

# Frontal White Matter and Cingulum Diffusion Tensor Imaging Deficits in Alcoholism

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**Background:** Alcoholism-related deficits in cognition and emotion point toward frontal and limbic dysfunction, particularly in the right hemisphere. Prefrontal and anterior cingulate cortices are involved in cognitive and emotional functions and play critical roles in the oversight of the limbic reward system. In the present study, we examined the integrity of white matter tracts that are critical to frontal and limbic connectivity.

**Methods:** Diffusion tensor magnetic resonance imaging (DT-MRI) was used to assess functional anisotropy (FA), a measure of white matter integrity, in 15 abstinent long-term chronic alcoholic and 15 demographically equivalent control men. Voxel-based and region-based analyses of group FA differences were applied to these scans.

**Results:** Alcoholic subjects had diminished frontal lobe FA in the right superior longitudinal fascicles II and III, orbitofrontal cortex white matter, and cingulum bundle, but not in corresponding left hemisphere regions. These right frontal and cingulum white matter regional FA measures provided 97% correct group discrimination. Working Memory scores positively correlated with superior longitudinal fascicle III FA measures in control subjects only.

**Conclusions:** The findings demonstrate white matter microstructure deficits in abstinent alcoholic men in several right hemisphere tracts connecting prefrontal and limbic systems. These white matter deficits may contribute to underlying dysfunction in memory, emotion, and reward response in alcoholism.

**Key Words:** Alcoholism, Diffusion Tensor Magnetic Resonance Imaging, White Matter, Reward System, Right Hemisphere.

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**L**ONG-TERM CHRONIC ALCOHOLISM adversely impacts brain systems involved in cognition and emotion and alters sensitivity to the effectiveness of acquired reinforcers (rewards) such as alcohol and other addictive substances (Blum et al., 2000; Bowirrat and Oscar-Berman, 2005). Alcoholism has been associated with a breakdown of the "reward cascade," leading to Reward Deficiency Syndrome (Blum et al., 2000; Bowirrat and Oscar-Berman, 2005). The reward cascade refers to brain neurotransmitter activity that contributes to a state of well-being, and Reward Deficiency Syndrome refers to an insensitivity in the effectiveness

of rewards (Blum et al., 2000; Comings and Blum, 2000), including a diminished ability to avoid negative affect created by repeated cycles of substance abuse and dependence (Baker et al., 2004).

Brain circuitry involved in alcoholism-related insensitivity to rewards includes the mesolimbic pathway linking the ventral tegmentum with the nucleus accumbens and the pallidum; these regions are especially important for modulating the effectiveness of reinforcement, both positive (reward) and negative (punishment) (Blum et al., 2000). The limbic aspects of this circuitry are modulated by inputs from the cortex, particularly from orbitofrontal, dorsolateral prefrontal, and cingulate regions. We have termed these combined cortical-subcortical circuits the Extended Reward and Oversight System (EROS). Furthermore, because there is overlap among the brain regions involved in memory, emotion, and sensitivity to reinforcement, these functions could be adversely impacted by damage to the relevant cortical and subcortical gray matter regions and/or by degradation of the white matter tracts that interconnect them. In a concurrent structural magnetic resonance imaging (MRI) study, we identified significant volume reductions in the cortical and subcortical components of EROS in abstinent long-term alcoholics (Makris et al., 2008). Several research groups have reported alcoholism-related damage in the frontal lobes, corpus callosum, cerebellum, and limbic structures (Mukamal, 2004;

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Oscar-Berman and Bowirrat, 2005; Oscar-Berman and Marinkovic, 2003; Sullivan et al., 2000). The goal of the present study was to assess the integrity of white matter tracts that connect to cortical regions involved in modulating reinforced behaviors (the "reward response") in abstinent alcoholic subjects and demographically equivalent nonalcoholic controls, with special attention being paid to possible hemispheric differences. Consideration of structural differences between the 2 cerebral hemispheres is important because, although both cerebral hemispheres contain EROS circuitry, their specific functions may be lateralized to reflect differential hemispheric sensitivities to stimulus materials (e.g., linguistic vs. visuospatial) and task demands (e.g., attention, perception, motor response, etc.). For example, alcoholics commonly display a pattern of deficits that includes visuospatial, attentional, and emotional abnormalities characteristic of patients with right hemisphere damage, suggesting that the right hemisphere may be more vulnerable to the effects of alcoholism than the left hemisphere (Ellis and Oscar-Berman, 1989; Oscar-Berman and Marinkovic, 2007).

Alcoholism is particularly damaging to cerebral white matter, as has been revealed by *postmortem* neuropathology (Harper et al., 1987, 2003; Paula-Barbosa and Tavares, 1985; Pentney, 1991; Putzke et al., 1998; Tarnowska-Dziduszko et al., 1995) and by *in vivo* structural MRI studies (Estruch et al., 1997; Pfefferbaum et al., 1992, 1995, 1996, 1997; Shear et al., 1994; Sullivan et al., 1996, 2000). Consistent with these findings, *postmortem* RNA analyses of superior frontal lobe samples found that genes related to myelin structure were down-regulated in alcoholics (Lewohl et al., 2000). Another MRI methodology, diffusion tensor MRI (DT-MRI), recently has been used for analyzing brain white matter integrity in alcoholics (Pfefferbaum and Sullivan, 2002; Sullivan and Pfefferbaum, 2003). By utilizing the principles of water diffusion and Brownian motion to determine the direction and magnitude of molecular water freedom and binding in tissue, DT-MRI is uniquely sensitive to the directional orientation and coherence of myelin within white matter microstructure (Basser et al., 1994; Pierpaoli and Basser, 1996). DT-MRI quantifies these properties on a voxel-by-voxel basis into fractional anisotropy (FA), which is a commonly derived scalar metric of DT-MRI data. FA measurements are especially well suited for white matter analyses because the diffusion of water in white matter axonal fibers is constrained by the structure of the tissue itself, i.e., the myelin sheath. This nonuniform constraint of water diffusion due to spatial orientation of tissue (for example, white matter tracts) is called anisotropy, whereas free diffusion is referred to as isotropy. Due to the anisotropic characteristic of white matter, images depicting white matter fiber coherence, orientation, and tractography can be obtained (Pierpaoli, 2002). Damage to white matter, or demyelination, along neuronal axons results in more isotropic water movement and is manifested as relatively low FA values.

When used to study white matter structure in alcoholics, DT-MRI has revealed microstructural damage in cerebral

areas that appeared intact based upon macrostructural analyses of structural MRI (Pfefferbaum and Sullivan, 2002; Sullivan and Pfefferbaum, 2003) or neuropathology (Tang et al., 2004). Prior DT-MRI studies have shown white matter tract damage in alcoholic subjects in the genu and splenium of the corpus callosum and the centrum semiovale (Pfefferbaum and Sullivan, 2002, 2005; Pfefferbaum et al., 2000, 2007), as well as widespread FA deficits in both hemispheres (Pfefferbaum et al., 2006).

