Published in final edited form as:

Eur Neuropsychopharmacol. 2012 October ; 22(10): 704–710. doi:10.1016/j.euroneuro.2012.02.003.

Alcohol consumption and premotor corpus callosum in older adults

Dimitrios Kapogiannis^{*}, Jason Kisser^{*}, Christos Davatzikos^{***}, Luigi Ferrucci^{*}, Jeffrey Metter^{*}, and Susan Resnick^{**}

^{*}National Institute on Aging/National Institutes of Health (NIA/NIH), Clinical Research Branch, 3001 South Hanover St., Baltimore, MD, 21225, U.S.A., kapogiannisd@mail.nih.gov, Telephone: 410-350-3953, Fax: 410-350-7308

^{**}NIA/NIH, Laboratory of personality and cognition (U.S.A.)

^{***}University of Pennsylvania, Department of Radiology (U.S.A.)

Abstract

Heavy alcohol consumption is toxic to the brain, especially to the frontal white matter (WM), but whether lesser amounts of alcohol negatively impact the brain WM is unclear. In this study, we examined the relationship between self-reported alcohol consumption and regional WM and grey matter (GM) volume in fifty-six men and thirtyseven women (70 $\pm$ 7 years) cognitively intact participants of the Baltimore Longitudinal Study of Aging (BLSA) with no history of alcohol abuse. We used regional analysis of volumes examined in normalized space (RAVENS) maps methodology for WM and GM segmentation and normalization followed by voxel based morphometry statistical parametric mapping (in SPM8) to examine the cross-sectional association between alcohol consumption and WM (and, separately, GM) volume controlling for age, sex, smoking, blood pressure and dietary thiamine intake. WM VBM revealed that in men, but not in women, higher alcohol consumption was associated with lower volume in premotor frontal corpus callosum. This finding suggests that even moderate amounts of alcohol may be detrimental to corpus callosum and white matter integrity.

Keywords

Alcohol; corpus callosum; premotor; white matter

1. Introduction

There is little doubt that heavy alcohol consumption is toxic to the brain (Harper, 2009; Harper and Matsumoto, 2005), in particular when aggravated by nutritional deficiencies (Charness, 1993; Kril, 1995). Heavy alcohol drinkers tend to have brain atrophy, the severity

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Conflict of interest

All authors declare that they have no conflicts of interest.

Contributors

Author DK designed the study, conducted the analysis and wrote the manuscript. Author JK contributed to the analysis and writing of the manuscript. Authors CD, JM and LF contributed to the study design and writing of the manuscript. Author SR contributed to the study design, analysis and writing of the manuscript. All authors contributed to and have approved the final manuscript.

of which is related to the level of alcohol consumption and which is largely attributed to white matter (WM) loss (de la Monte, 1988; Harper, 2009; Harper and Matsumoto, 2005; Kril, et al., 1997). In particular, alcoholics manifest prefrontal cortex (PFC) atrophy (Chanraud, et al., 2007), selective loss of PFC pyramidal neurons (Kril, et al., 1997), and decreased PFC N-acetylaspartate [a Magnetic Resonance Spectroscopy measure of neuronal integrity] (Bartsch, et al., 2007; Bendszus, et al., 2001). White matter atrophy in alcoholics also occurs predominantly in the frontal lobes and is attributable to both axonal loss and demyelination (Harper, 1998; Harper and Matsumoto, 2005). The fact that executive and other frontal functions are particularly disrupted in alcoholics (Ihara, et al., 2000; Moselhy, et al., 2001) provides additional support for an effect of alcohol on frontal systems.

While “Heavy” alcohol consumption is consistently associated with neurotoxicity, there are conflicting data regarding the effect of “mild” or “moderate” alcohol consumption to the brain (Anstey, et al., 2009; Harper, 2009; Harper and Matsumoto, 2005; Panza, et al., 2009). For instance, “moderate” consumption has been associated with a lower risk of dementia (Mukamal, et al., 2003; Panza, et al., 2009) and mild cognitive impairment (Anttila, et al., 2004), as well as with better preservation of cognitive function with aging (Ganguli, et al., 2005; Ngandu, et al., 2007). Even though some studies suggest a linear association of alcohol consumption with brain atrophy (Ding, et al., 2004; Mukamal, et al., 2001; Taki, et al., 2006), other studies suggest that moderate consumption is not associated with global or regional atrophy or fractional anisotropy abnormalities (Sasaki, et al., 2009). Data have been conflicting even in regards to ischemic cerebral infarctions, with some large studies showing a protective effect of moderate consumption (Ding, et al., 2004), while other studies reveal no such effect (Mukamal, et al., 2001).

