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Transcallosal White Matter Degradation Detected With Quantitative Fiber Tracking in Alcoholic Men and Women: Selective Relations to Dissociable Functions

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Abstract

Introduction—Excessive alcohol consumption can adversely affect white matter fibers and disrupt transmission of neuronal signals. Here, we examined six anatomically defined transcallosal white matter fiber bundles and asked whether any bundle was specifically vulnerable to alcohol, what aspect of white matter integrity was most affected, whether women were more vulnerable than men, and whether evidence of compromise in specific bundles was associated with deficits in balance, sustained attention, associative learning, and psychomotor function, commonly affected in alcoholics.

Methods—Diffusion tensor imaging quantitative fiber tracking assessed integrity of six transcallosal white matter bundles in 87 alcoholics (59 men, 28 women) and 88 healthy controls (42 men, 46 women). Measures included orientational diffusion coherence (fractional anisotropy, FA) and magnitude of diffusion, quantified separately for axial (longitudinal; λ_L) and radial (transverse; λ_T) diffusivity. The Digit Symbol Test and a test of ataxia were also administered.

Results—Alcoholism negatively affected callosal FA and λ_T of all but the sensory-motor bundle. Women showed no evidence for greater vulnerability to alcohol than men. Multiple regression analyses confirmed a double dissociation: higher diffusivity in sensory-motor and parietal bundles was associated with poorer balance but not psychomotor speed, whereas higher diffusivity in prefrontal and temporal bundles was associated with slower psychomotor speed but not balance.

Conclusions—This study revealed stronger alcohol effects for FA and radial diffusivity than axial diffusivity, suggesting myelin degradation, but no evidence for greater vulnerability to alcohol in women than men. The presence of brain-behavior relationships provides support for the role of alcoholism-related commissural white matter degradation as a substrate of cognitive and motor impairment. Identification of a double dissociation provides further support for the role of selective white matter integrity in specific domains of performance.

Keywords

Alcoholism; Corpus Callosum; Fiber Tracking; Sex; Ataxia; Digit Symbol Test

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In vivo structural magnetic resonance imaging (MRI) studies of chronic alcoholism commonly report smaller volumes of brain gray matter (Cardenas et al., 2005; Chanraud et al., 2007; Fein et al., 2002; Gazdzinski et al., 2005; Jernigan et al., 1991; Pfefferbaum et al., 1992) and white matter (Chanraud et al., 2007; Gazdzinski et al., 2005; Pfefferbaum et al., 1992) than normally expected for any given adult age. Also affected is the corpus callosum, the largest commissural fiber system in the brain and the major avenue for interhemispheric transfer of information, linking homologous cortical regions in left and right brain hemispheres. Structural MRI studies that examined the corpus callosum in a midsagittal view have shown that alcoholics typically have smaller corpora callosa than controls (Estruch et al., 1997; Hommer et al., 1996; Pfefferbaum et al., 1996, 2006a).

Magnetic resonance (MR) diffusion tensor imaging (DTI) has extended structural MRI by measuring the orientational displacement and distribution of water molecules (Basser and Pierpaoli, 1996), thereby enabling examination of the integrity of the microstructure of cerebral white matter. Fiber integrity is measured in terms of fractional anisotropy (FA), typically higher in fibers with a homogeneous or linear structure such as healthy white matter, and bulk mean diffusivity (MD) for which higher values, commonly due to larger presence of mobile fluid in a tissue sample (Pfefferbaum and Sullivan, 2003; Pfefferbaum et al., 2003; Pierpaoli et al., 2001), reflect diminished integrity. MD can be decomposed into two components: axial (longitudinal) diffusivity (λ_L), which can be altered with disruption of axonal integrity and axonal deletion; and radial (transverse) diffusivity (λ_T), which increases selectively with decline in myelin integrity (Song et al., 2002, 2005; Sun et al., 2006a,b). DTI has extended structural MR by revealing evidence for microstructural disruption of anterior and posterior regions of the corpus callosum in alcoholic men and women (Pfefferbaum et al., 2000, 2006a,b), even when no structural abnormalities were apparent (Pfefferbaum and Sullivan, 2002). DTI has been extended to provide visual depictions of white matter fiber systems (Lehericy et al., 2004; Stieltjes et al., 2001; Xu et al., 2002) and quantification of the integrity of specific fiber tracks (Gerig et al., 2005; Sullivan et al., 2006). These capacities enable assessment of interhemispheric white matter fiber tracks as they extend beyond the midsagittal band of the corpus callosum to link homologous regions of the left and right cortices.

Postmortem studies of patients with chronic alcoholism and animal studies have shown that callosal, supratentorial, and infratentorial white matter fibers sustain demyelination (Lewohl et al., 2000; Tarnowska-Dziduszko et al., 1995), microtubule disruption (De la Monte, 1988; Mayfield et al., 2002; Paula-Barbosa and Tavares, 1985; Putzke et al., 1998; Wiggins et al., 1988), and axonal deletion, possibly arising from regional neuronal loss (Alling and Bostrom, 1980; Badsberg-Jensen and Pakkenberg, 1993; Courville, 1955; De la Monte, 1988; Harper and Kril, 1991, 1993; Kril et al., 1997; Lancaster, 1993). Although in vivo DTI studies have revealed microstructural disruption in white matter regions, knowledge about the nature of this degradation would be enhanced by examination of the relative contribution of demyelination and axonal deletion, such as would be suggested by increases in either radial (λ_T) or axial (λ_L) diffusivity.

