

# **Cerebral White Matter Sex Dimorphism in Alcoholism: A Diffusion Tensor Imaging Study**

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**Running Head:** Diffusion Tensor Imaging, sex dimorphism, and alcoholism

## Supplemental Methods

For each subject, the diffusion magnetic resonance imaging (dMRI) scans were visually inspected in all 60-direction volumes. After skull-stripping with the Brain-Extraction Tool (BET), we used the FMRIB Diffusion Toolbox v2.0 (Behrens *et al*, 2003) to perform motion and eddy current distortion corrections (Jenkinson *et al*, 2002; Jenkinson and Smith, 2001; Smith, 2002), and to generate a diffusion tensor for each voxel, calculated using a least squares fit of the tensor model to the dMRI data. From the diffusion tensors, the eigenvalues of each tensor (which represent the magnitude of the three main diffusion directions) were calculated for each voxel. Maps of axial diffusivity, radial diffusivity, and FA were created for each participant. There were no statistically significant results from the axial or radial diffusivity analyses we specified. Therefore, the FA maps served as the primary measure of white matter microstructural integrity.

In order to prepare the single subject level data for group level analyses, all of the maps were aligned to the standard  $1 \times 1 \times 1$  mm<sup>3</sup> MNI152 brain, using nonlinear registration and subsequently skeletonized with a threshold of  $FA > 0.2$  to reduce the likelihood of partial voluming with the bordering gray matter and ventricular cerebrospinal fluid. To co-register the core white matter pathways among all of the subjects in this analysis, the following procedure was employed: A nonlinear registration was performed in order to coregister or align all FA images from all subjects to a predefined FA template image; then the FSL-based FA template (i.e., the target image) was derived from an averaged dataset of 58 FA maps from all healthy subjects, both male and female. The FA template was also in the standard  $1 \times 1 \times 1$  mm<sup>3</sup> MNI152 space. Using TBSS, the calculated nonlinear transformation was applied to the estimated

pathways for each individual subject, so all subjects were coregistered to MNI152 space for group level analysis. These maps were then binarized. The thresholded, normalized and nonlinearly warped and binarized maps were then summed across subjects to produce a group average probability map.

Group-level differences in dMRI data were assessed by standard Tract-Based Spatial Statistics (TBSS v1.1, [www.fmrib.ox.ac.uk/fsl/TBSS](http://www.fmrib.ox.ac.uk/fsl/TBSS)) analyses (Smith *et al*, 2006). To determine group-level differences in FA between the ALC and NC groups, whole brain voxel-wise statistical analyses were performed on the skeletonized data using FSL randomise (Winkler *et al*, 2014), a nonparametric permutation inference tool with threshold-free cluster enhancement (TFCE), which corrects for Type I error (Woo *et al*, 2014). The TFCE multiple comparison correction within TBSS analysis was performed on the comparison results by voxel-wise permutation (5000 permutations) testing, with a cluster-wise significance threshold of  $p < 0.05$ .

Clusters with significant Group by Sex interactions were extracted, and further *ad hoc* analyses were performed using R 3.3.2 (Daróczi and Tsegelskyi, 2015; Dowle *et al*, 2015; R Core Team, 2016; Robinson, 2014; Sievert *et al*, n.d.; Xie, 2013). Two-tailed Welch two-sample t-tests were used to compare the cluster FA values of the ALC to NC groups for men and women separately. The FA values for each cluster also were examined for relationships with age, and for immediate, delayed, and working memory for all participants, and interactions of those measures with group and sex. For the ALC group, interactions of drinking history (DHD, DD, and LOS) with sex were examined, followed by the direct relationships of drinking history to FA where significant interactions were not present.