An interesting issue is whether there are sex differences in regards to the brain effects of alcohol. This possibility has been explored in cohorts of alcoholic men and women, with most studies suggesting increased vulnerability of women for most brain regions examined (Hommer, et al., 2001; Mann, et al., 2005; Pfefferbaum, et al., 2009), although certain volumetric measures are more affected in men (Pfefferbaum, et al., 2001). Inconsistent findings across studies conducted in alcoholics may in part reflect differences in the ability to account for comorbid conditions (such as cardiovascular disease or nutritional deficiencies) related to alcohol use.

In the present study, we investigated the relationship between current alcohol consumption and regional WM and GM volume in a cohort of older adults controlling for demographic and cardiovascular risk factors. Given the effect of sex on macro and micro-structural characteristics of potentially involved brain regions [such as the CC (Davatzikos and Resnick, 1998; Shin, et al., 2005)] and its interaction with the regional effects of both aging (Resnick, et al., 2000) and alcohol (de Bruin, et al., 2005a; de Bruin, et al., 2005b; Pfefferbaum, et al., 2009; Sasaki, et al., 2009), we examined the effects of alcohol separately for men and women.

2. Experimental Procedures

The study cohort included 56 men and 37 women (70 $\pm$ 7 years old) drawn from the neuroimaging study of the Baltimore Longitudinal Study of Aging (BLSA) (Resnick, et al., 2000), for whom we had detailed data on current alcohol consumption, smoking habits, blood pressure and diet (Table 1). Participants were free of alcoholism, CNS disease, severe cardiovascular disease, severe pulmonary disease, or metastatic cancer. Participants quantified their alcohol consumption in a typical week in the last year, including beers (1 unit/can), spirits (1 unit/jig), sherry, port, and dessert wines (1 unit/4 oz), and other wines (1 unit/4 oz). Alcohol consumption at the time of the MRIs was highly correlated ($R = 0.828$; p

< 0.001) with consumption reported in prior BLSA visits (averaged over 2.7 ± 1.1 years). Based on their smoking habits, participants were classified as never smokers (< 100 cigarettes in their lifetime), former smokers and current smokers. Systolic blood pressure (SBP) was measured at the time of the visit. Associations between these measures and alcohol consumption were examined using ANOVA (for sex, race, smoking, glucose tolerance) or Pearson's correlation (for age and SBP). A nutritionist routinely instructs BLSA participants how to keep a qualitative and quantitative food diary for one typical week following their visit. Eighty-eight participants out of 93 (including 52 men) filled these diaries, allowing us to calculate the total amounts (in mg) of vitamins B1 (thiamine) consumed by the individual in a typical week.

MRI scans were acquired on a GE Signa 1.5T scanner (Milwaukee, WI) using a high-resolution volumetric spoiled-grass axial series (repetition time = 35 msec, echo time = 5 msec, field of view = 24 cm, flip angle = 45°, matrix = 256 × 256, number of excitations = 1, voxel dimensions 0.94 × 0.94 × 1.5 mm). The images were preprocessed according to previously validated and published techniques (Davatzikos, et al., 2001; Goldszal, et al., 1998). They were corrected for head tilt and rotation, and reformatted parallel to the anterior-posterior commissure plane. Extracranial tissue was removed using a semi-automated procedure followed by manual editing. The cerebellum and brainstem below the rostral midbrain level were also removed to improve the accuracy of segmentation and normalization. Next, images were segmented into WM, grey matter and cerebrospinal fluid, using a brain tissue segmentation method proposed in (Pham and Prince, 1999), followed by high-dimensional image warping (Shen and Davatzikos, 2002) to a standardized coordinate system, a brain atlas (template) aligned with the MNI coordinate space (Kabani, et al., 2008). Tissue-preserving image warping was used to create regional volumetric maps (RAVENS maps) for WM, GM and CSF separately (Davatzikos, et al., 2001; Goldszal, et al., 1998). Finally, GM and WM RAVENS maps were smoothed using an 8-mm full-width at half-maximum filter.

RAVENS maps quantify the regional distribution of GM, WM, and CSF, with one RAVENS map is formed for each tissue. If the image warping transformation registering an individual scan with the template applies an expansion to a GM or WM structure, the GM or WM density of the structure decreases accordingly to insure that the total GM or WM volume is preserved. Conversely, a RAVENS value increases during contraction, if tissue from a relatively larger region is compressed to fit a smaller region in the template (Misra, et al., 2009). Therefore, RAVENS values in the template's space are directly proportional to the volume of the respective structures in the original brain scan and regional volumetric measurements and comparisons can be performed via measurements and comparisons of the respective RAVENS maps (Misra, et al., 2009). The RAVENS approach has been extensively validated (Davatzikos, et al., 2001; Goldszal, et al., 1998) and applied to a variety of studies (Misra, et al., 2009; Resnick, et al., 2000). It uses a highly conforming high-dimensional image-warping algorithm that captures fine structural details. Moreover, it uses tissue-preserving transformations, which ensures that image warping preserves the amount of GM, WM and CSF tissue present in an individual's scan, thereby allowing for local volumetric analysis (Misra, et al., 2009).