The current DT-MRI study focused on changes in frontal and cingulum white matter tracts connecting cortical and limbic regions related to emotion, reward, and memory circuits, because of their relevance to alcoholism-related impairments. We hypothesized that alcoholic subjects would display deficits in white matter coherence, reflected by decreased FA values on DT-MRI, in white matter tracts connecting with fronto-limbic reward circuitry regions (such as the cingulate gyrus, orbitofrontal cortex, and dorsolateral prefrontal cortex). Specifically, we investigated white matter tracts projecting from dorsolateral prefrontal cortex [superior longitudinal fascicle (SLF) II and III], cingulate cortex (cingulum bundle), and orbitofrontal cortex (orbitofrontal cortex white matter; OF-Cwm), and we examined possible coherence differences between the 2 cerebral hemispheres.

## MATERIALS AND METHODS

### *Subjects*

The study included 15 alcoholic men (33- to 76-year old) who had been abstinent for at least 4 weeks before testing and scanning (abstinence mean  $\pm$  SD: 5.7  $\pm$  10.0 years; median: 0.25 years; range: 0.1 to 28 years; 11/15 subjects were sober 15 months or less), and 15 healthy nonalcoholic control subjects (men 46- to 77-year old). All of the participants were right-handed as determined by a handedness questionnaire (Briggs and Nebes, 1975) and were solicited from the Neurology, Psychology, Psychiatry, Medical, and Outpatient Services of Boston University Medical Center, the Department of Veterans Affairs (VA) Healthcare System Boston Campus, VA after-care programs, and advertisements (flyers, local newspapers, and websites). The groups performed comparably on neuropsychological screening tests (described below). As shown in Table 1, the 2 groups were similar with respect to IQ, memory scores, and education and did not differ on depression or anxiety measures. However, there was a trend toward the control subject group being older than the alcoholic subjects ( $p = 0.06$ ). The participants were native English speakers, with comparable socioeconomic backgrounds, and the ethnic distribution of the 2 groups was identical (13 White and 2 Black). Three of the alcoholics, but none of the control subjects, had a history of tobacco dependence. This study was approved by the human subjects investigational review boards of the participating institutions, and informed consent for participation in the research study was obtained from each subject prior to neuropsychological testing and also prior to scanning. Participants received monetary compensation for time and travel expenses.

### *Clinical and Diagnostic Procedures*

A medical history interview and a vision test were administered to the participants, as well as a series of questionnaires (e.g., handedness, alcohol, and drug use) in order to ensure that they met the inclusion criteria for the study. Participants also were given a computer-assisted, shortened version of the Diagnostic Interview

**Table 1.** Demographic, Neuropsychological, and Clinical Data

	Nonalcoholic control subjects <i>n</i> = 15, mean ± SD	Subjects with alcoholism <i>n</i> = 15, mean ± SD	<i>p</i> -value
Age at scan	56.4 ± 9.0	48.3 ± 13.1	0.06
Years of education	14.5 ± 1.8	13.8 ± 1.7	0.3
IQ and memory			
Full scale IQ <sup>(1)</sup>	110.6 ± 10.6	104.2 ± 10.1	0.10
Verbal IQ <sup>(1)</sup>	110.8 ± 12.1	105.7 ± 10.0	0.2
Performance IQ <sup>(1)</sup>	108.7 ± 10.2	101.8 ± 11.6	0.09
General memory <sup>(2)</sup>	105.4 ± 14.9	99.5 ± 10.3	0.2
Working memory <sup>(2)</sup>	108.2 ± 14.8	108.7 ± 20.8	0.9
WAIS-III performance Subtests <sup>(1)</sup>			
Digit symbol	10.4 ± 2.9	8.9 ± 2.2	0.1
Block design	11.3 ± 2.8	10.5 ± 2.9	0.4
Picture arrangements	11.3 ± 2.2	10.7 ± 1.8	0.5
Object assembly	10.4 ± 3.4	10.7 ± 2.8	0.8
Executive functioning			
WCST preservative errors (%) <sup>(3)</sup>	40.7 ± 30.7	45.6 ± 27.4	0.6
FAS word generation (%) <sup>(4)</sup>	48.7 ± 17.2	39.3 ± 25.2	0.2
Time to complete Trails A (seconds) <sup>(5)</sup>	35.4 ± 13.7	31.8 ± 16.5	0.5
Time to complete Trails B (seconds) <sup>(5)</sup>	83.0 ± 26.8	67.3 ± 33.5	0.2
Depression measures			
POMS <sup>(6)</sup>	37.5 ± 4.8	39.9 ± 8.3	0.4
MAACL <sup>(7)</sup>	45.3 ± 3.0	47.8 ± 10.3	0.4
Hamilton <sup>(8)</sup>	1.2 ± 1.2	2.4 ± 4.3	0.3
Anxiety measure			
MAACL*	42.9 ± 3.2	44.5 ± 6.8	0.4
Drinking behavior			
Quantity-frequency Index (QFI) <sup>(9)</sup>	0.4 ± 0.5	12.5 ± 10.1	<0.0001
Years of consuming 21+ drinks per week	–	16.0 ± 8.0	
Length of sobriety (years)	–	5.7 ± 10.0	

(1) WAIS-III (Wechsler, 1997a); (2) WMS-III (Wechsler, 1997b); (3) WCST (Berg, 1948; Grant and Berg, 1948); (4) FAS (Controlled Oral Word Association Test: Spreen and Strauss, 1998); (5) Trails A and B (US-Army, 1944); (6) POMS (McNair et al., 1981); (7) MAACL (Zuckerman and Lubin, 1965); (8) Hamilton Depression Scale (Hamilton, 1960); and (9) QFI (Cahalan et al., 1969). \*One alcoholic subject did not complete the MAACL. MAACL, Multiple Affect Adjective Check List; POMS, Profile of Mood States; WAIS, Wechsler Adult Intelligence Scale; WMS, Wechsler Memory Scale; WCST, Wisconsin Card Sorting Test.

Schedule (DIS) (Robins et al., 1989) that provides lifetime psychiatric diagnoses according to Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) criteria (APA, 1994). Participants were excluded if any source (i.e., DIS scores, hospital records, referrals, or personal interviews) indicated that they had one of the following: a history of neurological dysfunction (e.g., major head injury with loss of consciousness greater than 15 minutes, stroke, epilepsy, or seizures unrelated to alcohol withdrawal); electroconvulsive therapy; major psychiatric disorder (e.g., schizophrenia or primary depression); symptoms of depression within the 6 months prior to testing; current use of psychoactive medication; history of abuse of drugs besides alcohol; clinical evidence of active hepatic disease; history of serious learning disability or dyslexia; and uncorrected abnormal vision or hearing problem. Subjects also were excluded if their MRI scans demonstrated any gross neuroanatomic abnormalities.

