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Not lesser but Greater fractional anisotropy in adolescents with alcohol use disorders

Valerie A. Cardenas [a,*], David Greenstein [a], Jean-Paul Fouche [b], Helen Ferrett [b], Natalie Cuzen [b], Dan J. Stein [b], George Fein [a]

[a] Neurobehavioral Research, Inc., Ala Mona Pacific Center, 1585 Kapiolani Blvd. Suite 1030, Honolulu, HI 95814, USA
[b] Department of Psychiatry, University of Cape Town, South Africa

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ABSTRACT

Objective: The objective of this study is to examine white matter microstructure using diffusion tensor imaging (DTI) in a sample of adolescents with alcohol use disorders (AUD) and no psychiatric or substance co-morbidity.
Methods: Fifty adolescents with AUD and fifty non-alcohol abusing controls matched on gender and age were studied with DTI, neurocognitive testing, and a clinical assessment that included measures of alcohol use and childhood trauma. Maps of fractional anisotropy (FA) and mean diffusivity (MD) were computed, registered to a common template, and voxel-wise statistical analysis used to assess group differences. Associations between regions of altered WM microstructure and clinical or neurocognitive measures were also assessed.
Results: Compared with controls, adolescent drinkers without co-morbid substance abuse or externalizing disorder, showed 1) no regions of significantly lower FA, 2) increased FA in WM tracts of the limbic system; 3) no MD differences; and 4) within the region of higher FA in AUD, there were no associations between FA and alcohol use, cognition, or trauma.
Discussion: The most important observation of this study is our failure to observe significantly smaller FA in this relatively large alcohol abuse/dependent adolescent sample. Greater FA in the limbic regions observed in this study may index a risk for adolescent AUD instead of a consequence of drinking. Drinking behavior may be reinforced in those with higher FA and perhaps greater myelination in these brain regions involved in reward and reinforcement.

1. Introduction

The effects of alcohol on the brain have been studied extensively, revealing regions of white matter (WM) and gray matter atrophy and neuropsychological impairment (Fein and McGillivray, 2007; Fein et al., 2008, 2009a,b; Pfefferbaum et al., 1992; Sullivan et al., 1995, 2000). More recently, diffusion tensor imaging (DTI) has allowed researchers to study the effects of alcohol on WM microstructural integrity that are not revealed by conventional magnetic resonance anatomical imaging. Microstructural WM changes may include a host of alterations, including demyelination, microtubule disruption, cytoskeletal change, membrane degradation and axonal deletion (Moseley, 2002). DTI affords a means of examining WM microstructure in vivo, by measuring the random mobility of tissue water thereby obtaining an imprint of the intrinsic structural consistency of white matter, such as integrity of white matter fiber bundles.

In particular, fractional anisotropy (FA), which is an index of the orientation dependence of water diffusion within a voxel, is thought to provide a sensitive measure for the integrity of fiber bundles with decreases in FA reflecting compromised integrity of WM. Mean diffusivity (MD) is an index of the local magnitude of diffusion regardless of the direction of the movement of tissue water, and high values for MD are expected in the CSF and fluid filled regions of tissue degradation. Reductions in FA associated with alcohol use in adults have been observed both regionally and globally (Pfefferbaum and Sullivan, 2005; Pfefferbaum et al., 2006a,b; Schulte et al., 2005). In adolescent drinkers, both reductions (Bava et al., 2009; Jacobus et al., 2009; McQueeny et al., 2009) and increases (De Bellis et al., 2008) in FA have been observed. MD differences are also inconsistent between studies, with MD reductions in the isthmus observed in participants with alcohol and co-morbid mental disorders (De Bellis et al., 2008), MD reductions and increases reported in different brain regions of marijuana and alcohol using subjects (Bava et al., 2009), and no MD differences reported in binge drinkers or binge drinkers who also used marijuana (Jacobus et al., 2009). Interpreting these conflicting results is complicated by the differences in the subject populations studied.