For statistical parametric mapping, we used the VBM estimation module of SPM8 (Wellcome Department of Imaging Neuroscience, Institute of Neurology, UCL). We entered smoothed WM RAVENS maps into separate factorial models for men and women, with alcohol consumption as covariate of interest, controlling for smoking, SBP and age (all covariates were entered in a single step). We performed Analysis of Covariance (ANCOVA) global normalization for ICV to identify regions where the trends in WM volume differ from global effects on ICV (Ashburner and Friston, 2000). Intracranial volume was calculated

using the template-warping algorithm modified for head image registration (Goldszal, et al., 1998). We adopted a threshold of $p < 0.001$ at the whole brain level; subsequently, to correct for multiple comparisons we applied Family-Wise Error (FWE) correction to clusters ($p < 0.05$) and report only FWE-corrected results. To visualize associated clusters, we used MRICron (<http://www.cabiatl.com/mricron/>) to overlay and/or surface-render SPM images on average WM images (calculated in SPM8 from participants' RAVENS maps). To localize clusters we report MNI coordinates; for localization regarding WM tracts, we consulted the atlases by Mori (Mori, 2005) and Orrison (Orrison, 2008), which use DTI data for tractography. To conduct follow-up analyses, we used the MarsBaR toolbox for SPM8 to extract the intensity of significant clusters, which, since the source images were RAVENS maps, represent the volume contained within the cluster. To assess the strength of the association of frontal CC cluster volume with alcohol consumption in men, we performed linear regression using SPSS 17.

3. Results

Cohort characteristics: Table 1 contains the descriptive characteristics of the cohort. Mean age was 70.22 ± 7.17 years; age was not associated with alcohol consumption by linear regression, including sex to the model ($\text{Beta} = -0.057$, $p = 0.587$). Men consumed greater amounts of alcohol compared to women [fixed effect of sex on alcohol consumption, with age as covariate: $F(1) = 4.598$, $p = 0.037$]. There was no effect of smoking status (never smokers vs. former smokers vs. current smokers) on alcohol consumption [mixed effects model including sex as a factor and age as a covariate, fixed effect of smoking on alcohol consumption: $F(2) = 1.484$, $p = 0.234$]. Moreover, there were no associations by linear regression, including age and sex to the model, between alcohol consumption and systolic blood pressure ($\text{Beta} = 0.110$, $p = 0.327$) or calculated dietary thiamine intake ($\text{Beta} = 0.046$, $p = 0.677$). Finally alcohol consumption did not have an effect on total intracranial volume by linear regression, including age and sex to the model ($\text{Beta} = -0.026$, $p = 0.796$).

WM VBM (Table 2)

In women, there were no WM areas associated with alcohol consumption. In men, alcohol consumption was negatively associated with the volume of a frontal CC cluster extending to the white matter of the (R) middle cingulate gyrus (peak voxel: 2, 10, 24; left-most voxel: -5, 10, 25; right-most voxel: 10, 10, 26; anterior-most CC voxel (midline): 0, 18, 22; posterior-most CC voxel (midline): 0, 4, 26; size = 2374 voxels; t -statistic = 4.11; uncorrected $p < 0.001$; cluster-level FEW-corrected $p = 0.045$; Figure a, b, c). Based on atlas definitions, this cluster appears to contain commissural fibers with multiple orientations and probably some cingulum bundle fibers. Of the commissural fibers crossing through this region: some are forwardly oriented towards bilateral anterior corona radiata, with a portion of those terminating on the anterior-most anterior cingulate gyrus; some are oriented towards the near premotor and motor areas; and, finally, some terminate on the near portions of bilateral middle cingulate gyrus.

A follow-up analysis of the frontal CC cluster volume performed to assess the magnitude of the association showed that in men a negative association exists with alcohol consumption ($\text{Beta} = -0.386$, $p = 0.007$; Figure 1d) and age ($\text{Beta} = -0.303$, $p = 0.026$), but no association exists with dietary thiamine ($\text{Beta} = 0.022$, $p = 0.869$). In women, none of these factors was associated with the frontal CC cluster volume (alcohol consumption: $\text{Beta} = 0.028$, $p = 0.871$; age: $\text{Beta} = 0.080$, $p = 0.645$; dietary thiamine: $\text{Beta} = -0.197$, $p = 0.270$; Figure 1d).

There were no positive or negative regional volumetric effects of smoking for WM or GM in this limited sample of BLSA participants.

