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Alcohol Use in Emerging Adults Associated with Lower Rich-Club Connectivity and Greater Connectome Network Disorganization

Jessica P.Y. Hua[a,b,c,d,*], **Siemon C. de Lange**[e,f], **Martijn P. van den Heuvel**[f,g], **Cassandra L. Boness**[d,h], **Constantine J. Trela**[d], **Yoanna E. McDowell**[d], **Anne M. Merrill**[d], **Thomas M. Piasecki**[d], **Kenneth J. Sher**[d], **John G. Kerns**[d]

[a]Sierra Pacific Mental Illness Research Education and Clinical Centers, San Francisco VA Medical Center and the University of California, San Francisco, CA

[b]Mental Health Service, San Francisco VA Medical Center, San Francisco, CA 94121

[c]Department of Psychiatry and Behavioral Sciences, University of California San Francisco, San Francisco, CA 94143

[d]Department of Psychological Sciences, University of Missouri, Columbia, MO 65211

[e]Department of Sleep and Cognition, Netherlands Institute for Neuroscience, an institute of the Royal Netherlands Academy of Arts and Sciences, Amsterdam, The Netherlands.

[f]Department of Complex Trait Genetics, Center for Neurogenomics and Cognitive Research, Vrije Universiteit Amsterdam, Amsterdam Neuroscience, Amsterdam, The Netherlands.

[g]Department of Child Psychiatry, Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam Neuroscience, Amsterdam, The Netherlands.

[h]Center on Alcohol, Substance use, and Addictions, University of New Mexico, Albuquerque, NM 87106.

Abstract

Background: Emerging adulthood is a critical neurodevelopmental stage, with alcohol use during this period consistently associated with brain abnormalities and damage in anatomical structure and white matter integrity. However, it is less clear how alcohol use is associated with the

[*]To whom correspondence should be addressed: Jessica P. Y. Hua, Ph.D., tel: 415-221-4810 ×26403, Jessica.Hua@ucsf.edu.

Contributors

JGK, KJS, and TMP were responsible for the study concept and design. JGK contributed to the acquisition of data. CLB, CJT, YEM, and AMM were responsible for scoring the alcohol use variables. JPYH processed the neuroimaging data and performed the analyses on the main dataset. SCdL and MPvdH processed the discovery dataset and created the connectome pipeline. JPYH and JGK drafted the manuscript. All authors critically reviewed the manuscript and approved the final version for publication.

Data Availability Statement

The data that support the findings of the current study are openly available in the Open Science Framework repository, osf.io/ezhr9.

Conflict of Interest

Declarations of interest: none.

brain's structural organization (i.e., white matter connections between anatomical regions). Recent connectome research has focused on rich-club regions, a collection of highly-interconnected hubs that are critical in brain communication and global network organization and disproportionately vulnerable to insults.

Methods: For the first time, we examined alcohol use associations with structural rich-club and connectome organization in emerging adults (N=66).

Results: Greater lifetime drinks and current monthly drinks were significantly associated with lower rich-club organization (r_s=−.38, ps<.003) and lower rich-club connectivity (r_s<−.34, ps<.007). Additionally, rich-club connectivity was significantly more negatively correlated with alcohol use than connectivity among non-rich-club regions (ps<.035). Examining overall structural organization, greater lifetime drinks and current monthly drinks were significantly associated with lower network density (i.e., lower network resilience; r_s<−.36, ps=.004). Additionally, greater lifetime drinks and current monthly drinks were significantly associated with higher network segregation (i.e., network's tendency to divide into subnetworks; r_s>.33, ps<.008). Alcohol use was not significantly associated with network integration (i.e., network's efficiency in combining information across the brain; ps>.064).

Conclusions: Results provide novel evidence that alcohol use is associated with decreased rich-club connectivity and structural network disorganization. Given that both are critical in global brain communication, these results highlight the importance of examining alcohol use and brain relationships in emerging adulthood.

Keywords

alcohol; connectome; MRI; structural networks; young adult

1. Introduction

Adolescence through emerging adulthood is a critical neurodevelopmental period during which the brain is especially vulnerable to neural insults (Jacobus and Tapert, 2013; Squeglia and Gray, 2016). However, this period has been associated with the highest alcohol use rates (Chen et al., 2004). Previous research has consistently found alcohol use to have a neurotoxic effect on the brain in adolescence through emerging adulthood, with alcohol use associated with abnormalities in anatomical structure (e.g., abnormal gyrification, white and gray matter volumetric decline, abnormal cortical thickness) and white matter connectivity (e.g., decreased white matter integrity in cortical and subcortical tracts; e.g. Brown et al., 2008; Heikkinen et al., 2017; Hua et al., 2020b, 2020c; Jacobus and Tapert, 2013; Meda et al., 2017, 2018; Smith et al., 2017; Weiland et al., 2014; Welch et al., 2013). Although previous studies have greatly improved our understanding of neural effects of alcohol use, studies often focus solely on anatomical structure or connectivity abnormalities between select brain regions. Given that brain structure and connectivity coexist, it is critical that we understand how brain networks as a whole can serve as a predisposing factor of and/or a consequence of alcohol use.

