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Alcoholism and sexual dimorphism in the Middle Longitudinal Fascicle: A pilot study

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Abstract

Introduction—Alcoholism can lead to a complex mixture of cognitive and emotional deficits associated with abnormalities in fronto-cortico-striatal-limbic brain circuitries. Given the broad variety of neurobehavioral symptoms, one would also expect alterations of postrolandic neocortical systems. Thus, we used diffusion tensor imaging (DTI) to study the integrity of the middle longitudinal fascicle (MdLF), a major postrolandic association white matter tract that extends from the superior temporal gyrus to the parietal and occipital lobes, in individuals with a history of chronic alcohol abuse.

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Disclosure of potential conflicts of interest

The Authors Johanna Seitz, Kayle S. Sawyer, Susan M. Ruiz, George Papadimitriou, Isaac Ng, Antoni Kubicki, Palig Mouradian, Marlene Oscar-Berman, Marek Kubicki, Gordon J. Harris, and Nikos Makris have declared that there are no conflicts of interest in relation to the subject of this study.

Compliance with ethical standards

Research involving human participants and/or animals

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed Consent

Informed consent was obtained from all individual participants included in the study.

Methods—DTI data were acquired on a 3 Tesla scanner in 30 abstinent alcoholics (AL; 9 men) and 25 nonalcoholic controls (NC; 8 men). The MdLF was determined using DTI-based tractography. Volume of the tract, fractional anisotropy (FA), radial (RD), and axial (AD) diffusivity, were compared between AL and NC, with sex and hemispheric laterality as independent variables. The association of DTI measures with neuropsychological performance was evaluated.

Results—Men showed bilateral reduction of MdLF volume and abnormal diffusion measurements of the left MdLF. Analyses also indicated that the left MdLF diffusion measurements in AL men were negatively associated with Verbal IQ and verbal fluency test scores.

Conclusions—Abstinent alcoholic men display macrostructural abnormalities in the MdLF bilaterally, indicating an overall white matter deficit. Additionally, microstructural deficits of the left MdLF suggest more specific alterations associated with verbal skills in men.

Keywords

alcohol dependence; addiction; diffusion imaging tractography; DTI; sexual dimorphism; middle longitudinal fascicle/middle longitudinal fasciculus

Introduction

Alcoholism is a chronically relapsing disorder characterized by aspects of compulsion to seek and consume alcohol with loss of control over limiting its intake (Koob, 2014). Long-term chronic alcoholism thereby can result in a breakdown of the “reward cascade”, leading to Reward Deficiency Syndrome (Blum et al., 2000; Bowirrat & Oscar-Berman, 2005), which is manifested as insensitivity to rewards and inefficient modulation of both positive (rewarding) and negative (punishing) reinforcement (Blum et al., 2000). Additionally, deficits in executive functions further reduce the effectiveness of inhibitory control over reward behaviors (Oscar-Berman et al., 2014) and emotional responses (Foisy et al., 2007; Marinkovic et al., 2009; Oscar-Berman, Hancock, Mildworf & Hutner, 1990).

Many clinical as well as animal studies in alcoholism, have demonstrated that long-term chronic alcohol consumption disrupts the normal ability to engage fronto-cortico-striatal-limbic circuitries (Barbas, 2000; Barbas, Saha, Rempel-Clower, & Ghashghaei, 2003; Hariri, Mattay, Tessitore, Fera, & Weinberger, 2003; Marinkovic et al., 2009; Ochsner et al., 2004; Oscar-Berman & Bowirrat, 2005; Oscar-Berman & Marinkovic, 2007). These circuitries involve prefrontal, cingulate, and ventral striatal regions, as well as the amygdala, limbic brainstem, and their fiber connections, and have been termed as the “Extended Reward and Oversight System” (Makris, Gasic, et al., 2008; Makris, Oscar-Berman, et al., 2008).

Diffusion tensor imaging (DTI), provides the possibility to study structural alterations in these circuitries in vivo in humans (e.g., Fortier et al., 2014; Oscar-Berman et al., 2014; Zahr, 2014). Widespread white matter abnormalities have been found in people who express a variety of disease states. DTI alterations are seen in people with family history of alcohol abuse (Acheson et al., 2014; Squeglia et al., 2015), in alcoholics with long periods of abstinence (e.g., Fortier et al., 2014; Harris et al., 2008; Zorlu et al., 2014), short periods of

abstinence (Alhassoon et al., 2012), or following episodes of acute drinking (Kong, Zheng, Lian, & Zhang, 2012).

