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Associations between fractional anisotropy and problematic alcohol use in juvenile justice-involved adolescents

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Abstract

Background—Studies have shown associations between heavy alcohol use and white matter alterations in adolescence. Youth involved with the juvenile justice system engage in high levels of risk behavior generally and alcohol use in particular as compared to their non-justice-involved peers.

Objectives—This study explored white matter integrity among justice-involved adolescents. Analyses examined fractional anisotropy (FA) and mean diffusivity (MD) between adolescents with low and high levels of problematic alcohol use as assessed by the Alcohol Use Disorders Identification Test (AUDIT).

Methods—Participants (N = 125; 80% male; 14–18 years) completed measures assessing psychological status and substance use followed by diffusion tensor imaging (DTI). DTI data for low (n = 51) and high AUDIT (n = 74) adolescents were subjected to cluster-based group comparisons on skeletonized FA and MD data.

Results—Whole-brain analyses revealed significantly lower FA in clusters in the right and left posterior corona radiata (PCR) and right superior longitudinal fasciculus (SLF) in the high AUDIT group, as well as one cluster in the right anterior corona radiata that showed higher FA in the high AUDIT group. No differences in MD were identified. Exploratory analyses correlated cluster FA with measures of additional risk factors. FA in the right SLF and left PCR was negatively associated with impulsivity.

Conclusion—Justice-involved adolescents with alcohol use problems generally showed poorer FA than their low problematic alcohol use peers. Future research should aim to better understand the nature of the relationship between white matter development and alcohol use specifically as well as risk behavior more generally.

Keywords

Adolescence; alcohol; fractional anisotropy; juvenile justice

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Declaration of interest

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Introduction

Healthy white matter is synonymous with structural connectivity of the brain, and ongoing processes of pruning and myelination refine neural connections throughout adolescence to support increased functionality (1). Diffusion tensor imaging (DTI), a form of structural magnetic resonance imaging (MRI), examines the microstructure of white matter pathways by measuring diffusion of water molecules. Water diffuses freely without the structural barriers presented by myelinated fibers, as in gray matter and cerebrospinal fluid (2). Mean diffusivity (MD), or overall diffusion, and fractional anisotropy (FA), or directionality of diffusion, allow for characterization of highly myelinated bundles. These measures of white matter integrity are influenced by properties of axon size and density, pathway geometry and fiber intersections (3).

Changes in the progressive development of two neural systems during adolescence, a prefrontal control network and a limbic reward network, have been postulated to leave adolescents with a distinct and arguably developmentally appropriate propensity for risk taking (4–6). Subcortical regions mature considerably earlier than prefrontal regions, and the prefrontal cortex may not provide sufficient top-down control over reward seeking behaviors that have potential for negative consequences (4). Delayed white matter maturation and functional connectivity between these prefrontal and limbic areas may further contribute to impulsive and risky behaviors during this developmental period (7).

While engagement in some risky behaviors, such as alcohol use, is normative in adolescence, heavy substance use during this period may interfere with structural brain development (8,9). A number of studies have described deleterious effects of adolescent alcohol abuse on white matter microstructure (10–12) as well as lasting downstream negative cognitive effects (13), although the effects of other substances are less certain. Chronic alcohol abuse has been clearly linked with loss of white matter integrity in adults (14), but the developing brain may be particularly vulnerable to neurotoxic effects of alcohol exposure, especially given heavy episodic consumption (15). Neural changes associated with heavy alcohol use, particularly in long-range tracts connecting the rest of the brain to frontal cortices (16), may then contribute to increased, generalized risk-taking behaviors.

In the United States, tens of millions of adolescents fall under juvenile court jurisdiction (17). This large subsample represents adolescents whose risky behaviors have already had negative personal or societal impact, with increased risk for poor long-term outcomes. This population may represent an intermediary between community and treatment samples (i.e. they demonstrate high risk but have not typically sought treatment for substance use), thus providing unique opportunities to replicate and extend models elucidating neural correlates of risk behavior with direct implications for prevention and intervention programs.

This study examined FA and MD in a sample of juvenile justice-involved adolescents with varying alcohol use. Voxelwise analyses were conducted to identify diffusivity differences between adolescents reporting low versus problematic alcohol use. Covariates for gender, age and years of substance use were included in these analyses due to potential confounds with alcohol consumption, related problems and white matter architecture (18). For

identified clusters, additional analyses explored possible associations between white matter indices and factors that may share comorbidity or be exacerbated by alcohol use, including impulsivity, externalizing behaviors, attention deficits and hyperactivity, and depression (19,20). Based on previous research (9,10), it was hypothesized that adolescents with greater problematic alcohol use would show lower FA and higher MD than their peers with low alcohol use in major tracts such as the superior longitudinal fasciculus and corona radiata, and that diffusivity measures in significant clusters would be associated with other indicators of risk behavior, such as other drug use and psychological symptomatology.