Abbreviations: AUD, alcohol use disorders; DTI, diffusion tensor imaging; FA, fractional anisotropy; MD, mean diffusivity.

* Corresponding author at: Neurobehavioral Research Inc., Ala Moana Pacific Center, 1585 Kapiolani Blvd. Suite 1030, Honolulu, HI 96814, USA. Tel.: +1 808 283 1120; fax: +1 808 442 0980.
E-mail address: vcardenas-nicolson@nbresearch.com (V.A. Cardenas).

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Despite the approximately 10.7 million underage drinkers in the United States, obtaining a large sample of adolescents with alcohol use disorders (AUDs) who are free of comorbidities with other substance use disorders (SUDs) and other internalizing and externalizing psychiatric disorders is very difficult. In fact, among adolescents in the United States meeting criteria for alcohol dependence, drug use is the norm, as are other behavioral aspects of an externalizing diathesis such as conduct disorder or oppositional defiant disorder. In such samples it is difficult to separate out those brain effects which are a consequence of alcohol abuse from those reflecting predisposing differences in brain organization or structure or those which are the effects of comorbid drug use. Another confounding variable is early environmental adversity, which is a predisposing factor to AUDs and externalizing disorders, and which is associated with neural changes that resemble some of those associated with AUDs (Cohen et al., 2006; Rao et al., 2009).

To isolate the effects of alcohol abuse on the developing brain, it is important to recruit samples that are representative of the larger AUD population, and to minimize the confounding effects of predisposing factors, such as those mentioned above. The Cape Town region of South Africa is historically a wine-growing region, where a range of risk factors creating vulnerability to hazardous alcohol use in adolescence exists. Alcohol is the most highly abused substance among adolescents in this region (Parry et al., 2004; Pluddemann et al., 2008). Furthermore, surveys in Cape Town schools demonstrate lower incidence of mixed substance abuse than found in the USA (Parry et al., 2004). We have recruited a community-dwelling (i.e., treatment-naïve) adolescent cohort from this region that is ideal for studies attempting to isolate the effects of alcohol abuse on the developing brain because of the low rates of substance (other than alcohol) use, and our ability to recruit a sample with relatively modest externalizing behavioral problems (not meeting criteria for any lifetime externalizing diagnoses) among heavy drinkers. Early exposure to adversity is common in South Africa and in the study samples — its influence on DTI results will be measured.

In this report, DTI was used to measure white matter integrity in South African treatment-naïve adolescents with AUDs. Since FA and MD results conflict in previous studies, we decided to use a voxelwise whole brain exploratory approach to comparing groups instead of comparing groups on FA and MD measures within a priori regions of interest. We hypothesized that WM microstructure would be degraded in adolescents with AUD due to the damaging effects of alcohol, indexed by lower FA and higher MD, and that these changes would be associated with alcohol use variables, performance on cognitive testing, and increased exposure to early adversity.

2. Material and methods

2.1. Participants

Participants were screened for eligibility after written informed assent/consent was obtained from volunteers and parents or guardians. Screening involved detailed medical history-taking, physical and psychiatric examination, and urine analysis and breathalyzer testing (to confirm that the adolescents were not intoxicated during the testing procedures), all performed by a fully qualified and licensed psychiatrist. The Schedule for Affective Disorders and Schizophrenia for School Aged Children (6–18 years) Lifetime Version (K-SADS-PL) (Kaufman et al., 1997), a semi-structured clinician-rated diagnostic scale, was used to ascertain current and past psychiatric diagnoses, as reported by the participants. The subjects then completed demographic and Childhood Trauma — Short Form Questionnaires and underwent MRI brain scans. A research assistant was available to assist participants in completing the self-report demographic and early adversity questionnaires. All test materials were available in the participant's language of preference. Cognitive testing was individually administered. Participants were provided with meals and refreshments, and at the conclusion of the session were compensated for their time with gift vouchers (to the value of ZAR 50 per visit). All study information was kept confidential, except where statutory requirements dictated the reporting of newly identified or ongoing threats to the safety of minor participants. The study protocol and procedures complied with and were conducted in strict adherence to the guidelines contained in the Declaration of Helsinki (W.M. Association, 2008). Full written approval to conduct the study was obtained from the Western Cape Education Department and the Research Ethics Committee of the Stellenbosch University Faculty of Health Sciences.