While several studies have focused on regions within the Extended Reward and Oversight System (Moselhy, Georgiou, & Kahn, 2001; Oscar-Berman et al., 2014; Schulte, Muller-Oehring, Pfefferbaum, & Sullivan, 2010; Segobin et al., 2015), other alterations, e.g., of the corpus callosum (Ruiz et al., 2013), as well as superior longitudinal fascicles I and II and arcuate fascicle, have been reported to be altered in chronic alcoholism (Harris et al., 2008). In the later study, our team interestingly also found abnormalities in postrolandic areas such as the right superior temporal gyrus using exploratory voxel-based analyses of FA.

Based on these observations, we hypothesized that the middle longitudinal fascicle (MdLF), the principal long association fiber pathway of the superior temporal gyrus and dorsal temporal pole (Makris, 1999; Makris et al., 2009) is also abnormal in long-term chronic alcoholism. To our knowledge, no study examining the relationship of alcohol abuse to structural defects of the MdLF has been conducted to date.

The MdLF may be associated with right-sided dominant visuospatial and attention functions, as well as with verbal skills on the left hemisphere. Verbal/language and visual/attentional functions are affected by alcoholism possibly independently from the aforementioned executive and limbic impairments. For example, patients with Fetal Alcohol Syndrome (FAS) show hearing, speech, and language pathologies (Church & Abel, 1998; Korkman, Hilakivi-Clarke, Autti-Ramo, Fellman, & Granstrom, 1994; Rasmussen et al., 2013; Wyper & Rasmussen, 2011). Youth who abuse alcohol, as well as alcoholic patients at treatment entrance, experience language and semantic problems (Pitel et al., 2007; Sher, 2007). Furthermore, limitations of semantic fluency can be observed after long-term alcohol abuse as persistent symptoms (Mlinarics, Kelemen, Sefcsik, & Nemeth, 2009). Respectively, poorer visuospatial attention can be observed for different alcohol related stages in FAS (Rasmussen et al., 2013), youth with misuse behavior (Sher, 2007), and in association with long-term alcohol abuse (Fitzpatrick, Jackson, & Crowe, 2008; Smith & Oscar-Berman, 1992).

Therefore, we hypothesized that white matter alterations of the MdLF would be present in individuals who have experienced a substantial period of alcohol abuse despite long periods of abstinence. We further expected that right MdLF alterations would be associated with visuospatial performance and that left MdFL alterations would correspond with deficits in language-based performance.

Finally, we expected that group differences between nonalcoholic controls (NC) and subjects with history of alcohol abuse (AL) would be more pronounced in men than in women. This assumption is based on previous findings showing that structural deficits resulting from alcohol abuse are more prominent in men (Oscar-Berman & Song, 2011; Pfefferbaum, Adalsteinsson, & Sullivan, 2006; Sawyer et al., 2015), while women also showed greater structural recovery after an abstinent period (Ruiz et al., 2013).

Methods

Participants

We examined 30 individuals (9 men) who had experienced a substantial duration of heavy drinking (minimum = 3 years, mean = 14.30 years; AL) as well as prolonged periods of abstinence (minimum = 1 month, mean = 6.94 years), and 25 demographically equivalent nonalcoholic control subjects (8 men; NC). All participants were right-handed, native English speakers from comparable socioeconomic backgrounds (for further information please see Table 1).

Participants were recruited from the Department of Veterans Affairs (VA), Healthcare System Boston Campus and advertisements (flyers, local newspapers, and websites) in the greater Boston area. After a brief pre-screening phone interview, an extensive neuropsychological test battery was conducted, including the Computerized Diagnostic Interview Schedule (Robins, Helzer, Cottler, & Goldring, 1989), which provides psychiatric diagnoses according to criteria established by the American Psychiatric Association (American Psychiatric Association, 1994). This standardized interview is intensive, and covers history of drug and alcohol use and abuse.