Methods

Sample and procedure

A sub-sample of participants from a large longitudinal risk behavior study completed questionnaires assessing psychological status and substance use followed by a single session of diffusion tensor imaging. Research assistants from the University of New Mexico (UNM) recruited adolescents from the Youth Reporting Center (YRC), a juvenile justice diversion program. The YRC is a day-treatment program which requires youth to participate 12 hours a day, 7 days a week and aims to promote healthy behavior and life skills for youth wanting to re-enter society. The program welcomes first time and repeat offenders who have enrollment periods that are typically short (days or weeks) and vary as a function of individual probation sentences. Of the 566 adolescents initially approached regarding participation, 496 were assented (70 refused assent and/or did not meet inclusion criteria), and 236 completed both the questionnaires and magnetic resonance imaging. Of the 236 participants with imaging data, 192 had available diffusion tensor imaging.

Further exclusions occurred due to regular heavy other drug use (e.g. cocaine; $n = 13$), prescribed psychotropic medication use and/or bipolar disorder diagnosis ($n = 16$), history of head trauma ($n = 4$) and missing substance use data ($n = 13$). Of the remaining 146 available scans, 21 were excluded due to poor image data quality ($n = 17$ due to signal dropout and $n = 4$ due to motion). The final dataset contained 125 adolescents. Participants were predominantly male (80%) with a mean age of 16.57 ($SD = 1.07$) and were ethnically diverse (63.2% Hispanic, 15.2% Caucasian, 8.8% Multiracial, 7.2% African American, 3.2% American Indian, 1.6% Pacific Islander and 0.8% not specified).

Participants were fluent in written and spoken English, between the ages of 14–18 years, and had no current MRI contraindications (e.g. current pregnancy, irremovable metal implants or piercings, claustrophobia). Prior to scanning, female participants were required to test negative for pregnancy, but subjects were not tested for illicit drug use. All participants were assented and parental/legal guardian consent was obtained via audio recording prior to participation. UNM's Human Research Review Committee and Internal Review Board approved the study and a federal certificate of confidentiality was obtained from the National Institutes of Health and National Institute of Alcoholism and Alcohol Abuse.

Measures

To accommodate suboptimal literacy levels among participants, self-report questionnaires were completed on laptop computers via MediaLab, an Audio Computer-Assisted Self-Interviewing (ACASI) program (21). Participants were informed that their answers would be completely confidential and they were not required to answer any questions that made them uncomfortable.

Alcohol use severity—The Alcohol Use Disorders Identification Test (AUDIT; $\alpha = 0.81$) (22) was used to assess problematic drinking behavior. This 10-item scale asks participants to indicate the frequency of alcohol use and alcohol-related problems by choosing “never” (0), “less than monthly” (1), “monthly” (2), “weekly” (3) or “daily or almost daily” (4; e.g. “How often during the last 6 months have you been unable to remember what happened the night before because you had been drinking?”). A score of 4 or more has been suggested to have good sensitivity and clinical significance in designating hazardous drinking among youth (23) and was used as criteria to define problematic alcohol use groups. More than half (59.2%) of participants received a total score of 4 or greater (high AUDIT; $n = 74$; range: 4–32), suggesting an increased potential for alcohol dependence compared to those with a total score of 3 or less (low AUDIT; $n = 51$; range: 0–3). Age ranges (14–18) did not differ between groups. Participant characteristics by group are displayed in Table 1.

Behavioral and psychological risk—Levels of impulsivity and sensation seeking were assessed with the Impulsive Sensation Seeking Scale (IMPSS; $\alpha = 0.75$) (24). This 19-item scale asks participants to indicate how much they agree or disagree with a statement by selecting “true” (1) or “false” (0; e.g. “I like doing things just for the thrill of it”), and is scored as the sum of true responses to items indicative of higher impulsivity/sensation seeking.

The rule breaking and aggressive behaviors subscales of the Youth Self-Report Survey (YSR; $\alpha = 0.94$) (25) were used to examine frequency of externalizing behaviors. These subscales together are comprised of 32 items describing behaviors such as destruction of property, fighting and opposing authority (e.g. “I break rules at home, school, or elsewhere”). Respondents indicate whether each item is “not true” (0), “somewhat/sometimes true” (1) or “very/often true” (2). Raw summed scores are reported here due to a lack of norms for juvenile justice samples.