Multimodal neuroimaging has allowed researchers to map the human connectome and analyze brain network organization (i.e., white matter connections between anatomical

regions). In particular, research has focused on the rich-club, a phenomenon occurring when highly-connected brain hubs are more densely connected among themselves than nodes with fewer connections (van den Heuvel and Sporns, 2011). Due to high centrality and greater metabolic resource usage, rich-club regions are vulnerable to brain dysconnectivity and disproportionately affected across many sub-clinical and clinical groups (de Lange et al., 2018; Gollo et al., 2018; Schmidt et al., 2017; Zorlu et al., 2019). Rich-club damage could lead to impaired information processing, since it plays a critical role in efficient global brain communication (van den Heuvel et al., 2013; van den Heuvel and Sporns, 2013). In addition to the rich-club, commonly-assessed metrics of network organization across the whole connectome are network density, modularity, transitivity, and global efficiency (Rubinov and Sporns, 2010). Briefly, network distribution, as measured by density, is a marker of network development and resilience with greater density representing a more resilient and connected network. Network segregation measures, such as modularity and transitivity, represent the brain's ability for specialized processing within subgroups of brain regions. Network integration measures, such as global efficiency, represent the brain's ability to efficiently combine information across the brain. Optimal brain function is vital for information processing, with brain function impaired when network segregation and integration are not balanced (Lynall et al., 2010). Using this connectome-based structural network approach, for the first time, we examined alcohol use associations with rich-club connectivity and network organization in emerging adulthood.

To date, the majority of connectome-based studies combining anatomical structure with white matter or resting-state connectivity in individuals drinking alcohol (e.g., Chumin et al., 2019; Kuceyeski et al., 2013; Mayhugh et al., 2016; Morris et al., 2017; Mueller & Meyerhoff, 2021; Sjoerds et al., 2017; Wang et al., 2018; Zorlu et al., 2019) have been conducted in older populations of individuals with, or siblings of individuals with, alcohol dependence. Of these diffusion-weighted imaging (DWI) connectome papers, Chumin et al., (2019) specifically examined global network metrics, including global connectivity (i.e., network strength) and global efficiency in patients with alcohol use disorder (AUD) compared to controls. They found increased global connectivity (i.e., network strength) and global efficiency in AUD, and they did not examine relationships between network metrics and alcohol use. Critically, network strength consists of both connections between rich-club regions and non-rich-club regions, and it is possible that a metric combining across connection types could obscure the differential pattern between rich-club connections and non-rich club connections. In the sole DWI rich-club study examining both global network and rich-club organization of patients with AUD, Zorlu et al. (2019) found that patients with AUD had higher modularity and no significant difference in global efficiency. They also found a significant ordered difference in rich-club organization (AUD < siblings < controls), which suggests that rich-club disorganization may be a predisposing factor. Within the AUD group, drinking onset age and alcohol dependence duration were not significantly associated with global network and rich-club organization metrics. Thus, this study provides evidence for rich-club disorganization in AUD. Although, to our knowledge, there are no structural connectivity papers focused on alcohol use in emerging adulthood, Hua et al. (2020b) examined alcohol use and whole-brain gyrification associations in a study using the current sample. They found that cumulative lifetime drinks and past year hangover symptoms were

associated with hypogyria in multiple cortical regions, including right orbitofrontal, bilateral parahippocampal gyrus, and right anterior insula. Abnormal gyrification is a structural marker of abnormal neurodevelopment and inefficient neuronal connectivity (White et al., 2010). Thus, structural results from Hua et al. (2020b) suggest that alcohol use in emerging adults might be associated with connectivity abnormalities among brain networks and highlight the importance of concurrently examining anatomical structure and structural connectivity. As such, in the current study using an emerging adulthood sample, we examined alcohol use associations with structural networks by combining both structural data as well as DWI data.

Although the current study focused on structural connectomes, it is important to note that some previous studies focused on functional connectomes (i.e., resting-state connectivity between anatomical regions; Kuceyeski et al., 2013; Mayhugh et al., 2016; Morris et al., 2017; Sjoerds et al., 2017; Wang et al., 2018). Although not focusing on structural connectomes *per se*, structural and functional connectivity are strongly associated (Hagmann et al., 2010; Honey et al., 2010). The majority of these functional connectivity studies found no significant differences in overall network organization metrics between participants with alcohol dependence and no dependence/light-drinking groups (Kuceyeski et al., 2013; Morris et al., 2017; Sjoerds et al., 2017) or between older adults with light/moderate alcohol use (Mayhugh et al., 2016). Examining associations with alcohol variables in AUD groups, Morris et al. (2017) and Wang et al. (2018) did not find alcohol use to be associated with network organization metrics, whereas Sjoerds et al. (2017) found that longer alcohol dependence duration was associated with reduced network density. None of these studies examined the rich-club.

Taken together, research provides mixed evidence of connectome-based abnormalities related to alcohol use, and it is important to further explore these associations in a neurodevelopmentally critical period, such as emerging adulthood. To address this gap, we examined whether alcohol use in emerging adulthood was associated with rich-club connections and structural network organization. For our main analyses of interest, we hypothesized that greater alcohol use would be associated with fewer structural connections between rich-club regions. Based on prior research, we additionally hypothesized that greater alcohol use would be associated with lower network density and higher network segregation, but not network integration (Sjoerds et al., 2017; Zorlu et al., 2019).

2. Materials and Methods

2.1. Participants

Participants were University of Missouri undergraduates (N=66), who were about to celebrate their 21st birthday (participants were 20 years old and on average 11 days from their 21st birthday). Recruitment was targeted to undergraduates; however, student status was not systematically collected, so a few non-students may have participated by word of mouth. Exclusion criteria included: MRI contraindications (e.g., metal medical devices, being claustrophobic), head injury history resulting in loss of consciousness for over two minutes, or taking prescribed medication (except birth control). Participants were instructed not to consume alcohol, other drugs, ibuprofen, or antihistamines for at least 24 hours

prior to scanning and to abstain from smoking for at least 30 minutes prior to scanning. Participants were 50.00% female, 84.85% White, 1.52% Black/African American, 1.52% Asian American, and 12.12% did not disclose ethnicity.

2.2 Procedure

Participants were recruited for a three-session study on alcohol use in emerging adults. For session 1, participants completed alcohol use measures and a neuroimaging scan. Data reported in the current manuscript are from session 1 (study data: Hua et al., 2020a). Structural morphometric results on session 1 participants and on a subset of participants after their 21st birthday have been reported previously (Hua et al., 2020b, 2020c).

