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Associations Between Cerebellar Subregional Morphometry and Alcoholism History in Men and Women

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Abstract

Background—Alcoholism has been linked to deficits in cognitive, behavioral, and emotional functions, and the cerebellum is important for optimal functioning of these abilities. However, little is known about how individual differences such as gender and drinking history might influence regional cerebellar abnormalities.

Methods—Volumetric analyses of the cerebellum and its subregions were performed in relation to the interaction of gender and measures of drinking history. Structural magnetic resonance imaging (MRI) scans of 44 alcoholic individuals (23 men) and 39 nonalcoholic controls (18 men) were obtained. In addition to measuring total cerebellar gray and white matter volumes, we measured 64 individual cerebellar parcellation units, as well as functionally-defined a priori regions of interest that have been shown to correspond to functions impaired in alcoholism.

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Results—Total cerebellar white matter volume was smaller in alcoholic relative to nonalcoholic participants. Moreover, volumes of parcellation units varied with drinking history, showing negative associations between years of heavy drinking and the anterior lobe, the vestibulocerebellar lobe, and the spinocerebellar subdivision. The negative association between anterior volume and years of heavy drinking was driven primarily by alcoholic men. Additionally, we observed larger white and gray matter volumes for alcoholic women than for alcoholic men.

Conclusions—The identification of drinking-related abnormalities in cerebellar subregions lays a foundation that can be utilized to inform how cerebro-cerebellar networks are perturbed in this pathological condition. These results also provide estimates of how gender and individual differences in drinking history can predict cerebellar volumes.

Keywords

Alcohol; MRI; gender; cerebellum; brain; volume

Introduction

Alcoholism is a pervasive disease that negatively impacts not only the medical, psychological, and social well-being of those afflicted, but also the lives of people with whom alcoholics interact (Nutt et al, 2010). Chronic exposure to alcohol has effects on multiple bodily systems, including the brain. Within the brain, not all regions are affected equally, and the cerebellum, one of the more affected regions, is involved in many of the functions observed to be abnormal in association with chronic alcoholism. Specifically, motor abnormalities, postural instability, vestibular reflex abnormalities, as well as a range of cognitive and affective impairments are associated with both chronic alcoholism and cerebellar dysfunction (DeLong and Strick, 1974, Sullivan et al, 2003). Thus, chronic alcohol abuse could affect any or all such processes via cerebellar perturbations (Oscar-Berman and Marinkovic, 2007).

Indications that the cerebellum might represent a brain focus in alcoholism date back to early clinical reports by Bekhterev (1900), and there has been a long history in the medical literature dealing with cerebellar pathology in alcoholic patients (Victor et al, 1959, Cavanagh et al, 1997). The literature has provided a background of extensive and valuable neuropathological observations of degeneration within cerebellar lobes, which has formed the basis of the present study: We used high field magnetic resonance imaging (MRI) to quantitate the relationship between chronic alcoholism and abnormalities in cerebellar subregional morphology. Thus, while it is clear that global volumetric assessments of the cerebellum (e.g., gray matter, white matter, and total cerebellum) have indicated smaller volumes in alcoholics (AL) relative to nonalcoholics (NA) (Sullivan et al, 2000a), volumetric assessments of specific cerebellar subregions have rarely been conducted, with few exceptions: separate hemispheric volumes (e.g., Chanraud et al, 2007), and total or partial vermal volumes (e.g., Cavanagh et al, 1997, Phillips et al, 1987). Therefore, our primary objective was to address regional cerebellar involvement in alcoholism by taking a more fine-grained and novel approach to delineating meaningful structurally and functionally defined cerebellar volumetric regions of interest. Such an approach, which avoids potentially diluting effects (i.e., only measuring large regions when a small sub-

region is meaningful), is important because of the cerebellum's functional diversity and its regional and connective specificity. Thus, localized anatomic or functional reductions might have been overlooked in previous work.

The cerebellum is somatotopically organized with respect to function and structure such that specific regions are associated with different functions and are also connected to specific cerebral regions. For example, the anterior lobe and lobule VIII are associated with motor functioning, whereas the lateral hemispheres (especially Crus I and II) are commonly associated with various cognitive functions, and regions of the vermis have been found to be involved in emotional processes (Stoodley and Schmahmann, 2010). Using non-human primates, Strick, Dum, and Fiez (2009) have shown that neurons project (via relay nuclei) from Brodmann's (1909) area 9 to lobule VII of the cerebellum, and neurons from primary motor cortex project to lobules in the anterior cerebellar lobe. These data provide an anatomical substrate for the role of the cerebellum in both motor and non-motor processes. They also establish the significance of carefully parcellating the cerebellum into meaningful functionally defined units in order to understand its possible role in alcoholism and alcoholism-related deficits.

To address this issue, we used a manual parcellation method developed by Makris and colleagues (2003, 2005) to parcellate the cerebellum into predefined units. First, we examined broad regions to replicate and extend findings from prior literature: total cerebellum, total gray and white matter, along with total anterior and total posterior lobe volumes. Second, we examined regions bounded mediolaterally by their histological cerebral connections: vestibulocerebellum (i.e., flocculonodular lobe), the spinocerebellum, and the cerebrocerebellum. Third, we examined regions associated with the cerebellar functions related to domains shown to be impaired in alcoholism: motor (Fitzpatrick et al, 2012), somatosensory (Ammendola et al, 2001), spatial (Kopera et al, 2012), language (Davies et al, 2005; Fernandez-Serrano et al, 2010), working memory (Pitel et al, 2007), executive function (Oscar-Berman et al, 2009), and emotion (Gilman et al, 2010; Valmas et al, 2014); also see review by Oscar-Berman and colleagues (2014).