The Children’s Depression Inventory-Short Form (CDI-S; $\alpha = 0.72$) (26) was used to assess current levels of depression. Participants rated 10 items indicative of mood disturbance, such as feelings of loneliness and crying, over the past 2 weeks. A total summed score of 7 or more suggests clinical depression; 9.6% ($n = 12$) of this sample met that threshold.

The short form of the Conners-Wells Self-Report Scale (CASS-S; $\alpha = 0.90$) (27) was used to assess attention deficit and hyperactivity symptoms. This 27-item scale asks participants to rate items (e.g. “I have too much energy to sit still for long”) by selecting “not at all true” (0), “just a little true” (1), “pretty much true” (2) or “very much true” (3).

Substance use—Consistent with prior studies (21,28), participants reported on their past and present substance use, including alcohol, tobacco and marijuana use, as well as hard drugs including crack/cocaine, heroin, ketamine, ecstasy, methamphetamine, lysergic acid diethylamide (LSD), gamma-hydroxybutyric acid (GHB), mushrooms and non-prescribed medications. Total years of use for each substance were calculated by subtracting age of first use from current age. Nearly all of the participants ($N = 116$, 93%) reported lifetime use of at least one substance, most commonly alcohol ($N = 109$, 87%), marijuana ($N = 100$, 80%) and tobacco ($N = 96$, 77%) use. Additionally, participants were asked about their quantity of alcohol and tobacco use in the last 3 months as well as frequency of alcohol and marijuana use in the last 3 months. Response options ranged from 1 to 10 for quantity (e.g. “none” to “more than 20 drinks”) and from 1 to 9 for frequency (e.g. “never” to “every day”). Consistent with prior research (29), composite variables for other drug use were computed due to relatively low rates of drug use other than alcohol, tobacco or marijuana. Total years of other drug use was coded by greatest number of years across drugs other than alcohol, tobacco and marijuana, while past 3-month frequency was computed as an average of the frequencies of all other drug use.

Image acquisition and processing

DTI scans were acquired on a 3 T Siemens Trio (Erlangen, Germany) whole body scanner 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/mm².

DTI data were preprocessed using FMRIB's Software Library (FSL) (30) Diffusion Toolbox (Oxford, UK) (31). Data quality checks entailed visual inspection of each volume slice-by-slice for signal dropout and other artifact including excessive motion. Data were then corrected for eddy current distortion. All images were registered to a $b = 0$ s/mm² image using 6 degrees of freedom affine transformation using FSL's linear registration algorithm (FLIRT). Diffusion tensor and FA maps were calculated using Dtifit.

FA and MD values were obtained using FSL Tract-Based Spatial Statistics (TBSS) (32). A nonlinear registration algorithm (FMRIB's Nonlinear Image Registration Tool) aligned each FA image to Montreal Neurological Institute (MNI) standard space (voxel size: $1 \times 1 \times 1$ mm). All transformed FA images were merged into a single 4D image file, and a mean image was created and then skeletonized. 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 MD images to obtain a single skeletonized 4D image for MD data.

Statistical analyses

Voxelwise statistics on skeletonized FA and MD data were conducted using Analysis of Functional Neuroimaging (AFNI) (33,34) program 3dttest++ with gender, age, years of alcohol use, years of tobacco use, years of marijuana use and years of other drug use

included as covariates. Multiple comparisons were corrected using AFNI's 3dClustSim through Monte Carlo simulation of combined individual voxel probability and cluster size thresholding. With first-nearest neighbor clustering (i.e. connectivity of 1 mm), individual voxel probability $p < 0.01$ and brain-wise $\alpha < 0.05$, clusters ≥ 24 voxels were considered significant. Cohen's d effect sizes (35) were computed from averaged t -values across voxels within significant clusters. Anatomical structures were identified using Johns Hopkins University white matter atlases (36,37). For significant clusters, FA values were extracted for partial correlations that explored relationships between FA in each cluster and additional measures related to risk taking, which also controlled for gender, age and years of substance use.

Results

Voxelwise statistics

Whole-brain analyses revealed four FA clusters and no MD clusters of significant between-group difference. The FA clusters were located in the right and left posterior corona radiata (PCR), right superior longitudinal fasciculus (SLF) and right anterior corona radiata (ACR; see Figure 1 and Table 2). Interestingly, higher FA values were found among adolescents with lower AUDIT scores in the right and left PCR and right SLF, and higher FA values were found among adolescents with higher AUDIT scores in the right ACR, when gender, age, and years of alcohol, tobacco, marijuana and other drug use were included as covariates.