In addition to the Computerized Diagnostic Interview Schedule, to examine drinking patterns further, questionnaires and a structured interview were given to the participants (MacVane, Butters, Montgomery, & Farber, 1982), and the alcoholics met DSM-IV criteria (APA, 1994) for alcohol abuse or dependence. The following information was obtained from these interviews: Length of Sobriety (in years), Duration of Heavy Drinking (in years), and Daily Drinks (DD). The Length of Sobriety, refers to the period between the MRI scan date and the last drink participants reported having. The Duration of Heavy Drinking is the number of years that participants drank more than 21 drinks per week (one drink: 355 ml beer, 148 ml wine, or 44 ml hard liquor). The Daily Drinks are the ounces of ethanol per day the participants consumed during the last six months before cessation of drinking. A Quantity Frequency Index score (Cahalan, Cisin, & Crossley, 1969), which factors the amount, type, and frequency of alcohol usage (roughly corresponding to number of drinks per day, at approximately one ounce of ethanol per drink) over either the last six months (for nonalcoholics) or over the six months preceding cessation of drinking (for abstinent alcoholics) was calculated for each participant. To supplement information obtained from the interviews, questionnaires, and the above-noted inclusionary and exclusionary criteria, we required that alcoholic participants must have a history of consuming a minimum of 21 drinks per weeks for at least five years during their life, and had abstained from alcohol for at least four weeks prior to testing. Although our minimum drinking criteria were low, our sample of alcoholic participants had severe drinking histories: mean Daily Drinks = 9.67 (SD = 9.18; ounces of ethanol per day); and mean Duration of Heavy Drinking = 14.30 (SD = 7.87; years with over 21 drinks per week). Additionally, the mean Length of Sobriety was 6.94 (SD = 8.62; years). A Breathalyzer test also was administered prior to testing.

Exclusion criteria were Korsakoff's syndrome or other neurobehavioral disorders (e.g., stroke, epilepsy or seizures unrelated to alcoholism, head injury with loss of consciousness greater than 20 minutes), electroconvulsive therapy, HIV, hepatic disease, or major

psychiatric disease. Other exclusion criteria were a history of serious learning disability or dyslexia or uncorrected abnormal vision or hearing problems. Furthermore, participants who revealed poly-drug abuse, i.e., a history of drug use in excess of once per week less than five years prior to testing, were excluded.

The present study was approved by the human subjects investigational review boards of the participating institutions. Informed consent was obtained for each subject prior to enrollment, and participants received monetary compensation.

Procedures

Imaging Parameters—Images were acquired on a 3 Tesla Siemens Trio scanner (Siemens Medical Solutions USA, Inc., Malvern, PA) on an 8-channel head coil. The dMRI data were constructed based on a 70-shot acquisition (10 T2-weighted “lowb” anatomical reference with b-value = 0 s/mm², and 60 directional images). The following imaging parameters were used: TR = 9800 ms, TE = 94 ms, number of axial slices = 64 to cover the entire brain, FOV = 256 mm², data matrix = 128 × 128, in-plane resolution = 2 × 2 mm², slice thickness = 2 mm, skip = 0 mm, bandwidth = 1,860 Hz/pixel, b-value = 700 s/mm², and imaging time of approximately 10 minutes.

Image Processing—DTI images were visually inspected and corrected for motion, rotation, and eddy current distortion using affine registration with a reference volume (FLIRT, FSL, Oxford; <http://fsl.fmrib.ox.ac.uk/fsl> (Jenkinson, Bannister, Brady, & Smith, 2002)).

Tractography was performed with Diffusion Toolkit and TrackVis (R. Wang, Benner, Sorensen, & Wedeen, 2007). Diffusion tensors were estimated using the linear least-squares fitting method. The MdLF was delineated growing from a single region of interest (ROI) placed on a single coronal section in the superior temporal gyrus white matter (Makris et al., 2009) (see Figure 1). Specifically, this ROI was set by sampling all voxels within the white matter of the STG in a single coronal section in the rostral one third of the STG, precisely 17 mm caudal to the frontotemporal junction (FTJ). It is important to note that FTJ corresponds to Y = +4 mm in the rostrocaudal dimension of the Talairach coordinate space system (Lancaster et al., 2000). Given that the STG spans +4 mm to −55 mm in the Talairach Y rostrocaudal dimension, the white matter STG ROI is located approximately at Y = −13 mm and, thus within the rostral third of STG in Talairach space. This is important for assuring that fibers of the MdLF course through the anterior part of the STG (Makris, Preti, Asami, et al., 2013). From this seeding ROI in the STG, tracts were reconstructed using the standard *fiber assignment by continuous tracking* (FACT) algorithm (Mori, Crain, Chacko, & van Zijl, 1999). Tracking starts from every brain voxel defined within a brain mask, while tract delineation is determined through sudden changes of fiber orientation (indicated by angle >35°) in a voxel when compared to its neighbors. Tracts were visually inspected and fibers crossing the mid-sagittal plane were eliminated.