The second objective of this study was to examine cerebellar volumes in relation to drinking habits and abstinence, since these are known to influence volumetric measures of other brain structures (Oscar-Berman et al, 2014; Ruiz et al, 2013). Finally, because alcoholism can have gender-specific biomarkers and/or divergent underlying neural consequences for men and women (Ruiz and Oscar-Berman, 2013), the third and final objective was to examine potential gender differences in cerebellar volumes, especially as they might relate to drinking history.

Methods

Participants

The study included 44 abstinent long-term chronic alcoholic participants (21 women) and 39 nonalcoholic control participants (21 women). Table 1 provides participant characteristics, and the source data for the entire study are provided in the Supplemental Dataset. Participants were recruited through flyers posted in Boston University Medical Center, the

Veterans Affairs Healthcare System, and the Boston metropolitan area, as well as through newspaper and web-based advertisements. The research was approved by the Institutional Review Boards of the participating institutions, and informed consent was obtained from each subject.

During an initial screening phase, potential participants were given handedness and drug-use questionnaires, and they underwent a medical history interview and vision testing to ensure they met inclusion criteria. Qualifying participants were given the Computerized Diagnostic Interview Schedule (Robins, 2004), which provides psychiatric diagnoses according to criteria established by the American Psychiatric Association (American Psychiatric Association, 2000). Participants were excluded from further participation if English was not one of their first languages, if they were predominantly left-handed, or if they had one of the following: Korsakoff's syndrome; HIV; cirrhosis; major head injury with loss of consciousness greater than 15 minutes unrelated to alcoholism; stroke; epilepsy or seizures unrelated to alcoholism; schizophrenia and other psychotic disorders; bipolar II; Hamilton Rating Scale for Depression (HRSD; Hamilton, 1960) score over 17; or history of drug use once per week or more within the past five years (except for two AL (one woman) with occasional marijuana use more than five months before testing).

A number of participants were taking medications for a variety of conditions, had used illicit drugs at some point over five years prior to enrollment, or had a potentially confounding medical history (e.g., hepatitis or current psychotropic medications). Therefore, to confirm that results were independent of these potential confounds, we created a subgroup (referred to hereafter as the *unconfounded* subsample; see Supplemental Table 1) consisting of 49 participants (9 AL women, 7 AL men, 18 NA women, 15 NA men) without these confounding factors. This subgroup also excludes 20 individuals (13 men) who had used marijuana more than once per week for at least one year, four people who had used cocaine more than once per week (one for ten years, and three for less than two years), and two people who had used amphetamines more than once per week (both for one year or less). This subgroup also was restricted to include only individuals for whom no source indicated hepatitis or any current recurrent major depressive, bipolar I, or generalized anxiety disorder.

All participants received the Alcohol Use Disorders Identification Test (AUDIT), a questionnaire developed by the World Health Organization that has been shown to be a reliable and valid screening instrument for detecting hazardous and harmful drinkers (Reinert and Allen, 2007). For the AL group, we modified the questionnaire to indicate past tense, and asked participants to answer regarding the time they were drinking heavily. Participants also were administered the Alcohol Use Questionnaire, a structured interview regarding their drinking patterns (Cahalan et al, 1969), i.e., length of sobriety (LOS, in years), duration of heavy drinking (DHD, in years), and a quantity frequency index (ounces of ethanol per day; roughly equivalent to daily drinks [DD]). The LOS refers to the period between the MRI scan date and the last drink participants remembered having. The DHD represents the total number of years participants drank at least 21 drinks per week (i.e., an average of 3/day). The DD measure refers to alcohol consumed during the last six months (for NA participants), or to the six months preceding cessation of drinking (for AL participants). Five AL participants drank fewer than 3/day during the six months prior to

cessation; therefore, as a more accurate measure of the amount consumed, DD was scored as the number of drinks per day during last six months of heavy drinking. Subjects also were asked about family history of alcoholism (see Supplemental Table 2).

Full Scale IQ scores were obtained using the Wechsler Adult Intelligence Scale, Fourth Edition (Wechsler, 2008), and are reported in Table 1, along with age, education, DHD, DD, LOS, and AUDIT scores. Participants' ages ranged from 26 to 81, with an overall mean age of 55 years. The AL men had significantly higher DHD, DD, and shorter LOS than the AL women. Therefore, to address the potential confounding effect of gender differences in drinking histories, we analyzed a subsample (48 participants, split evenly) whereby subjects' drinking histories were selected to be similar for AL men and AL women (referred to hereafter as the *matched* subsample; Supplemental Table 1).

Scan Acquisition Protocol

MRI scans were obtained at Massachusetts General Hospital, Boston (MGH) on a 3 Tesla Siemens (Munich, Germany) MAGNETOM Trio Tim scanner with a 32-channel head coil. Image acquisitions included two T1 weighted multi-echo MP-RAGE series for volumetric analysis (one AL man had only one series) with these parameters: TR = 2530 ms; TE = 1.79 ms, 3.71 ms, 5.63 ms, 7.55 ms (root mean square [RMS] average used); flip angle = 7 degrees; field of view = 256 mm; matrix = 256 × 256; slice thickness = 1 mm with 50% distance factor; 176 interleaved sagittal slices; GRAPPA acceleration factor = 2. The two RMS multi-echo MP-RAGE scans were averaged.

MRI Cerebellar Morphometric Analysis

Our method was adapted from the *MRI Atlas of the Human Cerebellum* (Schmahmann et al, 1999) to identify landmarks in the cardinal planes according to CardViews software for quantitative labeling (Caviness et al, 1996; Makris et al, 2005). These procedures, developed by the Center for Morphometric Analysis at MGH (Makris et al, 2003, 2005), have shown good validity and reliability (Makris et al., 2005), and have been used to examine cerebellar abnormalities associated with other disorders (e.g., autism, Hodge et al, 2010; and trichotillomania, Keuthen et al, 2007). As of the writing of this report, updated versions of these manually-based structural MRI analysis methods were not yet available for release to interested investigators.