## Supplemental References

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## Supplemental Tables

Group Measure	Alcoholic Men		Alcoholic Women		Nonalcoholic Men		Nonalcoholic Women	
	Min	Max	Min	Max	Min	Max	Min	Max
Age (yrs)	27	77	27	71	24	75	28	76
Education (yrs)	10	20	10	19	12	18	12	20
FSIQ	75	140	70	137	90	152	86	135
VIQ	73	145	78	138	95	148	83	144
PIQ	78	140	67	142	79	146	90	132
IMI	78	130	63	144	82	146	95	142
DMI	84	128	52	140	84	150	84	140
WMI	81	124	74	136	76	136	79	136
HRSD**	0	18	0	13	0	3	0	7
DHD (years)*	5	37	3	25	0	3.5	0	2
DD (ounces/day)*	2.43	38.4	1.49	28.05	0	2.57	0	1.28
LOS (years)	0.01	27.6	0.02	31.65	0	20.12	0	31.87

**Table S1. Ranges for participant demographic characteristics and drinking histories.**

Abbreviations: Wechsler Adult Intelligence Scale (WAIS-III) measures are FSIQ: Full-Scale IQ; VIQ: Verbal IQ; PIQ: Performance IQ. Wechsler Memory Scale (WMS-III) measures are: IMI: Immediate Memory Index; DMI: Delayed Memory Index; WMI: Working Memory Index. HRSD: Hamilton Rating Scale for Depression. WAIS-III and WMS-III scores were not available from one alcoholic woman and one alcoholic man, and WMS-III scores were not available from an additional alcoholic man. DHD: Duration of Heavy Drinking (years); DD: Daily Drinks (ounces of ethanol per day); LOS: Length of Sobriety (years).

Clusters	Alcoholic Men		Alcoholic Women		Nonalcoholic Men		Nonalcoholic Women	
	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)
SLFII & SLFIII	0.44	(0.05)	0.50	(0.04)	0.47	(0.05)	0.45	(0.06)
AF & EmC	0.43	(0.05)	0.49	(0.06)	0.47	(0.04)	0.45	(0.05)
CC2, CC3, & CC4	0.68	(0.06)	0.72	(0.04)	0.73	(0.04)	0.69	(0.06)
PTR	0.54	(0.08)	0.59	(0.05)	0.60	(0.04)	0.59	(0.03)

**Table S2. Fractional anisotropy values for significant clusters.**

The mean and standard deviation (SD) fractional anisotropy values are listed separately by group and sex for each cluster. The first three clusters (CC2, CC3 & CC4: the anterior portions and body of the corpus callosum; AF & EmC: the left arcuate fasciculus and extreme capsule; and SLFII & SLFIII: the left superior longitudinal fasciculi) were obtained using a TBSS contrast examining the interaction of Group by Sex, with TFCE correction. The last cluster (PTR: posterior thalamic radiation), was obtained from a TBSS contrast comparing ALC men with NC men.

<b>Group</b>	<b>Alcoholic Men</b>		<b>Alcoholic Women</b>		<b>Nonalcoholic Men</b>		<b>Nonalcoholic Women</b>	
	<b>Min</b>	<b>Max</b>	<b>Min</b>	<b>Max</b>	<b>Min</b>	<b>Max</b>	<b>Min</b>	<b>Max</b>
SLFII & SLFIII	0.35	0.54	0.43	0.58	0.41	0.58	0.33	0.58
AF & EmC	0.32	0.51	0.33	0.61	0.41	0.53	0.38	0.57
CC2, CC3, & CC4	0.57	0.80	0.65	0.85	0.66	0.79	0.56	0.77
PTR	0.31	0.65	0.47	0.66	0.50	0.66	0.52	0.64

**Table S3. Ranges of fractional anisotropy values for significant clusters.**

The ranges of fractional anisotropy values are listed separately by group and sex for each cluster. The first three clusters (CC2, CC3 & CC4: the anterior portions and body of the corpus callosum; AF & EmC: the left arcuate fasciculus and extreme capsule; and SLFII & SLFIII: the left superior longitudinal fasciculi) were obtained using a TBSS contrast examining the interaction of Group by Sex, with TFCE correction. The last cluster (PTR: posterior thalamic radiation), was obtained from a TBSS contrast comparing ALC men with NC men.