GM VBM (Table 2)

In both men and women, we found a negative association between alcohol consumption and (L) lateral temporal areas.

4. Discussion

This study demonstrated that, in older men, higher alcohol consumption was associated with lower volume of a region of the frontal CC, controlling for cardiovascular risk factors that may affect the WM. This association was shown for a range of alcohol consumption generally considered as safe. This decrease in volume may be a factor that renders the frontal CC preferentially vulnerable to higher amounts of alcohol. Previous neuroimaging research has demonstrated frontal WM and callosal atrophy with alcoholism (Chanraud, et al., 2007; Estruch, et al., 1997; Pfefferbaum, et al., 2006; Schulte, et al., 2004). This study adds important new information by demonstrating atrophy in association with a wider range of alcohol consumption, including consumption within the “normal” range. Moreover, by performing global normalization by ANCOVA, we detected a region where the trend in WM volume differs from global effects, therefore identifying the premotor portion of the CC as its most vulnerable sub-region.

Factors determining the vulnerability of WM, in general, and of CC, in particular, to alcohol have largely been explored in the setting of alcoholism. Reduction of glial cells has been described in a dog model of alcoholism (Hansen, et al., 1991) and down-regulation of gene expression of glial fibrillary acidic protein, myelin-associated glycoprotein, and myelin basic protein, all critical for myelin formation, has been shown in alcoholism (Lewohl, et al., 2005). The WM damage in alcoholism is not uniform across brain regions, since frontal WM bundles (Pfefferbaum, et al., 2009) are most severely affected. Regarding the CC in alcoholism, it manifests up to 10% atrophy [mainly involving its trunk (body), genu and less so the splenium] (Chanraud, et al., 2007; Estruch, et al., 1997; Pfefferbaum, et al., 2006; Schulte, et al., 2004) and damage to its myelin, axons and vessels (Harper and Kril, 1988; Pfefferbaum, et al., 2006; Tarnowska-Dziduszko, et al., 1995). CC atrophy in alcoholics is correlated with total lifetime alcohol consumption (Estruch, et al., 1997) and is particularly pronounced (especially in the prefrontal CC subregion) in cases of alcoholic Wernicke’s encephalopathy (Lee, et al., 2005). The extreme manifestation of alcohol toxicity to the CC is Marchiafava-Bignami disease, which typically affects older alcoholic men and is characterized by demyelination, necrosis and cystic degeneration of the middle layer of the CC (Charness, 1993; Kohler, et al., 2000), especially at its frontal region (Heinrich, et al., 2004; Khaw and Heinrich, 2006). Data from a rat model of alcoholism suggest a synergistic effect of alcohol consumption and thiamine depletion for CC pathology (He, et al., 2007). Apart from atrophy, the CC of alcoholics’ shows lower fractional anisotropy and higher diffusivity, suggestive of decreased orientational coherence of CC fibers, which is further aggravated by age (Pfefferbaum, et al., 2006; Schulte, et al., 2005). This white matter disruption may be attributable to the accumulation of intracellular and extracellular fluid in excess of that occurring in aging (Pfefferbaum and Sullivan, 2005). The functional consequence of these changes could have adversely affect interhemispheric transfer, a previously reported functional change associated with alcohol (Schulte, et al., 2004; Schulte, et al., 2005). Reduced efficiency of interhemispheric transfer could, in turn, be related to decreased performance on tests of memory and executive function, which is observed in association with CC atrophy in alcoholics (Chanraud, et al., 2007; Estruch, et al., 1997).

In the absence of Diffusion Tensor Imaging (DTI) data, we cannot be certain about the cortical origin of the fiber tracts that cross the frontal CC cluster region. Based on the atlases by Mori (Mori, 2005) and Orrison (Orrison, 2008), commissural fibers from motor and especially premotor areas seem to be the majority in the area of the frontal CC cluster (Mori,

2005; Orrison, 2008). Recent studies have provided evidence to the fact that this region of the CC contains pre-motor fibers to the point of referring to this area as the “premotor” portion of the CC (Hofer and Frahm, 2006; Wahl and Ziemann, 2008). This finding may have implications for bilateral (especially bimanual) motor coordination in association with alcohol that require further investigation.

The negative association of left lateral temporal regions with alcohol consumption was an unexpected finding and its interpretation is currently unclear. Nevertheless, the finding is statistically strong and it holds independently for men and women. Therefore, we do consider it reliable and report it here, with the hope that it will generate new testable hypotheses and inform future research. We would simply like to note that (left greater than right) lateral temporal cortical thinning has been observed as a result of heavy fetal alcohol exposure (Sowell, et al., 2008; Zhou, et al., 2011). Our results suggest that the preferential vulnerability of this language-related region to alcohol seen during development may also be true during later life.