The cerebellum was first segmented into gray and white matter, and global measures of gray, white, and total cerebellar volumes were computed. We obtained regional cerebellar volumes by semi-automatically segmenting each coronal slice of the cerebellum. Next, the cortex of the cerebellum was parcellated into lobules I through X. The lobules were subdivided into vermal, medial, and lateral zones. The parcellation units are bounded by eleven subdivisions landmarked mediolaterally by fissures (Makris et al, 2003), intersected by two longitudinal sagittal borders and the longitudinal paravermian sulcus (Makris et al, 2005). Thus, the lateral zones of Crus I and Crus II of lobule VIIA were subdivided into medial and distal portions, and a total of 32 units were specified within each hemisphere (for a total of 64 units). An example of labeled raw MR cerebellar images can be found in Figure 8 of the paper by Makris and colleagues (2003).

Segmentation of the cerebellar exterior, gray matter, and white matter, along with parcellation of the cerebellar cortex, were carried out by a research assistant with training in neuroanatomy, supervised by an expert neuroanatomist. Blindness of group assignment was maintained during analysis. High inter-rater and intra-rater reliability of these methods has been established (Makris et al., 2005). Estimated total intracranial volume was obtained by using a scaling factor from the whole head to an atlas (Buckner et al, 2004) included in the FreeSurfer software package version 5.3.0 (<https://surfer.nmr.mgh.harvard.edu>). All cerebellar regions were examined as a proportion of estimated total intracranial volume. Additionally, the raw volumes of all of the cerebellar regions are provided in Supplemental Table 3.

We followed a disciplined a priori procedure by combining parcellation units selected from the 64-unit scheme (Makris et al, 2003) into relevant regions justified by prior literature. Eight of these newly constructed volumes were anatomically-defined regions, and seven were functionally-defined regions. The anatomically-defined regions (Makris et. al., 2005) were: total cerebellar volume (gray and white matter combined), total cerebellar gray matter (cerebellar cortex), total cerebellar white matter, anterior cerebellar cortex, posterior cerebellar cortex, vestibulocerebellum, spinocerebellum, and cerebrocerebellum. The functionally-defined regions were delineated in a meta-analysis by Stoodley and Schmahmann (2009), along with an fMRI study by Stoodley et al. (2010): motor, somatosensory, spatial, language, working memory, executive function, and emotion. Importantly, these neuropsychological abilities are impaired in alcoholism (Oscar-Berman et al, 2014). The loci from Stoodley and Schmahmann's (2009) meta-analysis were superimposed on the regions delineated in Schmahmann's atlas (1999) and adapted with a quantitative framework for cerebellar morphometric analyses (Figure 1).

Statistical Analyses

We used JMP Pro software (Version 11, SAS Institute, Inc., Cary, NC) for statistical analyses. For each region examined, analysis of covariance was used to delineate group and gender differences. A factorial model was constructed with factors of age, group, gender, and the interaction of group and gender. Next, independent comparisons between the four subgroups were conducted to quantify the observed differences. Confidence intervals (CI) of the mean differences are provided in Tables 1 and 2.

Multiple regression analyses with age as a covariate were conducted to assess the impact of drinking history. Measures of DHD, DD, and LOS were investigated for the AL group alone. The slopes are reported for significant findings (Tables 3-5).

Each volumetric outcome measure was evaluated for normality by examining normal probability plots. No regions were significantly abnormally distributed (Shapiro-Wilk W, all $p > 0.05$). Results were examined to ensure that each group did not differ by variability using Levene's test, and homoscedasticity and linearity of regression assumptions were confirmed by examining residual by predicted plots. For each model, participants were removed if the Cook's D values indicated disproportionate influence. This resulted in the exclusion of zero to two subjects per model.

All effects reported (alcoholism, DHD, DD, LOS, and gender interactions) were consistently observed within the unconfounded and matched subsamples (i.e., the subgroup effects were within the 95% CI of the total group effects), indicating that the reported results were not caused by subject confounds or gender differences in alcohol histories. As such, we present the results for only the total sample.

Following the a priori analyses, in order to take full advantage of the meticulous manual parcellation, we employed a false discovery rate (FDR) corrected multiple regression exploratory analysis of all 64 cerebellar units. Age was included as a covariate, and robust fit Huber M-estimates were used to reduce outlier sensitivity for all exploratory analyses.

Results

Between-group differences in cerebellar volumes

Significant cerebellar white matter volumetric deficits were observed for the AL group compared to the NA group (6.1% smaller; see Table 2 and Figure 2). Total cerebellar white matter was significantly smaller for AL than NA men (8.7% reduction), and a similar trend was identified for women. There were no group by gender interactions. However, within-group gender differences were observed. That is, the AL women had 7.7% larger total cerebellar volumes than AL men, and a similar gender effect size was observed for the NA group, though it did not reach statistical significance. Table 2 lists the a priori cerebellar subregions that were larger for women than for men as a percentage of estimated total intracranial volume.

Our exploratory FDR-corrected analyses of group and gender effects for the 64 cerebellar parcellation units revealed no significant differences.

Relationships between drinking variables and cerebellar volumes

Duration of heavy drinking—Widespread effects of years of drinking heavily were observed, with estimates centered at roughly 0.5% to 1.0% smaller volumes per year (Table 3). For the AL group, significant associations with DHD were observed for volumes of several regions (Figure 3): the total cerebellum (-0.3%/year), gray matter (-0.3%/year), anterior lobe (-1.0%/year), vestibulocerebellum (-0.8%/year), spinocerebellum (-0.5%/year), and the motor region (-0.5%/year). There was a group by gender interaction for the anterior lobe, whereby the volumes for men were 1.4% smaller per year of heavy drinking, but the volumes for women were slightly, but insignificantly larger (Figure S1).