We recruited English- and Afrikaans-speaking adolescents from 19 schools within the Cape Flats region of the greater Cape Town area. All participants were from moderately low socioeconomic backgrounds, residing in permanent housing with potable water and electricity, but mostly without luxury items such as computers and cars. The median gross annual income level per household was ZAR 62 035. From those studied, 50 pairs of participants (one abusing alcohol, one not) with artifact free DTI were individually matched for age (within 1 year) and gender, which resulted in a total of 28 female pairs and 22 male pairs.

Exclusion criteria for study participation were: mental retardation, lifetime DSM-IV Axis I diagnoses other than AUD (including depressive, anxiety, psychotic, post-traumatic stress, elimination, eating, tic, attention-deficit/hyperactivity, oppositional defiant, and conduct disorders); lifetime dosages exceeding 30 cannabis joints or 3 methamphetamine doses; current use of sedative or psychotropic medication; signs or history of fetal alcohol syndrome or malnutrition; sensory impairment; history of traumatic brain injury with loss of consciousness exceeding 10 min; presence of diseases that may affect the CNS (e.g., meningitis, epilepsy, HIV); less than 6 years of formal education; and lack of proficiency in English or Afrikaans. Collateral information verifying the absence of medical, psychiatric, and psychosocial problems was obtained from consenting parents by a social worker at the consent explanation interview.

2.2. Clinical measures

We measured early adversity, a predisposing factor to AUDs, with the Childhood Trauma Questionnaire-Short Form (CTQ-SF; Bernstein et al., 2003). The CTQ-SF is a 28-item retrospective self-report questionnaire comprising five subscales, each of which is aimed at measuring a distinct dimension of childhood mistreatment: physical abuse, sexual abuse, emotional abuse, physical neglect, and emotional neglect. From a general-purpose neuropsychological test battery three composite measures were made to index cognitive function likely to be affected by alcohol: (1) Verbal Story Memory, (2) Self-Monitoring, and (3) Psychomotor Speed and Coordination. The Timeline Followback (TLFB) procedure (Sobell and Sobell, 1992), a semi-structured, clinician-administered assessment of lifetime history of alcohol use and drinking patterns, was used in collaboration with the K-SADS-PL to elicit alcohol-use data. A standard drink was defined as one beer or wine cooler, one glass of wine, or one 1.5-oz shot of liquor (alone or in a mixed drink). AUD group membership was defined by a lifetime dosage in excess of 100 units of alcohol plus a DSM-IV diagnosis of alcohol abuse or dependence. The control group comprised non-drinkers (who had never consumed alcohol) and light drinkers (lifetime dosage not exceeding 76 units of alcohol), with no history of an AUD. Relationships between these measures of childhood trauma, cognitive function, and alcohol use and white matter integrity were explored in this study.

2.3. DTI

Acquisition: diffusion tensor images were acquired at the Cape Universities Brain Imaging Centre on a Siemens Magnetom 3-T Allegra scanner with the following parameters: repetition time 8800 ms, echo time 88 ms, diffusion weighted volumes in 30 directions with b =

1000 s/mm^2 and a single unweighted volume (b = 0 s/mm^2). The in-plane resolution was 2 × 2 mm^2, and the slice thickness was 2.2 mm. The sequence was repeated 3 times.

Analysis: we created smoothed FA and MD images in standard space using FSL tools (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/). The 3 acquisitions were examined manually for artifacts, and the least noisy image was selected for eddy current correction and fitting of the tensor model. An artifact occurred consistently for one of the diffusion directions, and this direction was excluded from all further analysis. The b0 images were coregistered to the b0 images of the first acquisition and averaged, and the average used as the reference b0 image for eddy current correction. Fractional anisotropy (FA) and mean diffusivity (MD) images were created by fitting a diffusion tensor model at each voxel using FSL's DTIFIT (Behrens et al., 2003). The participants' FA images were then aligned into a common space, using as the reference image one subject automatically chosen to be the most "typical" subject of the adolescents studied. These same nonlinear transforms were also used to bring the MD images into common space. The aligned FA and MD images were spatially smoothed using a Gaussian kernel with standard deviation of 2 mm.