Participants provided written informed consent. Study procedures were in accordance with the ethical standards of the University of Missouri's Institutional Review Board and the latest version of the Declaration of Helsinki.

2.3. Alcohol Use Measures

Using a timeline follow-back approach, the Lifetime Drinking History interview (Jacob, 1988) retrospectively assesses lifetime alcohol use patterns starting from when a participant began drinking regularly and ending with the participant's current alcohol use pattern. *Lifetime drinks* was defined as the estimated sum of alcoholic drinks in a participant's lifetime. *Current average monthly drinks* was defined as the average number of alcoholic drinks in the last month. *Drinking onset age* was defined as the age when a participant started drinking alcohol regularly. To better reflect the relationship between younger age and alcohol-related problems and dependence (e.g., Hingson et al., 2006; Squeglia and Gray, 2016), we reversed the statistical direction of associations with drinking onset age and examined associations with earlier drinking onset.

The Hangover Symptoms Scale (Slutske et al., 2003) assesses hangover symptoms. As recommended by scale developers, we dichotomized symptoms as having "never occurred" or "ever occurred" in the past year. *Past year hangover symptoms* was defined as the sum of 13 dichotomized items. Higher scores have been associated with increased frequency of drinking and getting drunk (Slutske et al., 2003) and have been found to predict daily-life hangover occurrence (Robertson et al., 2012).

2.4. Other Substance Use and Possible Psychiatric Diagnoses

Alcohol use associations could be confounded by other drug use or psychiatric diagnoses. Based on clinical interview, we collected information on whether participants had ever used other drugs or met lifetime diagnostic criteria for a psychiatric diagnosis (see Supplemental Methods for more details). None of these variables was significantly correlated with connectome variables (ps>.052; Supplemental Table 1). Results should be interpreted with caution since these data were missing for many participants (n=16–17 depending on the variable of interest; n=18 missing at least one of the variables) due to time constraints.

2.5. Image Acquisition and Processing

Structural T1-weighted MRI and DWI were acquired using a Siemens Trio 3T scanner equipped with an 8-channel head coil (for scanning parameters, see Supplemental Methods). Structural images were processed using FreeSurfer's morphometric pipeline (Han et al., 2006; Jovicich et al., 2006) and parcellated into 68 Desikan-Killiany cortical regions (Desikan et al., 2006) and 14 subcortical regions (left/right thalamus, pallidum, caudate, putamen, accumbens, hippocampus, and amygdala).

2.6. Structural Network Construction

Structural networks were processed and constructed using the Connectivity Analysis TOolbox (CATO; de Lange and van den Heuvel, 2021). For processing details, see Figure 1 and Supplemental Methods. Structural networks were constructed by combining each participant's T1 FreeSurfer parcellation map with their reconstructed tractography streamlines (Figure 1). Each participant's network can be expressed as a connectivity matrix: $G=(V,E)$, with V defined as the 82 cortical/subcortical network nodes and E as the collection of reconstructed streamline network edges between network nodes. As recommended, networks were not thresholded, and analyses were performed on weighted networks (van den Heuvel et al., 2017).

Networks were weighted by number of streamlines (NOS), such that connection weight of network edges was equal to the NOS between network nodes. Accounting for potential volume effects, in exploratory analyses, we examined streamline density-weighted (SD) networks, such that connection weight of networks edges was equal to the NOS divided by average cortical volume of connected network nodes. NOS-weighted and SD-weighted network results showed a very similar pattern (see Supplemental Tables 2-4 for SD-weighted results).

2.7. Analyses

2.7.1. Rich-Club Organization & Rich-Club Node Identification—Using the MATLAB-based Brain Connectivity Toolbox (Rubinov and Sporns, 2010), we calculated rich-club organization($\Phi[k]$; for more details, see Supplemental Methods). A normalized rich-club coefficient ($\Phi_{norm}[k]$) was computed as the ratio between $\Phi(k)$ and the average rich-club coefficient $\Phi_{\text{random}}(k)$ of 1,000 null networks obtained by degree-preserved random rewiring of the original networks (van den Heuvel & Sporns, 2011). Due to non-normality of alcohol use variables (Shapiro-Wilk ps<.037) and to reduce outlier influence, we computed Spearman correlations between alcohol use variables and rich-club coefficients at degree (k) equal to 15.

To avoid selection bias, we identified rich-club nodes using the 1200 Human Connectome Project (HCP) young adult dataset as our discovery dataset. Data were obtained from the HCP database (https://ida.loni.usc.edu/login.jsp; principal investigators: Rosen, Toga, and Weeden) and is the result of efforts of co-investigators from the University of Southern California, Martinos Center for Biomedical Imaging at Massachusetts General Hospital (MGH), Washington University, and the University of Minnesota. This dataset consisted of 1502 young adults (22–35 years old). Since current participants were approximately 11

days from their 21st birthday, we also identified rich-club nodes in a HCP subset (n=220) restricted to ages 22–25. For both the entire HCP discovery dataset and age-restricted dataset, a group-averaged unweighted structural network was computed by selecting streamline connections present in at least 75% of participants (van den Heuvel et al., 2013; van den Heuvel and Sporns, 2011).

2.7.2. Structural Connection Types—We next applied the categorization of rich-club nodes and peripheral nodes (i.e., non-rich-club nodes) from the HCP discovery dataset to our current sample and examined three connection categories (rich-club, feeder, and local; Supplemental Figure 1). Rich-club connections were defined as the sum of the weights of edges between all pairs of rich-club nodes. Feeder connections were defined as the sum of the weights of edges between all pairs of a rich-club node and a peripheral node. Local connections were defined as the sum of the weights of edges between all pairs of peripheral nodes.