The exploratory FDR-corrected analyses revealed significant main effects of DHD for the left vermal lobule X (smaller by 0.9%/year) and right lateral lobule X (smaller by 0.6%/year). These analyses also revealed three DHD by gender interactions. The interactions were significant for the volumes of the right lobule VIIA (Crus II) medial region, the right lobule V medial region, and the left lobule V lateral region. The Crus II interaction showed that the volumes for alcoholic women were 2.4% larger per year drinking, whereas for alcoholic men, the volumes were 0.7% smaller per year. For the right medial lobule V, the men tended to have 1.3% smaller volumes for each year drinking; the deficits were less for the women.

The interaction for the left lateral lobule V also indicated a negative relationship for the men (2.8%/year) but positive for the women (2.2%/year larger).

Daily drinks—Our analyses of a priori volumes, as well as our exploratory analyses, showed no significant relationships to daily drinks (Table 4).

Length of sobriety—When examining LOS, the vestibulocerebellum was identified to be 0.6% larger for each year of abstinence (see Figure S2). Significant relationships were not identified for AL men or AL women examined independently, and no significant interactions of LOS with gender were observed (see Table 5).

The exploratory analyses uncovered significant interactions of LOS with gender for vermal lobule I/II bilaterally. For AL men, positive relationships were identified (right 7.2%/year, left 6.5%/year), while the positive associations for women were not as extreme. Main effects of LOS were significant for the same regions, with men driving the overall relationship.

Discussion

Our results support and extend prior reports that cerebellar white matter volume is smaller in individuals with chronic alcoholism histories relative to individuals with no such histories (Sullivan et al, 2000a). Our finding of a substantially smaller total cerebellar volume, which was on the order of 5 to 10%, also expands upon prior work that highlighted *cerebral* white matter volume reductions in association with chronic alcoholism (Ruiz et al, 2013).

Additionally, our findings support early reports showing restricted degeneration of the cerebellum's anterior lobe (Victor et al, 1959).

We also found connections between duration of heavy drinking (DHD) and cerebellar volumes. Average declines were on the order of about half a percent of volume per year of heavy drinking, but some declines were larger. For regions most affected, males and females combined showed smaller volumes of lobule X (left vermal 0.9% per year; left lateral 0.6% per year), which could possibly play a role in the postural (lateral lobule X) and autonomic (vermal lobule X) deficits observed in alcoholics (Rosenbloom et al, 2007; Sawyer et al, 2015; Sullivan et al, 2000c, 2004). The smaller volumes of this region, also called the vestibulocerebellum, is notable in light of literature showing gait, balance, and other motor deficits in association with heavy drinking (Rosenbloom et al, 2007; Sullivan et al, 2004).

Regarding gender differences, the volume of the anterior lobe of the cerebellum, involved in motor functions (Stoodley and Schmahmann, 2009), was negatively associated with DHD for AL men (1.4% reduction of volume per year), a relationship that was significantly stronger than the one observed for women. Our exploratory analyses revealed that alcoholic women (but not men) had 2.4% larger volumes of lobule VIIA, involving emotion and language (Stoodley and Schmahmann, 2009), in association with more years drinking. The observation that DHD has a larger negative relationship to some cerebellar volumes in men than in women might reflect greater vulnerability in these structures for men than women.

In addition, negative associations with DHD were observed for the spinocerebellum (-0.5%/year) and for the motor region (-0.5%/year). These results are congruent with research that

has shown motor ability and postural deficits in alcoholics (Sullivan et al, 2000c, 2002, 2006). The spinocerebellum is heavily involved in motor function, as is demonstrated by the high degree of overlap with the functionally-defined motor region.

Regarding the relationship between cerebellar volumes and number of drinks per day, our results revealed that any possible declines for all of the a priori and exploratory subregions are small. In other words, drinks per day was a poor predictor of volume, which is somewhat surprising in light of the evidence that binge drinking is more detrimental than is drinking less but on a regular basis (Wetterling et al, 1999).

Duration of abstinence was positively associated with larger volume of the vestibulocerebellum. In exploratory regions, we also observed potential recovery of the volume of the vermal portion of lobule I/II. The vestibulocerebellum and the vermal portion of lobule I/II (part of the anterior lobe) serve functions involving motor control. As a consequence, and on the basis of our results, we predict that future studies would show that alcoholics with longer periods of sobriety have better postural and motor control. In all other a priori and exploratory subregions, LOS, like DD, was a poor predictor of volume. However, and as noted below, our participants were sober for an average of eight years. Therefore, it is also possible that volumetric recovery might have occurred early-on in the abstinence period and then plateaued. If so, the temporal pattern of recovery could have been obscured by analyses examining linear relationships. Assessments of cerebellar volume after variable shorter durations of abstinence, and assessments at multiple time-points post sobriety, would help address this issue.

The effect of aging on cerebellar atrophy has been estimated at below 2% per year (Luft et al, 1999). Our present findings showed a negative association between years of heavy drinking and cerebellar volume (0.6% to 1.0%). This suggests that (a) the effects of heavy drinking might amplify age-related changes in cerebellar volume, and (b) with abstinence, such changes might be reversed, especially for the vestibulocerebellum (lobule X). It is also intriguing that while aging appears to affect much of the cerebellum, the regions that were particularly related to DHD and LOS were the anterior- and posterior-most (i.e., lobule I/II and lobule X) portions of the cerebellum. Cavanagh and colleagues (Cavanagh et al, 1997) have suggested that these regions are most susceptible to alcoholism because they may be most heavily perfused by cerebrospinal fluid, being adjacent to the fourth ventricle.

