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Anterior Cingulate Cortex Metabolites and White Matter Microstructure: A Multimodal Study of Emergent Alcohol Use Disorder

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Abstract

Multimodal imaging is increasingly used to address neuropathology associated with alcohol use disorder (AUD). Few studies have investigated relationships between metabolite concentrations and white matter (WM) integrity; currently, there are no such data in AUD. In this preliminary study, we used complementary neuroimaging techniques, magnetic resonance spectroscopy (MRS), and diffusion weighted imaging (DWI), to study AUD neurophysiology. We tested for

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Author Contributions

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Compliance with Ethical Standards

The Institutional Review Board of Indiana University approved this study. All participants provided written informed consent.

Conflicts of Interest

The authors report no conflicts of interest.

relationships between metabolites in the dorsal anterior cingulate cortex (dACC) and adjacent WM microstructure in young adult AUD and control (CON) subjects. Sixteen AUD and fourteen CON underwent whole-brain DWI and MRS of the dACC. Outcomes were dACC metabolited, and diffusion tensor metrics of dACC-adjacent WM. Multiple linear regression terms included WM region, group, and region×group for prediction of dACC metabolites. dACC myo-inositol was positively correlated with axial diffusivity in the left anterior corona radiata (p<0.0001) in CON but not AUD (group effect: p<0.001; region×group: p<0.001; Bonferroni-corrected). In the bilateral anterior corona radiata and right genu of the corpus callosum, glutamate was negatively related to mean diffusivity in AUD, but not CON subjects (all model terms: p<0.05, uncorrected). In AUD subjects, dACC glutamate was negatively correlated with AUD symptom severity. This is likely the first integrative study of cortical metabolites and WM integrity in young individuals with AUD. Differential relationships between dACC metabolites and adjacent WM tract integrity in AUD could represent early consequences of hazardous drinking, and/or novel biomarkers of early-stage AUD. Additional studies are required to replicate these findings, and to determine the behavioral relevance of these results.

Keywords

alcohol use disorder; diffusion weighted imaging; magnetic resonance spectroscopy; white matter; anterior cingulate cortex

Introduction

Rodent and human neuroimaging studies have demonstrated that alcohol misuse is associated with pathological changes in the brain (Zahr & Pfefferbaum, 2017). These alterations likely contribute to the morbidity and mortality associated with heavy alcohol use. Magnetic resonance imaging (MRI) techniques permit deeper understanding of *in vivo* alcohol-associated neuropathology in humans through characterization of the structural integrity (e.g., white matter (WM) microstructure via diffusion weighted imaging (DWI)) and chemical composition of the brain (via magnetic resonance spectroscopy (MRS)).

In older populations, heavy alcohol use is associated with impaired white matter (WM) microstructure (Buhler & Mann, 2011; Pfefferbaum et al., 2009; Pfefferbaum et al., 2014; Yeh et al., 2009). We recently reported data from a young adult population with alcohol use disorder (AUD) that demonstrated that emergent AUD had lower fractional anisotropy (FA) values in cerebellum and insula, which could represent a deficit in axonal integrity and possibly altered function (Chumin et al., 2019). Concurrently, we noted that young AUD had higher FA and lower mean diffusivity (MD) and radial diffusivity (RD) throughout major WM tracts (Chumin et al., 2019).

Similarly, MRS studies have demonstrated variations in metabolite levels in heavy-drinking and AUD subjects. *N*-acetylaspartate (NAA) has been reported to be lower in several brain regions of AUD subjects, and generally recover with abstinence (Gazdzinski et al., 2010; Meyerhoff, 2014; Mon et al., 2012; Silveri et al., 2014; Wang et al., 2009). Levels of choline-containing compounds (Cho) are also typically lower in studies of individuals with AUD. There is evidence that myo-Inositol (mI) is higher in AUD subjects (Meyerhoff, 2014;

Schweinsburg et al., 2000). Glutamate (Glu) levels vary across studies as a function of age, stage of abstinence, and severity of disease burden (Ende et al., 2013; Meyerhoff, 2014; Prisciandaro et al., 2016, 2019; Streit et al., 2018; Thoma et al., 2011). Taken together, the DWI and MRS literature point to both micro- and macro-structural consequences of heavy alcohol consumption.

Given that MRS metabolites are involved with cellular metabolism and other normal physiological functions of neurons and glia, it is possible that alterations in NAA, Cho, mI, and Glu may to be related to WM structural changes that occur in the brains of individuals with AUD. For instance, demyelination as a function of glutamatergic excitoxocity (Matute et al., 2007)could theoretically impact DWI metrics. Additionally, increased Cho and decreased NAA in grey matter (GM) regions are hypothesized to reflect compromised neuronal viability. This could presage axonal degeneration, and hence result in altered diffusion metrics. Therefore, combining these complementary neuroimaging modalities may offer additional information about the pathophysiology of AUD (Soares et al., 2013; Wang et al., 2009). However, dual MRS and DWI studies in the field of alcohol research are infrequent, with just one MRS/DWI study that reported no association between WM microstructure and WM metabolites in recently-abstinent alcoholics (Gazdzinski et al., 2010). To our knowledge, no other work has been done examining relationships between the metabolite profiles of GM regions of interest and the characteristics of the WM that contains pathways to and from those regions. We recently published qualitative observations that suggest that information from WM tractography may inform us about pathology in GM regions (Chumin et al., 2018). It is also plausible that MRS data from GM are related to the relative integrity of the WM tracts that carry the afferent and efferent connections. Disruption of normal interactions between GM neurochemistry and associated WM integrity may yield novel biomarkers of addictive disorders such as AUD.