**Table S4A. Duration of Heavy Drinking**

	<i>Dependent variable:</i>							
	SLFII and SLFIII	AF and EmC	CC2, CC3, and CC4	PTR	SLFII and SLFIII	AF and EmC	CC2, CC3, and CC4	PTR
DHD	-0.002 (0.001)*	-0.001 (0.001)	-0.002 (0.001)*	-0.003 (0.001)*	-0.001 (0.001)	-0.001 (0.001)	-0.002 (0.001)	-0.003 (0.002)
Women					0.028 (0.029)	0.005 (0.038)	0.014 (0.036)	-0.021 (0.044)
DHD:Women					0.002 (0.002)	0.004 (0.002)	0.001 (0.002)	0.005 (0.003)
Constant	0.501 (0.016)***	0.484 (0.019)***	0.737 (0.017)***	0.608 (0.022)***	0.459 (0.021)***	0.451 (0.027)***	0.716 (0.026)***	0.591 (0.032)***
Observations	49	49	49	49	49	49	49	49
Adjusted R <sup>2</sup>	0.073	0.009	0.072	0.070	0.345	0.216	0.099	0.193

Note: \**p*<0.05; \*\**p*<0.01; \*\*\**p*<0.001

**Table S4B. Daily Drinks**

	<i>Dependent variable:</i>							
	SLFII and SLFIII	AF and EmC	CC2, CC3, and CC4	PTR	SLFII and SLFIII	AF and EmC	CC2, CC3, and CC4	PTR
DD	-0.002 (0.001)*	-0.0005 (0.001)	-0.002 (0.001)	-0.001 (0.001)	-0.0001 (0.001)	0.001 (0.001)	-0.0002 (0.001)	0.0003 (0.001)
Women					0.074 (0.020)***	0.080 (0.026)**	0.057 (0.024)*	0.064 (0.031)*
DD:Women					-0.001 (0.001)	-0.002 (0.002)	-0.002 (0.002)	-0.0003 (0.002)
Constant	0.488 (0.011)***	0.469 (0.014)***	0.723 (0.012)***	0.577 (0.016)***	0.438 (0.015)***	0.415 (0.020)***	0.688 (0.018)***	0.531 (0.024)***
Observations	49	49	49	49	49	49	49	49
Adjusted R <sup>2</sup>	0.067	-0.015	0.058	-0.006	0.337	0.190	0.126	0.112

Note: \**p*<0.05; \*\**p*<0.01; \*\*\**p*<0.001

**Table S4C. Length of Sobriety**

	<i>Dependent variable:</i>									
	SLFII and SLFIII	AF and EmC	CC2, CC3, and CC4	PTR	SLFII and SLFIII	AF and EmC	CC2, CC3, and CC4	PTR	CC2, CC3, and CC4 (men)	CC2, CC3, and CC4 (women)
LOS	0.001 (0.001)	0.001 (0.001)	0.002 (0.001)*	-0.00003 (0.001)	0.001 (0.001)	0.001 (0.002)	0.004 (0.001)**	0.003 (0.002)	0.004 (0.002)**	0.0002 (0.001)
Women					0.073 (0.016)***	0.069 (0.021)**	0.059 (0.018)**	0.099 (0.023)***		
LOS:Women					-0.002 (0.001)	-0.002 (0.002)	-0.004 (0.002)*	-0.006 (0.002)**		
Constant	0.464 (0.010)***	0.457 (0.011)***	0.691 (0.010)***	0.567 (0.013)***	0.430 (0.011)***	0.426 (0.014)***	0.662 (0.012)***	0.520 (0.016)***	0.662 (0.014)***	0.721 (0.011)***
Observations	49	49	49	49	49	49	49	49	23	26
Adjusted R <sup>2</sup>	0.009	-0.007	0.084	-0.021	0.339	0.181	0.236	0.245	0.243	-0.039

Note:

\* $p < 0.05$ ; \*\* $p < 0.01$ ; \*\*\* $p < 0.001$

**Table S4. Regression reports for cluster FA predicted by drinking history measures.**

Linear regression results are reported for the relationship of fractional anisotropy to the three measures of drinking history: duration of heavy drinking (DHD; years), daily drinks (DD; ounces of ethanol per day), and length of sobriety (LOS; years). Models examining interactions of these drinking measures with Sex and Group are reported as well. Table S4C additionally shows the relationship of LOS with the CC2, CC3, & CC4 cluster FA for alcoholic men and women separately.