Regarding the associations among drinking, gender, and cerebellar volume, although there were no group by gender interactions for a priori specified volumes, significant gender differences were observed. For the AL group, many cerebellar regions were larger for women than for men, and the NA group showed a similar gender trend. Of note, because all cerebellar volumes were analyzed as a proportion of estimated total intracranial volume, the gender effects do not reflect differences in body size between men and women. While other studies reported either no significant gender differences in total cerebellar volume (Nopoulos et al, 2000) or that men have larger cerebellar volumes than women (Fan et al, 2010; Raz et al, 2001), the participants were younger (Fan et al, 2010), and they either did not control for intracranial volume (Nopoulos et al, 2000; Raz et al, 2001), or the difference was significant only when not controlling for intracranial volume (Fan et al, 2010).

Overall, we have demonstrated how alcoholism and gender interact with cerebellar volume in long-term abstinent individuals with a history of chronic alcoholism. We observed widespread cerebellar volume abnormalities in relation to drinking history, especially negative associations in relation to the number of years drinking heavily. Although this study was cross-sectional, were we to assume causality, these reductions could be interpreted as a volume loss at a rate of about half a percent to one percent per year of heavy drinking. Supposing a duration of heavy drinking of approximately a decade, this would indicate a volume loss of around five to ten percent.

Limitations

There are several limitations to the present research. We recruited from a random sample of participants from the area in and around Boston, MA. We did not selectively recruit our AL subjects from families with a high prevalence of alcoholism, and the volumetric abnormalities we observed may be better defined in alcoholics by analyzing larger samples that allow for distinguishing those with clear positive family history from those without. However, by recruiting randomly, our sample is more representative of the general population. Additionally, the alcoholics in this sample not only had relatively lengthy alcohol sobrieties (average abstinence of eight years, and longer for the women), but some of the alcoholics also had a history of drug use (mostly marijuana). Therefore, the generalizability of our conclusions could be considered in relation to a history of marijuana as well as alcohol use. Nonetheless, comorbid marijuana use is common among alcoholics, so our results can be considered to be ecologically valid. Moreover, the findings for the unconfounded and matched subsamples were congruous with those obtained for the total sample, indicating results that appear to be robust to issues such as psychiatric comorbidity, marijuana use, and possibly abuse of other harmful substances. Details for all of the participants can be found in the Supplemental Dataset, which contains the source data for the entire study.

Although only a handful of cerebellar regions showed statistically significant effects with alcoholism or drinking history, the effect sizes observed across most other regions were modest, and in general, regions tended to be non-significantly smaller in alcoholics relative to controls. The modest effect sizes we observed may be related in part to recovery effects given the average abstinence period of eight years. Studies that have examined recently detoxified alcoholics have identified extensive cerebral volumetric reductions (e.g., Durazzo et al, 2011), whereas studies of longer-term abstinent alcoholics have shown evidence of recovery of volume with short periods of abstinence (e.g., Eijk et al, 2013).

Notably, evidence suggests that volume recovery of the cerebellum may occur more quickly than some other brain regions (Eijk et al, 2013) and also that recovery of volume has been noted in only two weeks of sobriety (Eijk et al, 2013). More widespread cerebellar volume deficits may have been observable immediately following cessation of drinking, before tissue recovery had time to occur if that were the case. Finally, this study utilized a cross-sectional approach, and the alcoholic participants had a history of at least five years of heavy drinking. This prevented us from determining whether the relationships we observed

predated the onset of heavy drinking (and thus could be considered risk factors for alcoholism) or were actually consequences of heavy drinking.

Conclusions

Together, the findings from the present study not only have fortified prior research that has examined cerebellar abnormalities in relation to alcoholism metrics (LOS, DHD, and DD), but also has extended it to describe relationships between alcoholism and more finely specified structurally and functionally defined regional volumes within the cerebellum. Furthermore, the quantitative approach to drinking history taken in this project provided a concrete benchmark to judge the impact each additional year of drinking, and each year of sobriety, have on the brain, findings that could have intuitive impact for the public.

In sum, we see reductions in cerebellar white matter and also associations between years of heavy drinking with gray matter regions in the anterior lobes, vestibular and spinocerebellar lobes, and with the functionally-defined motor region. At a more global level of analysis, the lateral hemispheres and associated cognitively-defined regions appeared to be relatively spared. It is only when we further parcellate the cerebellum that we see potential effects of heavy drinking on the more cognitive/language regions of the cerebellum, mainly lobule VIIA, where there also was a significant gender by DHD interaction. This suggests that using a fine-grained parcellation scheme has utility and could be beneficial in helping to pinpoint possible cerebellar abnormalities that are related to specific non-motor deficits in alcoholism.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Parcellation units that comprise each of the seven functionally-defined regions
 The cortical surface of the cerebellum is displayed in flattened schematics (Makris et al., 2003; 2005), with left hemispheres shown on the left. Regions were determined from a meta-analysis conducted by Stoodley and Schmahmann (2009). The regions identified in the meta-analysis were superimposed on the Schmahmann (2000) atlas used in this study and adapted with a quantitative framework for cerebellar morphometry.

Figure 2. Cerebellar white matter is smaller in alcoholic men and women

Boxplot whiskers represent the most extreme value within double the interquartile range. (There was one outlier, indicated by the red dot, but results did not change when the value was removed.) Stars indicate significant differences ($p < 0.05$). eTIV: Estimated Total Intracranial Volume.