Tract volume, Fractional Anisotropy (FA), Radial Diffusivity (RD) and Axial Diffusivity (AD) were calculated and averaged over each tract. Tract volume was obtained by summing up all voxels that were touched by streamline tractography. FA often is used as marker for

overall white matter abnormalities (Basser & Pierpaoli, 1996), whereas RD alterations have been suggested to be associated with myelin and AD changes with axonal pathologies (Song et al., 2003).

Statistical analyses—Statistical analyses were conducted using the Statistical Package for Social Sciences (SPSS) version 22.0 (IBM Corp, 2013) and Prism 6 (GraphPad Software, 2014).

In analyses of white matter volume, we used normalized volume (tract volume of each participant divided by total brain volume) to test for possible macrostructural (tract volume) differences between AL and NC groups. To this end, we used ANCOVA with volume as dependent and group, sex, and group x sex as independent variables. Age was a covariate, and each hemisphere was analyzed separately.

Subsequently, we conducted *post hoc* Mann-Whitney U tests (a non-parametric procedure appropriate for our small sample size) for both sexes combined, and each sex separately. In instances of significant group differences, we investigated how structural abnormalities were associated with neuropsychological functions. Thus, we correlated the left volume with verbal performance and the right volume with visual attention.

We used two general measures, and two specific measures, of verbal and of visual/attentional functions. The tests were selected because they measure different aspects of the abilities of interest. As such, these assessments represent a wide spectrum of functions controlled primarily by the left and the right hemispheres, respectively. For verbal abilities, we chose the WAIS III Verbal IQ score (Wechsler, 1997a) and the Controlled Oral Word Association Test (COWAT) (Benton, 1969; Schmidt et al., 2004). While the Verbal IQ scale assesses general Verbal IQ, the COWAT assesses word fluency, a function that has been reported to be impaired after chronic alcohol abuse (Mlinarics et al., 2009). To assess visual attention, we used the Performance IQ (Wechsler, 1997a), which assesses general visuospatial abilities, and the Trail Making Test A (Arnett & Seth, 1995; Tombaugh, 2004), which assesses visual search speed, scanning, and speed of processing.

Finally, we were interested whether white matter volume group differences were influenced by differences in *length of tract* or *streamline tractography* of the MdLF. We used the same ANCOVA as described below, with number of fibers and streamline tractography of the right and left MdLF as dependent variables.

For diffusion measurements, we conducted three ANCOVAs with FA, RD, and AD as dependent variables. Independent variables were group, sex, and group x sex, and age was a covariate for the right and the left hemisphere separately. In cases of significant group effects, we explored group, hemisphere, and sex differences separately by using *post hoc* Mann-Whitney U tests. Specifically, we examined group differences for RD for both sexes combined, followed by group differences for men and women separately. In cases of significant group differences, we further investigated the relationship of structural abnormalities (as indicated by altered diffusion parameters) with the aforementioned measurements for verbal performance.

To examine the influence of drinking patterns, we conducted Pearson's correlations of Length of Sobriety, Duration of Heavy Drinking, and Daily Drinks with FA, RD, AD, and MdLF volume for both sexes combined, and for each sex separately.

Results

Tractography

Using DTI-based tractography with a single ROI we were able to delineate MdLF that, in each subject, reliably extended from the temporal pole and superior temporal gyrus to the inferior and superior parietal lobules and the occipital lobes (Figure 2).

White matter volumes

First, we examined macrostructural tract differences between AL and NC. We conducted an ANCOVA with normalized volume as dependent variable; group, sex and group x sex as main and interaction effects, and age as covariate. The ANCOVA showed significant group effects for the right and left hemispheres, as well as a trend for a group x sex interaction in the left hemisphere (see Table 2).

Additional analyses showed that these differences in white matter volume can be explained by group differences of streamline tractography, as well as length of tract (Supplemental Table 1) indicating an overall white matter reduction in association with alcoholism.

Post-hoc analyses for each hemisphere are reported in Table 3 (descriptive statistics) and Table 4 (statistical tests). We observed significant group differences for both sexes combined, for the right and left hemispheres, with AL showing lower tract volume than NC. The results were significant for men analyzed separately, and a similar trend was observed for women (Figure 3).

Since the left MdLF was hypothesized to be related to verbal skills, we investigated this further by correlating volume of the MdLF of both sexes, together and separately, with Verbal IQ and Verbal Fluency scores. We did not find any significant correlations (Supplemental Table 2). Further, since the right MdLF is hypothesized to be associated with visual attention we also looked at the association of the right MdLF of alcoholic men with Performance IQ scores (Wechsler, 1997a) and with Trails A Time (Arnett & Seth, 1995; Tombaugh, 2004). We did not find any correlations of volume with visuospatial ability that were significantly different from zero (Supplemental Table 2).