**Table S5A. Age**

	<i>Dependent variable:</i>													
	SLFII and SLFIII	AF and EmC	CC2, CC3, and CC4	PTR	SLFII and SLFIII	AF and EmC	CC2, CC3, and CC4	PTR	PTR (men)	CC2, CC3, and CC4 (alcoholic men)	CC2, CC3, and CC4 (alcoholic women)	CC2, CC3, and CC4 (nonalcoholic men)	CC2, CC3, and CC4 (nonalcoholic women)	
Age	-0.001 (0.0004)*	-0.002 (0.0004)***	-0.002 (0.0004)***	-0.002 (0.0005)**	-0.001 (0.001)	-0.002 (0.001)*	-0.002 (0.001)**	-0.004 (0.001)***	-0.004 (0.001)**	-0.002 (0.001)*	0.001 (0.001)	-0.002 (0.001)**	-0.003 (0.001)***	
GroupNonalcoholic					0.021 (0.066)	0.001 (0.066)	0.019 (0.063)	-0.080 (0.070)	-0.080 (0.083)					
GenderWomen					-0.016 (0.065)	-0.060 (0.065)	-0.120 (0.063)	-0.101 (0.070)						
Age:GroupNonalcoholic					0.0002 (0.001)	0.001 (0.001)	0.0003 (0.001)	0.003 (0.001)	0.003 (0.002)					
Age:GenderWomen					0.001 (0.001)	0.002 (0.001)	0.003 (0.001)*	0.003 (0.001)*						
GroupNonalcoholic:GenderWomen					0.039 (0.089)	0.072 (0.089)	0.133 (0.086)	0.089 (0.096)						
Age:GroupNonalcoholic:GenderWomen					-0.002 (0.002)	-0.003 (0.002)	-0.004 (0.002)*	-0.003 (0.002)						
Constant	0.517 (0.024)***	0.556 (0.024)***	0.805 (0.023)***	0.667 (0.026)***	0.492 (0.049)***	0.559 (0.049)***	0.812 (0.047)***	0.739 (0.053)***	0.739 (0.062)***	0.812 (0.062)***	0.692 (0.038)***	0.831 (0.028)***	0.844 (0.040)***	
Observations	90	90	90	90	90	90	90	90	42	23	26	19	22	
Adjusted R <sup>2</sup>	0.039	0.151	0.176	0.106	0.209	0.275	0.309	0.293	0.346	0.137	-0.012	0.417	0.427	

Note:

\* $p < 0.05$ ; \*\* $p < 0.01$ ; \*\*\* $p < 0.001$

**Table S5B. Immediate Memory Index**

	<i>Dependent variable:</i>								
	SLFII and SLFIII	AF and EmC	CC2, CC3, and CC4	PTR	SLFII and SLFIII	AF and EmC	CC2, CC3, and CC4	PTR	PTR (men)
IMI	0.001 (0.0003)	0.0003 (0.0003)	0.001 (0.0003)*	0.001 (0.0003)	0.001 (0.001)	0.0003 (0.001)	0.001 (0.001)	0.0005 (0.001)	0.0005 (0.001)
GroupNonalcoholic					0.160 (0.113)	0.142 (0.118)	0.140 (0.116)	0.077 (0.117)	0.077 (0.136)
GenderWomen					0.147 (0.101)	0.061 (0.105)	0.048 (0.103)	0.109 (0.104)	
IMI:GroupNonalcoholic					-0.001 (0.001)	-0.001 (0.001)	-0.001 (0.001)	-0.0002 (0.001)	-0.0002 (0.001)
IMI:GenderWomen					-0.001 (0.001)	-0.0001 (0.001)	-0.0002 (0.001)	-0.001 (0.001)	
GroupNonalcoholic:GenderWomen					-0.348 (0.167)*	-0.182 (0.174)	-0.086 (0.170)	-0.140 (0.172)	
IMI:GroupNonalcoholic:GenderWomen					0.002 (0.001)	0.001 (0.002)	0.0001 (0.001)	0.001 (0.002)	
Constant	0.396 (0.039)***	0.429 (0.040)***	0.613 (0.039)***	0.517 (0.039)***	0.340 (0.079)***	0.406 (0.083)***	0.555 (0.081)***	0.497 (0.082)***	0.497 (0.095)***
Observations	87	87	87	87	87	87	87	87	40
Adjusted R <sup>2</sup>	0.027	-0.003	0.053	0.022	0.176	0.110	0.149	0.112	0.153

