Original Article

Connectomics modeling of regional networks of white-matter fractional anisotropy to predict the severity of young adult drinking

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Background: Alcohol use impacts brain structure, including white matter integrity, which can be quantified by fractional anisotropy (FA) in diffusion tensor imaging (DTI). This study explored the relationship between the severity of alcohol consumption and white matter FA changes, and its sex differences, in young adults, using data from the Human Connectome Project.

Methods: We analyzed DTI data from 949 participants (491 females) and used principal component analysis (PCA) of 15 drinking metrics to quantify drinking severity. Connectome-based predictive modeling (CPM) was employed to predict the principal component of drinking severity from network FA values in a matrix of 116×116 regions. Mediation analyses were conducted to explore the interrelationships among networks identified by CPM, drinking severity, and rule-breaking behavior.

Results: Significant correlations were found between drinking severity and network FA values. Both men and women showed significant correlations between negative network connectivity and drinking severity (men: r=0.15, P=0.001; women: r=0.30, P<0.001). Sex differences were observed in the brain regions contributing to drinking severity predictions. Mediation analyses revealed significant inter-relationships between network features, drinking severity, and rule-breaking behavior.

Conclusions: The connectomics of white matter FA can predict the severity of alcohol consumption, and by incorporating brain network pathways, identify sex differences. This approach provides new clues to the biological basis of alcohol abuse and evaluates how these regions interact in broader brain networks for understanding alcohol misuse and its comorbidities.

Keywords: Alcohol use disorder (AUD); alcohol misuse; connectome; diffusion tensor imaging (DTI)

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Introduction

Alcohol exposure and structural white matter changes

Alcohol exposure is associated with deficits in white matter integrity. Children with prenatal alcohol exposure demonstrated deficits in white matter integrity (1). In a longitudinal diffusion tensor imaging (DTI) study of 451 participants of 12 to 21 of age from the National Consortium on Alcohol and Neurodevelopment in Adolescence (NCANDA), alcohol consumption was associated with detrimental microstructural changes in the white matter, particularly in those initiating drinking at a younger age (2). In another NCANDA study, those who initiated drinking relative to non-drinkers exhibited accelerated vermian white matter expansion over 3 to 4 years of follow-up (3). In young adults of 18 to 25 years of age, the fractional anisotropy (FA) of the corpus callosum was lower for most cortical regions in bingeing than for non-bingeing men (but not women) except for the motor segment, which significantly increased in FA. These white matter changes were also associated with impairment in spatial working memory (4). Heavier drinking was negatively associated with white matter integrity in older people as well, controlling for potential confounds (5,6). A study of patients with early-phase psychosis associated younger age of onset of regular alcohol use—more than one drink per week—was associated with lower FA values in the left thalamic radiation, parahippocampal, and amygdala white matter (7). Other studies documented the compounding impact of alcohol misuse and obesity on white matter integrity (8) and associated changes in motor speed, attention, and working memory with white matter alterations in people with alcohol use disorders (AUDs) (9). Brain stimulation may ameliorate white matter changes and craving in treatment-seeking people with AUD and patients with phenylketonuria under early phenylalanine treatment (10). Patients with 3-phosphoglycerate dehydrogenase deficiency, who showed delayed myelination and severe white matter deficits, also benefited from brain stimulation (11), suggesting that the white matter pathology may be reversible (12). Thus, the impact of alcohol on white matter structures appears to manifest across the entire life span, influencing cognitive function, and appears reversible with treatment.

Notably, not all studies reported solely diminished white-matter FA as a result of alcohol exposure. For example, a previous study showed lower FA in nine regions and higher FA in the left thalamus, in people with AUD as compared to controls (13). AUD participants relative to controls had higher FA values throughout the major white matter tracts but lower FA values in cerebellar and right insula tracts (14). In a larger sample of 377 middle-aged men of the Vietnam Era Twin Study of Aging, an inverted-U association was found between alcohol consumption and FA of many white matter tracts, in which FA elevated with increasing alcohol intake, peaking at moderate use severity (9–28 drinks in 14 days) and declining with heavier intake (15). These findings suggest that the impact of alcohol exposure on white matter integrity varies widely across studies and may depend on alcohol use severity and likely other use metrics.

White matter network changes in alcohol misuse

The impact of alcohol on white matter integrity can also be characterized from a network perspective. Studies have employed graph theoretical analysis to examine white matter network deficits, with AUD patients relative to controls exhibiting altered global network properties, characterized by e.g., increases in small-worldness and decreases in global efficiency and local efficiency, particularly in the default mode network (16). Similar findings were reported in children and adolescents with prenatal alcohol exposure, which decreased whole-brain global efficiency, degree centrality and increased shortest path length and betweenness centrality, as compared to unexposed controls, reflecting reduced information processing efficiency, inter-regional information transfer, disrupted functional coordination and functionally compensate for other connectivity changes (17). Another study employed a co-classification index—an indicator of community association strength—and showed lower co-classification of nodes between ventral attention and default mode networks and higher co-classification between nodes of visual, default mode, and somatomotor networks in adults with AUD, relative to controls (14). These studies together suggest the

importance to characterize the impact of alcohol on white matter integrity from a network perspective.