A commonly selected region for MRS studies in substance-dependent individuals is the dorsal anterior cingulate cortex (dACC), which is implicated in higher-order cognition and reward monitoring (Bush et al., 2002; Cheng et al., 2018; Kalivas & Volkow, 2005; Meyerhoff, 2014; Yeo et al., 2013). In addition, the dACC is of great interest due to its role as a hub within the cortical salience network (CSN), which is a structurally and functionally defined cortical pathway that assigns valence and importance to interoceptive events (Cauda et al., 2011; Galandra et al., 2018; Ghaziri et al., 2017; Gorka et al., 2018; Seeley et al., 2007). The CSN has been implicated as being a relevant network in addiction (Halcomb et al., 2019; Vergara et al., 2017), and neuroimaging studies have reported that both alcohol endophenotypes (Grodin et al., 2017) and AUD-related cognitive impairments (Galandra et al., 2018) are associated with changes in the CSN. Additionally, several recent studies have reported that in AUD, there are differences in dACC MRS metabolites (Cheng et al., 2018; Prisciandaro et al., 2016, 2019; Prisciandaro et al., 2017).

The work presented here is a retrospective extension of two previous studies of AUD in young, college-aged adults. Cheng et al. (2018) reported that, in AUD subjects, dACC Glu was reduced in response to alcohol cues relative to baseline; this effect was not observed in control subjects. Although there were no group differences in baseline dACC Glu, in the AUD sample, a significant negative correlation was found between baseline Glu levels and

self-reported drinking. Subsequently, Chumin et al. (2019) found altered WM microstructure throughout WM tracts in a subset of subjects from Cheng et. al. (2018)). We sought to pursue a novel exploratory approach that integrated both MRS and DWI information in subjects that underwent *both* MRS and DWI (i.e., in subjects from both Cheng et al., 2018; Chumin et al., 2019). This multi-modality analysis is analogous to the approach of our colleagues, who examined the intersection of dACC MRS metabolites and functional connectivity in dACC-related networks in cannabis users and controls (Newman et al., 2019). The goal of our preliminary study was to examine the putative association between dACC metabolites and WM in dACC-adjacent tracts that contain its efferent and afferent projections. We hypothesized that young adults with AUD and social-drinking controls (CON) would have differential relationships between dACC metabolites and adjacent WM tract integrity.

Materials and Methods

Subjects

Study procedures were approved by the Institutional Review Board at Indiana University. Informed consent was obtained from all subjects. Sixteen subjects with AUD and 14 healthy controls (CON) were recruited from the community as part of a larger study (Finn et al., 2015). Participants were 18–30 years old, had at least an 6th grade level of English comprehension, had consumed alcohol previously, and had no history of psychiatric illness or head trauma. AUD subjects had a lifetime diagnosis of AUD. One AUD participant also had a past lifetime diagnosis of a substance use disorder. In the AUD group, the age of first drink was <15 years of age; age of onset of AUD was <20 years of age. The Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA) was used to assess AUD severity (Bucholz et al., 1994) via the number of positive responses to all SSAGA questions in the Alcohol Diagnosis section (SSAGA score). Recent alcohol consumption was quantified as the number of self-reported drinks two weeks prior to interview. CON subjects had no history of AUD. Prior to study day, subjects were asked to abstain from alcohol for 12 hours. Breathalyzers confirmed sobriety at the MRI facility on scan day (Alco-Sensor IV; Intoximeters®).

Imaging Protocol

DWI and MRS imaging protocols are described elsewhere (Cheng et al., 2018; Chumin et al., 2019). Briefly, subjects were scanned on a Siemens 3T Trio-Tim (Siemens, Erlangen, Germany). Diffusion-weighted data were collected with a single-shell (b=1000 s/mm2) 2D acquisition; 64 diffusion directions and 8 b = 0 volumes; A-P phase encoding; 128×128 matrix; 72 slices; voxel size 2×2×2 mm3 voxels, iPAT factor = 2. A high-resolution T1-weighted 3D anatomic sequence was also acquired (Field of view = 192×168 matrix, 160 sagittal slices, and 1.3×1.3×1.3 mm voxels). A single-voxel MRS scan in the dorsal ACC (voxel size 15×20×30 mm^3; Figure 1) was acquired with the PRESS sequence: TR/TE = 2000/30 ms, bandwidth = 2000 Hz, 2048 data points, number of measurements = 120, scan time = 4 min, followed by a water reference scan (8 averages). Manual shimming was performed. The linewidth of the water signal after shimming was below 14 Hz.