There are several limitations of this study. First, women in our cohort did not consume large quantities of alcohol, limiting our ability to detect possible associations in them. Therefore, the absence of an association between WM and alcohol consumption in our cohort of women should be interpreted with caution. Second, our alcohol consumption data were based on the subjects’ self-report, which correlates moderately with objective measures of alcohol consumption (Babor, et al., 2000; Whitford, et al., 2009); still self-report can be considered an adequate source of information, even for the purpose of clinical trials (Babor, et al., 2000). Third, the measures used in the current study to estimate alcohol consumption go back only 2.7 $\pm$ 1.1 years from the time of scanning. Thus we have not measured lifetime exposure in this analysis (Estruch, et al., 1997). Finally, the image processing methodology we followed requires the removal of the brainstem and cerebellum; therefore, we were unable to assess the effect of alcohol on these structures.

On the other hand, combining the RAVENS methodology for segmentation and normalization with statistical inference in SPM represents a major strength of this study, since the RAVENS approach is a validated mass-preserving methodology that quantifies tissue volumes rather than tissue density.

Future neuropathological studies should confirm and identify the microstructural changes associated with the neuroimaging finding of decreased CC volume. Alcohol-induced effects on the brain are partially reversible with abstinence, including frontal atrophy and metabolic abnormalities, as well as cognitive performance (Bartsch, et al., 2007; Bendszus, et al., 2001). In particular, the partial reversal of white matter atrophy may be attributable to myelin re-growth, whereas some non-reversible damage may be related to axonal loss (Bartsch, et al., 2007; Harper, 2009). An accurate characterization of these processes is critical in order to establish truly safe limits to alcohol consumption.

Acknowledgments

This research was supported in part by the Intramural Research Program of the NIH/NIA and in part by N01-AG-3-2124. We thank the neuroimaging and BLSA staffs at the NIA and Johns Hopkins University and the BLSA participants for their continued dedication to the study.

Role of the funding source

This research was supported in part by the Intramural Research Program of the NIH/NIA and in part by N01-AG-3-2124. The study was conducted as part of official duty for U.S. Government employees DK, JK, JM, LF and SR. The present manuscript underwent clearance for publication by NIA.

References

- Anstey KJ, Mack HA, Cherbuin N. Alcohol consumption as a risk factor for dementia and cognitive decline: meta-analysis of prospective studies. *Am J Geriatr Psychiatry*. 2009; 17(7):542–555. [PubMed: 19546653]
- Anttila T, Helkala EL, Viitanen M, Kareholt I, et al. Alcohol drinking in middle age and subsequent risk of mild cognitive impairment and dementia in old age: a prospective population based study. *BMJ*. 2004; 329(7465):539. [PubMed: 15304383]
- Ashburner J, Friston KJ. Voxel-based morphometry--the methods. *Neuroimage*. 2000; 11(6 Pt 1):805–821. [PubMed: 10860804]
- Babor TF, Steinberg K, Anton R, Del Boca F. Talk is cheap: measuring drinking outcomes in clinical trials. *J Stud Alcohol*. 2000; 61(1):55–63. [PubMed: 10627097]
- Bartsch AJ, Homola G, Biller A, Smith SM, et al. Manifestations of early brain recovery associated with abstinence from alcoholism. *Brain*. 2007; 130(Pt 1):36–47. [PubMed: 17178742]
- Bendszus M, Weijers HG, Wiesbeck G, Warmuth-Metz M, et al. Sequential MR imaging and proton MR spectroscopy in patients who underwent recent detoxification for chronic alcoholism: correlation with clinical and neuropsychological data. *AJNR Am J Neuroradiol*. 2001; 22(10):1926–1932. [PubMed: 11733327]
- Chanraud S, Martelli C, Delain F, Kostogianni N, et al. Brain morphometry and cognitive performance in detoxified alcohol-dependents with preserved psychosocial functioning. *Neuropsychopharmacology*. 2007; 32(2):429–438. [PubMed: 17047671]
- Charness ME. Brain lesions in alcoholics. *Alcohol Clin Exp Res*. 1993; 17(1):2–11. [PubMed: 8452204]
- Davatzikos C, Genc A, Xu D, Resnick SM. Voxel-based morphometry using the RAVENS maps: methods and validation using simulated longitudinal atrophy. *Neuroimage*. 2001; 14(6):1361–1369. [PubMed: 11707092]
- Davatzikos C, Resnick SM. Sex differences in anatomic measures of interhemispheric connectivity: correlations with cognition in women but not men. *Cereb Cortex*. 1998; 8(7):635–640. [PubMed: 9823484]
- de Bruin EA, Hulshoff Pol HE, Bijl S, Schnack HG, et al. Associations between alcohol intake and brain volumes in male and female moderate drinkers. *Alcohol Clin Exp Res*. 2005a; 29(4):656–663. [PubMed: 15834232]
- de Bruin EA, Hulshoff Pol HE, Schnack HG, Janssen J, et al. Focal brain matter differences associated with lifetime alcohol intake and visual attention in male but not in female non-alcohol-dependent drinkers. *Neuroimage*. 2005b; 26(2):536–545. [PubMed: 15907310]
- de la Monte SM. Disproportionate atrophy of cerebral white matter in chronic alcoholics. *Arch Neurol*. 1988; 45(9):990–992. [PubMed: 3415529]
- Ding J, Eigenbrodt ML, Mosley TH Jr, Hutchinson RG, et al. Alcohol intake and cerebral abnormalities on magnetic resonance imaging in a community-based population of middle-aged adults: the Atherosclerosis Risk in Communities (ARIC) study. *Stroke*. 2004; 35(1):16–21. [PubMed: 14657449]
- Estruch R, Nicolas JM, Salameiro M, Aragon C, et al. Atrophy of the corpus callosum in chronic alcoholism. *J Neurol Sci*. 1997; 146(2):145–151. [PubMed: 9077511]
- Ganguli M, Vander Bilt J, Saxton JA, Shen C, et al. Alcohol consumption and cognitive function in late life: a longitudinal community study. *Neurology*. 2005; 65(8):1210–1217. [PubMed: 16247047]
- Goldszal AF, Davatzikos C, Pham DL, Yan MX, et al. An image-processing system for qualitative and quantitative volumetric analysis of brain images. *J Comput Assist Tomogr*. 1998; 22(5):827–837. [PubMed: 9754125]
- Hansen LA, Natelson BH, Lemere C, Niemann W, et al. Alcohol-induced brain changes in dogs. *Arch Neurol*. 1991; 48(9):939–942. [PubMed: 1953418]
- Harper C. The neuropathology of alcohol-specific brain damage, or does alcohol damage the brain? *J Neuropathol Exp Neurol*. 1998; 57(2):101–110. [PubMed: 9600202]