Note:

\* $p < 0.05$ ; \*\* $p < 0.01$ ; \*\*\* $p < 0.001$

**Table S5C. Delayed Memory Index**

	<i>Dependent variable:</i>								
	SLFII and SLFIII	AF and EmC	CC2, CC3, and CC4	PTR	SLFII and SLFIII	AF and EmC	CC2, CC3, and CC4	PTR	PTR (men)
DMI	0.001 (0.0003)	0.0003 (0.0004)	0.0004 (0.0004)	0.0003 (0.0004)	0.002 (0.001)	0.0004 (0.001)	0.001 (0.001)	0.0001 (0.001)	0.0001 (0.001)
GroupNonalcoholic					0.227 (0.122)	0.156 (0.127)	0.147 (0.126)	0.114 (0.127)	0.114 (0.147)
GenderWomen					0.201 (0.113)	0.049 (0.118)	-0.006 (0.117)	0.068 (0.118)	
DMI:GroupNonalcoholic					-0.002 (0.001)	-0.001 (0.001)	-0.001 (0.001)	-0.0005 (0.001)	-0.0005 (0.001)
DMI:GenderWomen					-0.001 (0.001)	0.00004 (0.001)	0.0003 (0.001)	-0.0002 (0.001)	
GroupNonalcoholic:GenderWomen					-0.358 (0.166)*	-0.134 (0.173)	0.027 (0.171)	-0.192 (0.172)	
DMI:GroupNonalcoholic:GenderWomen					0.002 (0.001)	0.001 (0.002)	-0.001 (0.001)	0.001 (0.002)	
Constant	0.391 (0.040)***	0.427 (0.041)***	0.654 (0.041)***	0.549 (0.041)***	0.274 (0.095)**	0.389 (0.099)***	0.605 (0.098)***	0.535 (0.099)***	0.535 (0.114)***
Observations	87	87	87	87	87	87	87	87	40
Adjusted R <sup>2</sup>	0.029	-0.002	0.007	-0.003	0.185	0.117	0.138	0.114	0.152

Note:

\* $p < 0.05$ ; \*\* $p < 0.01$ ; \*\*\* $p < 0.001$

**Table S5D. Working Memory Index**

	<i>Dependent variable:</i>								
	SLFII and SLFIII	AF and EmC	CC2, CC3, and CC4	PTR	SLFII and SLFIII	AF and EmC	CC2, CC3, and CC4	PTR	PTR (men)
WMS_WMI	0.0003 (0.0004)	0.0004 (0.0004)	-0.0001 (0.0004)	0.00001 (0.0004)	0.001 (0.001)	0.0004 (0.001)	-0.0002 (0.001)	-0.001 (0.001)	-0.001 (0.001)
GroupNonalcoholic					0.226 (0.132)	0.133 (0.138)	0.134 (0.139)	0.016 (0.137)	0.016 (0.159)
GenderWomen					0.153 (0.119)	0.043 (0.124)	-0.024 (0.125)	0.041 (0.123)	
WMS_WMI:GroupNonalcoholic					-0.002 (0.001)	-0.001 (0.001)	-0.001 (0.001)	0.0004 (0.001)	0.0004 (0.002)
WMS_WMI:GenderWomen					-0.001 (0.001)	0.0001 (0.001)	0.001 (0.001)	0.0001 (0.001)	
GroupNonalcoholic:GenderWomen					-0.382 (0.173)*	-0.202 (0.180)	-0.111 (0.182)	-0.084 (0.180)	
WMS_WMI:GroupNonalcoholic:GenderWomen					0.003 (0.002)	0.001 (0.002)	0.0002 (0.002)	0.0002 (0.002)	
Constant	0.433 (0.046)***	0.423 (0.046)***	0.718 (0.046)***	0.582 (0.046)***	0.339 (0.096)***	0.393 (0.100)***	0.702 (0.101)***	0.597 (0.100)***	0.597 (0.115)***
Observations	87	87	87	87	87	87	87	87	40
Adjusted R <sup>2</sup>	-0.005	-0.003	-0.011	-0.012	0.178	0.119	0.098	0.112	0.151

