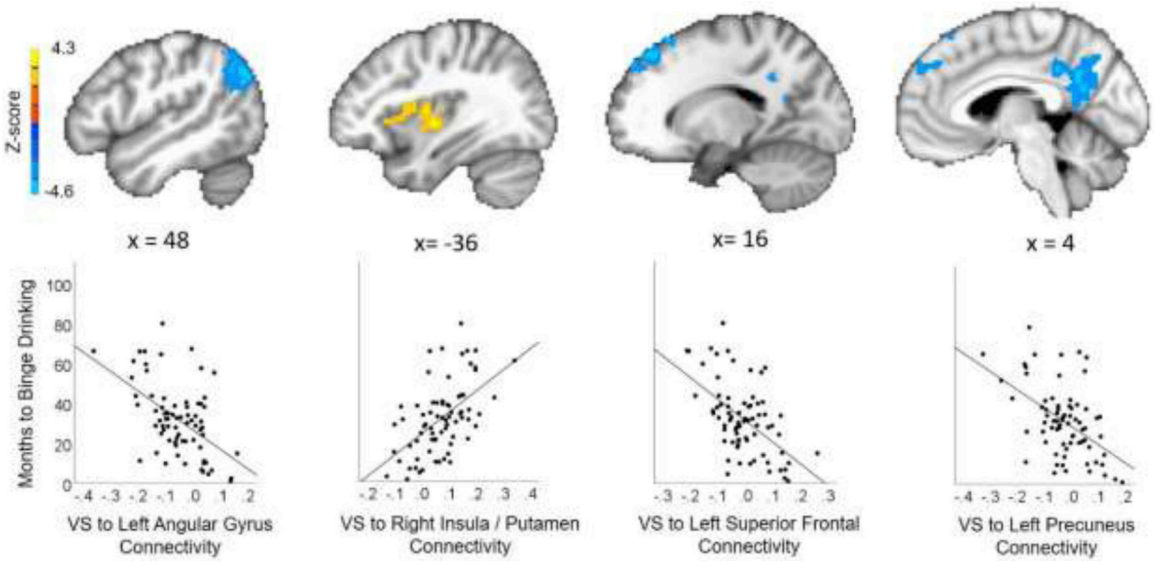

Figure 2. Associations between ventral-striatal resting-state functional connectivity and duration to onset of binge drinking.

Whole-brain voxel-wise statistical maps displayed in the top row show brain regions where there was a significant association between connectivity to the ventral striatum and duration to onset of binge drinking (cluster-forming threshold $p < 0.01$, cluster-level corrected for multiple comparisons $p < 0.05$). Scatter plots show that adolescents who began binge drinking sooner have greater connectivity of the ventral striatum to the superior parietal cortex, superior frontal gyrus, and precuneus. In contrast, adolescents who began binge drinking sooner have less connectivity of the ventral striatum to the insula and putamen. Values in the scatterplots are adjusted for the effects of age, sex, and mean framewise displacement.

Table 1.

Associations Between Ventral Striatal Resting-State Functional Connectivity and Onset of Binge Drinking.

Location and size of clusters where a significant association between ventral striatal resting state functional connectivity and duration to onset of binge drinking was detected.

Cluster Location	Cluster Size[a]	Peak z-score	MNI Coordinates[b]		
			x	y	z
Left Precuneus	917	−4.64	−12	−54	24
Left Angular Gyrus	576	−4.88	−48	−69	36
Right Insula / Putaman	573	4.18	33	−3	12
Left Superior Frontal Gyrus	544	−4.67	−18	39	51

[a]MNI, Montreal Neurological Institute; size in number of 2 mm voxels

[b]Coordinates reported in LPS convention (left, posterior, superior, i.e. neurological convention)