Whether women are more vulnerable to the deleterious effects of chronic heavy alcohol use than men is controversial (Mann et al., 2005). Several studies have reported comparable deficits, relative to same-sex controls, in alcoholic men and women despite lower alcohol consumption in the women. Such evidence derives from MRI volumetric studies of cerebral white and gray matter and cerebrospinal fluid (Hommer et al., 2001), the corpus callosum (Hommer et al., 1996), and hippocampal volumes (Agartz et al., 1999). Other studies found that men had greater abnormalities than women in size of the lateral ventricles, cortical gray matter (Pfefferbaum et al., 2001) and white matter, corpus callosum, and pons (Pfefferbaum

et al., 2002), once differences in intracranial volume, age, and lifetime alcohol consumption were taken into account.

Chronic excessive alcohol use is also associated with a number of behavioral deficits including poorer performance on tests involving visuospatial and psychomotor skills (Fein et al., 2006; Nixon et al., 2002; Oscar-Berman and Marinkovic, 2007; Sullivan et al., 2000b, 2002) and impairments in balance and gait. Performance of the Digit Symbol Test involves multiple sensory, motor, and cognitive processes, requiring integration across neural sites and functions. Processes include visual scanning, psychomotor speed, cognitive processing speed, sustained attention, associative learning, and sequencing (Sassoon et al., 2007). These processes are likely to require interhemispheric coordination of multiple cortical regions, including frontal (for the executive components of the task) and temporal (for the associative learning component of the task). The systems involved in maintaining balance, particularly with eyes closed, are largely different from those involved in the Digit Symbol Test and require integration of sensory-motor and parietal systems for motor control and updating body location as one sways while maintaining balance.

In this study, we used quantitative fiber tracking to examine the effect of alcoholism on three metrics of fiber quality of the corpus callosum divided into six transcallosal bundles based on the anatomy of their cortical destinations (Pandya and Seltzer, 1986). Potential sex differences in vulnerability to the effects of chronic heavy alcohol use and whether deficits in specific bundles were related to performance on tasks requiring adequate functioning of frontal, sensory-motor, parietal, or temporal cortical structures were also investigated.

Methods

Participants

Alcoholic participants in this study were drawn from two studies, for which extensive clinical and demographic descriptions of participants are available elsewhere (Rosenbloom et al., 2005, 2007). Prior reports of effects of alcohol on brain structure and/or white matter integrity are available for each study separately (Pfefferbaum et al., 2006a,b,c, 2007; Schulte et al., 2005b, 2008) or combined across both studies, as in the current report (Pfefferbaum et al., 2009). Reports of performance on psychomotor sustained attention (Rosenbloom et al., 2009; Sassoon et al., 2007), visuospatial construction (Rosenbloom et al., 2009), conflict processing (Schulte et al., 2005a), interhemispheric processing (Schulte et al., 2005b), working memory (Fama et al., 2009), and upper and lower motor function (Fama et al., 2007; Sullivan et al., 2010b) are available for one or other of these samples. Only the tests of ataxia and psychomotor sustained attention reported herein were obtained across both studies and are available for the combined sample reported. Control data were from men and women who matched the alcoholic groups in age range (Sullivan et al., 2010c).

Demographic data of the 175 men and women in the current analysis appear in Table 1. The fiber tracking analysis of the corpus callosum in the alcoholic men and women and the brain DTI-neuropsychological test correlations are novel and have not been published previously. Participants with alcoholism were recruited by referral from outpatient substance abuse treatment centers. Informed consent followed procedures approved by the Institutional Review Boards of SRI International and Stanford University.

Clinical Evaluation

Study criteria were based on the Structured Clinical Interview for DSM-IV (SCID) (First et al., 1998), administered to all subjects by clinicians. Prospective subjects meeting lifetime criteria for schizophrenia or bipolar disorder or for nonalcohol substance dependence or abuse within the prior 3 months were excluded, as were prospective controls meeting DSM-

IV criteria for any Axis I disorder. All alcoholics met DSM-IV criteria for alcohol dependence. Global Assessment of Functioning (GAF) was derived from the SCID (Endicott et al., 1976). All subjects were HIV-negative either by self-reported medical history or blood test. Autobiographical history of alcohol consumption (Pfefferbaum et al., 1992; Skinner, 1982; Skinner and Sheu, 1982) yielded quantitative lifetime consumption of alcohol and time since last drink. Interviews and questionnaires assessed current depression symptoms using the Beck Depression Inventory (BDI)–II (Beck et al., 1996); socioeconomic status (SES) using a two-factor scale based on education and occupation (Hollingshead and Redlich, 1958); handedness (Crovitz and Zener, 1962); history of smoking (current, past, or never); and body mass index (BMI) (height cm/weight kg²).