Note:

\* $p < 0.05$ ; \*\* $p < 0.01$ ; \*\*\* $p < 0.001$

**Table S5. Regression reports for cluster FA predicted by age and memory scores.**

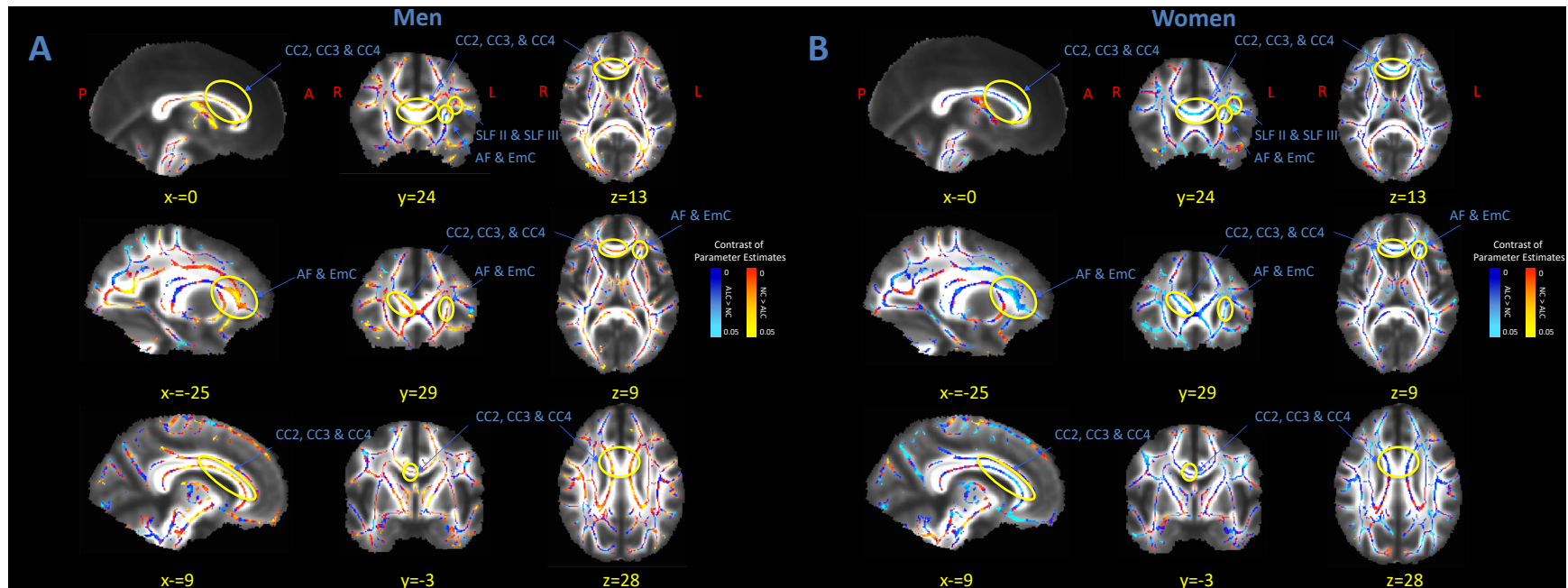
Linear regression results are reported for the relationship of fractional anisotropy to age and the three measures of memory from the Wechsler Memory Scale, Third Edition: Immediate Memory Index (IMI), Delayed Memory Index (DMI), and Working Memory Index (WMI). Models examining interactions of these measures with Sex and Group are reported as well.