We computed Spearman correlations between alcohol use variables and connection types. To further examine if alcohol use associations were specific to rich-club connections or overall general connectivity, we conducted Meng's z-tests (Meng et al., 1992) to compare our rich-club, feeder, and local connections correlations. Additionally in post-hoc analyses of significant associations between alcohol use variables and rich-club connections, we parsed the associations by examining rich-club connections by each rich-club node separately.

2.7.3. Structural Network Organization Metrics—Following-up on structural connection type results and examine structural network organization (i.e., whole connectome organization), for network organization metrics, we calculated measures of network distribution (network density), segregation (modularity and transitivity), and integration (global efficiency) using MATLAB's Brain Connectivity Toolbox (Rubinov and Sporns, 2010). Network density is a marker of neurodevelopment and resilience and represents the "wiring cost" of a network. It was computed as number of actual connections divided by total number of potential connections between brain regions. Modularity is the degree to which a network can be subdivided into clearly delineated subnetworks. Transitivity is the probability of a network to have interconnected adjacent nodes that form tightly connected clusters around individual nodes and is equal to the ratio between the actual number of closed triplets (i.e., triangles formed by three connected nodes) to the maximum number of closed triplets. Global efficiency is the average inverse of shortest path length and is a measure of efficiency of distant information transfer. As graph theoretical metrics are influenced by network distribution characteristics, in exploratory analyses we calculated normalized modularity and normalized global efficiency with respect to 1,000 null networks that preserved network distribution (Rubinov and Sporns, 2010). For further explanation of these metrics, see Supplemental Methods and Figure 1. We computed associations between alcohol use variables and overall network organization metrics using Spearman correlations.

2.7.4. Multiple Comparison Correction—We used a false discovery rate (FDR) correction of p_{FDR}<.05 across n=32 associations (i.e., 4 correlations between alcohol use variables with rich-club organization, 12 correlations between alcohol use variables with

structural connection types and 16 correlations between alcohol use variables with network organization metrics).

2.7.5. Missing Data—Using Little's Missing Completely at Random Test (Little, 1988), missing data were determined to be missing completely at random for lifetime drinks and drinking onset age (n=6), current average monthly drinks (n=3), and past year hangover symptoms (n=1). Since data were missing completely at random, we used pairwise deletion in which all participants that had data for the specific analysis were included (results were similar with listwise deletion in which only participants without any missing data were included).

3. Results

3.1. Alcohol Use Descriptives and Correlations

Alcohol use in the current sample was similar to national levels in emerging adults. Specifically, drinking onset age (M=17.48 years; Table 1) was approximately the same as the national average in young adults (M=17.4 years; Chen et al., 2004). Additionally, participants experienced on average 6.22 hangover symptoms, which was one symptom greater than the average of 5 symptoms endorsed by a large sample of undergraduates (Slutske et al., 2003). As expected, alcohol use variables were strongly intercorrelated (Table 2).

3.2. Alcohol Use Associated with Rich-Club Organization and Structural Connection Types

Overall, participants in the current study showed a rich-club organization to their structural connectomes as evidenced by an increasing rich-club curve with normalized rich-club coefficients greater than 1 (see Supplemental Table 5 for distribution of rich-club organization, Supplemental Figure 2). At degree (k) equal to 15, greater lifetime drinks (r_S=−.38, p=.003) and current average monthly drinks (r_S=−.38, p=.002) were significantly associated with lower rich-club organization. Associations between drinking onset and past year hangover symptoms were not significant (ps>.375). Note that associations showed a similar pattern at different thresholds of k.

As mentioned previously, rich-club nodes were identified in the HCP data by selecting the top 12% of highly-connected nodes (e.g., van den Heuvel et al., 2013; van den Heuvel and Sporns, 2011): left/right putamen, left/right superior parietal, left/right superior frontal, right insula, left/right thalamus, and left medial orbitofrontal (Figure 2). Each rich-club node was connected to at least 30 other brain regions. Identified rich-club nodes were the same for all HCP young adults and HCP young adults restricted to ages 22–25 at the 75% threshold as well as at group-averaged thresholds of 80% and 85% (Supplemental Table 6). Note that all of these same rich-club nodes were identified in the current study sample, with the exception of the left thalamus and the addition of the left insula, caudate, precentral, and rostral middle frontal.

Based on these 10 identified rich-club nodes from the HCP dataset, we examined alcohol use associations with structural network connections in the current sample (Table 3; see

Supplemental Table 5 for distributions of connection types and Supplemental Figure 3 for representative examples of high alcohol use and low alcohol use matrices). Greater lifetime drinks (r_s=−.35, p=.007) and current average monthly drinks (r_s=−.34, p=.007) were significantly associated with lower rich-club connections (Figure 3). There was evidence that greater lifetime drinks, current average monthly drinks, and greater past year hangover symptoms were in turn associated with more local connections (r_s=.26 to .33, ps<.044), however, results did not survive FDR correction across n=32 associations. Note that associations between rich-club connections with lifetime drinks and current average monthly drinks as well as local connections with past year hangovers symptoms showed a similar pattern when using different rich-club identification thresholds (i.e., top 9% and 17% of highly-connected nodes; Supplemental Table 7). Additionally, in post-hoc analyses, we included analyses in which we dropped any participant (n=18) that had missing other substance use or psychiatric diagnostic data (Supplemental Table 8; note that results were in the same direction as those in the full sample; however, results should be interpreted with caution due to low statistical power).

Further, we post-hoc parsed the associations between greater lifetime dinks and current average monthly drinks with rich-club connections, by examining rich-club connections by each rich-club node separately (Supplemental Table 9). Greater lifetime drinks was significantly associated with lower rich-club connections for the left putamen, left superior parietal, left superior frontal, and left thalamus. Greater current average monthly drinks was significantly associated with lower rich-club connections for the left superior parietal and left thalamus.