Groups differed in education, Global Assessment of Function rating, lifetime alcohol consumption, BDI score, SES, and smoking history (see Table 1 for descriptive and group statistics and comparisons). Only the alcohol consumption variable showed a group-by-sex interaction: alcoholics drank more than controls, and alcoholic men had drunk almost twice as much as the alcoholic women over their lifetime. Men were over-represented in the alcoholic group, but alcoholic men and women were not significantly different from each other in age, education, handedness, SES, age of onset of alcoholism, length of illness, current depressive symptoms, or prior history of nonalcohol substance abuse. However, alcoholic women were of lower body mass than alcoholic men, more likely to be smokers, and had been sober for a longer time before examination (average 6 months) than men, (average 3 months).

Image Acquisition Protocol

Imaging was performed on a 1.5-Tesla GE clinical whole body system. A dual-echo fast spin-echo (FSE) coronal structural sequence was acquired (47 contiguous, 4-mm-thick slices; TR/TE1/TE2 = 7500/14/98 ms; matrix = 256 × 192). DTI was performed with the same slice location parameters as the dual-echo FSE, using a single shot spin-echo echo-planar imaging technique (47 contiguous, 4-mm-thick slices, TR/TE = 10,000/103 ms, matrix = 128 × 128, in-plane resolution = 1.875 mm², b-value = 860 s/mm²). Diffusion was measured along six noncollinear directions (6 NEX) with alternating signs to minimize the need to account for cross-terms between imaging and diffusion gradients (Neeman et al., 1991). For each slice, six images with no diffusion weighting (b = 0 s/mm²) were also acquired.

Image Processing

The structural data were passed through the FSL Brain Extraction Tool (Smith, 2002) to extract the brain. Eddy current-induced image distortions in the diffusion-weighted images for each direction were minimized by alignment with an average made of all 12 diffusion-weighted images using a 2-D 6-parameter affine correction on a slice-by-slice basis (Woods et al., 1998). The DTI data were then aligned using the FSE data by a nonlinear 3D warp (3rd-order polynomial), which provided in-plane and through-plane alignment. On a voxel-by-voxel basis, FA and MD, the latter decomposed into its longitudinal ($\lambda_L = \lambda_1$) and transverse ($\lambda_T = [\lambda_2 + \lambda_3]/2$) components, were computed. FA ranged from 0 to 1, and diffusivity was expressed in units of 10⁻⁶ mm²/s.

Warping to Common Coordinates

To achieve common anatomical coordinates across subjects, a population-average FA template (Sullivan et al., 2010c) was constructed from the FA data of 120 control subjects (20–81 years old) with group-wise affine registration (Learned-Miller, 2006) followed by iterative nonrigid averaging (Rohlfing and Maurer, 2003; Rohlfing et al., 2001). Each subject's FA data set was registered to the population FA template with a 9-parameter affine

transformation followed by nonrigid alignment using a multi-level, 3rd-order B-spline, with 5-mm final control point spacing (Rohlfing and Maurer, 2003; Rueckert et al., 1999).

Fiber Tracking

A more detailed description of fiber tracking procedures can be found in an earlier report (Sullivan et al., 2010c). The fiber tracking procedure (Mori et al., 1999; Xu et al., 2002), distributed by Gerig and colleagues (2005) applies a target-source convention that restricts the fibers to ones originating in source voxels and passing through target voxels (Sullivan et al., 2010c). For the corpus callosum, six midsagittal 5.625-mm thick, geometrically defined targets (Sullivan et al., 2006), modified to reflect colossal anatomical projections (Pandya and Seltzer, 1986), were identified on the population FA template. Sources were defined as 5.625-mm-thick planes spaced 9.375 mm bilaterally from the targets subtending the entire anterior-posterior extent of the brain. For each subject, the targets and sources were mapped from the population FA template to that subject's native image space and passed to the fiber tracking routine. Tracking parameters specified minimum FA (0.17) and threshold (0.125), maximum voxel-to-voxel coherence, and minimum (11.25 mm) and maximum (45 mm) fiber length, with essentially no limit on the number of fibers (other than the number of source pixels). For quantification, fiber length was limited to the width of the corpus callosum defined by the extent of the sources with the requirement that they pass through both sources to ensure identification of callosal fibers that extended to both hemispheres. We refer hereafter to the group of fibers coursing through each target region as "fiber bundles." For each fiber bundle, the mean FA, λ_L , and λ_T were the units of analysis. After fiber detection, the fiber locations were transformed back to common co-ordinates (i.e., population FA template space) for display (see Fig. 1).

Neuropsychological Tests

Using the Digit Symbol Subtest of the Wechsler Adult Intelligence Scale – Revised (WAIS-R) (Wechsler, 1981), participants were presented with 93 randomly assigned digits from 1 to 9, each in a box with a blank box below and were required to fill in the blank box by pairing each digit with a symbol from a key displayed above the grid. The scores were the number of boxes correctly completed in 90 seconds (standard score), time to complete the entire grid (Sassoon et al., 2007), and an incidental recall test of the symbols. *Ataxia* was assessed by the stand-on-one-foot balance test from the Fregly Graybiel ataxia battery (Fregly et al., 1972), performed with eyes closed (Sullivan et al., 2010b). Testing was terminated after 2 minutes, and the score was the mean of two trials.