In summary, we identified significant volume differences between NC and AL for the whole group and for men for the right and left MdLF.

Diffusion measurements

We explored group differences using three ANCOVAs with FA, RD, and AD as dependent variables; group, sex, and group x sex as independent variables, and age as covariate for the right and the left hemisphere separately. We found significant group and sex effects for RD, significant sex effects for AD and a trend toward significance group differences for FA and AD for the left hemisphere (see Table 2).

Subsequently, we conducted Mann-Whitney U tests to explore group differences for the left hemisphere. When investigating males and females combined, no significant group differences in RD were found. However, for the men alone, RD showed significant group differences (see Table 4).

Because RD was lower for AL men than NC men, we examined whether MdLF diffusivity was also related to the two aforementioned verbal tests for men. The alcoholic men showed significant positive correlations of RD with the COWAT score (Pearson's $r=0.80$, $p=.0090$, see also Figure 4 and Supplemental Table 2).

Additional analyses

Pearson's correlations were not significant for LOS, DHD, and DD with FA, RD, AD, and volume for both sexes combined, nor for separate analyses of men and women (Supplemental Table 3).

Discussion

In this study we delineated the MdLF using DTI-based tractography (Ito, Mori, & Melhem, 2002; Melhem et al., 2002; Mori et al., 1999) from the dorsal temporal pole and the superior temporal gyrus as has been described in previous reports (Makris et al., 2009; Makris, Preti, Asami, et al., 2013; Makris, Preti, Wassermann, et al., 2013; Maldonado et al., 2013; Martino, da Silva-Freitas, et al., 2013; Martino, De Witt Hamer, et al., 2013; Menjot de Champfleury et al., 2013; Y. Wang et al., 2013). We investigated the relationship between history of chronic alcoholism and MdLF structure and function. We found that alcoholism is associated with macroscopic, gross volumetric white matter abnormalities of the right and left MdLF for men, and with microstructural abnormalities pronounced on the left hemisphere. Further, abnormal microstructure was associated with deficits on verbal tests.

Previous studies have shown white matter alterations in prefrontal and mesocorticolimbic circuits (Oscar-Berman et al., 2014; Schulte et al., 2010; Segobin et al., 2015) in association with chronic alcoholism. However, other systems such as the language system and visuospatial attention are also impaired (Fitzpatrick et al., 2008; Mlinarics et al., 2009). Consequently, alterations of other white matter fiber bundles including the corpus callosum (Ruiz et al., 2013) and the superior longitudinal fascicle (Harris et al., 2008) have been observed. The latter study also presented exploratory results that indicated alterations in postrolandic areas (the superior and inferior parietal lobules and the superior temporal gyrus). We therefore hypothesized that white matter alterations of the MdLF would be present in individuals with a history of chronic alcohol abuse. To our knowledge, this is the first study investigating the relationship between chronic alcoholism and abnormalities of the MdLF. We expected that the AL group would have lower white matter volume and FA, but higher RD and AD, as compared to the NC group.

In concordance with previous literature (Makris et al., 2009), we used our tractography method to identify the MdLF, which connects the inferior parietal lobule with the superior temporal gyrus. We found volume differences between the AL and NC participants for the right MdLF. We also found structural differences (indicated by diffusion measurements and

white matter volume) of the left MdLF between AL men and NC men. The volume differences of the right and left MdLF might reflect an overall white matter volume decrease.

We investigated volume and biophysical diffusion measurements, because both are independent measures that interrogate different aspects of underlying white matter biology (Caviness, Lange, Makris, Herbert, & Kennedy, 1999; Makris, 1999). These diffusion findings, however, may be associated with specific neurobiological characteristics of the MdLF. The combination of higher AD and RD values in individuals with an alcohol history may indicate axonal degeneration, as well as myelin pathologies (Song et al., 2003). This is in line with clinical, post mortem and mice model studies, which report alcohol-related structural alterations in axons and myelin (Samantaray et al., 2015). Axonal damage as a sequelae of alcohol abuse is consistent with peripheral system neuropathy — a commonly reported disease caused by alcohol abuse that is characterized by axonal degeneration (Maiya & Messing, 2014) of large and small fibers (Mellion, Nguyen, Tong, Gilchrist, & De La Monte, 2013; Mellion et al., 2014) as well as demyelination and degeneration of myelin proteins (Nguyen et al., 2012). Additionally, axonal degeneration (Lai et al., 2013) and affected myelin sheaths (Poser, 1973) also have been observed in the central nervous system.