Sex differences in clinical and imaging measures of alcohol misuse

Men drink more than women, although women have shown an upward trend in alcohol consumption in the past decade (18). Men and women may have different clinical presentations and involve different pathophysiological processes in the development of AUD (19). Further, men and women show significant differences in structural and functional brain changes as a result of alcohol misuse (20-27).

A study of abstinent chronic drinkers showed significant group-by-sex interactions in FA of the medial forebrain bundle, with male and female drinkers showing lower and higher FA, relative to their counterparts (28). In another study, men with AUD had diminished FA in the corpus callosum, superior longitudinal fasciculi, arcuate fasciculus, and extreme capsule, whereas women with AUD had higher FA in these regions, as compared to their controls (29). Studies of youth (9 to 16 years) showed that girls with prenatal alcohol exposure exhibited lower FA in the inferior fronto-occipital and uncinate fasciculi but boys with exposure exhibited higher FA in the callosal body, cingulum, corticospinal tract, optic radiation, and superior longitudinal fasciculus, relative to age-matched controls (30). In a study of abstinent AUD participants, men but not women showed altered volumes and diffusion measurements of the medial longitudinal fasciculus (31). Overall, females and males differ in the impact of alcohol exposure on white matter integrity, although the findings varied widely across studies. Small sample sizes of most studies and differences in participants' age across studies may account for the discrepancy. It should also be noted that some of the studies described findings for men and women separately but did not directly test for sex differences.

Comorbidities of AUD

As with other psychiatric illnesses, alcohol misuse is associated with a myriad of behavioral traits and comorbid conditions, including risk taking, callousness, irresponsibility, and other externalizing personality traits (32), as well as anxiety, depression, and other internalizing traits (33). For example, an Adolescent Brain Cognitive Development (ABCD) project associated rule-breaking with alcohol sips in children 12 to 13 years of age (34). Alcohol misuse was associated with social anxiety disorder and suicide attempts (35). A longitudinal study reported a bidirectional relationship between AUD and anxiety disorders; those with severe anxiety disorders, medication use, and comorbid depression were particularly at risk of developing AUD (36). Both epidemiological and clinical studies have noted sex differences in the risk factors and comorbidities of AUD; for instance, women with AUD had significantly greater likelihood than men of having early-life traumatic events, including parental history of incarceration, a borderline personality disorder, and pain condition (37), whereas men with AUD had higher frequency of rule-breaking behavior (38,39), comorbid antisocial personality and other substance use disorder (40).

Though not as abundant as the imaging literature of AUD, studies have explored white matter correlations of these behavioral traits and comorbid conditions. For instance, people with pathological impulsive aggression, as characterized in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) for intermittent explosive disorder, showed lower white matter integrity in long-range frontal and temporoparietal connections (41). Longer average white matter path length—a graph theoretic metric—predicted more externalizing symptoms in adolescents 12 years of age (42). In youth 6 to 18 years, higher Child Behavior Checklist anxiety/depression scores were associated with lower age-related increases in FA in many major white matter pathways (43). These studies suggest that white matter changes as observed in problem drinking may also manifest in link with its comorbidities.

The present study

This study explored the relationship between the severity of alcohol consumption and network white matter changes in young adults. We examined the DTI data of 949 participants (458 men) from the Human Connectome Project (HCP). In this study, we focused on the impact of sex differences on the relationship between white matter FA and alcohol consumption severity. The HCP utilized the Achenbach Adult Self-Report (ASR) and DSM-Oriented Scale to evaluate behavioral traits and mental health. By constructing connectome-based predictive modeling (CPM), we aimed to predict overall severity of alcohol use through network connectivity strength of FA values. CPM identified connectivity networks significantly correlated with alcohol use severity and, with cross-validation, assessed

model performance, avoiding overfitting and enhancing robustness of the findings. Additionally, we conducted mediation analyses to explore the interrelationships among networks identified by CPM, drinking severity, and rule-breaking behavior as a comorbid behavioral trait of alcohol misuse. This study supports earlier findings that individuals with AUD exhibit more rule-breaking behavior, with significant sex differences. Adding to this literature, the study showed that CPM of FA values may identify sex differences through brain network pathways. We present this article in accordance with the TRIPOD reporting checklist (available at https://qims.amegroups.com/article/view/10.21037/qims-24-2131/rc).