We next examined if alcohol use associations were specific to rich-club connections or overall general connectivity among brain regions. Based on Meng's z-tests (Table 4), rich-club connections were significantly more negatively correlated with all alcohol use variables than local connections (zs=−4.46 to −2.12, ps<.035). Rich-club connections were also significantly more negatively correlated with lifetime drinks (z=−2.59, p=.010) and current average monthly drinks (z=−2.03, p=.043) than feeder connections. Additionally, feeder connections were significantly more negatively associated with alcohol use than local connections (zs=−3.89 to −2.62, ps<.009; comparison with earlier drinking onset age was not significant).

3.3. Alcohol Use Associated with Structural Network Organization Metrics

To examine whether only the rich-club was affected or also overall network organization, we examined alcohol use associations with network organization metrics (Table 5; see Supplemental Table 5 for distributions of network organization metrics). Greater lifetime drinks (r_s=−.37, p=.004) and current average monthly drinks (r_s=−.36, p=.004) were significantly associated with lower network density (Figure 4a). For network segregation, greater lifetime drinks was significantly associated with higher modularity (r_s=.38, p=.003; Figure 4b), and greater lifetime drinks (r_s=.43, p=.001) and current average monthly drinks (r_s=.33, p=.008) were significantly associated with higher transitivity (Figure 4c). There was some evidence that earlier drinking onset was similarly associated with these network organization metrics, however, these results did not survive FDR correction across n=32

associations ($|r_s|$=.27 to .28, ps<.041). For network integration, there were no significant associations between alcohol use variables and global efficiency (ps>.064). Normalized modularity and normalized global efficiency metrics showed a similar pattern of results (Supplemental Table 4).

4. Discussion

Emerging adulthood is a critical period for examining alcohol use effects on the brain due to it being a period in which the brain is developing and is vulnerable to neural insults (Jacobus and Tapert, 2013; Squeglia and Gray, 2016). Additionally, longitudinal studies have shown neural damage related to alcohol use can be reversible through abstinence from alcohol (e.g., Bartsch et al., 2007). Consistent with the view that alcohol use during emerging adulthood has a neurotoxic effect, many studies have found alcohol use during this period to be associated with abnormalities in anatomical structure and white matter connectivity (e.g., Brown et al., 2008; Hua et al., 2020b, 2020c; Jacobus and Tapert, 2013; Meda et al., 2017, 2018). However, anatomical structure and white matter connectivity coexist, and it is important to understand how connectivity and organization of structural brain networks (i.e., combination of anatomical structure and white matter connectivity) can serve as a predisposing factor of and/or a consequence of alcohol use.

Due to their centrality in the brain network, rich-club nodes are critical in global brain communication and disproportionately vulnerable (e.g., Gollo et al., 2018; van den Heuvel et al., 2013). Examining connections between HCP-identified rich-club regions in our study, we found novel evidence that greater lifetime drinks and current average monthly drinks were significantly associated with less rich-club organization and fewer structural rich-club connections in emerging adults. Critically, alcohol use was specifically associated with fewer rich-club connections but not feeder or local connections. If anything, there was a trend for local connections being positively associated with alcohol use. Additionally, using Meng's z analyses to compare the strength of the correlations, rich-club connections were significantly more negatively correlated with alcohol use than local and feeder connections. These rich-club findings are consistent with previous research finding rich-clubs to be affected in both sub-clinical and clinical populations (e.g., de Lange et al., 2018; Schmidt et al., 2017). Specific to alcohol, Zorlu et al. found that their AUD group had impaired rich-club organization compared to healthy controls. Although, Zorlu et al. did not find alcohol use variables (i.e., drinking onset age and alcohol dependence duration) to be associated with rich-club organization, it is possible that the rich-club is more sensitive to alcohol quantity consumption measures, such as our lifetime alcohol drinks and current average monthly drinks variables. Further, Chumin et al. (2019) found increased network strength to be greater in their AUD group relative to their control group. Of note, network strength is the sum of connection types (rich-club, feeder, and local), and by collapsing across the connection types, the differential pattern (i.e., decreased rich-club connections and increased local connections) is obscured. As rich-club nodes play a key role in global brain communication (van den Heuvel and Sporns, 2011), fewer rich-club connections and increased local connections could be one sign, among multiple factors, of impaired brain organization and communication. In turn, compromised global brain communication could be related to neurocognitive deficits present in individuals with heavy alcohol use (Squeglia

and Gray, 2016), as well as being a factor that predisposes, escalates, and maintains addiction.

Focus on the rich-club is useful in examining associations with the brain's core backbone, while the examination of overall network organization serves a complementary role in assessing for more global connectome effects. In particular, we examined associations with overall network distribution, network segregation, and network integration. Greater lifetime drinks and current average monthly drinks were both significantly associated with lower structural network density. For network segregation metrics, greater lifetime drinks was significantly associated with higher modularity, and greater lifetime drinks and current average monthly drinks were significantly associated with higher transitivity. Alcohol use was not significantly associated with network integration. Results were consistent with our hypotheses that alcohol use would be associated with greater brain segregation, with disrupted segregation (i.e., greater modularity and transitivity) characteristic of other psychiatric disorders and associated with impaired global brain communication (e.g., Lynall et al., 2010). Although Zorlu et al. (2019) did not find significant associations with alcohol use variables (i.e., drinking onset age and alcohol dependence duration), they found that when compared to their no AUD control group, the AUD group had abnormalities in network distribution and no significant difference in global efficiency (i.e., network integration)., There are multiple possibilities for why we found significant associations in our sample. It is possible that our alcohol quantity consumption variables are more directly related to network measures (Kuceyeski et al., 2013; Rehm et al., 2013). It is also possible that associations are stronger in emerging adulthood due to this being a critical neurodevelopmental period. Further, Zorlu et al. only tested correlations in their AUD subgroup (n=18), resulting in restriction of range in alcohol use and lower statistical power.

