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Structural Neuroimaging Correlates of Alcohol and Cannabis Use in Adolescents and Adults

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Abstract

Background and Aims—Chronic alcohol use is associated with lower gray matter volume, and we recently reported that alcohol use showed negative associations with widespread gray matter (GM) volume even among young adults. The current study aimed to test the strength of association between (1) alcohol use and GM volume; (2) alcohol use and white matter (WM) integrity; (3) cannabis use and GM volume; and (4) cannabis use and WM integrity among adults and adolescents.

Design and Setting—General linear models within large pooled cross-sectional samples of adolescents and adults who had participated in studies collecting substance use and neuroimaging data in the southwestern United States.

Participants—The current analysis included adults ages 18–55 years (N=853) and adolescents ages 14–18 years (N=439) with a range of alcohol and cannabis use.

Measurements—The dependent variable was GM volume or WM integrity, with key predictors of alcohol use (AUDIT score) and cannabis use (past 30-day use).

Findings—Alcohol use showed large clusters of negative associations (η_p^2=.028 to .145, p<.001) with GM volume among adults, and to a lesser extent (one cluster; η_p^2=.070, p<.05) among adolescents. Large clusters showed significant associations (η_p^2=.050 to .124, p<.001) of higher alcohol use with poorer WM integrity, whereas adolescents showed no significant associations between alcohol use and WM. No associations were observed between structural measures and past 30-day cannabis use in adults or adolescents.

Conclusions—Alcohol use severity is associated with widespread lower gray matter volume and white matter integrity in adults, and with lower gray matter volume in adolescents.

Keywords

alcohol use; cannabis use; neuroimaging; voxel-based morphometry; diffusion tensor imaging

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Conflicts of interest: None

Introduction

Neuroimaging studies provide strong evidence of deleterious effects of chronic alcohol use on brain structure in adults and adolescents [1–2]. Chronic alcohol consumption is associated with lower gray matter (GM) volume globally [3–5] and in specific cortical structures [6–7]. Results of our recent large-scale study support a negative correlation between alcohol use severity and global GM volume in adults as young as 18 years [8]. Studies among adolescents suggest regional reductions in frontal [9–11], temporal and parietal [10], and cerebellar volume [12], or differences localized to specific structures such as the hippocampus [13]. Recent longitudinal research has reflected that even minor or moderate alcohol use may have teratogenic effects [14]; and further, that initiation of regular drinking in late adolescence dose-dependently disrupts GM development [15–16]. These findings support potential alcohol-associated GM reductions in widely distributed brain areas among adults and adolescents.

Similarly, widespread regional associations are found between alcohol and white matter (WM) measures in adults, although findings are less consistent among adolescents. Reduced WM integrity has been demonstrated in adult alcohol users compared to age-matched low or non-drinkers [1, 17–18] in frontal and temporal tracts, cortico-striatal tracts, and corpus callosum [18–21]. Among adolescents, some studies suggest reduced WM integrity in drinkers in long-range tracts spanning posterior to frontal regions [14, 22–23], while others have suggested small areas of increased WM integrity [24]. However, it remains unclear whether areas of positive association reflect premorbid risk or a causal association with alcohol use [24–25].

In contrast with the neuroimaging literature on alcohol consumption, studies present inconsistent recreational or chronic cannabis use associations with structural brain measures [26]. Much of the extant research employed region of interest analyses, and contradictory results can be found in orbitofrontal cortex, hippocampus, and amygdala [27–31]. In some cases, cannabis-using and non-cannabis-using groups differed on alcohol use [31]. Studies of WM integrity and cannabis use are likewise inconsistent. Where deficits are reported, their locations vary [32–34]. Adolescent literature on the relationship between GM or WM and cannabis use is sparse, partly due to frequent use of alcohol and cannabis in this age group [35–36]. Researchers therefore tend to include control groups who either use alcohol alone or are substance-naïve [25, 37–39]. Results suggest that combined cannabis- and alcohol-using adolescents exhibit GM and WM differences compared to alcohol-only and substance-naïve controls [25, 37–39], but the regions of difference vary among studies, and generally do not match adult findings. While these studies often employ sizable samples, it remains difficult to distinguish relative impacts of alcohol and cannabis in group-based analyses, and when considered overall, cannabis findings in GM average to a null effect [40].

We aimed to test the strength of association between (1) alcohol use and GM volume; (2) alcohol use and WM integrity; (3) cannabis use and GM volume; and (4) cannabis use and WM integrity among adults and adolescents. We examined general linear models (GLM) in GM and WM that included terms for alcohol and cannabis use, with follow up cannabis

models comprising participants reporting weekly or greater cannabis use. Based on our previous work [8], we hypothesized that negative associations between alcohol use and GM would be observed in adults throughout frontal and parietal regions and cerebellum, and similar but less widespread associations would be observed in adolescents. We also expected that alcohol use would show widespread negative association with WM integrity among adults, and to a lesser extent among adolescents. Finally, based on previous work [40], we expected that no significant associations between GM or WM and cannabis use would emerge in adults or adolescents.