<b>Table S6A. Mother's Alcohol History</b>	<b>Alcoholic Men</b>	<b>Alcoholic Women</b>	<b>Nonalcoholic Men</b>	<b>Nonalcoholic Women</b>	<b>Total</b>
Alcoholic	5	5	1	1	12
Alcoholic and Drug Abuse	1	1	0	0	2
Don't Know	1	0	0	0	1
Drug Abuse	0	1	0	0	1
Never	7	6	5	8	26
Social Drinker	9	13	13	13	48
Total	23	26	19	22	90
<b>Table S6B. Father's Alcohol History</b>	<b>Alcoholic Men</b>	<b>Alcoholic Women</b>	<b>Nonalcoholic Men</b>	<b>Nonalcoholic Women</b>	<b>Total</b>
Alcoholic	10	18	5	6	39
Alcoholic and Drug Abuse	1	1	0	0	2
Don't Know	2	0	1	1	4
Drug Abuse	0	0	1	0	1
Never	1	2	3	6	12
Social Drinker	9	5	9	9	32
Total	23	26	19	22	90
<b>Table S6C. First Degree Alcohol History</b>	<b>Alcoholic Men</b>	<b>Alcoholic Women</b>	<b>Nonalcoholic Men</b>	<b>Nonalcoholic Women</b>	<b>Total</b>
No	6	2	13	13	34
Yes	17	24	6	9	56
Total	23	26	19	22	90
<b>Table S6D. Second Degree Alcohol History</b>	<b>Alcoholic Men</b>	<b>Alcoholic Women</b>	<b>Nonalcoholic Men</b>	<b>Nonalcoholic Women</b>	<b>Total</b>
No	8	2	14	13	37
Yes	15	24	5	9	53
Total	23	26	19	22	90

**Table S6. Alcoholism family history.**

Cross tabulations are shown for participants' alcoholism family history, as reported by the research participants. Tables S6A and S6B represent the mother's and father's history of alcoholism. Table S6C indicates the presence of a first degree relative (parents, children, and siblings), while Table S6D shows the presence of a second degree relative (grandparents, grandchildren, aunts, and uncles).