DWI Processing

DWI processing procedures were described previously (Chumin et al., 2019). Data were preprocessed using an in-house, Matlab-based pipeline, which included denoising, skull stripping, and tissue segmentation of each subject's T1-weighted image. The DWI data were denoised, and the eight b0 volumes were registered to the first volume and averaged. The data were corrected for motion, eddy currents, and registered to each subject's anatomic MRI space. At each voxel, tensor estimation was done with Camino software package (Cook et al., 2006) , and scalar metrics of diffusion including FA, MD, RD, and axial diffusivity (AD) were then derived from tensor data. At each stage of processing, data were visually inspected for proper alignment and quality.

Each subject's FA maps were input into the Tract-Based Spatial Statistics (TBSS) workflow, in which the individual maps were nonlinearly registered onto the FMRIB58 template FA image (FSL's FNIRT) (Chumin et al., 2019; Smith et al., 2006). A mean FA volume was created and thinned to generate a skeleton representation of core WM tracts; each subject's FA data were then projected onto the skeleton. The transformations obtained from the FA registrations were applied to the other diffusion scalars and subsequently projected onto the FA skeleton. From skeletonized scalar data, we extracted average values for WM regions of interest (ROI) surrounding the dACC MRS. Four *a priori* ROIs in each hemisphere (Figure 2) were selected from the Johns Hopkins ICBM-DTI-81 WM atlas (http://cmrm.med.jhmi.edu/), based on the previously reported dACC afferent/efferent projections (Heilbronner & Haber, 2014). These projections are comprised of structural connections between primary nodes of the salience network (e.g., dACC and anterior insula). ROIs included the anterior corona radiata, anterior portions of the internal capsule and external capsule, and genu of the corpus callosum.

MRS processing

MRS processing was described previously (Cheng et al., 2018). MRS voxels were registered to the T1 image using an in-house Matlab code (https://github.com/echumin/IUSM-connectivity-pipeline), and the relative volumes for GM, WM and CSF in the voxel were computed. The MRS data were processed with LCModel (http://www.s-provencher.com/. Each spectrum was fitted as a weighted linear combination of a basis set of *in vitro* spectra derived from individual metabolite solutions. The unsuppressed water signal was used for eddy current correction and for scaling the metabolite concentrations. We applied default settings for water attenuation, estimated water concentration, and baseline modeling. LCModel also reports the Cramer-Rao lower bounds (CRLB) estimated as the relative standard deviation for each fitted component. Only results with CRLB values for metabolites <20% were used for statistical analysis. All estimated MRS metabolite values were normalized to creatine.

Statistical Analysis

All statistics were done in SPSS Statistics v.25 (IBM). Group demographics were assessed with independent-samples *t*-tests or χ^2 tests. Group differences in MRS and DWI metrics were tested with independent *t*-tests. Multiple linear regressions were performed with DWI scalar metrics of each WM region, group, and region×group as predictors of dACC

metabolites. Separate regressions were run for each metabolite/tensor metric pair (e.g., glutamate and FA). When significant group effects or group×region interactions were found, simple linear regression models characterized the associations. Although this was an exploratory study, we applied a Bonferroni-corrected threshold ($p < 0.002$, based on number of tests conducted) to each set of multiple regression models. Exploratory linear regression analyses were conducted to test for relationships between metabolite levels and drinking characteristics (recent drinking history, SSAGA score) in the AUD subjects.

Results

Subject Characteristics

Subject characteristics are in Table 1. There were no group differences in age, race, gender, education, smoking status, or history of substance use disorder. AUD reported significantly earlier age of first drink, higher SSAGA-scores, and more alcoholic drinks consumed in the two weeks prior to interview.

Group Differences in MRS Metabolites and Scalar DWI Metrics

Group differences in scalar DWI metrics (Supplemental Table 1) were minimal (i.e., ~2–4%) and did not meet Bonferroni correction.

There were no group differences in MRS metabolites (Supplemental Table 2), consistent with Cheng et al (2018).

Multiple Linear Regression

The most robust relationship (i.e., Bonferroni-corrected) was between AD in the left anterior corona radiata and mI in the dACC. AD significantly predicted dACC mI ($\beta = 1.09$; $p < 1\times10^{-4}$). Significant group ($\beta = 23.6$; $p < 0.001$) and group×region interaction ($\beta = -23.6$; $p < 0.001$) are illustrated in Figure 3: CON subjects had a positive association between AD and dACC mI (single linear regression parameters: $r = 0.87$; $p = 5\times10^{-5}$), whereas in AUD, this relationship was nonsignificant ($r = 0.13$; $p = 0.64$).