All participants were given a structured interview (Cahalan et al., 1969; MacVane et al., 1982) in which they were asked about their drinking patterns. Information was obtained about length of absti-

nence and the number of years of heavy drinking (quantified as greater than 21 drinks per week). A Quantity-Frequency Index (QFI), which takes into consideration the amount, type, and frequency of use of alcoholic beverages either over the last 6 months (for the nonalcoholics), or over the 6 months preceding cessation of drinking (for the alcoholics), was calculated for each participant (Cahalan et al., 1969). The alcoholic group, on average, had a QFI of 12.5 ± 10.1, and had 21 or more drinks per week for 16.0 ± 8.0 years. Controls had an average QFI of 0.4 ± 0.5. Alcoholic subjects met DSM-IV criteria (APA, 1994) for alcohol abuse or dependence for a period of at least 5 years in their lives, and had abstained from alcohol use for at least 4 weeks prior to testing.

### Neuropsychological Measures

Neuropsychological evaluations, which typically required from 7 to 9 hours of testing over a minimum of 2 days, were performed prior to DT-MRI scan sessions. Selected neuropsychological information is reported in Table 1. During the neuropsychological assessment sessions, participants were given frequent breaks, and a session was discontinued and rescheduled if a subject indicated fatigue. Tests of intelligence, memory, and affect were administered. They consisted of the Wechsler Adult Intelligence Scale, Third Edition (WAIS-III) for Verbal IQ, Performance IQ, and Full Scale IQ (Wechsler, 1997a), the Wechsler Memory Scale, Third Edition for General Memory and Working Memory (Wechsler, 1997b), the Hamilton Depression Scale (Hamilton, 1960), the Profile of Mood States (POMS) (McNair et al., 1981), and the Multiple Affect Adjective Check List Revised (Zuckerman and Lubin, 1965). Subtests of the WAIS that have been reported to be sensitive to alcohol-related visuospatial dysfunction are Digit Symbol, Picture Arrangement, Block Design, and Object Assembly (Ellis and Oscar-Berman, 1989; Oscar-Berman and Schendan, 2000; Rourke and Loberg, 1996). In addition to tests of IQ, memory, and affect, the subjects were administered the following tests sensitive to integrity of frontal brain systems: Trail Making Test versions A and B (US-Army, 1944); a computerized version (Heaton et al., 1993) of the Wisconsin Card Sorting Test (WCST) (Berg, 1948; Grant and Berg, 1948); and the Controlled Oral Word Association Test (the "FAS" test) (Spreen and Strauss, 1998).

### Imaging Parameters

3D T1-weighted anatomical magnetization-prepared rapid gradient echo (MP-RAGE) and DT-MRI scans were acquired on a 3.0-Tesla Siemens Trio scanner (Siemens Medical Solutions USA, Inc., Malvern, PA). The MP-RAGE series were obtained with the following parameters: echo time (TE) = 3.3 ms, repetition time (TR) = 2,530 ms, inversion time (TI) = 1,100 ms, flip angle = 7°, slice thickness = 1.33 mm, 128 contiguous sagittal slices, acquisition matrix = 256 × 256, in-plane resolution = 1 × 1 mm<sup>2</sup> (i.e., square field of view (FOV) = 256 mm), 2 averages and pixel bandwidth = 200 Hz/pixel. The DT-MRI data were constructed based on a 7-shot acquisition (1 T2-weighted "lowb" anatomical reference with b-value = 0 s/mm<sup>2</sup>, and 6 directional images). The following parameters were used: TR = 200 ms, TE = 9 ms, averages = 10, number of axial slices = 60 to cover the entire brain, FOV = 256 mm (square), data matrix = 128 × 128, in-plane resolution = 2 × 2 mm<sup>2</sup>, slice thickness = 2 mm, skip = 0 mm, bandwidth = 1,860 Hz/pixel, b-value = 700 s/mm<sup>2</sup>, and imaging time of approximately 8 minutes.

### DT-MRI Processing Stream

The basic steps in our DT-MRI processing were as follows: (1) motion and Eddy current distortion correction; (2) corrected volume was used to generate FA maps (Pierpaoli and Basser, 1996) for each subject; (3) spatial transformation of each subject's lowb to an

average template created by co-registering (initial target was a T2-weighted 152-subject average template) and averaging all *lowb* volumes; (4) generation of voxel-wise group-difference statistical maps based on the common-space FA data; (5) assessment of group differences in anatomic white matter regions according to a priori hypotheses, guided by statistical thresholding; (6) FA values calculated on the spatially normalized data for each subject for the hypothesis-driven regions of interest (ROIs), identified in the above step (5). Additional detail is provided below.

### DT-MRI Methods

For the DT-MRI data analysis, we used a combination of the following 2 processing streams: Martinos Center Free Diffusion Tools (Salat et al., 2005a,b; Tuch et al., 2005), which include a set of processing scripts for reconstruction and analysis of DT-MRI data, developed at the Athinoula A. Martinos Center for Biomedical Imaging at Massachusetts General Hospital (Boston, MA); and FSL (<http://www.fmrib.ox.ac.uk/fsl>) (Jenkinson and Smith, 2001; Jenkinson et al., 2002; Smith, 2002; Smith et al., 2001).

The DT-MRI data were acquired as a 7-shot acquisition, consisting of 6 directional image volumes plus a *lowb* structural image set with no diffusion weighting. All of the above DT-MRI images were collected within the same sequence and with identical parameters. A 12-degree affine mutual information cost function transformation (procedure available with FLIRT, FSL-FMRIB's Linear Image Registration Tool, University of Oxford, England) was applied to all these volumes to help reduce Eddy current distortions and motion along different repetitions as follows: Each slice of the acquisition consisted of a *lowb* (T2) image and 6 directional images, which were repeated a total of 10 times (70 images per slice). The averaging step was to take the first *lowb* image (#1 of 70 images) and co-register all remaining images (*lowb* and directional images alike) to the first *lowb* image. Then, the DT was calculated for each voxel in the volume, using a least-squares fit to the diffusion signal (Basser et al., 1994). The FA was calculated from the DT (Pierpaoli and Basser, 1996).

### Spatial Normalization

Each subject's *lowb* volume was registered to the SPM (Statistical Parametric Mapping; <http://www.fil.ion.ucl.ac.uk/spm>) T2 152-subject average template (ICBM, NIH P-20 project, Principal Investigator, John Mazziotta). This template has a 2 mm isotropic resolution and was smoothed with an 8 mm full width at half maximum (FWHM) Gaussian filter (sequence details: dual echo spin echo, TE = 120 ms, TR = 3,300 ms, flip angle = 90°). Then, a subject-based T2 anatomical template was created by averaging the SPM-registered *lowb* volumes for the entire cohort of alcoholics and nonalcoholic controls. The FSL Brain Extraction Tool was used to skull-strip the input *lowb* volumes to facilitate more uniform and precise registrations. Each registration was performed using a 12-degree affine mutual information cost function transformation (procedure available with FLIRT).

Each subject's native *lowb* image was subsequently registered to the subject-based average template using FLIRT as above. The FA maps were then spatially transformed to the common coordinate space by using the transformations identified for their respective *lowb* volume.

### Group Maps

Group analyses were performed to examine the regional distribution of diagnostic-group related differences in FA, by performing a voxel-based two-tailed *t*-test between the 2 diagnostic groups. In this case, voxels that differed at  $p < 0.01$  using a two-tailed *t*-test (corresponding to  $t > 2.76$ ) were identified in an image that showed 2 types of colored regions: those where the alcoholic group had a sig-

nificantly higher FA value than the nonalcoholic control group (blue), and where the alcoholic group had a significantly lower FA value than that of the control group (red). This image of colored regions was then superimposed on the T2-weighted structural anatomical template volume (*lowb*) that was created as a group average for the entire cohort to get an anatomical reference for the regions of significant difference.