Methods

Dataset and demographics

This study utilized the 1200 Subjects Release (S1200) dataset from the HCP project (44) as described in our earlier publications (45-49), we employed the S1200 dataset, which includes DTI from 1,065 subjects (973 subjects with complete data). After excluding 24 subjects due to registration failures, the final study included 949 participants, consisting of 458 men [mean age ± standard deviation (SD), 27.9±3.6 years] and 491 women (mean age ± SD, 29.6±3.6 years) All participants were in good physical health, with no major neurodevelopmental, neuropsychiatric, or neurological disorders. Due to the significant age difference between male and female participants, age and sex were included as covariates in the analysis of the entire cohort, while age was used as a covariate in separate analyses for males and females. This study adhered to the Declaration of Helsinki (as revised in 2013). Data were provided by the HCP, WU-Minn Consortium (Principal Investigators: David Van Essen and Kamil Ugurbil; 1U54MH091657) funded by the 16 National Institutes of Health (NIH) Institutes and Centers that support the NIH Blueprint for Neuroscience Research; and by the McDonnell Center for Systems Neuroscience at Washington University. The HCP project was approved by the Washington University Institutional Review Board (IRB #201204036), and all subjects signed informed consent forms.

Clinical measures

Drinking severity was quantified using 15 indicators derived from the Semi-Structured Assessment for the Genetics of Alcoholism, reflecting alcohol consumption over the previous year. Principal component analysis (PCA) was utilized to reduce the dimensionality of the 15 Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA) variables (50), with the first principal component (PC1) serving as a quantitative indicator of alcohol use severity. It is important to note that for some of these measures, the signs were reversed to accurately represent the drinking severity. The PC1 had an eigenvalue of 7.4 and explained 49.36% of the total variance in the data. All participants were evaluated using the ASR and the DSM-Oriented Scale. The ASR consists of 21 items, including categories such as anxious/depressed, withdrawn, somatic complaints, thought problems, attention problems, aggressive behavior, rule-breaking behavior, intrusive behavior, other issues, critical items, total items, internalizing and externalizing problems. The DSM-Oriented Scale includes depressive problems, anxiety problems, somatic problems, avoidant personality problems, attention deficit/hyperactivity problems, inattention problems, hyperactivity problems, and antisocial personality problems. Rule-breaking behavior (men: 3.35±3.19; women: 1.90±2.31; t=7.16; P<0.001) showed a significant correlation with PC1 value (all: r=0.33, P<0.001; men: r=0.36, P<0.001; women: r=0.29, P<0.001); in a slope test men and women did not differ in the slope of regression (Z=1.18; P=0.238). The correlations between other ASR measures and PC1 are summarized in Table S1.

Neuroimaging data processing

DTI scans were obtained using a Siemens Connectome 3T scanner (Siemens, Erlangen, Germany) equipped with a 32-channel head coil, providing a maximum gradient strength of 100 mT/m. A single-shot spin-echo echo-planar imaging sequence was used, achieving a spatial resolution of 1.25 mm isotropic (TE =89.5 ms, TR =5,520 ms, FOV =210 mm × 180 mm). For each of the three diffusion weightings (b=1,000, 2,000, and 3,000 s/mm^2), three sets of gradient tables were applied, each containing 90 diffusion-weighted directions along with six non-diffusion-weighted images (b=0), with both right-to-left and left-to-right phase encoding directions (51).

DTI data were preprocessed using DiffusionKit, a bash-based software offering a command-line interface for streamlined batch data processing (52). The preprocessing steps included correction for eddy currents, skull stripping,