There were multiple strengths in the current study. A strength was the focus on both longstanding and more recent alcohol use in non-clinical emerging adulthood. By examining multiple measures, we better characterized lifetime and current alcohol use effects. Different metrics could also measure different characteristics of alcohol use that could refine our understanding of mechanisms underlying these associations. Additionally, to our knowledge, this is the only study that has examined alcohol use and connectome associations during emerging adulthood in a non-clinical sample. Use of a non-clinical younger cohort could help us better understand the relationship between alcohol use with rich-club and network disorganization without the confound of a prolonged history of heavy alcohol exposure. An additional strength was using multimodal neuroimaging approach and combining structural MRI data with DWI. Multimodal neuroimaging provides information on the complex interconnectedness of brain structure and connectivity that is not possible with a single imaging modality.

Despite these strengths, there were some limitations. A limitation was the relatively small sample size and the possibility that there might be some non-students in the sample. Another limitation was the cross-sectional design, which did not allow for directional interpretations of whether fewer rich-club connections and greater network disorganization are a precipitant of or consequence of alcohol use. Longitudinal data from before and after participants' 21st birthday celebration (i.e., key lifetime event often characterized by alcohol consumption)

will be analyzed and reported in a separate paper. Another limitation is the potential issue of co-occurring substance use and psychiatric comorbidity. Although we collected data on these variables, data were missing on a substantial number of participants. Further, although we asked participants to abstain from other substances prior to scanning, we did not include a urine toxicology screening to confirm that participants complied with instructions. Due to comorbidity with other substance use and psychiatric disorders, future research should continue to examine whether fewer richclub connections and connectome disorganization are specific to alcohol use or are more generally related to psychopathology. Lastly, the identification of rich-club nodes is dependent on the choice of rich-club node threshold, with this threshold varying across previous research (current study threshold was top 12% of highly connected nodes). Of note, the majority of our results, particularly the association between fewer rich-club connections and greater alcohol use, were robust to different rich-club node thresholds (top 9% and 17% of highly-connected nodes).

5. Conclusions

Overall, we found novel evidence that alcohol use is specifically associated with affected rich-club organization and connectivity as well as network disorganization (i.e., lower network connectivity) and higher network segregation in emerging adults. These results add to the growing literature that emerging adulthood is a critical period for examining alcohol use effects on the brain. Results also highlight the need to study the long-term course of these possible alcohol-induced effects and their potential reversibility through abstinence or adult maturation (Bartsch et al., 2007).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Young adulthood is a critical neurodevelopmental stage with high rates of drinking
- Examined alcohol use associations with connectome organization in emerging adults
- Specifically examined rich-club connectivity and structural network organization
- Greater alcohol use was associated with decreased rich-club connectivity
- Greater alcohol use was associated with greater structural network segregation

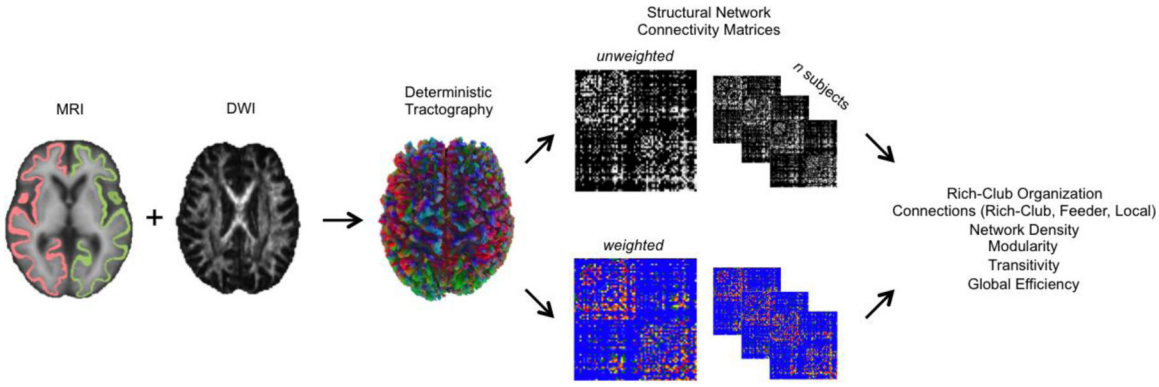

Figure 1.

Structural network construction pipeline. The magnetic resonance imaging (MRI) cortical parcellation map was combined with the diffusion-weighted image (DWI). The diffusion profile within each voxel of the gray matter/white matter mask was reconstructed and diffusion tensors were computed. White matter tracts were then reconstructed using the Fiber Assignment by Continuous Tracking (FACT) deterministic tracking algorithm. Structural networks were constructed by combining the MRI cortical parcellation map with the DWI reconstructed tractography streamlines. Structural networks could then be expressed as a structural network connectivity matrix for each participant. Unweighted connectivity matrices are binarized matrices, and weighted matrices are matrices weighted by number of streamlines (NOS-weighted) and cortical volume of nodes (i.e., streamline density; SD-weighted).