### Regions of Interest Procedures

We first executed a voxel-based analysis by creating regions of FA differences and taking clusters above a significance threshold ( $p < 0.05$ ) and size (greater than 5 contiguous voxels). Afterwards, these clusters were identified by one rater (NM) based on anatomical topography and the mapping of these fiber pathways from known literature (Makris et al., 1999, 2002b, 2005; Mufson and Pandya, 1984; Petrides and Pandya, 1988; Talairach and Tournoux, 1988; Yakovlev and Locke, 1961). Regions of FA difference located in predominantly gray matter were noted for discussion, but excluded from regional analyses as we were primarily interested in white matter tracts.

There were 4 principal clusters of anatomical interest corresponding to white matter tracts connecting to reward circuit cortical regions: The OFCwm, located in the ventral anterior sector of the frontal lobes (Caviness et al., 1996); the cingulum bundle, which included white matter voxels contained within the cingulate gyrus above the corpus callosum (Makris et al., 2002a); SLF II, in the region above the insula, the extreme capsule, the claustrum, the external capsule, the lenticular nucleus, and the internal capsule (Makris et al., 2005); and SLF III, within the parietal and frontal Sylvian opercula (Makris et al., 2005). We then created ROIs, defined by the extent of these clusters, and we calculated the average FA value in these clusters for each subject. These values were then compared between the 2 groups (alcoholic vs. control) with analyses of covariance (ANCOVA) to evaluate the group differences in FA values covaried for age. Furthermore, each of these ROIs was mirrored about the inter-hemispheric fissure to the contralateral hemisphere, and FA values in these contralateral hemisphere ROIs were determined and compared.

As an exploratory analysis, we also noted and discuss below the locations of other significant regions of FA group differences in regions beyond those connecting with specific reward-related regions of the EROS network.

### Data Analysis: ROI and Correlation Analyses

All statistical analyses were performed using JMP statistical analysis software (version 5.0.1.2; SAS Institute Inc., Cary, NC). Between-group ROI comparisons were made on regional FA measures using ANCOVA controlling for age. To assess laterality effects in the 4 index regions, we applied ANOVA including effects of group (alcoholic vs. control) and hemisphere (right vs. left), with subjects as a repeated factor, to determine whether there were group by hemisphere interaction effects. Correlation analyses then were applied to correlate regional FA measures in frontal ROIs with memory, IQ, age, and drinking history. Correlation coefficients were compared between groups using Fisher's *Z* transformation. Regions that had significant within group correlations in conjunction with significant between group differences in correlation coefficients are reported below.

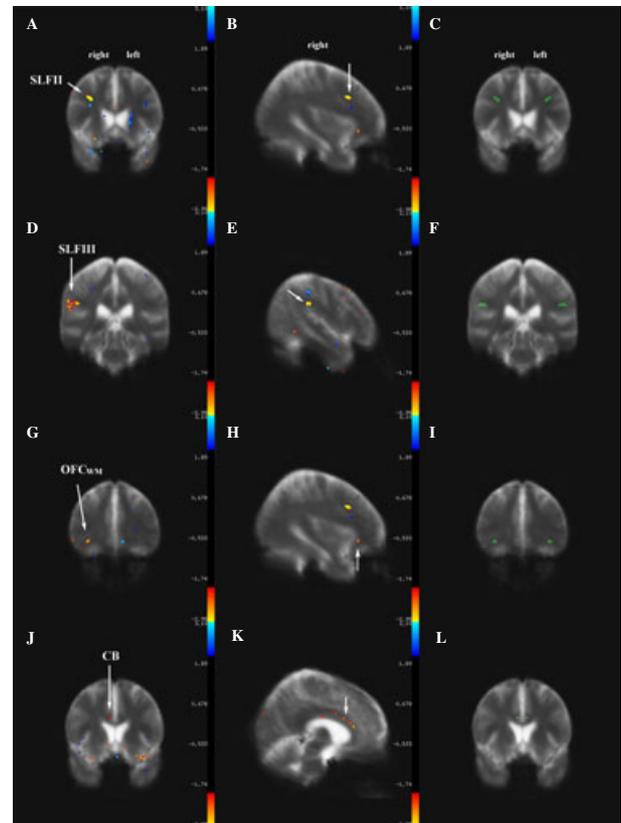
In order to determine how well the index regions could discriminate group membership, we performed linear discriminant function analysis (DFA) with and without partialling out the effect of age. Age was covaried by running the DFA on the residual FA values from the correlation of age with each ROI. In the absence of a second sample to test the discriminant function, we then created the discriminant function using  $n-1$  subjects and used it to classify the 1-out subject. This leave-one-out cross validation of the discriminant

analysis enables a test of the specificity and accuracy of the DFA within a sample using each subject as a test case of the discriminant function.

## RESULTS

### *FA Maps and a Priori Hypothesized ROIs*

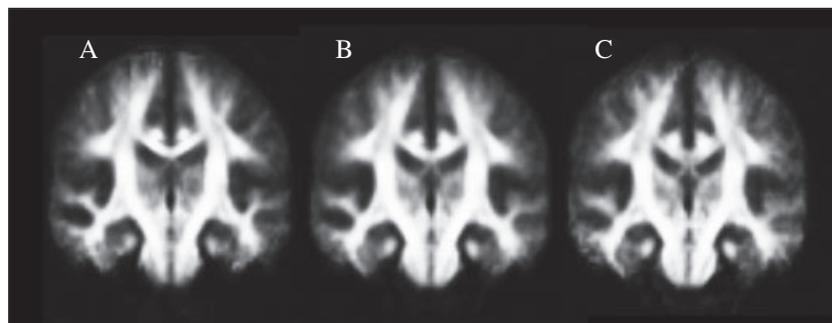
Averaged FA images of the control group, the alcoholism group, and the average of both groups combined are shown in Fig. 1, demonstrating consistent within- and between-group image registration and FA signal. These control and alcoholic FA group images were used as the basis for group FA comparisons. Intergroup FA maps (Fig. 2) show voxels of significant differences ( $p < 0.01$ ) in the principal index regions, where red voxels indicate that the nonalcoholic control group's FA is greater than the alcoholic group's FA, in the right SLF II and SLF III, the right cingulum bundle, and the right OFCwm. ANCOVA analyses examining these 4 right frontal ROIs demonstrated significant group effects in mean FA between the alcoholic group and the control group (see Table 2), which remained highly significant after covarying for age (no significant age effects were observed in the ANCOVA model for any ROI). To confirm hemispheric asymmetry and localization, we created ROIs mirrored across the inter-hemispheric fissure from the right ROIs to respective left hemisphere ROIs. Then we determined the mean FA values of the left hemisphere ROIs and ran ANCOVA analyses on these variables. There were no differences in the left hemisphere cingulum bundle, OFCwm, SLF II, or SLF III ROIs between the control and alcohol groups (all  $p > 0.20$ ). Table 2 shows the group means, standard deviations, and  $p$ -values between the groups for all 4 ROIs in each hemisphere. To confirm the lateralization of these regional differences, we applied ANOVA including effects of group (alcoholic vs. control), and hemisphere (right vs. left), with subjects as a repeated factor, for these 4 index ROIs in each hemisphere. For ANOVA including all 4 index ROI pairs, there were significant effects of group [ $F(1,208) = 35.6$ ;  $p < 0.0001$ ], and group by hemisphere interaction [ $F(1,208) = 18.4$ ;  $p < 0.0001$ ]. These effects were also significant for each of the 4 ROI pairs individually. Alcoholic subjects had signifi-