- Harper C. The neuropathology of alcohol-related brain damage. *Alcohol Alcohol*. 2009; 44(2):136–140. [PubMed: 19147798]
- Harper C, Matsumoto I. Ethanol and brain damage. *Curr Opin Pharmacol*. 2005; 5(1):73–78. [PubMed: 15661629]
- Harper CG, Kril JJ. Corpus callosal thickness in alcoholics. *Br J Addict*. 1988; 83(5):577–580. [PubMed: 3382816]
- He X, Sullivan EV, Stankovic RK, Harper CG, et al. Interaction of thiamine deficiency and voluntary alcohol consumption disrupts rat corpus callosum ultrastructure. *Neuropsychopharmacology*. 2007; 32(10):2207–2216. [PubMed: 17299515]
- Heinrich A, Runge U, Khaw AV. Clinicoradiologic subtypes of Marchiafava-Bignami disease. *J Neurol*. 2004; 251(9):1050–1059. [PubMed: 15372245]
- Hofer S, Frahm J. Topography of the human corpus callosum revisited—comprehensive fiber tractography using diffusion tensor magnetic resonance imaging. *Neuroimage*. 2006; 32(3):989–994. [PubMed: 16854598]
- Hommer D, Momenan R, Kaiser E, Rawlings R. Evidence for a gender-related effect of alcoholism on brain volumes. *Am J Psychiatry*. 2001; 158(2):198–204. [PubMed: 11156801]
- Ihara H, Berrios GE, London M. Group and case study of the dysexecutive syndrome in alcoholism without amnesia. *J Neurol Neurosurg Psychiatry*. 2000; 68(6):731–737. [PubMed: 10811696]
- Kabani N, Dorr AE, Lerch JP, Spring S, et al. High resolution three-dimensional brain atlas using an average magnetic resonance image of 40 adult C57Bl/6J mice. *Neuroimage*. 2008; 42(1):60–69. [PubMed: 18502665]
- Khaw AV, Heinrich A. Marchiafava-Bignami disease: diffusion-weighted MRI in corpus callosum and cortical lesions. *Neurology*. 2006; 66(8):1286. author reply 1286. [PubMed: 16636264]
- Kohler CG, Ances BM, Coleman AR, Ragland JD, et al. Marchiafava-Bignami disease: literature review and case report. *Neuropsychiatry Neuropsychol Behav Neurol*. 2000; 13(1):67–76. [PubMed: 10645739]
- Kril JJ. The contribution of alcohol, thiamine deficiency and cirrhosis of the liver to cerebral cortical damage in alcoholics. *Metab Brain Dis*. 1995; 10(1):9–16. [PubMed: 7596332]
- Kril JJ, Halliday GM, Svoboda MD, Cartwright H. The cerebral cortex is damaged in chronic alcoholics. *Neuroscience*. 1997; 79(4):983–998. [PubMed: 9219961]
- Lee ST, Jung YM, Na DL, Park SH, et al. Corpus callosum atrophy in Wernicke's encephalopathy. *J Neuroimaging*. 2005; 15(4):367–372. [PubMed: 16254403]
- Lewohl JM, Wixey J, Harper CG, Dodd PR. Expression of MBP, PLP, MAG, CNP, and GFAP in the Human Alcoholic Brain. *Alcohol Clin Exp Res*. 2005; 29(9):1698–1705. [PubMed: 16205370]
- Mann K, Ackermann K, Croissant B, Mundle G, et al. Neuroimaging of gender differences in alcohol dependence: are women more vulnerable? *Alcohol Clin Exp Res*. 2005; 29(5):896–901. [PubMed: 15897736]
- Misra C, Fan Y, Davatzikos C. Baseline and longitudinal patterns of brain atrophy in MCI patients, and their use in prediction of short-term conversion to AD: results from ADNI. *Neuroimage*. 2009; 44(4):1415–1422. [PubMed: 19027862]
- Mori, S. MRI atlas of human white matter. Vol. viii. Amsterdam ; Boston: Elsevier; 2005. p. 239
- Moselhy HF, Georgiou G, Kahn A. Frontal lobe changes in alcoholism: a review of the literature. *Alcohol Alcohol*. 2001; 36(5):357–368. [PubMed: 11524299]
- Mukamal KJ, Kuller LH, Fitzpatrick AL, Longstreth WT Jr, et al. Prospective study of alcohol consumption and risk of dementia in older adults. *JAMA*. 2003; 289(11):1405–1413. [PubMed: 12636463]
- Mukamal KJ, Longstreth WT Jr, Mittleman MA, Crum RM, et al. Alcohol consumption and subclinical findings on magnetic resonance imaging of the brain in older adults: the cardiovascular health study. *Stroke*. 2001; 32(9):1939–1946. [PubMed: 11546878]
- Ngandu T, Helkala EL, Soininen H, Winblad B, et al. Alcohol drinking and cognitive functions: findings from the Cardiovascular Risk Factors Aging and Dementia (CAIDE) Study. *Dement Geriatr Cogn Disord*. 2007; 23(3):140–149. [PubMed: 17170526]
- Orrison, WW. Atlas of brain function. Vol. xi. New York: Thieme; 2008. p. 304