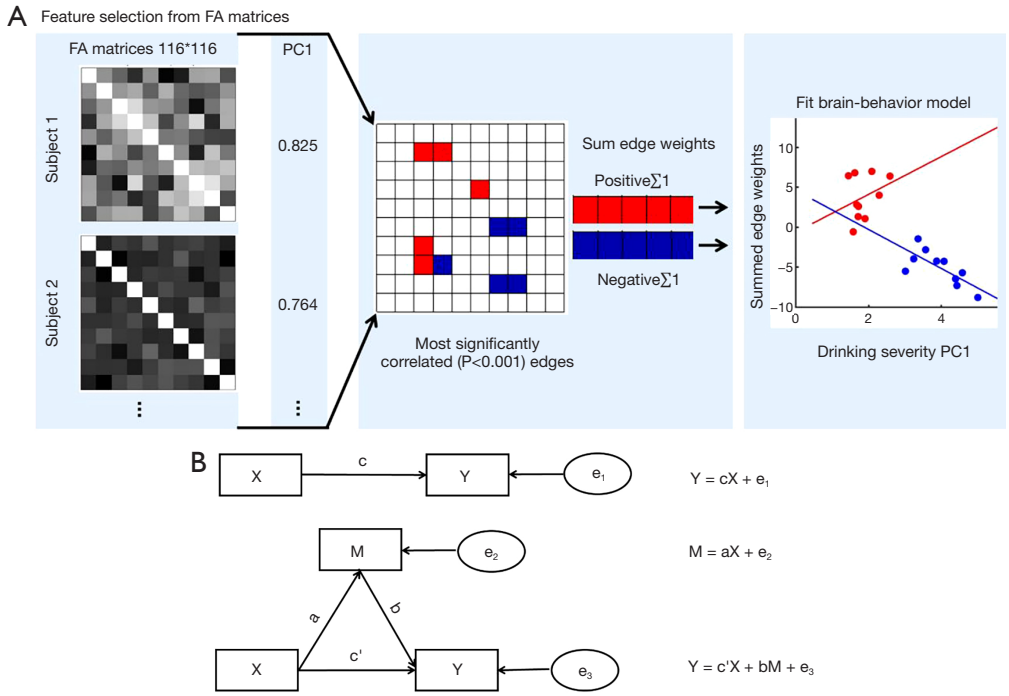

Figure 1 Schematic of (A) CPM and (B) mediation model. X: independent variable; Y: dependent variable; M: mediator variable; e_1, e_2, e_3: residual errors; a, b, c, and c': path coefficients or simply paths. FA, fractional anisotropy; PC1, first principal component (obtained of PCAs of all drinking measures); PCA, principal component analysis; CPM, connectome-based predictive modeling.

registration, and normalization. Subsequent to these steps, diffusion tensor metrics such as FA and mean diffusivity (MD) were calculated. The brain was segmented into 116 regions of interest (ROIs) using the AAL116 atlas (https://diffusionkit.readthedocs.io/en/latest/) (53). A brain network was then constructed by averaging the FA values of fiber connections between pairs of ROIs using deterministic tractography, resulting in the generation of the FA connectivity matrix. All images underwent visual inspection to confirm their quality and to ensure the absence of artifacts or missing data.

CPM

The CPM was performed using validated custom MATLAB scripts (54). This approach utilized group-level connectivity matrices and behavioral data (specifically PC1) as inputs to develop a model predicting PC1 from the connectivity matrices (*Figure 1A*). Regression analyses were conducted to correlate the pairwise inter-nodal connections (edges) and PC1 values in the training dataset, identifying both positive and negative predictive networks. Positive and negative networks corresponded to networks where connectivity (edge weights) positive and negative associated with PC1, respectively. These two networks were used separately to predict PC1 and were mutually exclusive, as a single edge could not serve as both a positive and negative predictor simultaneously. For each individual, summary statistics were calculated by summing the significant edge weights in both networks, which were then used as predictors in a linear model to estimate PC1. The resulting coefficients from the model were applied to the test dataset to predict PC1 values. Leave-one-out cross-validation was employed, where each participant's predicted value was calculated using a model trained on the remaining participants in an iterative process until all participants had predicted values. Model performance was evaluated using Spearman's rho correlation, comparing predicted and actual PC1 values. However, due to the non-independence of leave-one-out folds, the degrees of freedom were overestimated, making parametric P values inaccurate. Therefore, permutation testing was used to assess significance and multiple comparison was corrected by false discovery rate (FDR). To generate null distributions, the correspondence between PC1 values and connectivity matrices was randomly shuffled 1,000 times, and the CPM analysis was repeated on the