Statistical Analysis

To control for the normal effects of age on white matter fiber integrity (Sullivan et al., 2006, 2010c), all DTI measures were converted to age-corrected Z-scores, using age effects detected in the grand laboratory control sample of 120 subjects. Significant systematic sex differences in DTI metrics in the control sample were not found; thus, control men and women were combined for age modeling (Sullivan et al., 2010c). Each individual's Z-score indicates the extent to which they deviate from norms for their age, and the group mean Z-scores provides a measure of effect size. Behavioral scores were converted to age- and education-corrected Z-scores based on the performance of the normal control sample. We used Z-scores for all statistical analyses, but present raw scores for all fiber bundles studied in Table 2 to enable comparison with other reports. For analysis of group differences, we used the subset of control subjects who spanned the age range of the alcoholic men and women; of the full sample of 120 controls, 42 men and 46 women fell within the 20–60 year target age range.

Group (alcoholic and control) differences were assessed with repeated-measures ANOVA for the six corpus callosal bundles for each DTI metric, followed by *t*-tests. We predicted that the alcohol group would have lower FA and higher diffusivity values than normal controls. A series of six (one for each callosal sector) group-by-metric (FA, λL , and λT) repeated-measures ANOVAs sought interactions, which would indicate greater alcohol-related vulnerability of one metric over the others. Significant interactions were followed up by *t*-tests. For this analysis, FA values were inverted so that abnormal values would be in the same direction as λL and λT values. We also assessed sex differences with group (alcohol, control) by sex (male, female) ANOVAs for each bundle and DTI metric (FA, λL , and λT).

Associations between fiber tract metrics and demographic, alcohol use, and behavioral test performance within the combined group of alcoholic men and women and for each sex separately were tested with Pearson product-moment correlations (*r*). We predicted that lower FA and higher diffusivity would be associated with poorer test performance. For all tests, we applied family-wise Bonferroni correction for six interhemispheric corpus callosal fiber bundles (*p*-values ≤ 0.02 were considered significant).

Results

Effects of Chronic Alcoholism on Six Transcallosal Fiber Bundles

The six-bundle repeated measures ANOVA for FA revealed lower values across all fiber bundles in alcoholics than controls: group effect [$F(1,173) = 20.917, p < 0.0001$] but no bundle effect or group-by-bundle interaction. The repeated measures ANOVA for λL revealed higher values in alcoholics than controls [$F(1,173) = 11.51, p = 0.0009$] but no bundle effect or group-by-bundle interaction. The repeated measures ANOVA for λT revealed higher values in alcoholics than controls [$F(1,173) = 26.642, p < 0.0001$] and a trend toward a bundle-by-group interaction [$F(5,865) = 2.55, p = 0.027$]. Follow-up *t*-tests revealed significant group differences at the $p < 0.0001$ level for five bundles and a trend for the sensory-motor bundle [$t(193) = 2.39, p = 0.018$].

The group-by-three-DTI metric (FA, λL , and λT) repeated measures ANOVA revealed significant group effects at the $p = 0.0001$ level for five callosal bundles and a trend for the sensory-motor bundle [$F(1,173) = 4.8, p = 0.03$]. Metric [$F(2,346) = 7.67, p = 0.0006$] effect and metric-by-group interaction [$F(2,346) = 6.04, p = 0.0026$] were significant only for the frontal bundle, where FA [$t(173) = 4.8, p < 0.0001$] was lower and λT [$t(173) = 5.19, p < 0.0001$] was higher in alcoholics than controls, but λL only showed a trend in this direction [$t(173) = 2.03, p = 0.044$]. A similar but weaker pattern of results was seen for the occipital bundle: metric main effect [$F(2,346) = 4.675, p = 0.0099$]; group by metric interaction [$F(2,346) = 3.78, p = 0.024$].

Table 2 lists raw values for each metric and fiber bundle. Table 3 lists *t*-test comparisons between alcoholics and controls for each metric and fiber bundle.

Sex Differences in Regional FA and Diffusivity of Transcallosal Fibers

Figure 1 plots means and standard errors for each DTI metric at each corpus callosum bundle separately for men and women in each diagnostic group. Two-factor (group and sex) ANOVAs were performed to test for interactions that would support the putative greater vulnerability of women than men to the deleterious effects of alcoholism. Regardless of diagnosis, men had lower FA [$F(1,171) = 7.77, p = 0.006$] and higher λT [$F(1,171) = 7.37, p = 0.0073$] than women in the parietal bundle and higher λL in the sensory-motor bundle [$F(1,171) = 9.85, p = 0.002$]. However, there was no significant group-by-sex interaction for any bundle or metric.