Interestingly, when splitting the groups into men and women, we observed volume, as well as diffusion differences for men only. Similar findings have been reported (Oscar-Berman & Song, 2011; Pfefferbaum et al., 2006; Sawyer et al., 2015). Additionally, male adolescent binge drinkers already show more vulnerability than female adolescents (Squeglia et al., 2012). Collectively, these findings might indicate preexisting sex-specific vulnerability. In any case, it is crucial to examine sex differences since such findings emphasize the importance of more targeted approaches to prevention, treatment, and abstinence enhancement strategies (Bravo, Gual, Lligona, & Colom, 2013; Danielsson, Romelsjö, & Tengstrom, 2011; Prendergast, Messina, Hall, & Warda, 2011). This need of gender specific treatments is further emphasized by preliminary findings indicating a greater ability of structural recovery in women than in men (Ruiz et al., 2013).

In particular, the more pronounced alterations of the left MdLF for men are remarkable. The left MdLF has been proposed to play a role in higher auditory functions and language (Makris, Preti, Wassermann, et al., 2013; Y. Wang et al., 2013), and the language system has been reported to be vulnerable to alcohol (Church & Abel, 1998; Mlinaric et al., 2009; Pitel et al., 2007; Sher, 2007). We provide further evidence for such vulnerability, by not only showing an impairment of the left MdLF, but also by showing the relationship between diffusion measurements of alcoholic men with their performance on a verbal fluency test. This effect could be explained in many different ways. The language system may be stronger and therefore less vulnerable in women than in men (Sandu, Specht, Beneventi, Lundervold, & Hugdahl, 2008). This assumption is somewhat supported by a study investigating the influence of smoking on the brain (Hahn, Pogun, & Gunturkun, 2010), which found that smoking is associated with impairments of the speech dominant hemisphere in men but not in women. It also could be argued that the increased vulnerability of men is due to a stronger lateralization pattern in the male brain when compared to women, since it has been shown that less lateralization is associated with better and more stable cognitive performance

(Catani et al., 2007). Indeed, several studies reported different lateralization patterns of the language system for men and women (Clements et al., 2006; Vikingstad, George, Johnson, & Cao, 2000; Yu et al., 2014). However, others have not reported sex-related lateralization pattern differences (Sommer, Aleman, Somers, Boks, & Kahn, 2008). The divergent results may be explained by the fact that potentially sex-specific lateralization patterns are region-dependent (Kansaku & Kitazawa, 2001; Kansaku, Yamaura, & Kitazawa, 2000), task-dependent (Chiarello et al., 2009; Healey, Waldstein, & Goodglass, 1985), or dependent on family handedness (Piccirilli et al., 1988).

Limitations and future directions

The number of subjects in our sample was limited and we therefore might have missed real gender interactions, which otherwise would be observed with a larger sample. However, it is important to note that we greatly reduce our sample variability with our strict inclusion/exclusion criteria, thus substantially lowering the chance of making a Type II error. Additionally, we still did detect robust group differences in this relatively small sample size. Nevertheless, the potential association of alcoholism, the MdLF, and the language system identified in the current pilot study needs to be investigated further.

Another consideration is that the average Length of Sobriety of our research participants was about seven years, in contrast to the majority of research on abstinent alcoholics who have shorter durations (see Oscar-Berman et al., 2014 for review). Nonetheless, our findings confirm many independent reports that even after substantial periods of abstinence, alcoholics evidence structural brain changes, which are associated with functional impairments (Oscar-Berman et al., 2014).

Our results should be taken with a hint of caution (Jones, Knosche, & Turner, 2013) as tractography studies have their own limitations, e.g., misinterpretations in the case of crossing fibers within one voxel. However, tractography is currently the only *in vivo* method to investigate entire white matter tracts. Furthermore, we are confident in our preliminary findings because they are in line with results of previous neuroimaging (Oscar-Berman & Song, 2011; Pfefferbaum et al., 2006; Sawyer et al., 2015), *post mortem* (Harper et al., 2003), and nonhuman animal studies (Samantaray et al., 2015). Nevertheless, further research is needed using even more precise methods for modeling water diffusion within a voxel. For example, multi-tensor tractography can account for crossing fibres (Rathi et al., 2011), whereas separating each signal into two signals using a free water correction would account for partial volume effects (Pasternak et al., 2009).