2.4. Statistical analysis

Voxel-wise statistics were computed using valmap (http://www.nitrc.org/projects/valmap), correcting for multiple comparisons across space using permutation testing of suprathreshold clusters ($p < 0.025$) (Nichols and Holmes, 2002). Maps of FA or MD were the dependent variables, and factors were group and gender. Statistics were computed for all voxels where FA > 0.2 in the group average brain in common space. In regions of interest (ROIs) where a significant effect of alcohol was observed, the average FA or MD was computed for each individual, and these average ROI measures were correlated with measures of alcohol use, neurocognitive functioning, and early adversity.

3. Results

Table 1 shows participant demographics and alcohol use measures for the sample. The mean age was about 15 yrs and participants had completed about 8 yrs of education. The majority were native Afrikaans speakers. Of the alcohol users, 1 met DSM criteria for alcohol abuse and the other 49 met DSM criteria for alcohol dependence. Aside from the alcohol and nicotine use variables, there were no significant demographic differences between the AUD and non-drinking groups, except that the AUD participants were about 3 months older, which was clinically irrelevant. Of the controls, 44% had never drunk alcohol, and 48 of the 50 had never been intoxicated. None of the AUD participants were regular drinkers who drank more than 15 days per month. The vast majority (86%) classified themselves as weekend drinkers, with an average of about 50 drinks per month on 5 drinking days. As expected, nicotine use was more prevalent in the AUD participants, with only 4% reporting never smoking and 52% regularly smoking. In the light/non-drinking controls, 62% had never smoked and only 6% were regular smokers.

Table 1
Participant demographics.

		Non-abusing controls (N = 50)	Alcohol use disorder (N = 50)
Age (yrs)		14.8 ± 0.8	15.0 ± 0.7
Education (yrs)		7.8 ± 0.8	7.9 ± 0.8[a]
Home language	%English	22	26
	%Afrikaans	74	66
	%Bilingual	4	8
Nicotine use	%Never	62	14
	%Light (<100 cigarettes)	32	34
	%Regular (>100 cigarettes)	6	52
Age of first drink		11.9 ± 1.6	12.0 ± 1.9
Lifetime alcohol dosage (#drinks)		6.3 ± 14.4	1305.5 ± 1179.1
Duration of drinking (months)		NA	24.3 ± 19.3
Average drinking days/mo		NA	5.2 ± 2.9
Average drinks/mo		NA	60.9 ± 44.2

[a] Alcohol > controls, $p < 0.05$.

Table 2 shows the results from the trauma questionnaire and the cognitive testing. There were group by gender effects in the degree of physical abuse and sexual abuse suffered, with higher values in AUD boys. AUD participants showed deficits in memory and self-monitoring, scoring worse on the Verbal Story Memory composite (0.40 ± 0.96 vs. −0.41 ± 0.71, $t_{49} = 4.67$, $p < 0.001$) and the Self-Monitoring composite (−0.19 ± 0.35 vs. 0.18 ± 0.53, $t_{49} = -4.11$, $p < 0.001$). There were no significant differences in performance on the Psychomotor Speed and Coordination composite.

There were no regions where FA was significantly lower in AUD compared to controls. Fig. 1 shows the t-statistic map of voxels where FA was significantly greater in AUD participants compared to controls, after cluster correction for multiple comparisons (cluster volume is 10,190 mm^3, corrected $p = 0.05$). This cluster encompasses the fornix and stria terminalis, white matter pathways associated with the limbic system. FA values within this cluster were about 5% higher in AUD participants (AUD 0.41 ± 0.02, controls 0.39 ± 0.02). There were no differences in FA due to gender.