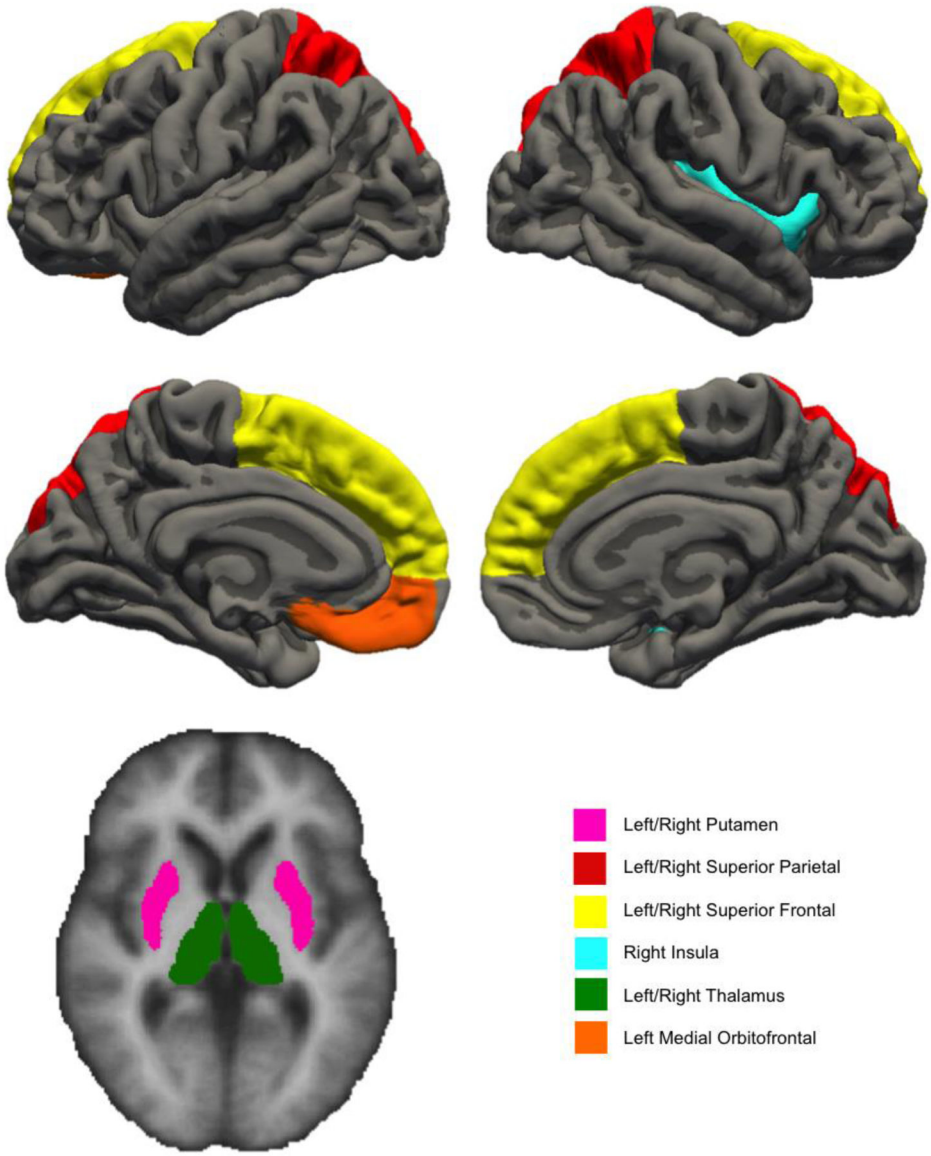

Figure 2.
Rich-club nodes.

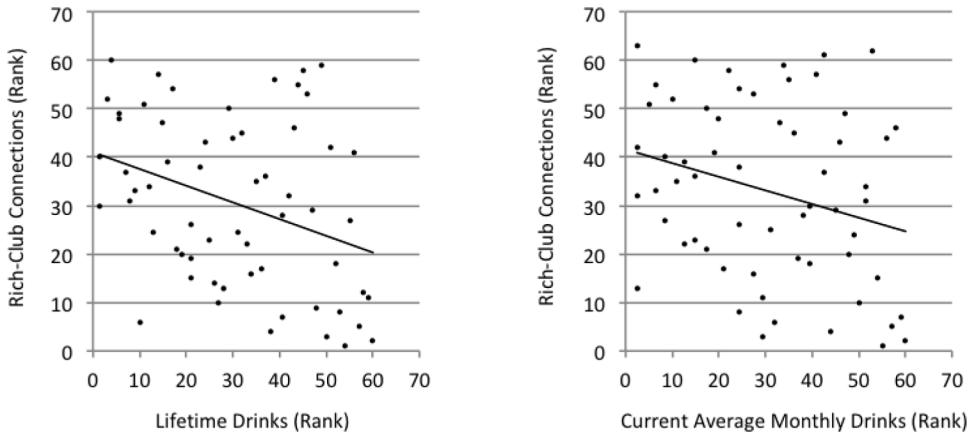

Figure 3.

Greater lifetime drinks and current average monthly drinks associated with lower rich-club connections.