The alcoholic women had been sober for about twice as long as the alcoholic men, and some men had drunk considerably more than any woman; both conditions may have mitigated observing greater vulnerability to alcohol in the women. Therefore, we derived a subgroup of 40 men and 25 women who were matched in length of sobriety (91 days for the men and 103 days for the women), age (45 years for men, 45.7 years for women), and lifetime consumption of alcohol (557 kg for men, 517 kg for women) and tested for sex differences in FA, λT , and λL in each callosal bundle. This analysis also found no evidence for differences between alcoholic men and women.

Other Contributors to Transcallosal Fiber Degradation

Regression analyses tested the hypotheses that among the combined group of alcoholic men and women, older age, higher current depressive symptom scores, greater lifetime alcohol consumption, a shorter period of sobriety, lower than normal body mass indicative of poor nutrition would contribute to greater deviations from age norms for each fiber bundle and DTI metric. Older age, greater lifetime alcohol consumption, or shorter sobriety were not associated with greater deficits in any of the age-normalized fiber bundle metrics. BMI, which was lower in alcoholic women than alcoholic men (Table 1), was negatively associated with λL ($r = -0.28$, $p = 0.0085$) of the premotor bundle.

BDI scores, available only on a subgroup of participants, were not associated with any DTI metrics in alcoholic or control groups examined separately. However, across a combined sample of 103 alcoholics and controls, higher BDI scores were associated with higher λL at prefrontal ($r = 0.255$, $p = 0.0092$) and parietal ($r = 0.295$, $p = 0.0025$) bundles. A follow-up ANCOVA, with BDI scores as covariate, was performed for λL at parietal bundle, where group differences met Bonferroni significance criteria (see Table 3). The alcohol group effect persisted [$F(1,100) = 4.09$, $p = 0.05$] after accounting for the BDI score.

Contributions from prior substance abuse and current/past cigarette smoking were assessed with separate ANOVAs (substance abuser vs. nonsubstance abuser; smoker vs. nonsmoker) each with an additional factor for sex. There were no main effects for either substance abuse or cigarette smoking and no interactions between either factor and sex. These negative results were also obtained when applied to the restricted sample of alcoholic men and women, matched on length of sobriety and lifetime alcohol consumption.

Performance Associations With DTI Metrics

Alcoholics showed marked deficits on the measure of balance [$t(161) = 7.183$, $p = 0.0001$], time to complete the Digit Symbol grid [$t(165) = 2.943$, $p = 0.0037$], and the traditional Digit Symbol score [$t(165) = 3.894$, $p = 0.0001$], but not on the unannounced recall test of the symbols [$t(162) = 1.123$, $p = 0.2633$]. See Table 4 for raw and Z-score means and standard deviations and comparisons. Two-factor ANOVAs with group and sex found that men took longer than women to complete the Digit Symbol grid [$F(1,163) = 16.24$, $p \leq 0.0001$] and completed fewer items within 90 seconds [$F(1,163) = 24.39$, $p \leq 0.0001$]. However, there were no sex differences in balance or Digit Symbol recall and no group-by-sex interactions for any test. Among all alcoholics, men performed worse than the women on the traditional Digit Symbol score [$t(81) = 3.3$, $p = 0.0014$] and time to complete the Digit Symbol grid [$t(81) = 2.29$, $p = 0.025$] but not on recall or balance. These sex differences persisted only for the Digit Symbol score [$t(61) = 2.2$, $p = 0.03$] in the restricted sample of alcoholic men and women, matched for lifetime alcohol consumption and length of sobriety. Among alcoholics, irrespective of sex, greater lifetime alcohol consumption correlated with poorer balance scores ($r = -0.334$, $p = 0.0019$) and lower scores on the Digit Symbol Test ($r = -0.30$, $p = 0.0057$); the parametric test results were confirmed with a nonparametric test (balance: $\rho = -0.328$, $p = 0.0026$; Digit Symbol: $\rho = -0.328$, $p = 0.0026$). Both of these

alcohol consumption performance associations were observed only in the men (balance: $r = -0.367$, $p = 0.005$; Digit Symbol Test: $r = 0.29$, $p = 0.027$) and not in the women (balance: $r = -0.165$, $p = 0.41$; Digit Symbol Test: $r = 0.055$, $p = 0.78$).

Two alcoholic men were excluded from correlational analyses involving the ataxia test and time to complete the Digit Symbol grid because they were statistical outliers. Pearson correlations between behavioral tests and each fiber bundle across the alcoholics are summarized in Table 5. In the combined group of alcoholic men and women, longer time to complete the Digit Symbol grid was associated with higher radial diffusivity (λT) measures in prefrontal ($r = 0.260$, $p = 0.017$) and higher axial (λL) diffusivity measures in temporal ($r = 0.302$, $p = 0.005$) fiber bundles. Shorter time maintaining balance was associated with greater axial diffusivity (λL) in both sensory-motor ($r = -0.364$, $p = 0.0007$) and parietal ($r = -0.321$, $p = 0.003$) bundles. No associations were found between DTI metrics and the Digit Symbol recall test.