Partial correlations

Partial correlations across all subjects showed significant negative associations between impulsivity scale score and FA in the right SLF ($p < 0.05$) and left PCR ($p < 0.03$) when controlling for gender, age, and years of alcohol, tobacco, marijuana and other drug use. Externalizing behaviors, depression symptoms, attention deficit and hyperactivity symptoms, and quantity and frequency of recent substance use (alcohol, marijuana, tobacco and other substance use) did not show significant associations with FA in any clusters. The sensation seeking and impulsivity subscales of the IMPSS were then correlated with FA to further explore possible relationships between FA and impulsivity. Controlling for gender, age and years of substance use, FA in the right SLF was negatively associated with the impulsivity subscale [$r(117) = -0.25, p < 0.01$], while FA in the left PCR and negatively associated with the sensation seeking subscale [$r(117) = -0.25, p < 0.01$].

Discussion

This study examined white matter correlates of problematic alcohol use in a sample of adolescents involved with the juvenile justice system. Further associations with broad measures of behavioral and psychological risk were explored. These cross-sectional analyses were exploratory in nature due to lack of existing data within juvenile-justice populations. This sample represents an ethnically diverse group of adolescents with a wide range of substance use whose involvement in the justice system reflects impactful levels of risky behavior with implications for prevention and intervention programs.

Adolescents in this study who endorsed higher levels of problematic drinking showed lower FA than their peers in the bilateral PCR and right SLF. The corona radiata consists of projection fibers from the internal capsule of the basal ganglia to the cerebral cortex, while the SLF is comprised of long-range fibers with connections in each lobe of the brain. These results represent medium effect sizes and are consistent with previous studies of white matter differences in adolescents with substance use disorders (38) and adolescents with subclinical heavy alcohol use showing poorer white matter integrity in several tracts, including the PCR and SLF (15,16). For example in a longitudinal study, increased alcohol use over an 18-month period was associated with higher mean diffusivity in the bilateral SLF and left PCR above and beyond poorer values at baseline (16). Although this study is cross-sectional, our findings within a juvenile justice-involved sample replicate poorer white matter microstructure in the PCR and SLF in heavy versus low drinking adolescents. Conversely, we report higher FA in the right ACR among the adolescents with higher AUDIT scores. The anterior portion of the corona radiata projects from the basal ganglia to the frontal lobes, and this finding may suggest a strengthened reward pathway among heavier drinkers (7). This preliminary finding should be further explored in samples with formal diagnoses of problematic drinking to better determine its possible relationship with heavy alcohol use.

In addition, self-report impulsivity and sensation seeking scores were negatively associated with FA in the right SLF and left PCR, respectively. Chronic marijuana smokers have also shown alterations in frontal FA related to impulsivity (39), although not specifically in adolescents. Adolescents with internet addiction disorder have widespread reductions in FA in major tracts compared to controls (40,41), though relationships among white matter microstructure, impulsivity and substance use were not explored. Further study is needed to explore how the SLF or PCR may be associated with impulsivity and problem drinking, which could inform future intervention strategies.

A number of considerations should inform interpretation of these results. First and foremost, the cross-sectional design limits our ability to infer causality or even directionality in the relationship of FA differences and alcohol use. The AUDIT is used only as an index of alcohol problems and does not provide formal diagnoses. It is also important to note the early ages of first substance use among participants in this sample. Group comparison analyses included years of substance use as covariates, but those measures may not fully characterize the extent of experience prior to study participation. Future research with older samples and a fuller range of age at first substance use should explore the relationship between age at first use and white matter development. Further, frequency of marijuana use among adolescents with alcohol problems was particularly high, and additional analyses are needed to explore possible interaction effects of co-occurring alcohol and marijuana or other polysubstance use. Exploratory correlations were not subjected to multiple comparison correction. Finally, analyses did not include any comparison group of non-justice-involved adolescents. However, the current analysis does incorporate adolescents with no or very little exposure to alcohol (i.e. non-drinkers and/or AUDIT score of 0).

This study is the first to explore alcohol use and white matter alterations within juvenile justice-involved youth. These data support and extend findings that heavy alcohol use during

adolescence is associated with poor white matter integrity, which may in turn be associated with additional risk factors. Group comparison results reached stringent thresholding criteria for FA but not MD, and future studies should continue to explore additional indices of white matter microstructure (e.g. radial and axial diffusivity). These data support the importance of conveying the potential impact of heavy alcohol consumption on the brain in the development of interventions targeting high-risk youth.