Methods

Design

The current study was cross-sectional and pooled data from existing studies that recruited substance-using adults, particularly alcohol, and collected neuroimaging data [41–42]. Data for adolescents were pooled from two existing neuroimaging studies among high-risk adolescents who were recruited to participate in a sexual health intervention [44–46]. Importantly, subsamples within the pooled dataset have been reported upon previously [8, 42], and were included here to maximize sample sizes and include a wide range of substance use. Key predictors of alcohol and cannabis use were treated as continuous measures, and participants with a wide range of use were included to test strengths of associations in GLM.

Sample and Procedures

Adult Participants—Participants were recruited from a southwestern metropolitan region of the United States through print and radio advertisements and online media. Exclusionary criteria across studies included traumatic brain injury with loss of consciousness >5 minutes, history of bipolar disorder or a psychotic disorder, or MRI contraindications (e.g., a positive pregnancy test, irremovable metal implants or piercings, claustrophobia). Subjects were asked to stop drinking 24 hours and abstain from smoking cigarettes 2 hours before scanning, and had to demonstrate a blood alcohol concentration of 0 prior to participation. Written informed consent, approved by the participating Institutional Review Board, was obtained from all participants.

Adolescent Participants—Research assistants recruited adolescents from juvenile justice partner programs to participate in interventions targeting risky health behaviors. All participants were assented and parental/legal guardian consent was obtained prior to study participation. Participants were between the ages of 14–18 years, and had no MRI contraindications. The participating Institutional Review Board approved the study and a federal certificate of confidentiality was obtained. Participants completed behavioral measures and a single neuroimaging session prior to participation in interventions.

Final Samples—Data were included for all available participants with complete measures needed for analyses. Among adult samples, 914 participants had anatomical neuroimaging data, and 904 participants had complete data for main variables across questionnaires. Following exclusions during initial processing, the final sample of adult participants for VBM models was N=853. Fewer participants completed diffusion tensor imaging (DTI),

such that 850 participants had completed both a DTI scan and questionnaire data. Following exclusions during initial processing (n=37), N=813 adults were included in DTI models.

Among adolescent samples, 526 participants completed an anatomical scan, but n=66 were missing substance use data. An additional n=21 participants were excluded during initial processing, for a total sample of N=439 adolescents in VBM models. Similar to adults, fewer participants had available diffusion tensor imaging (n=406), and n=3 participants were excluded during initial processing for a total sample size of N=403 in DTI models.

Measures

In addition to demographic information, participants responded to substance use questionnaires. All participants in both the adult and the adolescent studies completed the Alcohol Use Disorders Identification Test (AUDIT) [47–48] to assess alcohol use severity. Cannabis use was derived from the Time-line Follow-back (TLFB) [49], and was computed as days of use out of the past 30 days for both adult and adolescent samples. Both AUDIT score and days of cannabis use were subjected to square root transformation (i.e., due to positive skew) prior to inclusion in statistical analyses.

Image Acquisition

MRI was performed on a 3T Siemens Trio (Erlangen, Germany) whole body scanner with a 12-channel radio frequency coil. A high-resolution T_1-weighted structural image was acquired with a 5-echo multi-echo MPRAGE sequence with TE=1.64, 3.50, 5.36, 7.22, and 9.08 ms, TR=2.53 s, TI=1.20 s, flip angle=7°, NEX=1, slice thickness=1 mm, 192 sagittal slices, FOV=256×256 mm, resolution = 256×256×176, voxel size=1×1×1 mm, and pixel bandwidth=650 Hz.

DTI scans were acquired using a single-shot spin-echo echo planar imaging (EPI) sequence with a twice-refocused balanced echo to reduce eddy current distortions. Sequence parameters were: FOV=256×256 mm, 128×128 matrix, slice thickness=2 mm, NEX=1, TE=84 ms, and TR=9000 ms. A 12-channel radiofrequency (RF) head-phased array coil was used, with GRAPPA (X2), 30 gradient directions, and b=800 s/mm^2.

Voxel-Based Morphometry

Voxel-based morphometry (VBM) analyses were performed using FMRIB's Software Library's (FSL; v5.0.1) [50] FSLVBM analysis pipeline following standard automated processing [51–52], as in other publications [40, 53]. This pipeline uses modulation to incorporate the volumetric changes during normalization in the analysis for optimized VBM. The raw T1-weighted images were brain-extracted (i.e., removal of non-brain tissue and skull) using the FSL default BET brain extraction process. The resulting GM images were aligned to Montreal Neurological Institute (MNI) standard space using the affine registration tool FMRIB's Linear Image Registration Tool (FLIRT), followed by nonlinear registration using FMRIB's Nonlinear Image Registration Tool (FNIRT). Automated calculations for exclusion due to motion were used to accommodate the large sample sizes of pooled data. For T1 data, participants were excluded if the correlation between the spatially normalized image and the MNI template was <.93. Remaining images were then averaged into a study-

specific template (separate templates for adolescents and adults). Native GM images were then non-linearly re-registered to this template using FNIRT. The registered partial volume images were then modulated by dividing the Jacobian of the warp field. The modulated segmented images were then smoothed with an isotropic Gaussian kernel with a sigma of 3, yielding full-width half-maximum (FWHM) 3×2.3 mm = 6.9 mm.