To determine whether there was a double dissociation between the contribution of prefrontal and temporal bundles to Digit Symbol grid completion time and the contribution of sensory-motor and parietal bundles to balance, both Digit Symbol grid completion time and balance scores were entered as independent associates in multiple regression analyses for prefrontal λT , sensory-motor, parietal λL , and temporal λL . These associations are plotted in Fig. 2. For prefrontal λT , Digit Symbol grid completion time remained an independent associate (β coeff = 0.281, $p = 0.01$) after accounting for the association with balance (β coeff = -0.175 , $p = 0.105$). For sensory-motor λL , both Digit Symbol grid completion time (β coeff = 0.271, $p = 0.008$) and balance (β coeff = -0.404 , $p = 0.0001$) remained independent associates, together accounting for 22% of the variance. For parietal λL , balance remained an independent associate (β coeff = -0.349 , $p = 0.0013$) after accounting for the association with Digit Symbol grid completion time (β coeff = 0.163, $p = 0.122$). Finally, for temporal λL , Digit Symbol grid completion time remained an independent associate (β coeff = 0.309, $p = 0.005$) after accounting for the association with balance (β coeff = -0.018 , $p = 0.866$).

Discussion

We applied DTI anisotropy and diffusivity measures derived from quantitative fiber tracking to examine, in vivo, the effect of chronic excessive alcohol consumption on the microstructural integrity of six neuroanatomically defined transcallosal white matter bundles, using an extended sample combining participants from two earlier studies. This study extends our earlier reports of the macrostructural (Pfefferbaum et al., 1996, 2002) and microstructural (Pfefferbaum and Sullivan, 2002, 2005; Pfefferbaum et al., 2000) vulnerability of the corpus callosum to alcohol by examining more dimensions of white matter integrity and providing greater neuroanatomic specificity for the great mass of white matter fibers passing through the corpus callosum. FA and radial diffusivity were more affected than axial diffusivity, suggesting a greater role for demyelination (Lewohl et al., 2000; Tarnowska-Dzidusko et al., 1995) than axonal degeneration in the compromise of white matter integrity. This distinction provides convergent validity with postmortem findings for the DTI metrics as in vivo markers of white matter neuropathology. Additionally, anterior (prefrontal, premotor) and posterior (parietal, temporal, and occipital) bundles were all significantly affected, with smaller effects in sensory-motor bundle, a pattern consistent with relative preservation of motor cortex in a postmortem study of alcoholic cases (Harper et al., 2003). Although half of the alcohol sample had remote histories of prior substance abuse, this factor did not contribute to the effects observed.

We examined cigarette smoking (cf. Durazzo et al., 2007; Wang et al., 2009) and depressive symptoms (cf. Ma et al., 2007; Zanetti et al., 2009) as potential confounds to group

differences in white matter integrity. We found no evidence for a contribution from smoking but did detect associations in the total group of alcoholics and controls between depressive symptoms and axial diffusivity at prefrontal and parietal bundles. These findings are consistent with growing evidence for an association between depression and compromised white matter integrity, especially in prefrontal regions. Adding depression symptom scores as a covariate reduced but did not eliminate group differences at the parietal bundle.

Analysis of sex differences found that this sample of alcoholic men as a group had poorer integrity of parietal and sensory-motor bundles, completed fewer items within 90 seconds on the Digit Symbol Test, and took longer to complete the entire test grid than women. However, alcoholic men and women were not significantly different from each other, even in subgroups matched on lifetime alcohol and length of sobriety, on fiber integrity. Thus, the apparent “telescoping” found for some structural brain measures (e.g., Hommer et al., 1996, 2001; Mann et al., 2005) did not apply to DTI measures of integrity of white matter callosal tracts and is consistent with other reports using DTI or conventional MRI based on the alcoholic and control samples reported herein (Pfefferbaum et al., 2009; Sullivan et al., 2010b) or in independent samples (Pfefferbaum et al., 2001). Supplementary analyses showed that the higher rate of cigarette smoking in alcoholic women than men did not contribute to the effects observed. Associations between white matter integrity and behavior tended to be stronger in alcoholic men than in alcoholic women, possibly because of sample size differences and because men tended to perform worse on the tasks than women.

Associations between regional DTI metrics and behavior were consistent with involvement of sensory-motor and parietal cortices in maintaining postural stability and of prefrontal and temporal cortices in a task involving sustained attention and associative learning. The Digit Symbol test involves many component processes including executive function, sustained attention, associative learning, and psychomotor speed (Glosser et al., 1977; Joy et al., 2003; Sassoon et al., 2007). The association of both the Digit Symbol Test score and completion time with radial diffusivity of the prefrontal bundle is consistent with an executive function contribution to performance of this test. Time to complete the entire grid was also associated with the diffusivity in the temporal bundle, perhaps reflecting the contribution of associative learning of digits and symbols. These brain behavior relations were dissociated from those between balance and the sensory-motor and parietal cortices. Maintaining balance on one foot with eyes closed is a challenging task, even for healthy controls. Poor performance on this motor task by alcoholics is associated with alcohol-related effects on the cerebellum (Sullivan et al., 2000a) and pontocerebellar systems (Sullivan et al., 2010a). The current analysis highlights a further contribution of interhemispheric coordination of both sensory-motor and parietal cortices to this balancing task. The association of sensory-motor bundle integrity with ability to maintain balance and psychomotor speed measured by time to complete the Digit Symbol Test suggests a role of motor control for both these otherwise dissociated tasks.