Figure 3. Duration of heavy drinking (years) was significantly associated with regional volumes of the cerebellum in alcoholic participants

Figure 3 is presented in three parts. In the middle (B), the cortical surface of the cerebellum is displayed in flattened schematics (Makris et al, 2003, 2005). The parts at the top (A) and bottom (C) are leverage plots associated with the regions outlined in the middle (B). A. Spinocerebellar volumes were 0.5% smaller with each year of heavy drinking. This leverage plot (Sall, 1990) represents the relationship between duration of heavy drinking and spinocerebellum volume for alcoholic men and women, covaried for age. Red circles indicate AL women; blue triangles indicate AL men. The regression line and 95% confidence curve of the slope (dotted lines) are displayed ($F(1, 41) = 6.4, p < 0.05$). B. The

saturation of the color indicates the degree of association of duration of heavy drinking with each of the 64 cerebellar parcellation units: Red colors indicate smaller volumes (100% saturation = -3.0%/year), and blue patterns indicate larger volumes (100% saturation = 3.0%/year). C. Vestibulocerebellar volumes were 0.8% smaller with each year of heavy drinking. This leverage plot (Sall, 1990) represents the relationship between duration of heavy drinking and vestibulocerebellum volume for alcoholic men and women, covaried for age. Red circles indicate AL women; blue triangles indicate AL men. The regression line and 95% confidence curve of the slope (dotted lines) are displayed ($F(1, 41) = 7.3, p < 0.05$).

Table 1

Demographic characteristics

Means and standard deviations (SD) are presented for alcoholic (AL) and nonalcoholic control (NA) men and women separately, followed by the 95% confidence intervals (CI) of the mean differences. WAIS-IV FSIQ: Wechsler Adult Intelligence Scale Full Scale IQ, Fourth Edition (Wechsler, 2008); DHD: Duration of Heavy Drinking (years); DD: Daily Drinks (at one ounce of ethanol per drink); LOS: Length of Sobriety (years); AUDIT: Alcohol Use Disorders Identification Test. No significant group by gender interactions were identified. Effects significant at $p < 0.05$ are in bold. The minus signs in the column headings signify differences between the groups, which have been expressed as a CI (e.g., NA - AL indicates the 95% CI of the nonalcoholic group minus the alcoholic group).

	Alcoholic		Nonalcoholic Control		NA - AL		NA Men - AL Men		NA Women - AL Women		AL Men - AL Women		NA Men - NA Women	
	Women N=21	Mean (SD)	Men N=23	Mean (SD)	Women N=21	Mean (SD)	Men N=18	Mean (SD)	All N=83	95% CI	Men N=41	95% CI	Women N=42	95% CI
Age (years)	58.1 (11.6)	53.4 (11)	53.4 (11)	57.3 (13.7)	53.2 (14.3)	53.2 (14.3)	53.2 (14.3)	53.2 (14.3)	53.2 (14.3)	53.2 (14.3)	53.2 (14.3)	53.2 (14.3)	53.2 (14.3)	53.2 (14.3)
Education (years)	15.0 (1.9)	14.3 (2.0)	14.3 (2.0)	15.2 (2.7)	15.2 (2.7)	15.2 (2.7)	15.2 (2.7)	15.2 (2.7)	15.2 (2.7)	15.2 (2.7)	15.2 (2.7)	15.2 (2.7)	15.2 (2.7)	15.2 (2.7)
WAIS-IV FSIQ	103.4 (14.7)	104.8 (17.4)	104.8 (17.4)	108.9 (14.9)	110.7 (12.9)	110.7 (12.9)	110.7 (12.9)	110.7 (12.9)	110.7 (12.9)	110.7 (12.9)	110.7 (12.9)	110.7 (12.9)	110.7 (12.9)	110.7 (12.9)
DHD (years)	13.5 (5.3)	19.9 (10.4)	19.9 (10.4)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
DD (ounces ethanol/day)	7.3 (4.9)	11.3 (6.3)	11.3 (6.3)	0.2 (0.3)	0.1 (0.2)	0.1 (0.2)	0.1 (0.2)	0.1 (0.2)	0.1 (0.2)	0.1 (0.2)	0.1 (0.2)	0.1 (0.2)	0.1 (0.2)	0.1 (0.2)
LOS (years)	14.3 (12.8)	2.6 (3.0)	2.6 (3.0)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
AUDIT	25.8 (6.3)	28.1 (6.4)	28.1 (6.4)	1.6 (2.1)	2.2 (2.6)	2.2 (2.6)	2.2 (2.6)	2.2 (2.6)	2.2 (2.6)	2.2 (2.6)	2.2 (2.6)	2.2 (2.6)	2.2 (2.6)	2.2 (2.6)

Table 2
Cerebellar volumes in alcoholic (AL) and nonalcoholic control (NA) men and women as a percentage of estimated total intracranial volume

Means, standard deviations (SD), and 95% confidence intervals (CI) of the mean differences are presented, expressed as a percentage of the overall means. Age was included as a covariate in all regression analyses. No significant group by gender interactions were identified. Effects significant at $p < 0.05$ are in bold. The minus signs in the column headings indicate the mean differences between the groups, which have been expressed as a CI (e.g., NA - AL indicates the 95% CI of the nonalcoholic group minus the alcoholic group).