Voxel-wise analysis revealed no regions where MD was significantly different between AUD and controls, and no gender effects were observed in MD.

The average FA for each subject was computed within the cluster where FA was significantly greater in AUD vs. controls, and a scatterplot of these FA averages for each subject is shown in Fig. 2. Correlations were then computed between these average FA measures and measures of alcohol use, cognition, and trauma, controlling for gender on the trauma associations. There were no significant associations between the average FA measures and any alcohol use variable. When correlations were computed across the entire sample, higher FA was associated with better performance (e.g., faster reaction times) on the Psychomotor Speed and Coordination composite ($r = -0.193$, $p = 0.05$). There were no significant associations between average FA and any measure of early childhood trauma, computed across the entire group, AUD participants only, or controls only.

Higher FA in the corpus callosum of adolescent alcohol users has previously been reported (De Bellis et al., 2008). Our region of increased FA included the isthmus of the corpus callosum, and examination of our uncorrected T-statistic maps reveals higher FA in other corpus callosum regions that did not survive the stringent correction for multiple comparisons that must be applied to voxel-wise exploratory statistical analyses. To determine if a region of interest (ROI) analysis would reveal higher corpus callosum FA in our sample, we created corpus callosum ROIs using the ICBM-DTI-81 white-matter labels atlas from Johns Hopkins University, and compared the average FA in three corpus callosum regions. We found higher FA in the AUD participants in the posterior corpus callosum region (uncorrected $p = 0.04$), but not FA differences in the anterior or middle corpus callosum. De Bellis interpreted increased FA in his AUD population as accelerated prefrontal and temporo-parietal myelin maturation, and correlations between age and MD or FA within AUD supported that conclusion. In our sample, we found no relationship between age and FA within the posterior corpus callosum region.

4. Discussion

In this study, we found that adolescent drinkers with no co-morbid substance abuse or externalizing disorder, showed 1) higher FA in WM tracts of the limbic system, that was not associated with any alcohol use variable; 2) no MD differences; and 3) within the region of higher FA in AUD, no associations between FA and alcohol use, cognition, or trauma

Table 2
Early adversity and cognitive measures.

	Female non-abusers (N = 28)	Male non-abusers (N = 22)	Female alcohol use disorder (N = 28)	Male alcohol use disorder (N = 22)	Alcohol effect p-value	Alcohol × sex interaction p-value
Emotional abuse	8.2 ± 5.0	6.6 ± 2.2	8.7 ± 3.5	8.6 ± 4.3	NS	NS
Emotional neglect	10.2 ± 5.1	13.5 ± 6.9	12.6 ± 5.6	12.6 ± 7.0	NS	NS
Physical abuse	6.8 ± 4.1	5.9 ± 1.9	5.7 ± 1.2	8.2 ± 4.5	NA	0.013
Physical neglect	7.3 ± 3.2	9.0 ± 4.2	8.6 ± 2.6	9.2 ± 4.4	NS	NS
Sexual abuse	6.3 ± 2.9	5.3 ± 0.9	6.0 ± 2.4	7.6 ± 4.2	NS	0.019
Verbal Story Memory	−0.005 ± 0.928	0.176 ± 1.024	−0.086 ± 0.840	−0.094 ± 0.755	NS	NS
Self-monitoring	−0.235 ± 0.292	−0.140 ± 0.411	−0.040 ± 0.467	0.357 ± 0.559	<0.001	NS
Psychomotor speed and coordination	−0.226 ± 0.591	0.123 ± 0.995	−0.152 ± 0.562	0.095 ± 0.752	NS	NS

were found. Most surprising, however, was that FA was not smaller in AUD youth than controls in any brain region.