- Panza F, Capurso C, D'Introno A, Colacicco AM, et al. Alcohol drinking, cognitive functions in older age, predementia, and dementia syndromes. *J Alzheimers Dis.* 2009; 17(1):7–31. [PubMed: 19494429]
- Pfefferbaum A, Adalsteinsson E, Sullivan EV. Dysmorphology and microstructural degradation of the corpus callosum: Interaction of age and alcoholism. *Neurobiol Aging.* 2006; 27(7):994–1009. [PubMed: 15964101]
- Pfefferbaum A, Rosenbloom M, Deshmukh A, Sullivan E. Sex differences in the effects of alcohol on brain structure. *Am J Psychiatry.* 2001; 158(2):188–197. [PubMed: 11156800]
- Pfefferbaum A, Rosenbloom M, Rohlfing T, Sullivan EV. Degradation of association and projection white matter systems in alcoholism detected with quantitative fiber tracking. *Biol Psychiatry.* 2009; 65(8):680–690. [PubMed: 19103436]
- Pfefferbaum A, Sullivan EV. Disruption of brain white matter microstructure by excessive intracellular and extracellular fluid in alcoholism: evidence from diffusion tensor imaging. *Neuropsychopharmacology.* 2005; 30(2):423–432. [PubMed: 15562292]
- Pham DL, Prince JL. Adaptive fuzzy segmentation of magnetic resonance images. *IEEE Trans Med Imaging.* 1999; 18(9):737–752. [PubMed: 10571379]
- Resnick SM, Goldszal AF, Davatzikos C, Golski S, et al. One-year age changes in MRI brain volumes in older adults. *Cereb Cortex.* 2000; 10(5):464–472. [PubMed: 10847596]
- Sasaki H, Abe O, Yamasue H, Fukuda R, et al. Structural and diffusional brain abnormality related to relatively low level alcohol consumption. *Neuroimage.* 2009; 46(2):505–510. [PubMed: 19233298]
- Schulte T, Pfefferbaum A, Sullivan EV. Parallel interhemispheric processing in aging and alcoholism: relation to corpus callosum size. *Neuropsychologia.* 2004; 42(2):257–271. [PubMed: 14644111]
- Schulte T, Sullivan EV, Muller-Oehring EM, Adalsteinsson E, et al. Corpus callosal microstructural integrity influences interhemispheric processing: a diffusion tensor imaging study. *Cereb Cortex.* 2005; 15(9):1384–1392. [PubMed: 15635059]
- Shen D, Davatzikos C. HAMMER: hierarchical attribute matching mechanism for elastic registration. *IEEE Trans Med Imaging.* 2002; 21(11):1421–1439. [PubMed: 12575879]
- Shin YW, Kim DJ, Ha TH, Park HJ, et al. Sex differences in the human corpus callosum: diffusion tensor imaging study. *Neuroreport.* 2005; 16(8):795–798. [PubMed: 15891572]
- Sowell ER, Mattson SN, Kan E, Thompson PM, et al. Abnormal cortical thickness and brain-behavior correlation patterns in individuals with heavy prenatal alcohol exposure. *Cereb Cortex.* 2008; 18(1):136–144. [PubMed: 17443018]
- Taki Y, Kinomura S, Sato K, Goto R, et al. Both global gray matter volume and regional gray matter volume negatively correlate with lifetime alcohol intake in non-alcohol-dependent Japanese men: a volumetric analysis and a voxel-based morphometry. *Alcohol Clin Exp Res.* 2006; 30(6):1045–1050. [PubMed: 16737464]
- Tarnowska-Dziduszko E, Bertrand E, Szpak GM. Morphological changes in the corpus callosum in chronic alcoholism. *Folia Neuropathol.* 1995; 33(1):25–29. [PubMed: 8673416]
- Wahl M, Ziemann U. The human motor corpus callosum. *Rev Neurosci.* 2008; 19(6):451–466. [PubMed: 19317183]
- Whitford JL, Widner SC, Mellick D, Elkins RL. Self-report of drinking compared to objective markers of alcohol consumption. *Am J Drug Alcohol Abuse.* 2009; 35(2):55–58. [PubMed: 19322728]
- Zhou D, Lebel C, Lepage C, Rasmussen C, et al. Developmental cortical thinning in fetal alcohol spectrum disorders. *Neuroimage.* 2011; 58(1):16–25. [PubMed: 21704711]