The presence of brain-behavior relationships provides support for the role of alcoholism-related commissural white matter degradation as a substrate of cognitive and motor impairment. Indeed, identification of a double dissociation for relations between prefrontal and temporal callosal bundle integrity and psychomotor speed (indexed by Digit Symbol speed) but not balance and parietal fiber bundle integrity with balance but not psychomotor speed provides further support for the role of selective white matter integrity in specific domains of performance.

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Fig. 1.

Six transcallosal bundles from a 51-year-old alcoholic man are displayed in sagittal and axial views (top right). Mean $\pm$ SE for Z-scores for each bundle for control and alcoholic men and women for fractional anisotropy (FA) (top left), radial diffusivity (λ_T) (bottom left), and axial diffusivity (λ_L) (bottom right). Negative FA Z-score for the alcohol groups reflects lower anisotropy (lower integrity) relative to age norms, whereas positive λ_L and λ_T scores reflect higher diffusivity. See Table 3 for significant differences between alcoholics and controls. Control values are not zero because the control sample used in this analysis was selected from a larger sample of controls, spanning the full adult age range, to match the age range of the alcoholics in the current study.

Fig. 2.

Scatter plots illustrating associations between the two behavioral measures (balance on one foot with eyes closed and time to complete grid) used in multiple regressions with four diffusion tensor imaging metrics (prefrontal radial diffusivity, sensory-motor axial diffusivity, temporal axial diffusivity, and parietal axial diffusivity). Separate regression lines are drawn for men and women. Values for both the x- and y-axes are age-corrected Z-scores.

Table 1

Demographic and Clinical Characteristics of Study Participants

	Controls (42 men, 46 women)			Alcoholics (n = 87)		Alcoholics vs. controls		Alcoholic men (n = 59)		Alcoholic women (n = 28)		Alcoholic men vs. women
	Mean	SD	Mean	SD	p value	Mean	SD	Mean	SD	Mean	SD	p value
Age (years)	44.5	9.9	46.6	9.0	0.15	47.0	9.7	45.8	7.5			0.55
Years of education	15.8	2.3	14.2	2.3	<0.0001	14.3	2.4	14.0	2.0			0.54
Socioeconomic status ^a	26.5	13.0	30.7	13.2	0.042	30.1	14.3	32	10.8			0.55
Handedness (Crovitz) ^b	24.4	13.7	26.2	15.1	0.38	26.7	15.8	25.2	2.6			0.67
Body mass index	25.8	4.7	26.1	4.4	0.71	26.9	4.0	24.4	4.7			0.01
Global Assessment of Function	81.6	8.9	55.6	11.5	<0.0001	54.1	11.5	59.0	10.8			0.06
Beck Depression Inventory-II (BDI) ^c	2.6	2.9	9.8	8.1	<0.0001	8.9	8.8	11.5	6.7			0.29
Lifetime alcohol (kg)	42.0	60.6	854.4	770.6	<0.0001	1005	111.9	536.1	73.4			0.007
Length sober (d)	–	–	113.9	154.0	–	88.0	94.4	168.6	227.5			0.02
Age onset alcohol dependence	–	–	28.3	9.6	–	28.0	9.6	28.9	9.8			0.71
Smoker/nonsmoker ^d	20/59		63/23		<0.0001	39/19		24/4				0.07
Ethnicity ^e (Caucasian/minority)	54/34		64/23		0.007	47/12		23/5				0.78
Prior history of substance abuse	0		50%		<0.0001	50%		50%				0.94
Men/women	42/46		59/28		0.09	–		–				–

^aHollingshead 2-factor score (higher score = lower status).

^bTwelve alcoholics and 6 controls were left-handed (scored > 50).

^cBDI available on only 52 control and 51 alcoholic participants.

^dSmoking history not available for 9 controls and 1 alcoholic participant.

^eCaucasian non-Hispanic versus Hispanic plus other minorities.

Mean (SD) Values of Fractional Anisotropy (FA), λL, and λT at Six Corpus Callosum Bundles for 88 Healthy Controls and 87 Alcoholics

Table 2

Fiber bundles	Healthy controls (n = 88)			Alcoholics (n = 87)		
	FA	λL	λT	FA	λL	λT
Prefrontal	0.571 (0.048)	1.420 (0.083)	0.525 (0.062)	0.533 (0.052)	1.450 (0.101)	0.584 (0.086)
Prenotor	0.581 (0.053)	1.456 (0.099)	0.533 (0.082)	0.549 (0.061)	1.498 (0.111)	0.598 (0.111)
Sensory-motor	0.653 (0.046)	1.439 (0.088)	0.440 (0.078)	0.639 (0.047)	1.462 (0.083)	0.470 (0.079)
Parietal	0.646 (0.053)	1.480 (0.075)	0.467 (0.084)	0.610 (0.063)	1.528 (0.095)	0.532 (0.108)
Temporal	0.686 (0.036)	1.489 (0.070)	0.408 (0.052)	0.660 (0.048)	1.527 (0.084)	0.455 (0.083)
Occipital	0.676 (0.038)	1.481 (0.101)	0.424 (0.053)	0.655 (0.038)	1.500 (0.097)	0.462 (0.063)

FA can range from 0 (perfect isotropy) to 1 (perfect anisotropy). λL and λT are expressed in units of 10⁻³ mm²/s.