Structural regions	Alcoholic		Nonalcoholic Control		NA - AL		NA Men - AL Men		NA Women - AL Women		AL Men - AL Women		NA Men - NA Women	
	Women N=21	Mean (SD)	Men N=23	Mean (SD)	Women N=21	Mean (SD)	Men N=18	Mean (SD)	All N=83	Men N=41	Women N=42	AL N=44	NA N=39	95% CI
Total Cerebellum	9.4	(0.7)	8.8	(0.7)	9.4	(0.7)	9.1	(0.8)	[-2%, 5%]	[-2%, 9%]	[-5%, 4%]	[-13%, -3%]	[-9%, 2%]	
White Matter	1.9	(0.3)	1.7	(0.2)	1.9	(0.2)	1.9	(0.2)	[1%, 11%]	[2%, 15%]	[-3%, 10%]	[-16%, -1%]	[-9%, 3%]	
Gray Matter	7.6	(0.7)	7.1	(0.7)	7.5	(0.7)	7.2	(0.8)	[-4%, 5%]	[-4%, 9%]	[-7%, 4%]	[-13%, -2%]	[-10%, 3%]	
Anterior Lobe	0.9	(0.2)	0.9	(0.2)	0.8	(0.2)	0.9	(0.2)	[-16%, 4%]	[-19%, 14%]	[-22%, 3%]	[-20%, 6%]	[-13%, 18%]	
Posterior Lobe	6.5	(0.6)	6.0	(0.6)	6.5	(0.6)	6.2	(0.7)	[-3%, 6%]	[-4%, 10%]	[-6%, 5%]	[-13%, -2%]	[-11%, 2%]	
Vestibulocerebellum	0.1	(0.0)	0.1	(0.0)	0.1	(0.0)	0.1	(0.0)	[-6%, 9%]	[-8%, 15%]	[-12%, 7%]	[-25%, -3%]	[-17%, 3%]	
Cerebrocerebellum	4.4	(0.4)	4.2	(0.4)	4.4	(0.4)	4.3	(0.5)	[-2%, 6%]	[-2%, 11%]	[-6%, 5%]	[-12%, -1%]	[-8%, 5%]	
Spinocerebellum	3.1	(0.3)	2.9	(0.3)	3.0	(0.3)	2.9	(0.4)	[-6%, 4%]	[-8%, 7%]	[-10%, 4%]	[-16%, -2%]	[-14%, 2%]	
Functional regions														
Motor	1.3	(0.2)	1.2	(0.2)	1.2	(0.2)	1.3	(0.2)	[-5%, 8%]	[-3%, 14%]	[-13%, 6%]	[-16%, 1%]	[-8%, 13%]	
Somatosensory	1.2	(0.2)	1.2	(0.2)	1.3	(0.2)	1.2	(0.2)	[-4%, 9%]	[-8%, 12%]	[-7%, 12%]	[-17%, 4%]	[-15%, 4%]	
Spatial	0.5	(0.1)	0.5	(0.1)	0.5	(0.1)	0.5	(0.1)	[-3%, 13%]	[-10%, 15%]	[-5%, 17%]	[-19%, 6%]	[-19%, 2%]	
Language	2.0	(0.3)	1.8	(0.3)	2.0	(0.2)	1.8	(0.3)	[-5%, 9%]	[-8%, 13%]	[-7%, 8%]	[-21%, -4%]	[-19%, 0%]	
Working Memory	2.6	(0.3)	2.5	(0.3)	2.7	(0.2)	2.6	(0.4)	[-2%, 8%]	[-5%, 12%]	[-4%, 9%]	[-13%, 2%]	[-12%, 4%]	
Executive	2.9	(0.3)	2.7	(0.3)	2.9	(0.3)	2.8	(0.4)	[-3%, 7%]	[-4%, 13%]	[-7%, 5%]	[-17%, -3%]	[-12%, 5%]	
Emotion	2.1	(0.3)	1.9	(0.3)	2.1	(0.2)	1.9	(0.3)	[-6%, 8%]	[-10%, 12%]	[-8%, 8%]	[-21%, -3%]	[-19%, 0%]	

Table 3
Relationships of duration of heavy drinking (DHD, years) to cerebellar volume for AL men and women

The 95% confidence interval (CI) of the slope (B) for volumes (as a proportion of estimated total intracranial volume, expressed as a percentage of the overall means) and partial r^2 as a function of DHD are presented for all alcoholics combined, as well as AL men and women separately. Partial r^2 was calculated with the formula: $SS_{\text{term}}/(SS_{\text{term}} + SS_{\text{error}})$. Age was included as a covariate for all analyses. Effects significant at $p < 0.05$ are in bold. *DHD by gender interaction ($p < 0.05$).

Structural regions	Duration of Heavy Drinking (years)							
	All AL		AL Men		AL Women			
	95% CI	Partial r^2	95% CI	Partial r^2	95% CI	Partial r^2	95% CI	Partial r^2
Total Cerebellum	[-0.6, 0.0]	0.10	[-0.5, 0.3]	0.03	[-0.7, 0.7]	0.00		
White Matter	[-0.7, 0.2]	0.02	[-0.7, 0.6]	0.00	[-1.6, 0.6]	0.05		
Gray Matter	[-0.7, 0.0]	0.08	[-0.6, 0.3]	0.03	[-0.7, 0.9]	0.00		
Anterior Lobe*	[-1.8, -0.4]	0.18	[-2.3, -0.6]	0.37	[-1.1, 2.4]	0.03		
Posterior Lobe	[-0.6, 0.2]	0.03	[-0.5, 0.5]	0.00	[-0.8, 0.9]	0.00		
Vestibulocerebellum	[-1.5, -0.2]	0.15	[-1.6, 0.2]	0.11	[-2.2, 0.9]	0.05		
Cerebrocerebellum	[-0.6, 0.1]	0.03	[-0.5, 0.4]	0.00	[-0.7, 1.1]	0.01		
Spinocerebellum	[-0.9, -0.1]	0.13	[-0.9, 0.2]	0.08	[-1.0, 0.9]	0.00		
Functional regions								
Motor	[-0.9, 0.0]	0.08	[-0.8, 0.5]	0.01	[-2.0, 0.4]	0.09		
Somatosensory	[-1.0, 0.2]	0.04	[-1.0, 0.4]	0.05	[-1.7, 1.7]	0.00		
Spatial	[-1.3, 0.1]	0.06	[-1.8, 0.1]	0.15	[-1.5, 2.4]	0.01		
Language	[-0.9, 0.2]	0.05	[-1.0, 0.6]	0.01	[-0.7, 1.7]	0.04		
Working Memory	[-0.5, 0.3]	0.01	[-0.6, 0.6]	0.00	[-0.7, 1.3]	0.02		
Executive	[-0.7, 0.2]	0.03	[-0.7, 0.6]	0.00	[-0.7, 1.1]	0.02		
Emotion	[-0.9, 0.2]	0.05	[-1.1, 0.5]	0.03	[-0.5, 1.8]	0.07		

Table 4
Relationships of daily drinks (DD, at one ounce of ethanol per drink) to cerebellar volume for AL men and women

The 95% confidence interval (CI) of the slope (B) for volumes (as a proportion of estimated total intracranial volume, expressed as a percentage of the overall means) and partial r^2 as a function of DD are presented for all alcoholics combined, as well as AL men and women separately. Partial r^2 was calculated with the formula: $SS_{\text{term}}/(SS_{\text{term}} + SS_{\text{error}})$. Age was included as a covariate for all analyses. No significant group by gender interactions were identified. Effects significant at $p < 0.05$ are in bold.