Significant group and group×region effects were detected for the multiple regression of MD on dACC glutamate in the bilateral anterior corona radiata and right genu of the corpus callosum (uncorrected significance, $p < 0.05$; R^2 values and beta weights in Table 2). Figure 4 shows the data from the left anterior corona radiate: the observed negative relationship between MD and glutamate in AUD subjects ($r = -0.54$; $p = 0.03$) was absent in CON subjects ($r = 0.16$; $p = 0.58$). The results for the right anterior corona radiata were similar (graphical data not shown). A similar pattern emerged for the right genu of the corpus callosum, although only a trend-level relationship was present in AUD (AUD: $r = -0.46$, $p = 0.07$; CON: $r = 0.33$, $p = 0.25$; Figure 5).

Linear Regression

There was a significant negative correlation between dACC Glu and SSAGA score ($r = -0.61$; $p < 0.05$; Supplemental Figure 1). No other significant relationships existed between metabolite levels and SSAGA score or recent drinking history.

Discussion

This exploratory study took an integrative approach with MRS and DWI to study AUD during emergent adulthood, when brain maturation processes are still occurring (Mashhoon et al., 2014; Silveri, 2014; Silveri et al., 2014). The ACC is among the last brain regions to reach maturation (Mashhoon et al., 2014; Silveri et al., 2014), and concurrently, binge drinking and AUD rates are highest during emergent adulthood (Mashhoon et al., 2014; Silveri et al., 2014). Therefore, it is important to understand the neurophysiological consequences of alcohol drinking during this critical neurodevelopmental window. The present findings demonstrate that there may be differential relationships in AUD and CON with respect to dACC metabolites and WM integrity in the anterior corona radiata. Specifically, CON subjects, but not AUD, had a positive association between mI and AD. Conversely, AUD, but not CON, had a negative relationship between dACC Glu and MD in the anterior corona radiata. Although discerning the physiological meaning of these patterns will require additional research, the data could represent consequences of AUD in young adults, and/or biomarkers of emergent AUD that could prove useful for studying functional outcomes.

The observed relationship in controls between dACC mI and proximal WM AD was intriguing. mI is a critical neuronal osmolyte (Gullans & Verbalis, 1993), and has been associated with neuronal density (Sundkvist et al., 2000). Recent evidence suggests that mI plays a potentially important role in the electrical activity of neurons through its role in regulation of osmolytic balance (Dai et al., 2016). AD is thought to be an indicator of axonal strength, which theoretically would affect the efficiency of neuronal excitability . Taken together, it is plausible that these data comprise a biomarker for both normal neuronal function and dysfunction. Given that this relationship did not apparently exist in AUD, it is intriguing to speculate that lack of a positive relationship between mI and AD may indicate suboptimal neuronal firing in AUD. Alternatively, there may be other physiological substrates that underlie our observations.

There was a negative relationship between MD and Glu in AUD, but not CON subjects. As the data did not survive Bonferroni correction, interpretation should be viewed with caution. MD can be conceptualized as the inverse of membrane density; as such, lower Glu levels may be associated with lower membrane density in AUD. The presence of a linear relationship in AUD but not CON is counter-intuitive, especially given that the Glu levels were not different between groups. While this may reflect pathology in AUD, the putative mechanism is unclear, as the source of the Glu signal comes from multiple neuronal, glial, and metabolic pools. Therefore, additional research is needed to fully characterize the relationship between glutamatergic functioning and alterations in WM microstructure of emerging adults with AUD.

In the present emergent AUD sample, dACC Glu was negatively correlated with AUD severity (SSAGA score). We did not replicate previously reported correlations between Glu and recent drinking (Cheng et al., 2018; Prisciandaro et al., 2016, 2019). However, the SSAGA score is a robust index of overall AUD severity, and thus is consistent with prior

data with drinking behavior as a metric for AUD severity. Future studies will help determine whether AUD severity mediates the relationship between Glu and MD in emergent AUD.

Limitations

There are limitations to this work. This retrospective study had a modest number of subjects; larger studies are needed for replication. The primary result was localized to the left anterior corona radiata; larger sample sizes may have uncovered bilateral associations. We did not have extensive information on other important variables (e.g., time since last drink, cigarette and drug use histories), nor were urine toxicology screens available to rule out recent drug use. These variables could contribute variance to our metrics of WM microstructure and MRS metabolite levels. Lastly, both Glu and glutamine produce similar spectra which can be difficult to resolve independently; therefore, it is possible that the Glu concentrations may reflect some combination of Glu and glutamine (commonly referred to as ‘Glx’).