Tract-Based Spatial Statistics

For DTI data, motion exclusion for a single volume occurred if motion was greater than 4mm of root mean square displacement, and a participant was not considered for further analysis if more than 10% of gradient directions were dropped [42]. DTI data were preprocessed using FSL's Diffusion Toolbox [54]. Data were corrected for eddy current distortion and then all images were registered to a b=0 s/mm^2 image using 6 degrees of freedom affine transformation using FSL's linear registration algorithm (FLIRT). Diffusion tensor and index maps were calculated using Dtifit.

Fractional anisotropy (FA) and mean, axial, and radial diffusivity (MD, AD, and RD, respectively) values were obtained using FSL Tract-Based Spatial Statistics (TBSS) [55]. A nonlinear registration algorithm (FNIRT) aligned each FA image to Montreal Neurological Institute (MNI) standard space. All transformed FA images were merged into a single 4D image file, and a mean image was created and then skeletonized (separate skeletons for adolescents and adults). Finally, a threshold value of 0.2 was applied to the mean skeleton image, and all aligned FA data were projected onto the mean skeleton for use in voxelwise statistics. The nonlinear warps and projection vectors from the FA processing were then applied to AD, RD, and MD images to obtain a single skeletonized 4D image for each diffusivity index.

Data Analyses

GLMs conducted using FSL's Randomise program [56] evaluated relationships between brain structure (i.e., dependent variables of GM volume or WM integrity) and key predictors of AUDIT score and TLFB-derived cannabis use days (e.g., in order to examine each predictor while controlling for the other), with additional covariates for age, sex, and study cohort, as well as intracranial volume (ICV) in VBM models. Multiple comparison correction used voxelwise thresholding applied through FSL's Randomise permutation-based non-parametric testing with Monte Carlo simulations. A total of 5000 simulations were run for each permutation test, and threshold-free cluster enhancement [57] was used to identify clusters of significant association. Clusters are reported of sizes ≥1000 contiguous voxels in VBM models and ≥200 contiguous voxels in DTI models. In order to obtain partial eta squared values for each cluster, average values were extracted for inclusion in univariate GLMs in SPSS [58]. In order to further test possible associations between brain structure and cannabis use, the samples were restricted to participants who reported using cannabis at least once per week. Analyses were repeated but excluding the AUDIT predictor.

Results

Sample Characteristics

Sample characteristics are presented in Table 1. Based on AUDIT score, adults reported a mild to moderate degree of alcohol problems on average, while adolescents reported alcohol use below clinical thresholds on average. Across substance use measures (alcohol use in last 6 months, and cannabis use in last 30 days), 487 adult participants reported using only alcohol, 5 reported using only cannabis, and 28 reported using neither substance. Similarly, among adolescents, 113 participants reported using only alcohol, 35 reported using only cannabis, and 60 reported using neither substance. AUDIT score and TLFB cannabis use days were not correlated in adults [$t(851)=.04$], but were significantly correlated in adolescents [$t(437)=.30$, $p<.01$].

Alcohol Use Models

Consistent with previous results, AUDIT scores showed large clusters of negative association ($\eta_p^2=.028–.145$, $p<.001$) with GM volume among adults above and beyond cannabis use and covariates (see Table 2, Figure 1). Peak effects were observed in cerebellum, insula, caudate, and putamen. Among adolescents, negative association ($\eta_p^2=.070$, $p<.05$) between GM and AUDIT score was observed in one large cluster, with peak effects in the cuneus, precuneus, and posterior cingulate gyrus (see Table 2, Figure 2).

A similar pattern was observed among WM indices in adults, such that large clusters showed significant associations ($\eta_p^2=.050–.124$, $p<.001$) of higher AUDIT scores with poorer WM integrity (i.e., negative association with FA and positive association with diffusivity; see Table 3 and Figures 3–4). In particular, higher AUDIT scores were associated with large clusters (i.e., up to 37% of the entire WM skeleton in a single cluster) of greater diffusivity (MD, AD, and RD) with peak effects observed in inferior, superior, and inferior fronto-occipital fasciculi. Among adolescents, no associations were observed between WM and AUDIT score.

Cannabis Use Models

In adults and adolescents, no associations were observed between cannabis use and GM above and beyond other predictors, in either the full samples or when limited to weekly or greater users and excluding the AUDIT predictor. Further, among adults and adolescents, no associations were observed between cannabis use and WM indices above and beyond other model predictors, in either the full sample or restricted sample of weekly or greater cannabis users and excluding the AUDIT predictor.