**Fig. 2.** Voxel-based analysis maps of significant FA differences between groups at levels of the 4 principal index regions: Superior longitudinal fascicle (SLF) II (top row), SLF III (second row), orbitofrontal cortex white matter (OFCwm, third row), and cingulum bundle (CB, bottom row). Left column shows coronal views, middle column displays sagittal views, and right column depicts the 4 principal regions of interest (ROIs) in right hemisphere, and the mirror regions in left hemisphere. Red indicates control group FA is greater than that of alcoholic group, while blue regions have greater FA in the alcoholic group.

cantly reduced FA in right hemisphere ROIs compared with their respective left hemisphere ROIs and compared with the control group's right hemisphere ROIs. No left hemisphere effects were observed in these ROI analyses.

We performed a DFA on the 4 significant right hemisphere frontal ROIs to determine the discriminant ability of these



**Fig. 1.** Group-average FA images for controls (A), alcoholics (C), and the average across all subjects in both groups (B).

**Table 2.** Mean Differences of Average DTI FA Values in Selected ROI

Region	Cluster size (voxels)	Cluster coordinates*			Nonalcoholic control subjects <i>n</i> = 15, mean ± SD	Subjects with alcoholism <i>n</i> = 15, mean ± SD	Group effect	
		<i>X</i>	<i>Y</i>	<i>Z</i>			<i>F</i> (1,29)	<i>p</i>
Right Hemisphere								
SLF II	27	33	26	19	0.43 ± 0.05	0.25 ± 0.13	23.1	<0.0001
SLF III	33	48	28	-29	0.27 ± 0.07	0.15 ± 0.06	21.0	<0.0001
CB	15	5	26	11	0.46 ± 0.09	0.29 ± 0.10	19.9	<0.0001
OFCwm	6	34	-9	31	0.36 ± 0.12	0.23 ± 0.11	7.1	0.013
Left Hemisphere								
SLF II	27	-33	26	19	0.38 ± 0.11	0.33 ± 0.14	2.0	0.2
SLF III	33	-48	28	-29	0.28 ± 0.06	0.30 ± 0.11	0.2	0.7
CB	15	-5	26	11	0.37 ± 0.13	0.33 ± 0.12	0.7	0.4
OFCwm	6	-34	-9	31	0.32 ± 0.13	0.30 ± 0.17	0.1	0.7

*F*-values are for the ANCOVA group effect after covarying for Age. No significant age effects were observed in the ANCOVA model for any ROI. \*Talairach coordinates: *X* = right + and left -; *Y* = superior + and inferior -; and *Z* = anterior + and posterior -. Overall ANCOVA results (includes group and age effects in model): right SLF II  $F(2,27) = 12.6$ ,  $p = 0.0001$ ; right SLF III  $F(2,27) = 12.1$ ,  $p = 0.0002$ ; right CB  $F(2,27) = 10.8$ ,  $p = 0.0004$ ; right OFCwm  $F(2,27) = 6.8$ ,  $p = 0.004$ ; left SLF II  $F(2,27) = 1.3$ ,  $p = 0.3$ ; left SLF III  $F(2,27) = 0.1$ ,  $p = 0.9$ ; left CB  $F(2,27) = 0.4$ ,  $p = 0.7$ ; left OFCwm  $F(2,27) = 0.2$ ,  $p = 0.8$ . SLF, superior longitudinal fascicle; CB, cingulum bundle; OFCwm, orbitofrontal cortex white matter; FA, fractional anisotropy; ROI, regions of interest.

DT-MRI FA regional measures for categorizing the group membership of each subject. The DFA was highly effective for determining group membership; all controls and all but 1 alcoholic subject were correctly classified based on the 4 frontal right-hemisphere ROIs [29/30, 97% correct classification,  $F(4, 25) = 18.8$ ,  $p < 0.0001$ ]. After covarying for age, 93% were correctly classified [28/30, 1 alcoholic and 1 control subject misclassified,  $F(4, 25) = 10.7$ ,  $p < 0.0001$ ]. The leave-one-out cross validation of the DFA showed similar results: 29 of 30 correct classifications [ $F(4, 24) = 18.3$ ,  $p < 0.0001$ ], and 90% correct classifications with age as covariate [27/30, 1 alcoholic and 2 control subjects misclassified,  $F(4, 24) = 10.4$ ,  $p < 0.0001$ ].

In order to examine whether methodological artifacts might have contributed to hemispheric lateralization of frontal regional DT-MRI tract differences, we examined non-thresholded group-difference maps, and also examined whether applying a smaller cluster size threshold (3 contiguous voxels rather than 5), would demonstrate left hemisphere differences in these index regions that might have missed the statistical or cluster size thresholds, or been missed by the contralaterally mirrored ROI placement. However, we did not find evidence of systematic hemispheric artifacts that might have contributed to the lateralized results above. While reducing the cluster size threshold resulted in more regions being noted overall, the lateralization of DT-MRI deficits in alcoholics remained heavily weighted toward the right hemisphere; there were 12 right hemisphere regions versus 4 left hemisphere regions with clusters of 3 voxels or more, and none was located in left frontal lobe white matter tracts.

#### Behavioral Correlations With Regional FA Measures

Age at scan, drinking history, IQ, and memory scores were examined for correlation with mean FA of the index ROIs that were created in the study (right and left hemisphere cin-

gulum bundle, SLF II, SLF III, and OFCwm). Regions that had significant structure/behavior correlations within a subject group, combined with significant correlation differences between groups, are reported here. No group differences were observed in correlations between regional FA values and age, drinking history, or IQ scores. However, age was correlated with duration of abstinence [age vs. (log) years sober:  $r = 0.76$ ,  $p = 0.001$ ; nonparametric rank correlation  $\rho = 0.61$ ,  $p = 0.02$ ], which may have inhibited our ability to detect age or abstinence-related changes. In the nonalcoholic control group (but not in the alcoholic group), Working Memory was significantly correlated with right and with left SLF III FA (right:  $r = 0.69$ ,  $p = 0.005$ ; left:  $r = 0.72$ ,  $p = 0.002$ ). Correlation coefficients for right and left SLF III vs. Working Memory scores were significantly different between groups (right:  $Z = 3.5$ ,  $p = 0.0004$  and left:  $Z = 3.2$ ,  $p < 0.01$ ). Right SLF III was negatively correlated with Working Memory in the alcoholic group ( $r = -0.53$ ,  $p = 0.04$ ), but this negative correlation was influenced by an outlier subject with IQ of 155. Without including this subject, the alcoholic group correlation for right SLF III and Working Memory remained negative, but was no longer significant ( $r = -0.39$ ,  $p = 0.17$ ), and was comparable to the left SLF III correlation with Working Memory in alcoholics ( $r = -0.38$ ,  $p = 0.16$ ). However, even without including the outlier subject, the between-group Fisher *Z* comparison continued to demonstrate strongly significant difference between groups in correlation between right SLF III and Working Memory ( $Z = 3.01$ ,  $p = 0.003$ ).