The most important observation of this study is our failure to observe significantly smaller FA in this relatively large alcohol abuse/dependent adolescent sample; this result contrasts with findings of smaller FA in other smaller sample studies of alcohol abusing youth (Bava et al., 2009; Jacobus et al., 2009; McQueeny et al., 2009). A secondary observation is our finding of larger FA in the limbic system. The characteristics of our unique sample of adolescents from the Cape Town region in South Africa may partly account for our failure to find smaller FA values. We studied adolescents who met criteria for AUD and were very heavy pure alcohol users, but were without comorbid substance or psychiatric disorders. Moreover, both AUD and control adolescents had experienced substantial trauma, had low socioeconomic status (SES), and a substantial number were cigarette smokers. Prior studies from the United States primarily examined binge drinking adolescents, most of whom did not meet criterion for an AUD and had a lifetime consumption of alcohol of about 200 drinks, much lower than the 1300 drink average lifetime alcohol consumption of the AUD participants in the current study. Additionally, two of the cited manuscripts reporting smaller FA included participants with comorbid marijuana use. Furthermore, both controls and binge drinkers from previous United States studies had higher SES, smoked less, and probably experienced less trauma than our Cape Town samples. It is possible that the smaller FA values in alcohol binge drinking adolescents reported in other studies were driven by comorbid psychiatric or substance use disorders and were not a result of alcohol use per se. Additionally, exposure to trauma, low SES, and smoking may have resulted in smaller FA values within the Cape Town samples (both AUD and controls), such that the additional effect of alcohol on FA in the AUD adolescents was small, perhaps reaching a floor. Further study is necessary to assess these possible contributing factors.

Aside from differences in our subject population, our image analysis techniques were different, which may explain why previous studies (Bava et al., 2009; Jacobus et al., 2009; McQueeny et al., 2009) did not observe higher FA in limbic regions. In particular, these studies used tract based spatial statistics (Smith et al., 2004), a method that projects each subject's FA data onto a mean FA skeleton that represents the centers of all WM tracts common to the group. Although this may reduce errors due to inaccurate registration, it is not sensitive off-skeleton where we found some of our FA differences, and may explain why regions of higher FA similar to ours were not observed.

Our results are most consistent with those reported by De Bellis et al. (2008), who studied adolescents with alcohol use and co-morbid mental disorders, and reported higher FA in the rostral body and isthmus of the corpus callosum and lower MD in the isthmus. In a