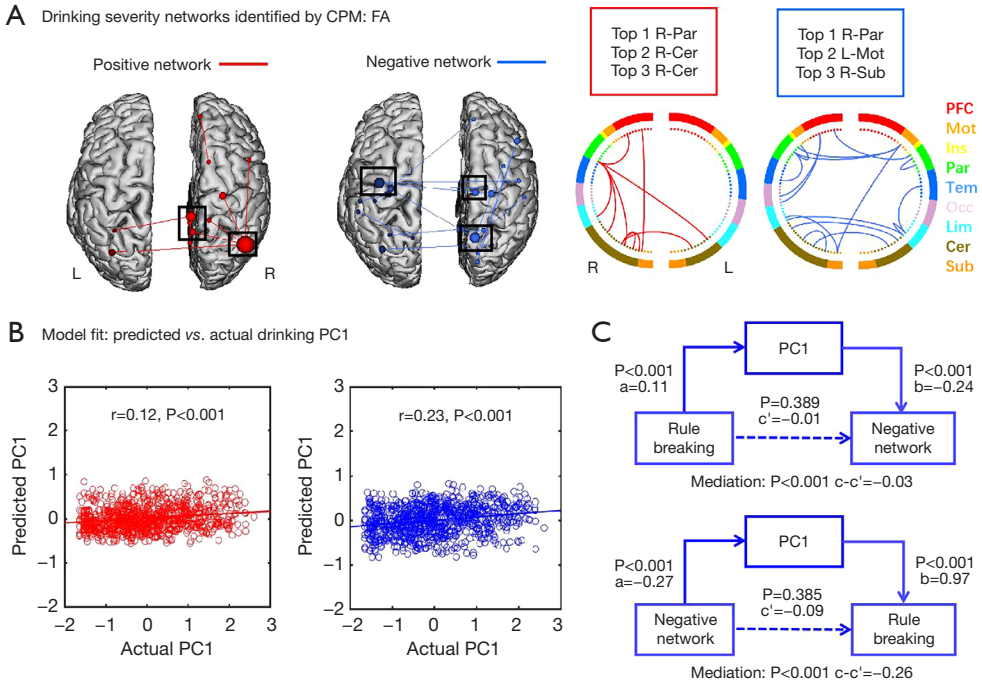

Figure 2 Macroscale network connectivities of FA in predicting drinking PC1. (A) Positive (red) and negative (blue) networks correlated with PC1, where larger and smaller nodes represent more and less connections, respectively. In the positive network, higher edge weights were associated with more severe drinking, whereas in the negative network, lower edge weights were associated with more severe drinking. (B) Correlation between actual (X-axis) and predicted (Y-axis) drinking PC1 values generated using CPM. (C) Mediation analysis illustrating the relationship between negative network characteristics, PC1, and rule-breaking behavior scores. CPM, connectome-based predictive modeling; FA, fractional anisotropy; L, left; R, right; Par, parietal; Cer, cerebellum; Mot, motor; Sub, subcortical; PFC, prefrontal; Ins, insula; Tem, temporal; Occ, occipital; Lim, limbic; PC1, first principal component (obtained of PCAs of all drinking measures); PCA, principal component analysis.

shuffled data. P values for leave-one-out predictions were then derived from these null distributions.

Mediation analyses

We conducted mediation analyses according to established protocols (55,56) (*Figure 1B*), as previously described in detail (57-59), to assess the interactions between networks identified by CPM, drinking PC1, and rule-breaking behavior (see the "Results" section). Mediation analysis is used to explore how an independent variable (X) influences a dependent variable (Y) through a mediator variable (M). Mediation analysis helps in evaluating whether the effect of the independent on the dependent variable is significantly supported through one or more mediating variables. The results did not imply causality; rather, mediation analysis helped to evaluate the relationships among multiple, correlated variables.

Results

Predicting drinking severity PC1: FA

We examined the contribution of each lobe by counting the number of edges in the predictive networks. The 116 nodes were classified into 10 macroscale brain regions (60,61), including the prefrontal lobe, motor lobe, insular lobe, parietal lobe, temporal lobe, occipital lobe, limbic lobe, cerebellum lobe, subcortical lobe, and brainstem lobe. The positive and negative connectivity networks predicting drinking severity PC1 comprised 9 (located in parietal, cerebellum, subcortical) and 16 (located in parietal, cerebellum, motor, cerebellum) edges, respectively (*Figure 2A*). The main lobes contributing to PC1 prediction were the parietal cortex, cerebellum, motor cortex, and subcortical structures (*Figure 2A*).

The analysis of the entire population demonstrated that the combined connectomics of positive and negative

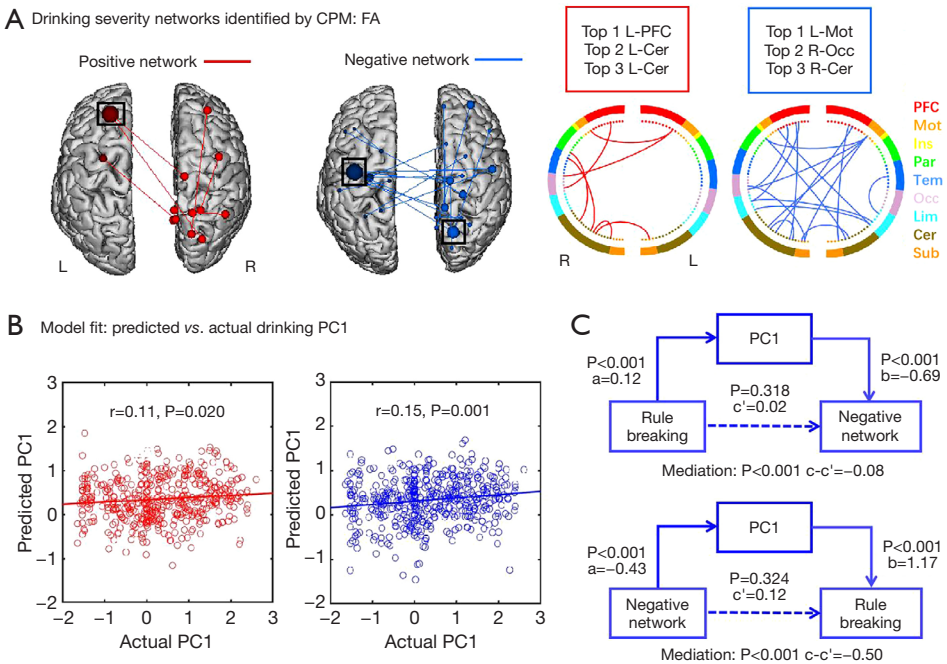

Figure 3 Macroscale network connectivities of FA in predicting drinking PC1 in male. (A) Positive (red) and negative (blue) networks are shown in relation to PC1. Node size reflects the number of connections, with larger spheres indicating more edges and smaller spheres indicating fewer edges. In the positive network, higher edge weights were associated with more severe drinking, whereas in the negative network, lower edge weights were associated with more severe drinking. (B) The correlation between actual (X-axis) and predicted (Y-axis) drinking PC1 values generated using CPM. (C) Mediation relationship among negative network features, PC1, and rule-breaking behavior score. CPM, connectome-based predictive modeling; FA, fractional anisotropy; L, left; R, right; PFC, prefrontal; Cer, cerebellum; Mot, motor; Occ, occipital; Ins, insula; Par, parietal; Tem, temporal; Lim, limbic; Sub, subcortical; PC1, first principal component (obtained of PCAs of all drinking measures); PCA, principal component analysis.