#### Additional Exploratory Regional Group FA Differences

In addition to the hypothesis-driven analyses of white matter tracts with direct connections to reward-related cortical regions involved in EROS, there were several white matter regions depicting group differences in other parts of the brain.

**Table 3.** All Exploratory Regions With Significant Between-Group FA Differences in the Parametric Map (their locations and average *t*-statistics for the clusters are shown)

Location	Direction	Cluster size (voxels)	Cluster coordinates*			<i>t</i>	<i>p</i>
			X	Y	Z		
SLF I right	Ctrl > Alc	9	15	46	-55	-3.34	0.002
STG-WM right	Ctrl < Alc	18	44	-17	0.2	3.27	0.003
AFh right	Ctrl < Alc	11	31	16	21	3.28	0.003
AFh left	Ctrl < Alc	15	-31	28	-9	3.12	0.004
AFv left	Ctrl < Alc	32	-44	18	-53	3.15	0.004
FTJ-LI left	Ctrl < Alc	33	-30	-14	-5	3.59	0.001

\*X: +, right and -, left; Y: +, superior and -, inferior; and Z: +, anterior and -, posterior. STG-WM, superior temporal gyrus white matter; AFh, arcuate fasciculus, horizontal part; AFv, arcuate fasciculus, vertical part; FTJ-LI, fronto-temporal junction, limen insula; Ctrl, nonalcoholic control subjects; Alc, alcoholic subjects; FA, fractional anisotropy; SLF, superior longitudinal fascicle.

Alcoholic subjects had decreased FA in right parietal SLF I. Alcoholic subjects had FA increases in left arcuate fascicle (both vertical and horizontal portions), as well as in right arcuate fascicle horizontal portion and right superior temporal gyrus white matter. Alcoholic subjects also had FA increases in the left fronto-temporal junction. The cluster sizes, average magnitude of region differences, and Talairach coordinates of these regions are presented in Table 3.

Other prior DT-MRI studies have reported FA differences in regions defined a priori in corpus callosum and centrum semiovale (Pfefferbaum and Sullivan, 2005; Pfefferbaum et al., 2000). While we did not specifically note differences in these regions, these prior reports included regions that were relatively broadly defined, and may have included or bordered on regions identified in the current study such as cingulum bundle and SLF II.

There were 4 FA difference clusters that were located in predominantly gray matter regions. However, because the focus of this study was white matter tracts, these predominantly gray matter regional FA differences are only noted and not discussed: left inferior insula and right cuneal cortex (greater FA values in controls), as well as right caudate and right supramarginal cortex (greater FA values in alcoholics).

## DISCUSSION

The results of our study depict alterations of white matter tracts connecting with right hemisphere cingulate and frontal lobe regions involved in the processing of reward, emotion, and memory functions. Thus, our observations support 3 theoretical notions concerning the effects of alcoholism that have been reported in the literature: (1) White matter is damaged at the microstructural level in alcoholism (Pfefferbaum and Sullivan, 2005; Pfefferbaum et al., 2000); (2) the reward circuitry is damaged in the brains of alcoholics, especially in the dorsolateral prefrontal, orbitofrontal, and cingulate regions (Blum et al., 2000; Bowirrat and Oscar-Berman, 2005; Com-

ings and Blum, 2000); and (3) alcoholism selectively affects the integrity of the right hemisphere (Bowirrat and Oscar-Berman, 2005; Ellis and Oscar-Berman, 1989; Makris et al., 2008) and the frontal lobes (Makris et al., 2008; Moselhy et al., 2001; Oscar-Berman and Marinkovic, 2003).

### Reward Circuitry

Our results demonstrated alcoholism-related dysfunction in white matter tracts connecting frontal lobe and cingulate regions of the EROS network. Specifically, we found lower white matter coherence in right SLF II and III, OFCwm, and the cingulum bundle in the alcoholic subjects, suggesting that fronto-limbic connections are damaged. A key area that provides oversight to the reward circuitry, the dorsolateral prefrontal cortex, while not directly involved in the primary reward circuit, is a higher level probability-judgment and decision-making structure that mediates the subcortical and paralimbic regions involving responses to positive and negative reinforcement (Fuster, 2003; Petrides and Pandya, 2002). Dorsolateral prefrontal cortex has connections with many other cortical regions and subcortical structures (Schmahmann and Pandya, 2006). SLF II and III connect frontal cortex with parietal regions. Orbitofrontal cortex and the anterior cingulate gyrus, which are major contributors and highly integrated with the reward circuit (Goldstein and Volkow, 2002; Volkow et al., 2002), are important for coding of stimulus reward value (Bowirrat and Oscar-Berman, 2005; Elliott et al., 2003; O'Doherty, 2004). These prefrontal regions seem to be tied to most aspects of the addiction cycle, e.g., there is increased cerebral blood flow in prefrontal cortex during alcohol administration and during drug craving, and there is decreased cerebral blood flow in prefrontal and frontal cortices during drug and alcohol withdrawal (Goldstein and Volkow, 2002). Our data suggest that white matter interconnecting areas involved in the reward cascade is less intact in the brains of alcoholic individuals than in the brains of people who have not abused alcohol, thereby supporting the idea of a Reward Deficiency Syndrome in alcoholics (Blum et al., 2000; Bowirrat and Oscar-Berman, 2005).

White matter damage as indicated by decreased FA in frontal regions linked with the fronto-limbic EROS network may be related to observations of damage at the molecular level in areas of the reward circuit. For example, decreased levels of D<sub>2</sub> dopamine receptors in the ventral striatum have been correlated with alcohol craving and greater cue-induced functional MRI (fMRI) activation of orbitofrontal, medial prefrontal, and anterior cingulate cortices (Goldstein and Volkow, 2002; Heinz et al., 2004; Volkow et al., 2002). A recent neuroimaging positron emission tomography (PET) report identified increased levels of dopamine D<sub>2</sub> receptors in ventral striatum in nonalcoholic members of alcoholic families, suggesting that higher levels of dopamine in the reward system may have a protective effect (Volkow et al., 2006). Furthermore, these investigators reported that striatal D<sub>2</sub> receptor availability in nonalcoholic family members correlated with

positive emotionality, as well as with metabolism in orbitofrontal, anterior cingulate, and prefrontal cortex, demonstrating a connection between behavior, subcortical D<sub>2</sub> neuroreceptors, and cortical function in reward circuit regions. In addition, decreased D<sub>2</sub> receptor numbers in frontal, temporal, and anterior cingulate cortices have been reported in both late-onset (Type I) and violent (Type II) alcoholic groups (Tupala et al., 2004). Serotonin and benzodiazepine receptors, also thought to be involved in the reward circuitry, seem to be decreased in alcoholic subjects in prefrontal and anterior cingulate areas (Abi-Dargham et al., 1998; Mantere et al., 2002). Notably, in all of these studies, deficiencies in prefrontal/limbic systems and anterior cingulate seem to coexist.