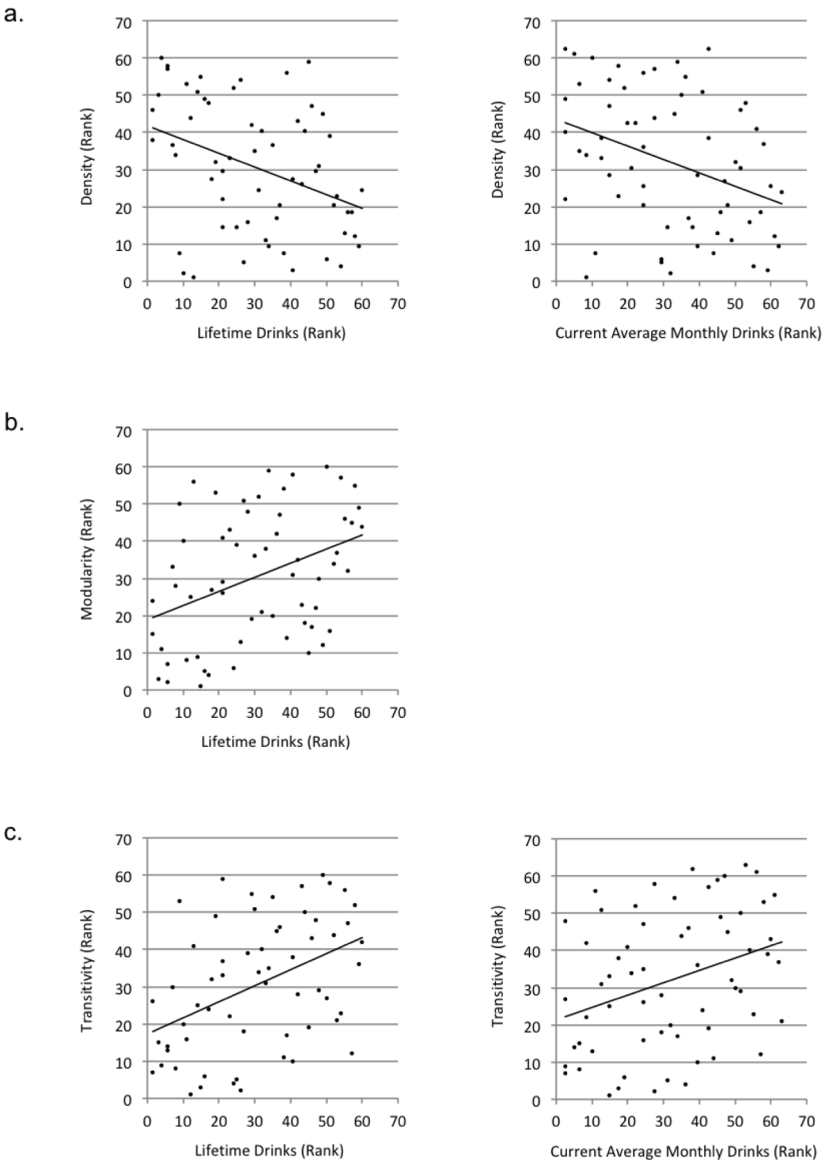

Figure 4.

Alcohol use associated with network organization metrics. a) Greater lifetime drinks and current average monthly drinks associated with lower density. b) Greater lifetime drinks associated with higher modularity. c) Greater lifetime drinks and current average monthly drinks associated with higher transitivity.

Table 1

Alcohol Use Variables Descriptive Statistics (N=66)

Variables	Mean (*SD*)	Range
Lifetime Drinks (in Standard Drinks)	1,318.62 (1,824.96)	0–10,542
Current Average Monthly Drinks (in Standard Drinks)	32.40 (37.09)	0–198
Drinking Onset Age (years)[a]	17.48 (1.57)	13–20
Past Year Hangover Symptoms	6.22 (3.22)	0–12

Note. SD=standard deviation.

[a]Two participants were non-drinkers, and results were similar when these participants were excluded from the analysis.

Table 2

Spearman Correlations Among Alcohol Use Variables

Variables	1	2	3	4
1. Lifetime Drinks	—			
2. Current Average Monthly Drinks	.84***	—		
3. Earlier Drinking Onset[a]	.64***	.43**	—	
4. Past Year Hangover Symptoms	.64***	.56***	.53***	—

[a]Drinking onset age was reversed scored (i.e., higher scores mean earlier age of onset).

** $p < .01$.

*** $p < .001$.

Table 3

Spearman Correlations Between Alcohol Use Variables With Rich-Club Organization and Network Connection Types.

Variables	Structural NOS-Weighted Matrices			
	Rich-Club Organization[a]	**Rich-Club Connections**	**Feeder Connections**	**Local Connections**
Lifetime Drinks	**−0.38****	**−0.35****	−0.10	0.33*
Current Average Monthly Drinks	**−0.38****	**−0.34****	−0.14	0.26*
Earlier Drinking Onset[b]	−0.12	−0.24	−0.10	0.10
Past Year Hangover Symptoms	−0.10	−0.07	0.01	0.30*

Note. Bolded text denotes regions that are significant after false discovery rate correction ($p_{FDR} < 0.05$); NOS-weighted = number of streamlines-weighted.

[a] Rich-dub coefficient calculated at degree = 15. Associations were similar when tested at multiple degree thresholds between 13 and 17.

[b] Drinking onset age was reversed scored (i.e., higher scores mean earlier age of onset).

* $p < .05$.

** $p < .01$.

Table 4

Correlated Correlations Comparisons Between Alcohol Use Variables and Network Connection Types.

	Structural NOS-Weighted Matrices		
Variables	**Rich-Club vs. Feeder (z)**	**Rich-Club vs. Local (z)**	**Feeder vs. Local (z)**
Lifetime Drinks	−2.59 **	−4.46 ***	−3.89 ***
Current Average Monthly Drinks	−2.03 *	−3.85 ***	−3.51 ***
Earlier Drinking Onset[a]	−1.44	−2.12 *	−1.64
Past Year Hangover Symptoms	−0.84	−2.45 *	−2.62 **

Note. NOS-weighted = number of streamlines-weighted.

[a]Drinking onset age was reversed scored (i.e., higher scores mean earlier age of onset).

* $p < .05$

** $p < .01$

*** $p < .001$.

Table 5

Spearman Correlations Between Alcohol Use Variables and Network Organization Metrics

Variables	Structural NOS-Weighted Matrices			
	Density	Modularity	Transitivity	Global Efficiency
Lifetime Alcohol Drinks	**−.37****	**.38****	**.43****	−.18
Current Average Monthly Drinks	**−.36****	.31*	**.33****	−.10
Earlier Drinking Onset[a]	−.28*	.27*	.27*	−.17
Past Year Hangover Symptoms	−.08	.13	.20	−.04

Note. Bolded text denotes regions that are significant after false discovery rate correction ($p_{FDR} < .05$); NOS-weighted=number of streamlines-weighted.

[a]Drinking onset age was reversed scored (i.e., higher scores mean earlier age of onset).

*$p < .05$.

**$p < .01$.