Discussion

The current study sought to expand previous work on associations between alcohol use and GM structure [8] by further examining WM microstructure; and by examining these associations among adults and adolescents. Given the inconclusive prior evidence regarding the possible relationship between cannabis use and brain structure [26], we also tested associations between structural measures and recent cannabis use. Our previous results

suggested widespread negative associations of medium effect size between alcohol use and GM throughout the brain and cerebellum, above and beyond important confounding variables such as age. Negative associations between alcohol use and GM volume were observed even among the youngest age group of the sample (ages 18 to 25 years) [8]. The current study supported previous VBM results among adults, such that large clusters of negative association between problem drinking and GM volume (e.g., accounting for approximately 15% of variance) were observed. Further, a large cluster of similar effect as adults was observed among adolescents. Additionally, we examined similar models among adults and adolescents for WM. Similar to VBM results, very large clusters showed negative association between alcohol use severity and WM integrity among adults (e.g., accounting for approximately 12% of variance), although no WM associations were observed in adolescents. No significant associations were observed between cannabis use and structural measures across any sample, even when limited to participants reporting weekly or greater use and removing the influence of the alcohol predictor.

Negative associations between GM volume and alcohol use were expected among the adult sample, and are consistent with existing literature [4, 59–60]. In adolescents, the cluster of negative association was larger than expected, but did not survive increasing the significance threshold above $p<.05$. While no causal conclusions may be drawn, adolescents showed lower cuneus, precuneus, and posterior cingulate volume associated with alcohol use, with about 4 years of drinking on average. These regions are more commonly reported among adult alcohol use disorder (AUD) patients [6], but overall this finding is comparable to results from a large consortium project, in which adolescent drinkers showed smaller cortical volumes and thickness than nondrinkers [61]. Several longitudinal projects have been able to extend these findings to examine predictors of future alcohol use or structural changes over time, and results may suggest a dose-dependent relationship between alcohol use and changes in GM emerging even during adolescence. Future binge drinking was predicted by lower GM volume in superior frontal gyrus but greater GM volume in middle and precentral gyrus [63]. Further, in another longitudinal study [16], adolescents who progressed from negligible to heavy drinking over 3 years had smaller baseline volumes of anterior cingulate and inferior frontal gyrus, and reduced temporal gyri and subcortical volumes at follow up compared to non-drinkers. These volume reductions appeared to be dose dependent, in that they positively correlated with lifetime alcohol use [16]. Another study found that individuals who started drinking regularly at approximately 18 years of age exhibited over-thinning of the middle frontal gyrus, an area key to executive processing, compared to non-drinkers at follow up after 2 years [15]. Taken together, these results suggest that initiation of regular alcohol use in adolescence may disrupt typical GM development [15–16], which has been associated with important functional changes in risk taking and reward responding [62–63].

Adult alcohol users consistently show lower WM volume and integrity compared to age-matched low- or non-drinkers [1, 17–18, 59], which exceed normal age-related decline [61]. These impairments have been found in widespread brain regions, including frontal and temporal tracts, corticostriatal tracts, and corpus callosum [18–21]. The current results suggest a pervasive association between reduced WM integrity and alcohol use. Consistent with these results, a meta-analysis concluded that AUDs are associated with significant WM

deficits with a small-to-moderate effect size [65]. Among adolescent populations, however, associations between WM measures and alcohol use are less conclusive. Greater number of lifetime drinks was associated with smaller subcortical WM volume [61], but another study using the same sample found no differences in WM integrity measures between adolescent drinkers and non- or low-drinkers [66]. Several cross-sectional studies of adolescent alcohol use and WM measures have found lower FA in corpus callosum, corona radiata, inferior and superior longitudinal fasciculi [14, 22–23, 67]. Other studies found greater FA among adolescents with AUDs compared to their non-drinking peers in limbic tracts even when matching groups for age [24], or that a higher number of lifetime drinking occasions was associated with increased superior longitudinal fasciculus integrity in adolescents [67]. Similar to these findings, the results of the current study did not indicate any regions of negative association between WM integrity and heavy alcohol use, and longitudinal studies will be important for clarifying alcohol effects on brain structural development.

The current study did not observe any associations of past 30-day cannabis use with GM or WM among adults or adolescents beyond other model predictors. This is consistent with our previous work suggesting that regionally specific differences between cannabis users and non-users are often inconsistent across studies and that some of the observed associations may actually be related to comorbid alcohol use [40]. The present results are also consistent with a recent study from a large consortium project that found no relationship between cannabis use and cortical GM (N=466) [68] and a large twin study (N=483) that found the association between cannabis use and GM volumes was explained by genetics rather than cannabis use [69]. While the analyses reported herein are consistent with the effects reported in studies with large sample sizes, future longitudinal studies will be important to clarify the effects of cannabis and alcohol use on brain structure.

Several limitations should be considered when interpreting the current results. Participants were pooled from several studies to maximize sample size, and the current study used a similar model for VBM and AUDIT score as a previous paper [8]. The AUDIT was selected as the primary measure of alcohol use due to its inclusion across adult and adolescent studies, and because it provides an estimate of behavior for a slightly longer period than other available measures (i.e., 30 days via the TLFB). The AUDIT offers high reliability and validity in terms of measuring risk of alcohol problems [47], but does not provide a detailed history. This could lead to an underestimation of long-term alcohol effects, which is particularly relevant for older participants. Similarly, the TLFB is a limited measure of cannabis use, and lacks detailed information on history of cannabis use and quantity of consumption. It was selected as the only available common metric of cannabis consumption across adult and adolescent samples, and the average use of the current samples was relatively low. We attempted to address this limitation by examining potential associations within weekly or greater users and without the influence of an alcohol use predictor (i.e., as in many other studies in the existing literature), but results are still limited to recent use. Future prospective studies should carefully select measures of cannabis use representing history, frequency, and quantity of use. Finally, collecting comparable measures of substance use could enhance interpretability of findings.