Our finding of a decreased coherence in the anterior cingulum bundle in the alcoholic group also points to a dysfunctional fronto-limbic system, as the anterior cingulate cortex connects to the frontal lobes, albeit indirectly, as well as to the limbic system, in a circuit that is related to emotional processing and drug reward/craving (Grusser et al., 2004; Heimer and Van Hoesen, 2006; Myrick et al., 2004). The orbitofrontal cortex also has a role in the processing of affective stimuli, specifically emotion-related learning, and damage to this region or its associated white matter tracts may be responsible for the inability in alcoholics to alter associations between a reward (positive reinforcement such as alcohol) and an affective stimulus (Hornak et al., 1996). There is strong evidence of deficiency in emotional processing in alcoholism that implicates orbitofrontal cortex and/or anterior cingulate cortex (Davis et al., 2005; Kornreich et al., 2001; Uekermann et al., 2005; Volkow et al., 1997).

#### *Frontal Lobe Hypotheses*

Previous literature consistently reported damage to the frontal lobes of alcoholics, as assessed with various methodologies (Moselhy et al., 2001), including neuropsychological tests of frontal function, *postmortem* neuropathological measurements, structural MRI, PET, single photon emission computed tomography, pneumoencephalogram analysis, and computerized tomography (CT). In the present study, the alcoholic group had decreased FA in right OFCwm and in SLF II. In addition, SLF III, which connects the middle and inferior frontal gyrus (*pars opercularis*) with the supramarginal gyrus of the inferior parietal lobule, had decreased coherence on the right side in the alcoholic group compared with the nonalcoholic controls. One possible mechanism proposed for frontal lobe damage in alcoholism is based on the observation that there is down-regulation of mitochondria-encoding proteins in the frontal cortex of alcoholics, which may result in oxidative stress and ultimately cellular damage (Flatscher-Bader et al., 2005).

The alcoholic and control groups in the present study were equivalent on Working Memory scores, although the DT-MRI FA results suggest alcoholism-related damage in frontal lobe white matter tracts associated with short-term memory

functions. Interestingly, however, Working Memory scores correlated positively with right SLF III FA in the control group but negatively with right SLF III FA in the alcoholic group. While the reason behind this negative correlation in the alcoholic group was influenced by an outlier who had an IQ of 155, this discrepancy between groups persisted even after excluding that subject, suggesting an abnormal association between working memory and frontal lobe white matter integrity in alcoholism. Similarly, an fMRI study demonstrated reduced dorsolateral prefrontal activation in alcoholic subjects relative to controls during tasks that engage working memory, even though the 2 groups showed similar behavioral performance (Pfefferbaum et al., 2001a). The current study identified FA deficits in right SLF II and SLF III in alcoholic subjects and may demonstrate a neuroanatomical basis for these fMRI working memory deficits: White matter FA deficits observed in SLF II and III may adversely impact the functioning of the dorsolateral prefrontal cortex, which is involved in short-term memory (Petrides, 2005). Together, these findings are supportive of prior evidence from neuropsychological studies showing alcoholism-related impairments in memory and visuospatial functions (Oscar-Berman and Markinkovic, 2003, 2007), and suggest that deficits in frontal white matter coherence has a detrimental impact on cognitive functions in alcoholism.

#### *Right Hemisphere Hypotheses*

Findings from the present study also support the Right Hemisphere Hypothesis, i.e., the idea that functions controlled primarily by the right side of the brain are more vulnerable to the effects of long-term alcoholism than are left-hemisphere functions (Demaree et al., 2005; Ellis and Oscar-Berman, 1989). The Right Hemisphere Hypothesis was first proposed to explain the visuospatial deficits commonly reported in alcoholics (Ellis and Oscar-Berman, 1989); it was later applied to account for emotional processing deficits (Hutner and Oscar-Berman, 1996; Oscar-Berman and Schendan, 2000), particularly as emotional processing is believed to involve right frontal and limbic regions of the brain (Morgane et al., 2005). In the present study, all of the major frontal/reward regional FA differences (OFCwm, cingulum bundle, SLF II, and SLF III) were in the right hemisphere, in white matter tracts with connectivity to cortical regions involved in the fronto-limbic system (dorsolateral prefrontal cortex, orbitofrontal cortex, and anterior cingulate cortex). Of interest, a recent DT-MRI study found more low FA values in the right versus left hemisphere in alcoholic, compared with nonalcoholic men, although this difference was not statistically significant (Pfefferbaum et al., 2006).

#### *Exploratory Regional Analyses*

In addition to the hypothesized regional FA differences in tracts connecting parts of EROS, several additional regional group FA differences were observed in our exploratory

analyses. Alcoholic subjects displayed FA decreases in right SLF I, which may denote connectional abnormalities between frontal areas (e.g., the supplementary motor area and the superior frontal gyrus) with parietal areas (e.g., the superior parietal lobule and precuneus areas). These cortical regions are known to be involved in the regulation of higher motor behaviors (Makris et al., 2005).

There were several regions where the alcoholic subjects had higher FA values than the control group. The observation of FA increases in alcoholic subjects supports the hypothesis that there is compensatory activity in brain regions relatively spared by alcoholism (Desmond et al., 2003). That is, while fMRI and neurobehavioral evidence in the literature supports the idea of frontal brain dysfunction in alcoholism (Oscar-Berman and Marinkovic, 2003), one group found that during a verbal working memory task, alcoholic subjects had increased fMRI activation in left frontal cortex and right superior cerebellum (Desmond et al., 2003). These 2 distant brain regions are neuroanatomically interconnected (Schmahmann and Pandya, 2006), and the findings by Desmond et al. suggest that in alcoholics, far-reaching regions within the fronto-cerebellar system are recruited in addition to those normally used. In other words, the *increased* activity in a fronto-cerebellar network suggests that this system is engaged in order to counteract deficient dorsolateral prefrontal input and maintain accuracy of behavioral performance (Oscar-Berman and Marinkovic, 2007). Other fMRI results have suggested subtle neuronal reorganization in alcoholics (Pfefferbaum et al., 2001a; Tapert et al., 2001, 2004). Thus, although chronic heavy drinking is associated with interference within neural systems typically used for certain tasks, neural compensation can produce intact performance levels by way of alternative, albeit potentially less suitable, systems (Oscar-Berman and Marinkovic, 2007). However, with increased task difficulty or brain compromise, performance problems become more severe (Ham and Parsons, 1997; Tapert et al., 2001, 2004).