Structural regions	Daily Drinks (ounces of ethanol per day)					
	All AL		AL Men		AL Women	
	N=44		N=23		N=21	
	95% CI	Partial r^2	95% CI	Partial r^2	95% CI	Partial r^2
Total Cerebellum	[-0.8, 0.2]	0.04	[-0.7, 0.5]	0.01	[-1.3, 1.5]	0.00
White Matter	[-1.5, 0.1]	0.08	[-1.2, 0.6]	0.03	[-2.3, 2.4]	0.00
Gray Matter	[-0.8, 0.3]	0.02	[-0.8, 0.6]	0.00	[-1.4, 1.7]	0.00
Anterior Lobe	[-2.0, 0.6]	0.03	[-2.5, 0.7]	0.06	[-3.9, 3.6]	0.00
Posterior Lobe	[-0.7, 0.4]	0.01	[-0.7, 0.8]	0.00	[-1.4, 1.8]	0.00
Vestibulocerebellum	[-1.2, 0.8]	0.00	[-1.0, 1.9]	0.02	[-3.2, 1.4]	0.04
Cerebrocerebellum	[-0.5, 0.6]	0.00	[-0.5, 0.8]	0.01	[-1.0, 2.1]	0.03
Spinocerebellum	[-1.2, 0.1]	0.06	[-1.2, 0.5]	0.04	[-2.4, 1.6]	0.01
Functional regions						
Motor	[-1.4, 0.3]	0.04	[-1.6, 0.4]	0.07	[-2.4, 3.0]	0.00
Somatosensory	[-0.5, 1.1]	0.01	[-0.7, 1.4]	0.02	[-1.4, 3.7]	0.05
Spatial	[-1.0, 1.2]	0.00	[-1.5, 1.6]	0.00	[-2.6, 3.6]	0.01
Language	[-0.9, 0.9]	0.00	[-0.6, 1.7]	0.05	[-2.5, 1.9]	0.00
Working Memory	[-0.6, 0.7]	0.00	[-0.6, 1.2]	0.02	[-1.6, 1.9]	0.00
Executive	[-0.7, 0.7]	0.00	[-0.5, 1.4]	0.05	[-1.5, 1.6]	0.00
Emotion	[-0.8, 1.0]	0.00	[-0.6, 1.8]	0.05	[-2.3, 2.2]	0.00

Table 5
Relationships of length of sobriety (LOS, years) to cerebellar volume for AL men and women

The 95% confidence interval (CI) of the slope (B) for volumes (as a proportion of estimated total intracranial volume, expressed as a percentage of the overall means) and partial r^2 as a function of LOS are presented for all alcoholics combined, as well as AL men and women separately. Partial r^2 was calculated with the formula: $SS_{\text{term}}/(SS_{\text{term}} + SS_{\text{error}})$. Age was included as a covariate for all analyses. No significant group by gender interactions were identified. Effects significant at $p < 0.05$ are in bold.

Structural regions	Length of Sobriety (years)					
	All AL		AL Men		AL Women	
	N=44		N=23		N=21	
	95% CI	Partial r^2	95% CI	Partial r^2	95% CI	Partial r^2
Total Cerebellum	[-0.2, 0.4]	0.02	[-1.7, 0.7]	0.03	[-0.6, 0.2]	0.07
White Matter	[-0.4, 0.4]	0.00	[-2.6, 1.0]	0.04	[-0.7, 0.5]	0.01
Gray Matter	[-0.2, 0.5]	0.02	[-1.7, 1.0]	0.02	[-0.6, 0.2]	0.06
Anterior Lobe	[-0.3, 1.0]	0.02	[-2.2, 4.3]	0.02	[-1.3, 0.6]	0.04
Posterior Lobe	[-0.2, 0.5]	0.01	[-2.1, 0.9]	0.04	[-0.7, 0.2]	0.05
Vestibulocerebellum	[0.0, 1.2]	0.10	[-1.2, 4.5]	0.07	[-0.5, 1.1]	0.03
Cerebrocerebellum	[-0.2, 0.5]	0.02	[-1.5, 1.2]	0.00	[-0.7, 0.3]	0.04
Spinocerebellum	[-0.2, 0.6]	0.03	[-2.4, 1.0]	0.03	[-0.7, 0.3]	0.05
Functional regions						
Motor	[-0.2, 0.7]	0.04	[-2.4, 1.7]	0.01	[-0.6, 0.7]	0.00
Somatosensory	[-0.4, 0.7]	0.00	[-1.8, 2.5]	0.00	[-1.1, 0.7]	0.02
Spatial	[-0.7, 0.6]	0.00	[-3.9, 2.1]	0.02	[-1.5, 0.6]	0.05
Language	[-0.3, 0.7]	0.02	[-3.1, 1.5]	0.03	[-0.9, 0.3]	0.05
Working Memory	[-0.4, 0.3]	0.00	[-2.9, 0.7]	0.08	[-0.8, 0.2]	0.08
Executive	[-0.2, 0.6]	0.02	[-2.8, 1.1]	0.04	[-0.7, 0.2]	0.05
Emotion	[-0.3, 0.7]	0.01	[-3.3, 1.6]	0.03	[-1.0, 0.3]	ss0.06