In addition, the present analyses do not account for psychopathology (other than excluding participants with history of bipolar disorder or psychosis) or use of substances other than alcohol and cannabis. Studies have demonstrated GM reductions with tobacco smoking [70–71], which has also been associated with exacerbated age-related brain atrophy [72–73]. Future studies primarily focusing on tobacco and cannabis use should control for alcohol use history [40]. Further, these data are cross-sectional, which prevents consideration of the contributions of preexisting conditions or causality. Although we do not believe the adolescents in this study represent a fundamentally different population than other adolescents given their justice involvement, the question of causality is particularly relevant for adolescents, and ongoing large consortium projects will inform whether any observed associations are likely premorbid or result from heavy alcohol use [74].

The current results extend previous findings on the significant, widespread associations between alcohol use severity and alterations in brain structure. These results were expected for GM [8], but the global nature of associations between alcohol use and WM integrity was surprising; even at an increased significance threshold, approximately 30% of voxels in the WM skeleton showed negative association between AUDIT score and WM integrity. WM damage in adult hazardous alcohol users may be partially reversed with extended abstinence [75–77], but the current results underline the importance of increasing efforts for early and effective treatments for AUDs. Further, identification of specific brain regions impacted by alcohol use throughout the lifespan may aid in the development of more efficacious pharmacological treatment options.

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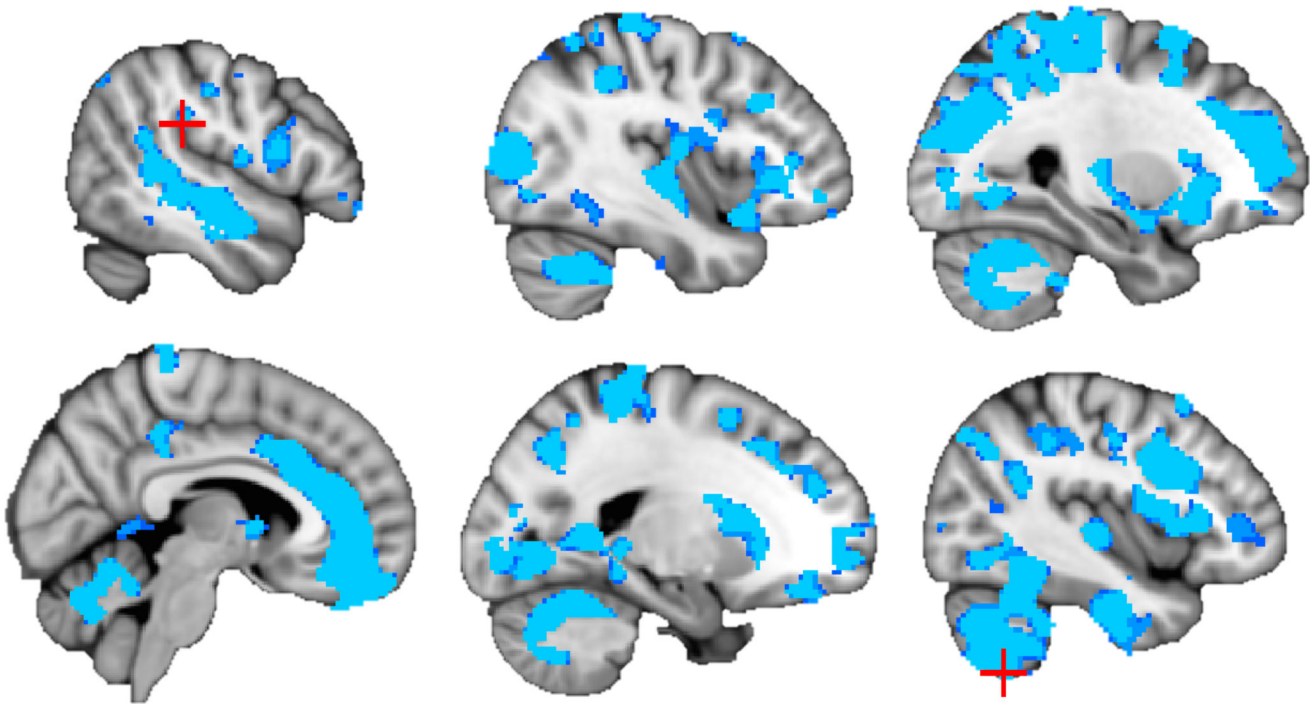

Figure 1.

Negative association ($p < .001$) between AUDIT score and gray matter volume among adults ($N = 853$). Peak voxels within each cluster are marked with red crosshairs (see Table 2; slices from top left: x = 38, 50, 62, 84, 110, and 130).