Conclusions

It remains unlikely that single neuroimaging modalities can comprehensively describe the neuropathology associated with chronic alcohol consumption (Newman et al., 2019; Schulte et al., 2012). We used MRS and DWI to assess whether relationships existed between dACC metabolites and WM integrity in tracts that communicate with the dACC, and whether these relationships were different between controls and emergent AUD. The main result was that dACC mI was positively correlated with AD in the left anterior corona radiata in CON, but not emergent AUD. These data suggest that such differential associations may be biomarkers of the consequences and/or risk for AUD. Additional work is required to confirm and extend these results.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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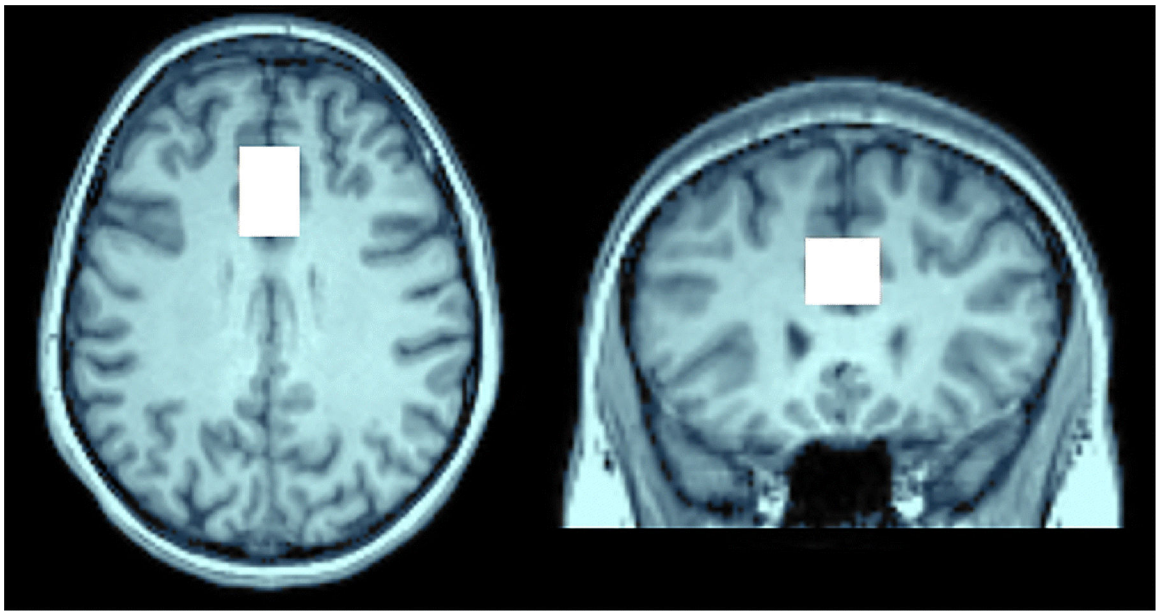

Figure 1.
Dorsal anterior cingulate cortex voxel placement for magnetic resonance spectroscopy.