## LIMITATIONS

Our use of DT-MRI allowed us to observe microstructural white matter damage in abstinent alcoholic individuals, specifically in those tracts that are involved in the reward circuitry. Interestingly, our study did not find significant corpus callosum or centrum semiovale damage in alcoholics as was reported in previous DT-MRI studies (Pfefferbaum and Sullivan, 2005; Pfefferbaum et al., 2000). This may be due to differences in methods employed in the various studies, including differences in ROI definition, as well as different subject populations or selection criteria. For example, the regions described by Pfefferbaum and Sullivan (2005) as corpus callosum and centrum semiovale were defined using relatively large, a priori defined ROIs, and there may be overlap between our tract-specific ROIs and these regions. Our cingulum bundle ROI may have been included within the broader region defining the corpus callosum, as the cingulum bundle

lies adjacent to this region. The broadly defined centrum semiovale region in the prior studies includes the SLF II as defined in our study, as well as other white matter tracts. Therefore, it may be that our tract-specific ROIs represent a subset of these broader a priori regions. Furthermore, subject population differences such as drinking history (e.g., duration of abstinence and QFI) may influence discrepancies between studies. For example, there is evidence of white matter regeneration with continued abstinence from alcohol (Crews et al., 2005; O'Neill et al., 2001; Pfefferbaum et al., 1995, 2001b). In the present study, the distribution of duration of abstinence in our alcoholic subjects was highly skewed, so we could not reliably assess the impact of duration of abstinence on outcome variables. Duration of abstinence also was correlated with age, and so these effects may work at odds: Whereas aging may produce a decline in FA, in contrast, abstinence may lead to improvement in white matter quality. In that case, the 2 effects may cancel each other so that neither age nor abstinence shows a correlation with FA variables. In sum, the broad variance and skewed distribution in duration of abstinence and QFI may have limited our ability to detect further associations between regional FA values and neurocognitive test performance. Furthermore, the variance and length of abstinence makes it uncertain whether the observed results reflect the effects of alcoholism per se, or rather the effects of long-term abstinence. For example, the finding of prominent FA deficits in a few white matter tracts of the right but not left hemisphere could potentially be a consequence of faster recovery of deficits on the left side rather than a reflection of right-sided deficits in alcoholism. Thus, we cannot be certain whether the results of the current study are direct effects of alcoholism, abstinence, or an interaction between the 2. Additional studies are required to determine whether these findings would be replicated in a sample of alcoholics with short-term abstinence. Additionally, a methodological limitation is that we cannot identify whether the reduced FA in alcoholism is due to decreased or damaged myelin, diminished axonal connections, increased fluid either intracellularly or extracellularly, or due to a disorganized white matter fiber structure (Pfefferbaum and Sullivan, 2005).

Some regions that were composed of predominantly gray matter depicted group differences in FA values: Right supra-marginal gyrus and right caudate showed FA increases in alcoholic subjects, while right cuneal cortex in the occipital lobe and left inferior insula had FA decreases in alcoholic subjects. This may indicate differences in fiber orientation in these cortical regions between groups. However, since this study was specifically focused on white matter tracts and related hypotheses, we noted these differences, but are also aware that such FA differences in gray matter regions are difficult to interpret.

Another limitation of our study is that our sample consisted of only male subjects. There are cerebral differences between male and female alcoholics, which have been reported in DT-MRI studies (Pfefferbaum and Sullivan, 2002) and also in a CT study (Uekermann et al., 2005).

Females are also reported to be more vulnerable to the effects of alcohol, but the evidence is inconclusive (Hommer, 2003; Prendergast, 2004). Therefore, additional alcoholism studies are needed with gender-specific controls. Another limitation of our study is the small sample size of 15 individuals in each group.

It may seem to be another limitation that our control group was somewhat older than the alcoholic group (see Table 1). However, prior DT-MRI studies have shown white matter tract degeneration with normal aging (Madden et al., 2004; Pfefferbaum and Sullivan, 2003; Pfefferbaum et al., 2005), and so we may have even underestimated the extent of FA deficits in the alcoholic group. In other words, if Age effects predominate over Group effects, the trend toward older control subjects would be expected to generate decreased FA in the control group compared with the alcoholic group in our study. However, despite the control group being slightly older than the alcoholic group, the alcoholic group displayed decreased FA in right frontal lobe white matter tracts, and these differences remained highly significant after covarying for age. It is possible, however, that the trend toward older control subjects may have contributed to the higher FA in alcoholics observed in several regions.

Finally, our ROI analyses may have bias due to the fact that we selected ROIs as the regions defined by significant FA clusters, and not as cytoarchitectonic or functional brain regions. Nevertheless, our ROIs seem to have high predictive value of whether an individual subject is classified as an alcoholic or a nonalcoholic control. A DFA was run to determine how well the right frontal FA ROIs classified group membership (i.e., alcoholic or control), and we noted 97% correct group classification (93% covarying for age). Thus, it is highly unlikely that artifacts or bias in methods could explain such a dramatic group discrimination effect. Another potential source of region bias was that we created the left hemisphere ROIs as mirrored regions from the right hemisphere regions, to estimate the location of the corresponding contralateral tracts. Because mirrored regions may not exactly match the location of the opposite hemisphere's tracts, the left hemisphere ROIs may be less accurate measures of the tract ROIs. However, the exploratory analyses reported all significant group difference clusters, and even after examining smaller cluster size thresholds and non-thresholded group difference maps to look for possible left-sided effects that may have been overlooked, we did not observe left hemisphere regional differences proximal to the index ROIs to suggest regional findings were simply missed by the ROI placement or thresholds, or resulted from methodological artifacts.

## CONCLUSIONS

This DT-MRI study is the first to report damage in right fronto-limbic and cortico-cortical white matter connectivity in alcoholism, evidenced by lower FA values in right SLF II, SLF III, OFCwm, and cingulum bundle in the alcoholic

group. The white matter abnormalities observed in our study support previous literature on alcoholism, specifically those studies showing damage to brain regions that comprise a system that is essential for normal emotional functioning and for modulating the effectiveness of positive and negative reinforcement in human behavior: the EROS network. The white matter abnormalities in reward-related white matter tracts that we observed were localized to the right hemisphere, a finding that is consistent with observations of visuospatial and emotional abnormalities in alcoholism. Lastly, our results also support previous studies that reported alcoholism-related deficits in working memory.

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## SUPPLEMENTARY MATERIAL

The following supplementary material is available for this article:

**Fig. S1.** Nonthresholded voxel-based analysis maps of FA differences between groups at levels of the four principal index regions (noted by white arrows): superior longitudinal fascicle (SLF) II (top row), SLF III (second row), orbitofrontal cortex white matter (OFCwm, third row), and cingulum bundle (CB, bottom row). Left column shows coronal views, middle column displays sagittal views through these right hemisphere index regions, and right column depicts sagittal views through the corresponding left hemisphere plane. Red indicates control group FA is greater than that of alcoholic group, while blue regions have greater FA in the alcoholic group. Nonthresholded maps do not demonstrate evidence of left frontal DT-MRI deficits comparable to the right-sided differences.

This material is available as part of the online article from: <http://www.blackwell-synergy.com/doi/abs/10.1111/j.1530-0277.2008.00661.x> (This link will take you to the article abstract).

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