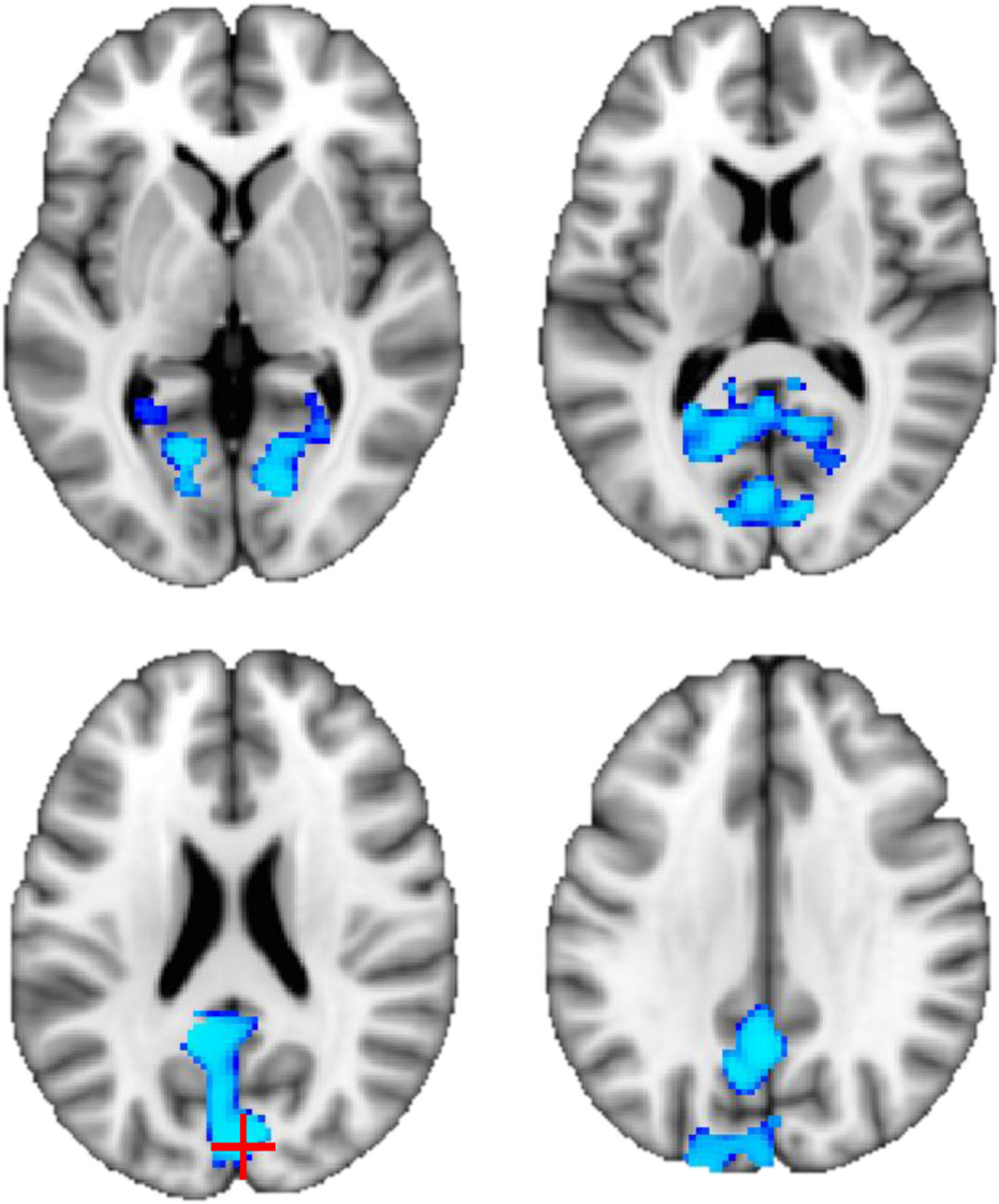

Figure 2.

Negative association ($p < .05$) between AUDIT score and gray matter volume among adolescents ($N = 439$). Peak voxel is marked with red crosshair (see Table 2; slices from top left: z = 74, 84, 94, and 104).