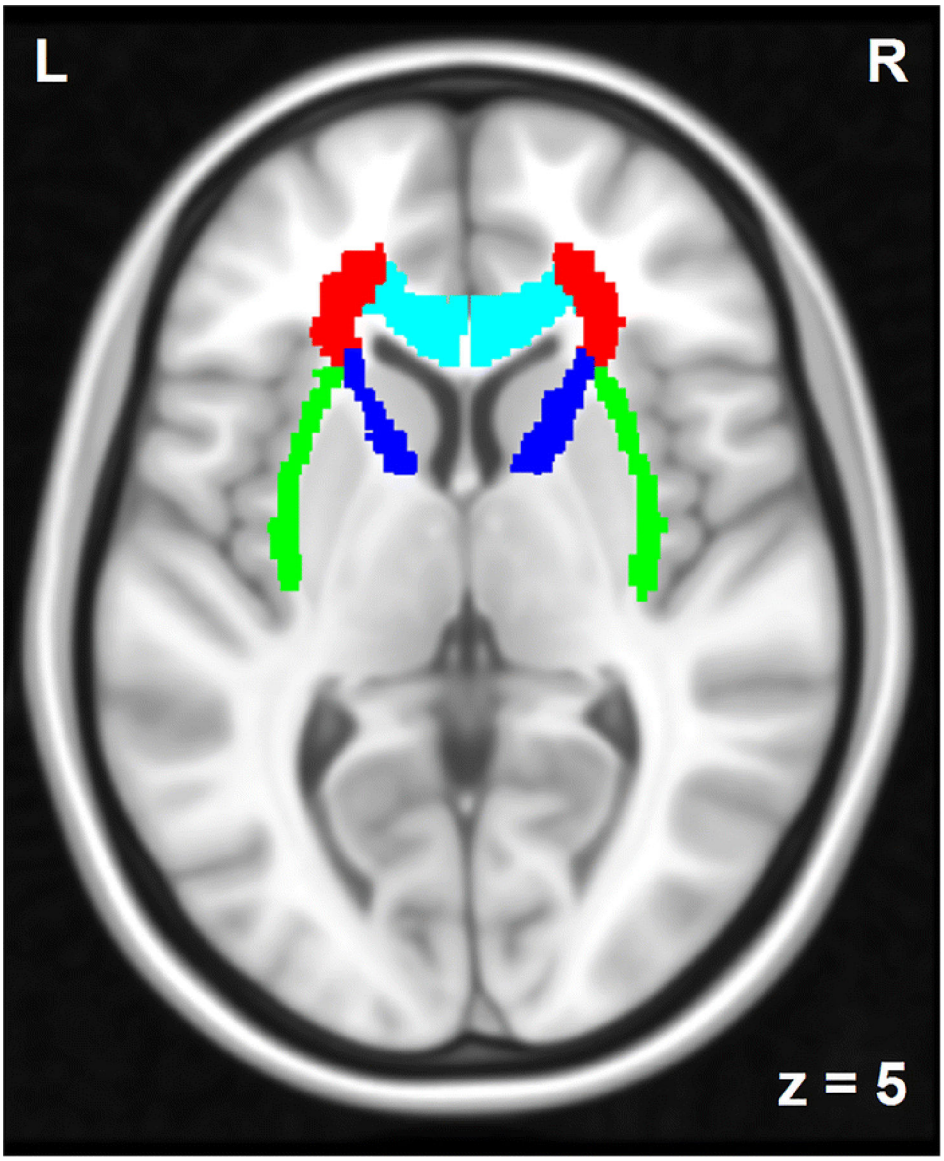

Figure 2.

White matter regions of interest used to extract diffusion weighted imaging scalar metrics (Left) Red: anterior corona radiata. Blue: internal capsule. Green: external capsule. Cyan: genu of the corpus callosum. Data were extracted separately for left (L) and right (R) hemispheres. Axial level is $z = 5$ mm in Montreal Neurological Institute coordinate system.

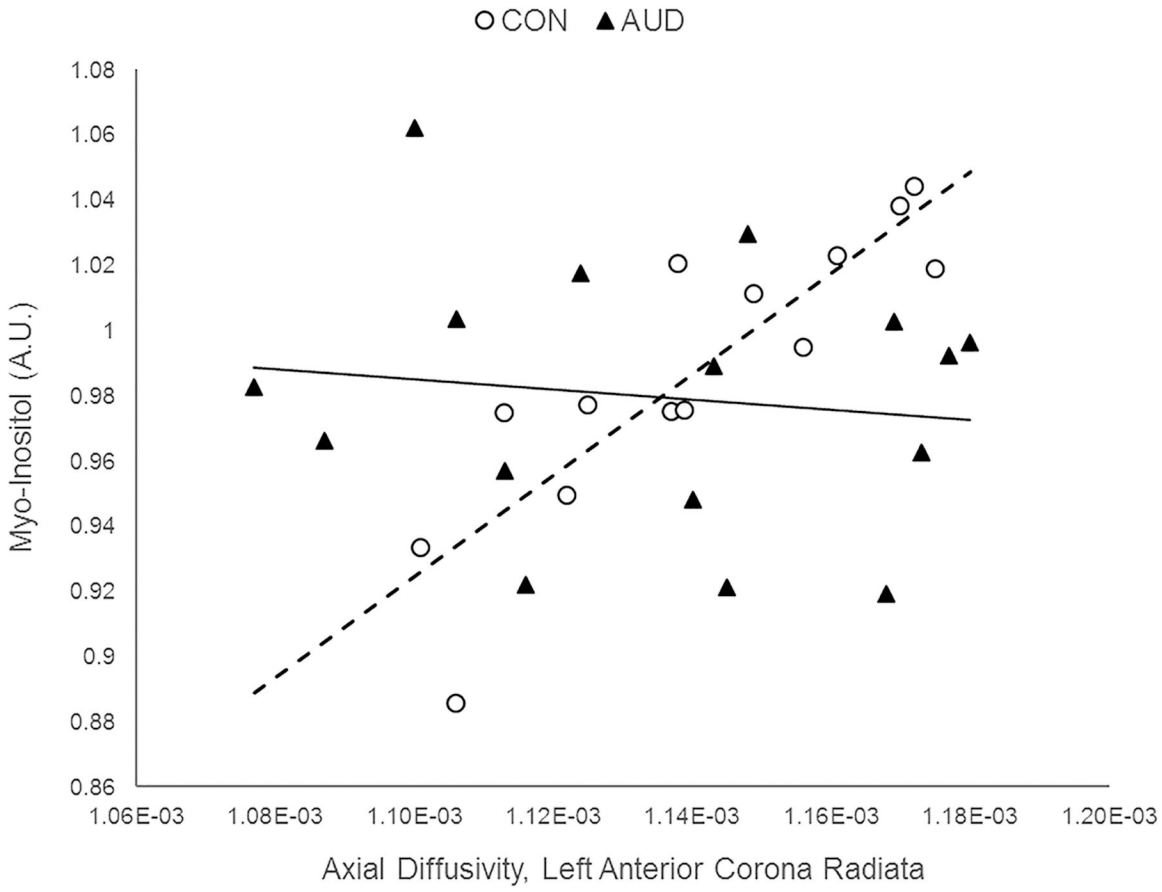

Figure 3.