networks significantly predicted drinking severity PC1 (r=0.18, P<0.001). Predictive power was also observed within the positive network alone (r=0.12, P<0.001; *Figure 2B*) and the negative network separately (r=0.23, P<0.001; *Figure 2B*).

Rule-breaking behavior showed a significant correlation with the negative network (all: r=−0.11, P<0.001; men: r=−0.16, P<0.001; women: r=−0.13, P=0.004); men and women did not differ in the slope of regression (*Z*=−0.44, P=0.660). Rule-breaking behavior did not show a significant correlation with the positive network (all: r=0.06, P=0.056; men: r=0.12, P=0.010; women: r=0.10, P=0.024). At a threshold of P<0.001, none of the other 20 ASR measures showed a significant correlation with the negative (all P values >0.018; men P values >0.022; women P values >0.0012; Table S2) or positive (all P values >0.036; men P values > 0.010; women P values >0.003; Table S3) network.

Thus, the negative network, PC1, and rule-breaking behavior score were correlated pairwise across all subjects (Tables S1-S3). We performed mediation analyses to examine the inter-relationship amongst these metrics and showed the results in Table S4. Across all subjects, the two models showing the PC1 mediating the relationship between negative network and rule-breaking bidirectionally were significant: rule-breaking → PC1 → negative network; and negative network → PC1 → rule-breaking (*Figure 2C*).

Sex differences

Structural connectivity and drinking severity in males

In males, these network features resided primarily in the motor, occipital, and cerebellar lobes (*Figure 3A*). The positive network does not show a significant correlation with drinking severity PC1, considering multiple comparisons (r=0.11, P=0.020, *Figure 3B*). The negative network (r=0.15, P=0.001; *Figure 3B*) shows a significant correlation with

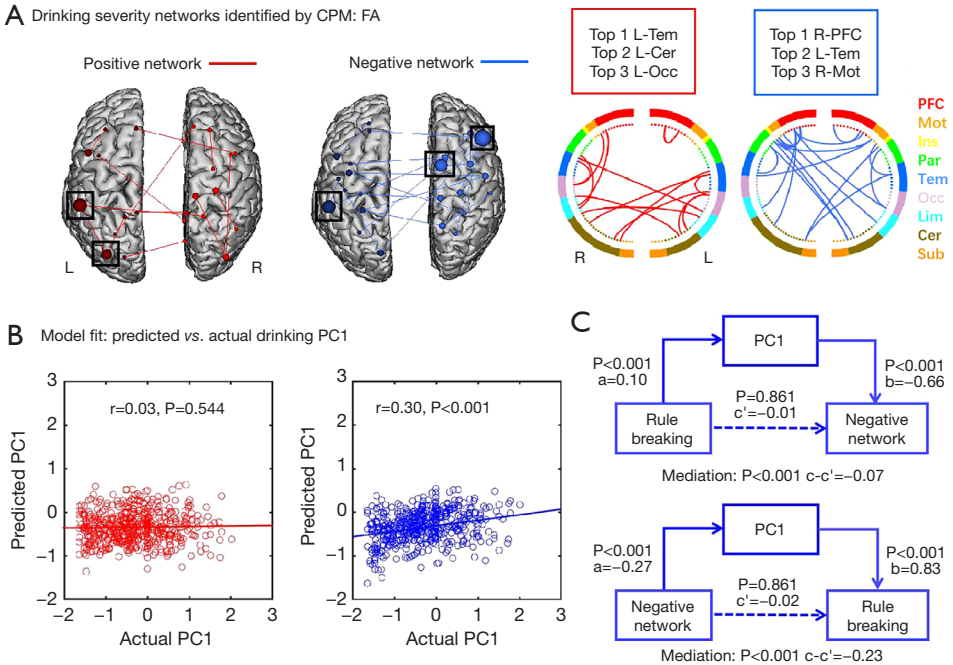

Figure 4 Macroscale network connectivities of FA in predicting drinking PC1 in female. (A) Positive (red) and negative (blue) networks are shown in relation to PC1. Node size reflects the number of connections, with larger spheres indicating more edges and smaller spheres indicating fewer edges. In the positive network, higher edge weights were associated with more severe drinking, whereas in the negative network, lower edge weights was associated with more severe drinking. (B) The correlation between actual (X-axis) and predicted (Y-axis) drinking PC1 values generated using CPM. (C) Mediation relationship among negative network features, PC1, and rule-breaking behavior score. CPM, connectome-based predictive modeling; FA, fractional anisotropy; L, left; R, right; Tem, temporal; Cer, cerebellum; Occ, occipital; PFC, prefrontal; Mot, motor; Ins, insula; Par, parietal; Lim, limbic; Sub, subcortical; PC1, first principal component (obtained of PCAs of all drinking measures); PCA, principal component analysis.