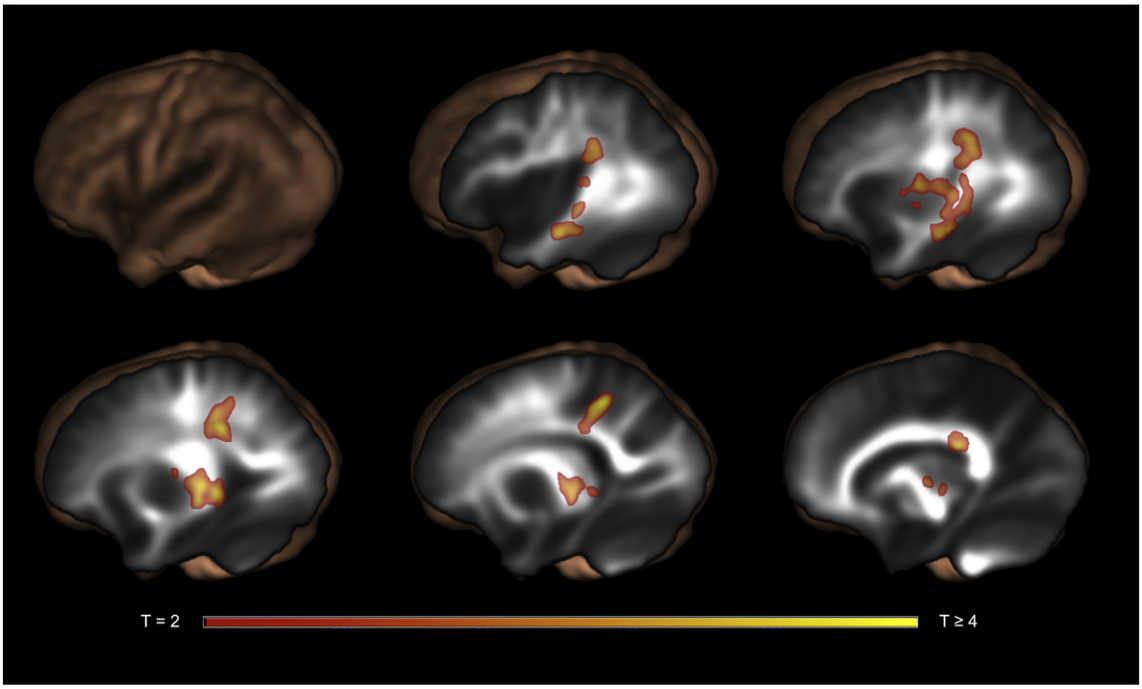

Fig. 1. The t-statistics within the cluster of voxels that significantly differentiates alcohol use disorder participants from controls are shown overlaid on the average FA image. Alcohol use disorder participants showed higher FA in a region that encompasses the fornix and stria terminalis of the limbic system.

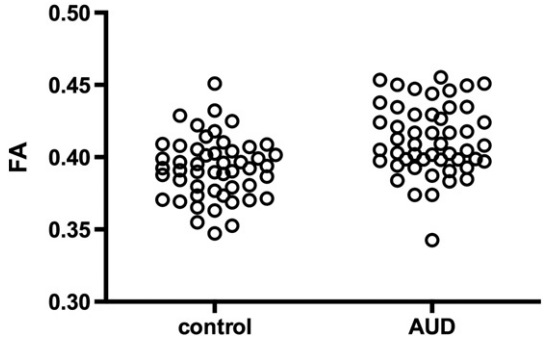

Fig. 2. Scatterplot of the average FA for each subject computed within the cluster where FA was significantly greater in AUD than controls.

confirmatory ROI analysis, we demonstrated higher FA in a posterior corpus callosum region, similar to DeBellis, but we did not observe an association between FA and age in this region. These correlation results do not support an interpretation of accelerated myelin maturation explaining higher FA, but it is possible that true associations with age were obscured by the narrow age range in our studied participants, and that drinking alcohol at abusive levels might modify the developmental trajectory.

Increased FA within the region of significance was associated with better performance on psychomotor tasks across all subjects. Since there was no group difference in performance on psychomotor tasks, this is probably not related to alcohol, but more reflective of greater myelination being related to greater motor speed and coordination.

The region of higher FA in AUD participants was not associated with any measure of alcohol use, arguing against the observed difference being a consequence of the direct toxic effects of alcohol. Although the AUD participants showed impairments in verbal memory and self-monitoring, these measures were not associated with increased FA in the limbic regions either. Therefore, increased FA in these regions may index a risk for adolescent AUD instead of a consequence of drinking. The WM tracts with higher FA in this study make connections with the septal nuclei, which play a role in reward and reinforcement. Drinking behavior may be reinforced in those with higher FA and perhaps greater myelination in these regions.

Our previous studies in this population have shown neither a strong family history of AUD nor the reduced P300 evoked electrical response that is a marker of genetic vulnerability to AUD (Cuzen et al., 2013), perhaps suggesting that increased risk indexed by higher FA is not genetic. Gene-imaging association studies could shed additional light on this question. However, despite the fact that this population drank very heavily on the occasions that they drank (nearly 12 drinks per occasion), very few hangover symptoms were reported. Using the Hangover Symptoms Scale, aside from feeling thirsty, the vast majority reported never or only occasionally experiencing hangover symptoms (>72% on all symptoms). It is possible that this resistance to hangover symptoms contributes to the development of AUD in adolescents. However, our interpretation of the finding of increased FA in the limbic system is speculative, and longitudinal DTI imaging studies would help us to understand whether increased FA is premorbid, and whether FA decreases over time with continued drinking.

4.1. Conclusions

Increased FA in the limbic regions observed in this study may index a risk for adolescent AUD instead of a consequence of drinking. Drinking behavior may be reinforced in those with higher FA and perhaps greater myelination in these brain regions involved in reward and reinforcement.

Acknowledgments

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