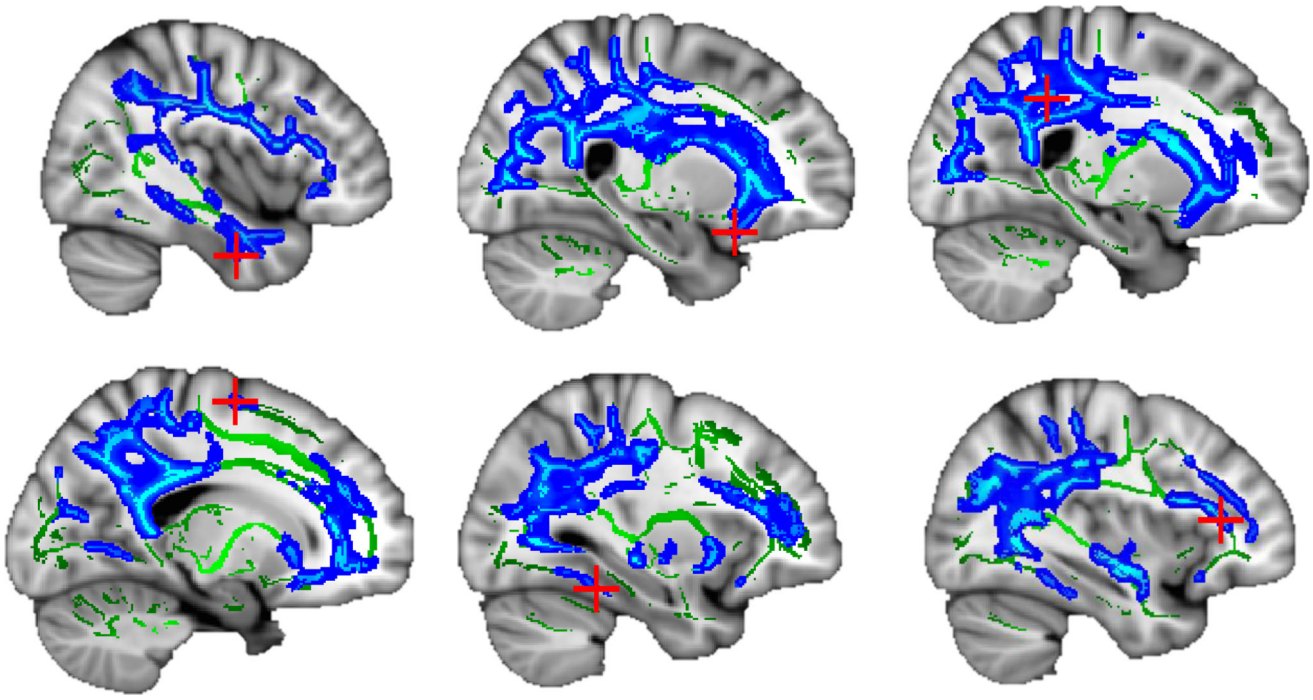

Figure 3.

Negative association ($p < .001$) between AUDIT score and white matter integrity among adults ($N = 813$). Mean diffusivity clusters (blue) overlaid on white matter skeleton (green); peak voxels marked with red crosshairs (see Table 3; slices from top left: x = 48, 65, 67, 107, 121, and 125).