Figure.

The frontal CC cluster (peak voxel MNI co-ordinates: 2, 10, 24) negatively associated with alcohol consumption in men. **a.** Axial interpolation of the cluster on the average image from the WM RAVENS maps of fifty-six men. **b.** 3D-rendering of the cluster on the average image from the WM RAVENS maps of fifty-six men (left sagittal view). **c.** 3D-rendering of the cluster on the average image from the WM RAVENS maps of fifty-six men (anterior coronal view). **d.** Frontal CC cluster volume and alcohol consumption. The y-axis depicts WM RAVENS map intensities for the corpus callosum cluster, which represent the WM volume contained in the cluster (for a detailed explanation of the RAVENS maps methodology, see Methods); the x-axis depicts alcohol consumption in units/week. ROI = region of interest; CC = corpus callosum; green dots/regression line = men; blue dots/regression line = women.

Table 1

Cohort characteristics.

Categorical variables	Levels	Alcohol consumption (units/week)
Sex *	Women (37)	2.98 (SE= 1.68)
	Men (56)	7.62 (SE= 1.27)
Smoking status	Never smokers (27)	2.82 (SE= 1.98)
	Former smokers (64)	7.89 (SE= 1.49)
	Current smokers (2)	2.50 (SE= 5.86)
Continuous variables		Mean (SD)
Age		70.22 (SD = 7.17) years
Systolic Blood Pressure		139.37 (SD= 20.55) mmHg
Dietary Thiamine		2.31 (SD= 1.17) mg
Intracranial volume		1.31 (SD = 0.12) lt

SE = standard error; SD = standard distribution.

Factors significantly associated with alcohol consumption ($p < 0.05$) are marked by *.

Table 2

VBM Results

	Contrast	Cluster size (voxels)	Peak-voxel Z score for t-statistic	Significance level for t-statistic (cluster-level FWE correction)	Localization (peak-voxel MNI coordinates, neuroanatomical and according to Brodmann)
WM: women	Negative correlation with alcohol	-	-	-	
WM: men	Negative correlation with alcohol	2374	4.11	p = 0.045	2, 10, 24 premotor CC
GM: women	Negative correlation with alcohol	1109	3.98	p = 0.009	-72, -42, -2 (L) MTG, BA 21
GM: men	Negative correlation with alcohol	1723	4.29	p < 0.001	-70, -33, 9 (L) STG, BA 22
		1748	3.96	p < 0.001	-60, -31, -4 (L) MTG, BA 21
		1396	3.61	p = 0.002	-64, -8, -4 (L) MTG, BA 21