Conclusions

The present study showed an association between chronic alcohol abuse and structural abnormalities of the MdLF. Alcoholic men especially, showed reduced bilateral MdLF volume, potentially reflecting overall white matter alterations in relation to alcoholism. Additionally, alcoholic men showed white matter alterations of the left MdLF, and correlation analyses showed that these abnormalities were associated with low verbally-based neuropsychological test scores. This emphasizes the importance of the left MdLF for

language and suggests that the language system may be more vulnerable in alcoholic men than in alcoholic women.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1. Method of tractography of the middle longitudinal fasciculus (MdLF)

Right lateral (a), frontal (b), and left lateral (c) views of the MdLF in a representative subject. The delineation of the white matter (WM) superior temporal gyrus (STG) region of interest (ROI) is shown (*red*) for the right (d) and left (e) hemisphere. Trackvis was used to create these images.

AG= gyrus angularis, IPS= intraparietal sulcus, SPL= superior parietal lobule

Fig. 2. Results of tractography of the middle longitudinal fasciculus MdLF

Right lateral (a), frontal (b), and left lateral (c) views of the MdLF in a representative subject. AG = gyrus angularis, IPS = intraparietal sulcus, SPL = superior parietal lobule, WM STG ROI = white matter superior temporal region of interest

Fig. 3.

Normalized tract volumes (absolute tract volume as extracted from diffusion data divided by brain volume as extracted from a brain mask). The boxes represent the interquartile range, and the whiskers are the 2.5–97.5 percentiles

Association of RD of AL with COWAT scores

Fig. 4. Association of radial diffusivity (RD) and the Controlled Oral Word Association Test (COWAT) (Benton, 1969; Schmidt et al., 2004) for abstinent alcoholic men (AL). The AL men showed significant correlations of RD with COWAT score

Table 1

Characteristics of the abstinent alcoholic participants (AL) and nonalcoholic control individuals (NC) in this study.

	AL (n=30)	NC (n=25)	Statistical test		
			<i>t</i>	<i>df</i>	<i>p</i>
Age (years)	53.73±10.58 ^a	54.81±15.23 ^a	.31	53	.072
Gender (male/female)	9/21	8/17	.026	1	.87
WAIS III-Full IQ ^b	109.07±16.27 ^a	111.92±11.79 ^a	.27	52	.47
Education (years)	15.15±2.92 ^a	15.40±2.48 ^a	.34	53	.74
WMS III-General Memory ^c	114.86±16.37 ^a	115.00±15.19 ^a	.032	52	.97
Tobacco dependence	6	0	6.68	1	.010

^aMean ± standard deviation

^bWAIS (Wechsler, 1997a) = Wechsler Adult Intelligence Scale

^cWMS (Wechsler, 1997b) = Wechsler Memory Scale

Table 2
Group differences in MdLF measurements between AL and NC explored by ANCOVA.

		Volume	FA	AD	RD
Right	Group	F=11.01, df=1, <i>p</i> =.002* , $\eta_p^2=.18$	F=2.81, df=1, <i>p</i> =.10 , $\eta_p^2=.053$	F=.034, df=1, <i>p</i> =.86 , $\eta_p^2=.001$	F=3.09, df=1, <i>p</i> =.085 , $\eta_p^2=.058$
	Sex	F=.52, df=1, <i>p</i> =.43 , $\eta_p^2=.009$	F=3.96, df=1, <i>p</i> =.05 , $\eta_p^2=.073$	F=8.10, df=1, <i>p</i> =.006* , $\eta_p^2=.14$	F=.22, df=1, <i>p</i> =.64 , $\eta_p^2=.004$
	Group x Sex	F=1.07, df=1, <i>p</i> =.31 , $\eta_p^2=.021$	F=.02, df=1, <i>p</i> =.88 , $\eta_p^2<.001$	F=.82, df=1, <i>p</i> =.37 , $\eta_p^2=.016$	F=.29, df=1, <i>p</i> =.60 , $\eta_p^2=.006$
Left	Group	F=10.12, df=1, <i>p</i> =.003* , $\eta_p^2=.17$	F=4.60, df=1, <i>p</i> =.037 , $\eta_p^2=.084$	F=6.54, df=1, <i>p</i> =.014 , $\eta_p^2=.12$	F=10.97, df=1, <i>p</i> =.002* , $\eta_p^2=.18$
	Sex	F=.20, df=1, <i>p</i> =.66 , $\eta_p^2=.004$	F=.029, df=1, <i>p</i> =.87 , $\eta_p^2=.001$	F=46.53, df=1, <i>p</i> <.0001* , $\eta_p^2=.48$	F=22.18, df=1, <i>p</i> <.0001* , $\eta_p^2=.31$
	Group x Sex	F=3.77, df=1, <i>p</i> =.058 , $\eta_p^2=.070$	F=1.17, df=1, <i>p</i> =.29 , $\eta_p^2=.023$	F=3.67, df=1, <i>p</i> =.061 , $\eta_p^2=.068$	F=3.45, df=1, <i>p</i> =.069 , $\eta_p^2=.064$