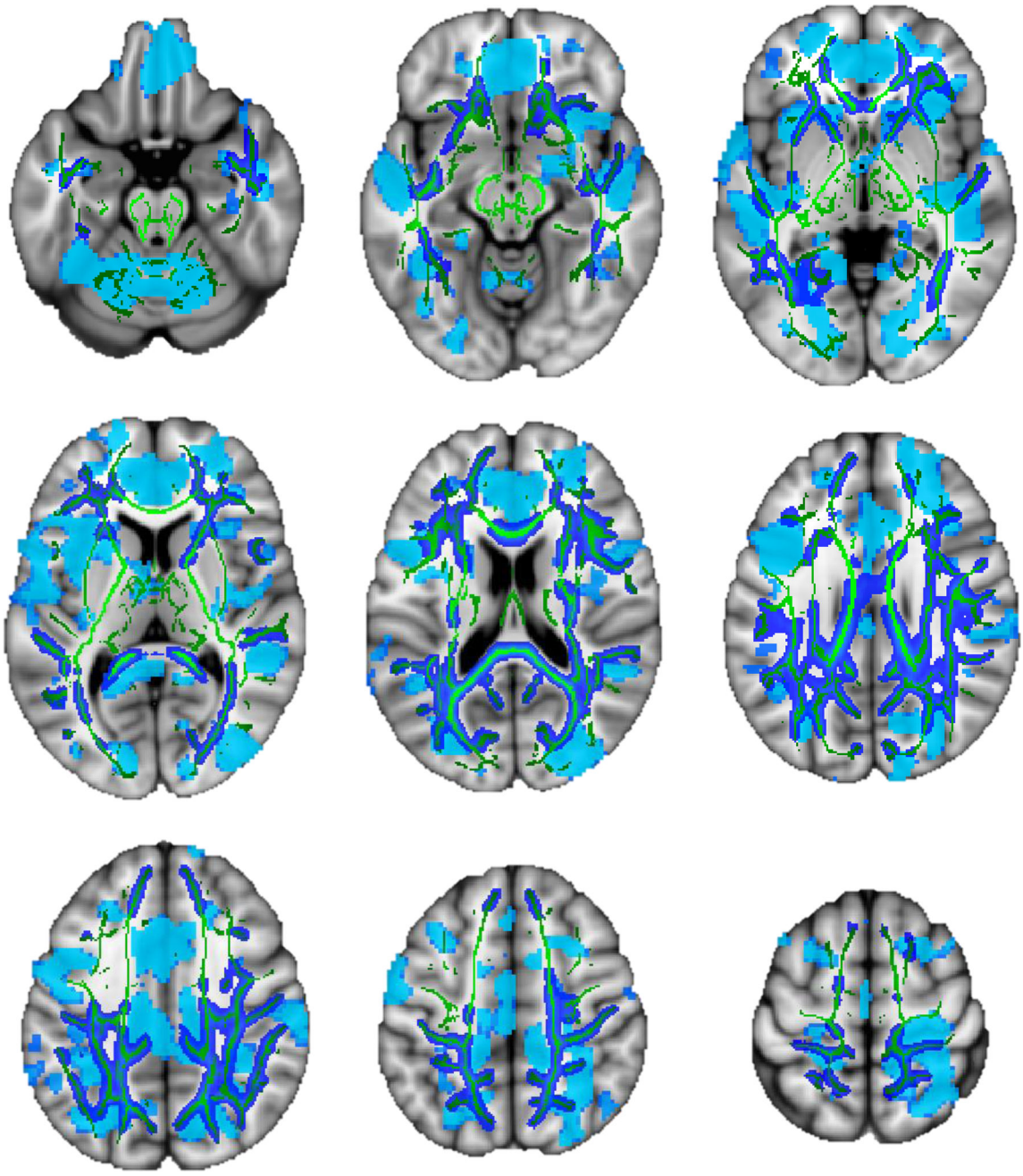

Figure 4.

Overlay of gray matter (light blue) and white matter mean diffusivity (dark blue, with mean white matter skeleton in green) associations with AUDIT score among adults ($p < .001$; slices from top left: z = 50, 60, 70, 80, 90, 100, 110, 120, and 130).

Table 1

Sample Characteristics.

	Adults		Adolescents	
	Whole Sample	**Weekly or Greater Cannabis Users**	**Whole Sample**	**Weekly or Greater Cannabis Users**
N	853	191	439	201
Ethnicity				
Caucasian	474 (56%)	111 (58%)	66 (15%)	29 (14%)
Latino	136 (16%)	19 (10%)	285 (65%)	133 (66%)
Native American	60 (7%)	13 (7%)	32 (7%)	17 (8%)
African American	25 (3%)	7 (4%)	28 (6%)	11 (5%)
Asian/Pacific Islander	10 (1%)	0 (0%)	6 (1%)	3 (1%)
Mixed	120 (14%)	30 (16%)	21 (5%)	8 (4%)
Unknown/Declined	28 (3%)	11 (6%)	1 (<1%)	0 (0%)
Females:Males	326:527 (62% Male)	64:131 (69% Male)	134:305 (69% Male)	52:149 (74% Male)
Age	31.64 (9.64)	28.81 (8.44)	15.97 (1.17)	16.00 (1.08)
AUDIT Total Score	13.14 (8.47)	14.00 (7.79)	6.39 (6.67)	8.48 (6.65)
TLFB Alcohol Drinking Days	12.78 (8.95)	13.81 (8.89)	2.17 (3.78)	3.39 (4.48)
TLFB Cannabis Smoking Days	4.33 (8.66)	18.19 (9.24)	9.69 (11.94)	20.60 (9.51)

AUDIT: Alcohol Use Disorders Identification Test; TLFB: Timeline Follow-Back (30 days).

Percentages approximate due to rounding error.

Table 2

Clusters (≥ 1000 voxels) of significant negative association between Voxel-Based Morphometry (VBM) and AUDIT scores.

Region[a]	Cluster Size (voxels)	MNI Coordinates[a] X	Y	Z	Peak *t*[b]	Partial Eta Squared[c]
Adults (*N* = 853; *p* < .001)						
Cerebellum VIIb L; Insula R; Caudate L, Central opercular cortex L, Putamen L	348256	130	66	12	8.06	.145
Parietal operculum cortex R; Anterior supramarginal gyrus R	5168	38	96	98	5.01	.028
Adolescents (*N* = 439; *p* < .05)						
Cuneus R; Precuneus L, Posterior cingulate gyrus L	27872	86	42	94	4.05	.070

[a] Corresponding to peak *t*; followed by local maxima

[b] FSL Randomise output

[c] SPSS GLM on extracted average cluster values

L = Left; R = Right

Table 3

Clusters (≥ 200 voxels) of significant association ($p < .001$) between white matter integrity and AUDIT scores in adults ($N = 813$).

Region[a]	Cluster Size (voxels)	MNI Coordinates[a] X	Y	Z	Direction	Peak *t*[b]	Partial Eta Squared[c]
Fractional Anisotropy							
Cingulum (cingulate gyrus) R; Inferior fronto-occipital fasciculus R	528	67	83	108	−	6.16	.072
Mean Diffusivity							
Inferior longitudinal fasciculus R; Superior longitudinal fasciculus L, Superior longitudinal fasciculus R	45154	48	120	38	+	7.80	.079
Radial Diffusivity							
Inferior longitudinal fasciculus L; Superior longitudinal fasciculus R, Superior longitudinal fasciculus L, Inferior fronto-occipital fasciculus R	39029	121	86	53	+	7.51	.079
Axial Diffusivity							
Inferior fronto-occipital fasciculus R; Superior longitudinal fasciculus L, Superior longitudinal fasciculus R	21352	65	143	52	+	8.01	.124
Inferior fronto-occipital fasciculus L; Superior longitudinal fasciculus L, Anterior thalamic radiation L	988	125	158	82	+	5.74	.073
Superior longitudinal fasciculus L	430	107	119	136	+	6.01	.050

[a] Corresponding to peak *t*; followed by local maxima

[b] FSL Randomise output

[c] SPSS GLM on extracted average cluster values

L = Left; R = Right