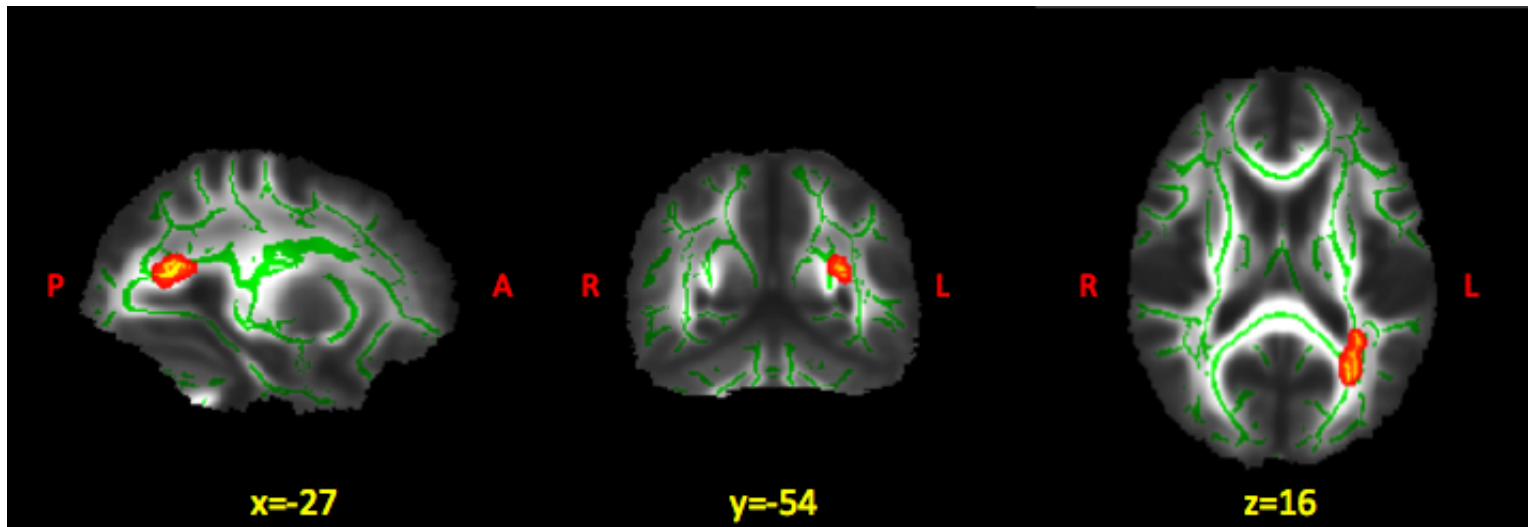
## Supplemental Figures



**Figure S1. Group by Sex interaction in fractional anisotropy differences in white matter.**

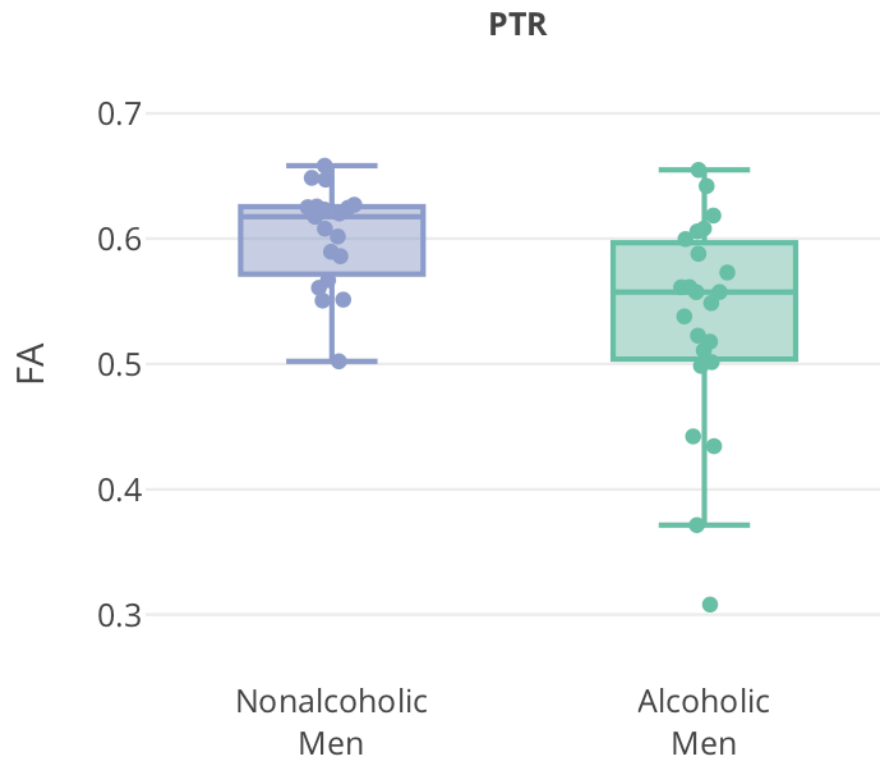
The non-thresholded contrast of parameter estimate FA map is displayed for (A) alcoholic men vs. nonalcoholic men, and (B) alcoholic women vs. nonalcoholic women, displayed in in sagittal, coronal, and axial views. Blue-light blue represents regions where the parameter estimate for the FA values in corresponding ALC group is higher than the NC group. Red-Yellow colors represent regions where the parameter estimate for the FA values in corresponding ALC group is lower than the NC group. Yellow circles indicate regions where the Group by Sex interaction TFCE analysis revealed significant clusters (Figure 1). The three clusters were located as follows: the anterior portions and body of the corpus callosum (CC2, CC3, & CC4); the left superior longitudinal fasciculi (SLF II & SLF III); and the left arcuate fasciculus and extreme capsule (AF & EmC); see Figure 2 for individual FA levels.





**Figure S2. Alcoholic men had lower fractional anisotropy than nonalcoholic men in the PTR cluster.**

The maps represent significant ( $p < 0.05$ , TFCE corrected) clusters from voxel-based FA value comparisons in alcoholic men vs. nonalcoholic men (in red-yellow) in sagittal, coronal, and axial views. The green represents the skeletonized mean FA map of all of the subjects, which has been overlaid on a mean FA map of all the subjects. The red-yellow clusters represent regions with significant effect. One cluster was identified, in the posterior thalamic radiation (PTR); see Figure S3 for individual FA levels.



**Figure S3. Alcoholic men had lower fractional anisotropy than nonalcoholic men in the PTR cluster.**

When examining the effect of alcoholism group for men and women separately, one cluster was identified after TFCE correction for multiple comparisons ( $p < 0.05$ ). For the posterior thalamic radiation (PTR), alcoholic men had 0.06 lower FA than nonalcoholic men; see Figure S2 for the cluster location.