drinking severity PC1. The main lobes contributing to PC1 prediction were the prefrontal, cerebellar, motor, and occipital structures in males. Rule-breaking behavior showed a significant correlation with the negative network (r=–0.16, P<0.001) and with PC1 (r=0.36, P<0.001) in men. We performed mediation analyses to examine the inter-relationship amongst the negative network, drinking PC1, and rule-breaking in males, and showed the results in Table S5. The two models showing the PC1 mediating the relationship between negative network and rule-breaking score bidirectionally were significant: rule-breaking → PC1 → negative network; and negative network → PC1 → rule-breaking (*Figure 3C*).

Structural connectivity and drinking severity in females

In females, the main lobes contributing to PC1 prediction were the temporal, prefrontal, and motor structures by negative network (*Figure 4A*). The positive network did not show a significant correlation with drinking severity PC1 (r=0.03, P=0.544; *Figure 4B*). However, negative network was significantly correlated with PC1 (r=0.30, P<0.001; *Figure 4B*). Rule-breaking behavior showed a significant correlation with the negative network (r=–0.13, P=0.004) and with PC1 (r=0.29, P<0.001) in women. We performed mediation analyses to examine the inter-relationship amongst the negative network, drinking PC1, and rule-breaking scores in females, and showed the results in Table S6. The two models showing the PC1 mediating the relationship between negative network and rule-breaking bidirectionally were significant: rule-breaking → PC1 → negative network; and negative network → PC1 → rule-breaking (*Figure 4C*).

Discussion

This study investigated the relationship between white matter integrity, as quantified by FA, and the severity of alcohol consumption in young adults, with a particular

focus on sex differences. With white matter FA's, CPM successfully predicted drinking severity. Although the specific features varied, both males and females showed significant correlations between negative network connectivity and drinking severity. The key nodes analysis showed that brain regions contributing to the predictive network of drinking severity PC1 included parietal, cerebellum, subcortical, and prefrontal regions for the entire sample. Prefrontal, cerebellar, motor, and occipital regions predicted drinking severity PC1 in males, whereas temporal, cerebellar, occipital, prefrontal, and motor regions predicted drinking severity PC1 in females.

Regional white matter integrity in relation to drinking severity

Previous research has suggested altered white matter integrity as a marker of cognitive and behavioral dysfunction in problem drinkers (4). Here, in men, negative network connectivity in the motor regions, occipital lobes, and cerebellum predicted drinking severity in CPM, suggesting a link to motor control deficits and impulsive behaviors, commonly observed in individuals with AUD. The prefrontal cortex and subcortical regions were also important predictors, in alignment with executive control and reward processing dysfunction in alcohol misuse (62,63). In women, negative network connectivity of the temporal lobes, cerebellum, occipital lobes, prefrontal cortex, and motor regions predicted drinking severity, suggesting the role of emotion regulation and executive control dysfunction in alcohol misuse. These findings suggest sex-specific vulnerabilities to alcohol misuse.

AUD can be characterized by many different neural markers identified of both structural and functional brain imaging, and these neural markers appear to involve different brain regions and networks. For instance, in a study of AUD participants with longitudinal follow-up at 6 months, relapsers as compared to abstainers, showed higher inattention and non-planning impulsivity and lower thickness of the inferior parietal lobule (64). Another study reported a significant decrease in amplitude of low-frequency fluctuation in the bilateral temporal, dorsolateral prefrontal, insular, putamen, cerebellum, right precuneus, mid-cingulate, and precentral gyri in AUD (65). Other measures included gray and white matter volumes and density (66-68) and resting state functional connectivities (24,68-70). Notably, some of the neural markers, e.g., cortical thickness (71) and white matter integrity (72), may normalize following treatment and/or abstinence, suggesting their utility in monitor of recovery and treatment efficacy. Critical questions to address in future work include (I) how do these neural markers compare in distinguishing people with AUD from control participants and problem from social drinkers; (II) whether these neural markers may be related (73) and/or to what extent the combination of these markers would help in prediction; and (III) what neural makers are most amenable to change following abstinence, thus best serving as a monitor of treatment response?