Table 3

Group Comparisons (*t*-tests) for Fractional Anisotropy (FA), λ L, and λ T in Six Transcallosal Fiber Bundles. Controls (*n* = 88) Versus Alcoholics (*n* = 87)

Fiber bundles	FA	λ L	λ T
Prefrontal			
<i>t</i>	4.805	2.030	5.189
<i>p</i>	0.0001	0.0439	0.0001
Premotor			
<i>t</i>	3.449	2.497	4.250
<i>p</i>	0.0007	0.0135	0.0001
Sensory-motor			
<i>t</i>	1.882	1.583	2.388
<i>p</i>	0.0615	0.1153	0.018
Parietal			
<i>t</i>	3.915	3.675	4.357
<i>p</i>	0.0001	0.0003	0.0001
Temporal			
<i>t</i>	3.824	3.583	4.590
<i>p</i>	0.0002	0.0004	0.0001
Occipital			
<i>t</i>	3.462	1.756	4.426
<i>p</i>	0.0007	0.0808	0.0001

Bold denotes family-wise Bonferroni correction for six corpus callosum fiber bundles. 1-tailed, *p* = 0.02.

Table 4

Mean (SD) for Uncorrected and Age- and Education-Corrected Z-Scores for Controls and Alcoholics

	Controls		Alcoholics		<i>t</i>	<i>p</i>
Raw scores	<i>n</i>	Mean (SD)	<i>n</i>	Mean (SD)		
Digit Symbol Test	82	56.92 (11.74)	82	48.37 (10.94)	85	4.87 <0.0001
DS grid completion time	82	146.45 (31.88)	82	167.25 (42.51)	85	-3.57 0.0005
DS recall	79	6.80 (1.94)	79	6.41 (2.07)	85	1.23 0.2202
Balance	79	26.23 (17.77)	79	10.54 (9.00)	85	7.20 <0.0001
Z-Scores						
Digit Symbol Test Z-score	82	0.00 (0.99)	82	-0.57 (0.89)	85	3.89 0.0001
DS Grid completion time Z-score	82	0.00 (0.99)	82	0.53 (1.29)	85	-2.94 0.0037
DS recall Z-score	79	0.00 (0.99)	79	-0.18 (1.06)	85	1.12 0.2633
Balance Z-score	79	0.00 (0.99)	79	-0.85 (0.64)	85	6.56 <0.0001

^aNot all subjects completed all tests.

Pearson Correlations (*r*) Between Regional Tractography Metrics and Neuropsychological Test Scores in Alcoholics

Table 5

Fiber bundles	Digit symbol time to finish (<i>n</i> = 84)			Digit symbol raw score (<i>n</i> = 85)			Ataxia-stand on one foot (<i>n</i> = 84)		
	Fractional anisotropy (FA)	λL	λT	FA	λL	λT	FA	λL	λT
Prefrontal									
<i>r</i>	-0.231	0.099	0.260	0.241	-0.088	-0.259	0.086	-0.186	-0.118
<i>p</i>	0.034	0.369	0.017	0.026	0.421	0.017	0.438	0.091	0.286
Premotor									
<i>r</i>	-0.067	0.126	0.113	0.019	-0.076	0.057	0.188	-0.225	-0.205
<i>p</i>	0.54	0.253	0.307	0.860	0.490	0.605	0.088	0.039	0.062
Sensory-motor									
<i>r</i>	-0.183	0.241	0.248	0.152	-0.100	-0.165	0.043	-0.364	-0.154
<i>p</i>	0.095	0.027	0.023	0.164	0.362	0.132	0.697	0.007	0.163
Parietal									
<i>r</i>	-0.120	0.141	0.156	0.046	-0.113	-0.092	0.169	-0.321	-0.195
<i>p</i>	0.278	0.202	0.156	0.680	0.302	0.401	0.125	0.003	0.075
Temporal									
<i>r</i>	-0.114	0.302	0.208	0.134	-0.218	-0.195	0.072	0.040	0.116
<i>p</i>	0.302	0.005	0.058	0.221	0.045	0.074	0.517	0.715	0.294
Occipital									
<i>r</i>	-0.087	0.128	0.143	0.117	-0.055	-0.147	0.057	0.107	0.056
<i>p</i>	0.432	0.246	0.194	0.286	0.615	0.181	0.605	0.337	0.605

Bold denotes family-wise Bonferroni correction for six interhemispheric corpus callosum fiber bundles, 1-tailed comparisons, *p* = 0.02.