Axial diffusivity in the left anterior corona radiata is positively correlated with dorsal anterior cingulate cortex myo-inositol in controls (CON), but not in emergent alcohol use disorder (AUD) subjects. See text for details regarding the statistical analysis. Myo-inositol concentrations were normalized to creatine. Controls: open circles, dotted trendline. Alcohol use disorder: filled triangles, solid trendline.

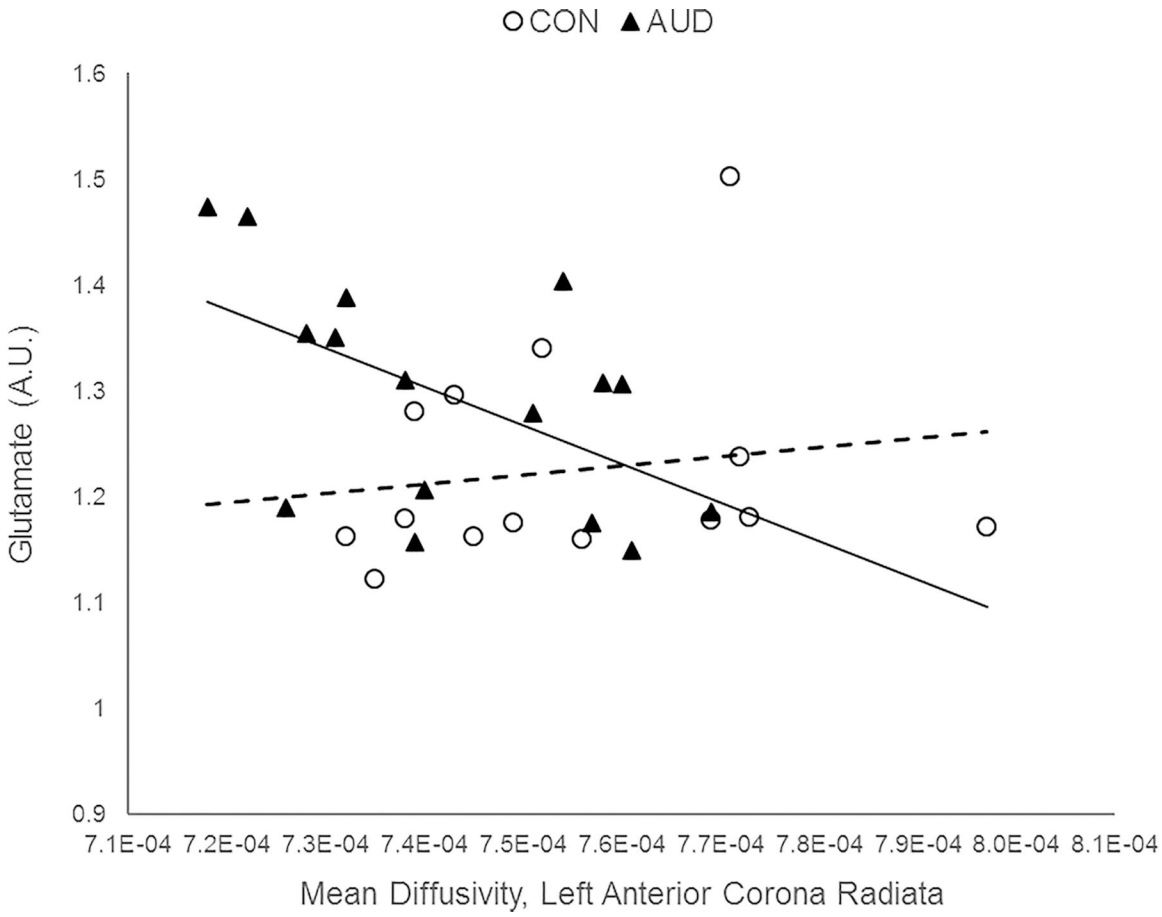

Figure 4.

Mean diffusivity in the left anterior corona radiata is negatively correlated with dorsal anterior cingulate cortex glutamate in emergent alcohol use disorder (AUD), but not control (CON) subjects. Data were similar for the right anterior corona radiata (not shown). See text for details regarding the statistical analysis. Glutamate concentrations were normalized to creatine. Controls: open circles, dotted trendline. Alcohol use disorder: filled triangles, solid trendline.