AL = abstinent alcoholic participants; NC = nonalcoholic control individuals

* Indicates statistical significance $p<.01$ (Bonferroni corrected for 8 tests) η_p^2 =partial eta-squared

Table 3

Descriptive statistics (mean $\pm$ sd) showing the volumes of the white matter, FA, AD and RD of the left and right MdLF

	Men + Women			Men			Women		
	NC	AL	NC	AL	NC	AL	NC	AL	AL
Volume left	.0036 $\pm$.0010	.0029 $\pm$.0011	.0041 $\pm$.00078	.0026 $\pm$.0010	.0034 $\pm$.0011	.0030 $\pm$.0011	.0034 $\pm$.0010	.0031 $\pm$.0012	.0030 $\pm$.0011
Volume right	.0040 $\pm$.0010	.0030 $\pm$.0012	.0040 $\pm$.00077	.0026 $\pm$.0010	.0039 $\pm$.0011	.0031 $\pm$.0012	.0039 $\pm$.0011	.0031 $\pm$.0012	.0031 $\pm$.0012
FA left	.32 $\pm$.042	.30 $\pm$.042	.33 $\pm$.040	.29 $\pm$.034	.31 $\pm$.043	.30 $\pm$.044	.31 $\pm$.043	.31 $\pm$.043	.30 $\pm$.044
FA right	.32 $\pm$.044	.30 $\pm$.040	.36 $\pm$.035	.31 $\pm$.039	.31 $\pm$.045	.29 $\pm$.039	.31 $\pm$.045	.31 $\pm$.045	.29 $\pm$.039
AD left	.00087 $\pm$.000053	.00089 $\pm$.000082	.00091 $\pm$.000036	.00098 $\pm$.000090	.00085 $\pm$.000049	.00085 $\pm$.000035	.00085 $\pm$.000090	.00085 $\pm$.000049	.00085 $\pm$.000035
AD right	.00088 $\pm$.000052	.00087 $\pm$.000061	.00089 $\pm$.000063	.00091 $\pm$.000071	.00087 $\pm$.000048	.00085 $\pm$.000048	.00087 $\pm$.000071	.00087 $\pm$.000048	.00085 $\pm$.000048
RD left	.00056 $\pm$.000065	.00060 $\pm$.000087	.00058 $\pm$.000067	.00068 $\pm$.000099	.00055 $\pm$.000063	.00056 $\pm$.000049	.00058 $\pm$.000067	.00055 $\pm$.000063	.00056 $\pm$.000049
RD right	.00056 $\pm$.000054	.00058 $\pm$.000062	.00055 $\pm$.000050	.00060 $\pm$.000074	.00057 $\pm$.000057	.00058 $\pm$.000057	.00057 $\pm$.000074	.00057 $\pm$.000057	.00058 $\pm$.000057

AL = abstinent alcoholics; NC = nonalcoholic controls; FA = fractional anisotropy; AD = axial diffusivity; RD = radial diffusivity; volumes are normalized for head size

Table 4

Group differences (in case of a significant ANCOVA effect) between the alcoholic and the nonalcoholic groups explored by Mann-Whitney U tests.

	Men + Women (combined)	Men	Women
Volume left^a	<i>U</i>=222.00, <i>p</i>=.010	<i>U</i>=10.00, <i>p</i>=.012	<i>U</i> = 140.00, <i>p</i> =.27
Volume right^a	<i>U</i>=199.00, <i>p</i>=.0030	<i>U</i>=11.00, <i>p</i>=.016	<i>U</i> =116.00, <i>p</i> =.067
RD left	<i>U</i> =267.00, <i>p</i> =.068	<i>U</i>=14.00, <i>p</i>=.036	<i>U</i> =136.00, <i>p</i> =.21

RD = Radial Diffusivity

^a normalized for head size