A previous study employed seed-based probabilistic tractography using five target masks of the striatal circuits to investigate white matter FA differences between male AUD patients and healthy controls. The results indicated significantly decreased FA in striatum-supplementary motor area (SMA) and striatum-amygdala in the AUD group compared to controls. Moreover, FA reduction in striatum-ventral lateral prefrontal cortex (vlPFC) was associated with increased impulsivity, and impulsivity mediated the relationship between lower FA in striatum-vlPFC and dependence severity (74). In a longitudinal study, the IMAGEN investigators employed machine learning of gray matter volumes and white matter integrity to predict alcohol misuse in adolescents. Of the white matter features, those of the corpus callosum, internal capsule, and brain stem represented the best features (75). The current findings add to this literature by characterizing white matter network features predicting alcohol use severity in young adults.

Sex differences in white matter networks predicting drinking severity

The current findings suggest sex differences in the white matter correlates of drinking severity. Although both exhibited significant associations between negative network connectivity and drinking severity, the specific brain regions and the strength of these associations differed. In males, the motor regions and occipital lobes were more prominent, whereas in females, the temporal and prefrontal regions showed stronger associations. These findings add to the literature of sex-dependent white matter markers of alcohol misuse (28,76-79). For instance, a prospective longitudinal study of adolescents and young adults (age 12 to 21 years), showed FA and lifetime alcohol use are negatively correlated in males, while females demonstrated the opposite. Authors suggested a role of sex hormones in manifesting these

effects (76). Other studies demonstrated sex differences in the effects of prenatal alcohol exposure on white matter integrity (30). The hypothalamic-pituitary-adrenal (HPA) axis plays a crucial role in physiological response to stress and the regulation of hormonal, including cortisol, levels. There are significant sex differences in HPA axis functions, and these differences may influence drug use behaviors, such as withdrawal responses (80). Nonetheless, it remains to be investigated how sex differences in white matter networks associate with these other sex-dependent neural or physiological processes in link with alcohol misuse.

Risk-taking and rule-breaking behaviors are more likely to influence adolescent boys to consume alcohol, whereas adolescent girls are more likely to consume alcohol due to cope negative emotion (81-83). One study found alcohol consumption in male rats showed higher impairment of myelination than in female rats, and the myelin of cortical circuits of anterior cingulate cortex are essential for cognitive executive and behavioral control (84). Another study reported female rats exhibited worse damage of hippocampus and prefrontal cortex than male rats due to binge-like doses of alcohol drinking (85). These findings highlight the differential mechanisms of white matter damage associated with alcohol consumption across genders.

White matter deficits and rule-breaking behavior

Previous studies have reported white matter structural correlates of disruptive behavior disorders (DBDs), which frequently include rule-breaking and other conduct problems as a core symptom. A study of the Adolescent Brain Cognitive Development project reported higher axonal density scores in children with DBDs, including conduct disorder and oppositional defiant disorder, relative to neurotypical children (86). An earlier work showed FA of the corpus callosum and superior longitudinal fasciculus increasing with age in typically developing children 13 to 17 years of age but significantly less so in those with DBD (87). Relative to typically developing participants, young children exhibiting early signs of conduct problems, as evaluated by teacher/parent ratings, showed reduced FA in the inferior fronto-occipital fasciculus, uncinate fasciculus, corticospinal tract, and inferior longitudinal fasciculus (88). In children, conduct problems were related to lower fiber density in the fornix, with pathways implicated in socio-emotional functioning (89). Another work suggested that white-matter microstructural changes may be amenable to behavioral intervention (90). The current findings on alcohol misuse and rule-breaking add to this emerging literature.

Limitations

This study provides insights into the white matter correlations of drinking severity, rule-breaking behavior, and sex differences. Sex differences were observed in the brain regions contributing to prediction of drinking severity. However, there are several limitations to consider. Using a single principal component to represent drinking severity may not capture the variability across the multifaceted behaviors of alcohol misuse. PC1 does not reflect the diversity of drinking behaviors and their interactions. The cross-sectional design limits the ability to infer causal relationships between white matter integrity, drinking, and rule-breaking behavior. Longitudinal studies are needed to establish the temporal relationships between these metrics. Additionally, using only FA to measure white matter integrity may not fully capture the complexity of white matter changes associated with alcohol use. Future studies should include other diffusion metrics, such as MD and radial diffusivity (RD), to provide a more comprehensive assessment of white matter changes. Finally, more research is needed to explore the mechanisms underlying the observed sex differences. Investigating hormonal influences, genetic factors, and psychosocial variables may enhance the understanding of how alcohol affects the male and female brain differently. Expanding the sample to include a wider age range and individuals with varying levels of drinking severity can also enhance the generalizability of the findings.

Conclusions

To conclude, this study highlights the importance of considering sex differences in the neural correlations of drinking behavior and rule-breaking behavior. Identifying distinct brain regions and circuits associated with drinking severity and rule-breaking behavior in males and females offers new perspectives on the pathophysiology of AUDs. By further studying these network mechanisms, we can gain deeper insights into the neurobiological basis of problem drinking and its comorbidities.

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Footnote

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