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Figure 1. Clusters of significant difference in FA between adolescents with low and high AUDIT scores in the a) right and left posterior corona radiata, b) right superior longitudinal fasciculus and c) right anterior corona radiata.

Table 1

Sample characteristics.

<i>Measures</i>	Low AUDIT[†] (<i>n</i> = 51) <i>Mean (SD)</i>	High AUDIT[†] (<i>n</i> = 74) <i>Mean (SD)</i>
<i>Demographics</i>		
Age	16.54 (1.14)	16.60 (1.03)
Gender (% Female)**	31.5	10.8
Ethnicity (% Hispanic)	56.9	67.6
<i>Total Scale Scores</i>		
Alcohol Use Disorders Identification Test (AUDIT)**	0.96 (1.15)	11.26 (6.52)
Impulsive Sensation Seeking (IMPSS)*	9.45 (3.98)	11.20 (3.61)
Youth Self-Report (YSR) Externalizing**	15.98 (14.06) ^a	23.69 (12.01)
Children's Depression Inventory-Short Form (CDI-S)	2.27 (2.86)	2.51 (2.42)
Conners-Wells Self-Report Scale-Short Form (CASS-S)	23.59 (13.97)	28.07 (13.30)
<i>Substance Use</i>		
Age of first alcohol use [†] ,**	13.76 (1.59) ^b	11.97 (2.14) ^c
Age of first tobacco use [†] ,**	13.79 (2.10) ^d	12.10 (2.77) ^e
Age of first marijuana use [†] ,**	13.33 (2.29) ^f	11.37 (2.24) ^g
Years of alcohol use**	1.41 (1.51)	3.18 (1.94)
Years of tobacco use**	1.08 (1.60)	2.20 (2.22)
Years of marijuana use**	1.84 (1.98)	3.90 (2.40)
Years of other drug use**	0.45 (0.86)	1.62 (1.48)
Past 3 months alcohol use quantity [§] ,**	2.10 (1.32)	4.03 (2.31)
Past 3 months tobacco use quantity [§] ,*	2.29 (2.04)	3.08 (2.00)
Past 3 months alcohol use frequency [◇] ,**	2.08 (1.48)	4.24 (2.39)
Past 3 months marijuana use frequency [◇] ,**	3.18 (3.19)	5.46 (3.58)
Past 3 months other drug use frequency [◇] ,**	1.03 (0.13)	1.19 (0.30)

[†] Low AUDIT total score <4, high AUDIT total score ≥ 4.

* $p < 0.05$;

** $p < 0.01$.

[†] In instances of no reported lifetime use, age of first use is missing data and years of use is 0.

^a $n = 50$;

^b $n = 41$;

^c $n = 67$;

^d $n = 33$;

^e $n = 63$;

$$f_n = 36;$$

$$g_n = 67.$$

[§]Past 3 months alcohol (drinks) and tobacco (cigarettes) use quantity value labels: “none” (1), “1” (2), “2–3” (3), “4” (4), “7–9” (5), “10–12” (6), “13–15” (7), “16–18” (8), “19–20” (9), “More than 20” (10).

◇ Past 3 months substance use frequency value labels: “Never” (1), “Occasionally” (2), “Once a month” (3), “2–3 times a month” (4), “4–5 times a month” (5), “Once a week” (6), “2–3 times a week” (7), “4–5 times a week” (8), “Everyday” (9).

Table 2
Clusters of significant difference in fractional anisotropy (FA) between adolescents with low and high AUDIT scores.

	Cluster Size (voxels)	MINI Coordinates ^a			Low AUDIT [†] (n = 51)		High AUDIT [†] (n = 74)		Direction	Effect Size (Cohen's d) ^b
		X	Y	Z	Mean FA	Mean FA	Mean FA	Mean FA		
Posterior Corona Radiata R	53	71	87	108	0.467	0.444			Low>High	0.54
Superior Longitudinal Fasciculus R	32	40	121	94	0.426	0.397			Low>High	0.59
Anterior Corona Radiata R	25	66	150	77	0.501	0.536			High>Low	0.57
Posterior Corona Radiata L	24	109	88	108	0.484	0.463			Low>High	0.53

[†]Low AUDIT total score <4, high AUDIT total score ≥4

^aCenter of mass

^bCalculated from average t-value across each cluster