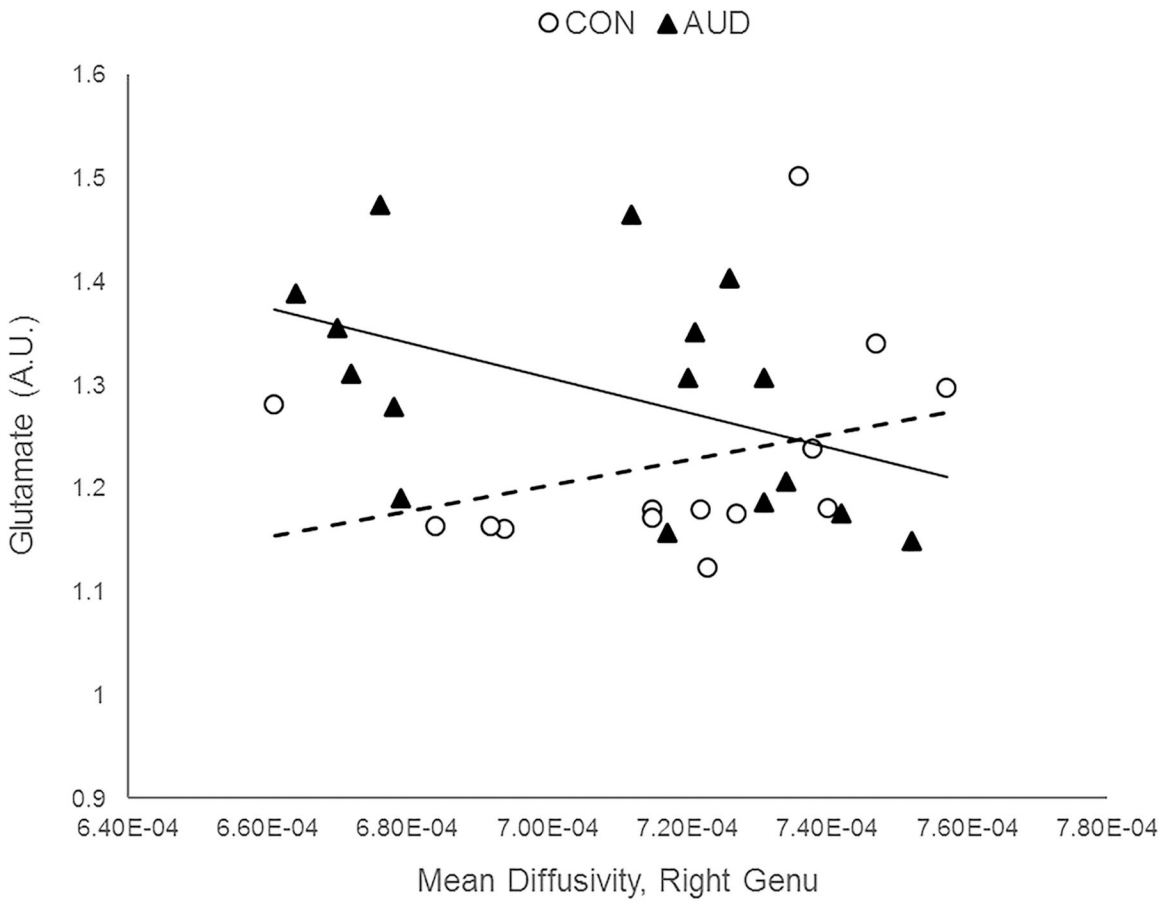

Figure 5.

Mean diffusivity in the right genu of the corpus callosum (Genu) radiata is negatively correlated with dorsal anterior cingulate cortex glutamate in emergent alcohol use disorder (AUD) subjects, but not controls (CON). See text for details regarding the statistical analysis. Glutamate concentrations were normalized to creatine. Controls: open circles, dotted trendline. Alcohol use disorder: filled triangles, solid trendline.

Table 1.

Subject Characteristics

	CON (*n* = 14)	**AUD (*n* = 16)**
Age	22.2 ± 3.42	22.2 ± 1.47
Gender	8 F	5 F
Race	11 C	15 C
Cigarette Use	3	6
Education (years)	14.0 ± 1.57	14.4 ± 1.20
History of SUD	0	1
Total Drinks (Last 2 Weeks)	4.93 ± 6.94	66.7 ± 54.2 *
Age of First Drink	17.7 ± 1.99	15.2 ± 1.42 **
Age of Onset of AUD	N/A	17.4 ± 1.50
SSAGA-score	2.57 ± 3.63	47.7 ± 22.6 ***

Data are mean ± standard deviation. CON: control. AUD: emergent alcohol use disorder. F: Female. C: Caucasian. SSAGA: Semi-Structured Assessment for the Genetics of Alcoholism. SUD: Substance Use Disorder.

* $p < 0.005$

** $p < 0.001$

*** $p < 1.0 \times 10^{-6}$

Table 2.

β values for the multiple linear regression of mean diffusivity on dACC glutamate.

Region	Overall R^2	Region β	Group β	Group×Region β
Left Anterior Corona Radiata	0.26	0.14	16.00 **	−15.64 **
Right Anterior Corona Radiata	0.39	0.10	19.81 **	−19.47 **
Left Genu of the Corpus Callosum	0.20	0.25	7.56 *	−7.21 *
Right Genu of the Corpus Callosum	0.25	0.32	10.10 **	−9.70 **

* trend-level, $0.05 < p < 0.1$

** $p < 0.05$, uncorrected