Parietal Gray Matter Volume Loss is Related to Spatial Processing Deficits in Long-Term Abstinent Alcoholic Men

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Acknowledgements

This work was supported by NIAAA Grants AA11311 and AA13659 and by NIDA (SBIR contract HHSN271200688434C). We also express our appreciation to the NRI recruitment and assessment staff, and to each of our volunteer research participants.
Abstract

Background. We previously demonstrated relatively intact cognitive function (with the exception of suggestive evidence for persistent deficits in spatial information processing) in middle-aged long-term abstinent alcoholics (LTAA, abstinent for 6 months or more) compared to age and gender comparable non-alcoholic controls (NAC) (Fein et al., 2006).

Methods. In the current study, we examine cortical gray matter volumes in the same samples to determine whether gray matter volumes in LTAA are consistent with the cognitive results – i.e., exhibiting gray matter volumes comparable to NAC in most brain regions, except for possible indications of persistent shrinkage in the parietal lobe subserving spatial information processing.

Results. We found gray matter shrinkage in LTAA in the parietal lobe consistent with the spatial processing deficits in this same sample. More compelling, in LTAA, the magnitude of parietal gray matter shrinkage was negatively associated with spatial processing domain performance and positively associated with alcohol dose. Gray matter volume deficits were present in the occipital and other cortical tissue, but poorer visuospatial test performance correlated significantly with smaller volumes in the parietal cortex only.

Conclusions. Taken together, the cognitive and structural imaging data provide compelling evidence that chronic alcohol abuse results in shrinkage of the parietal cortex with associated deficits in spatial information processing.

Keywords: alcohol abstinence; structural MRI; brain shrinkage; gray matter; parietal lobe
1. **Introduction**

   It has been well documented that long-term alcohol dependence is associated with cognitive impairments and brain atrophy; however, there is evidence that both phenomena may be at least partially reversible with abstinence, especially long-term abstinence. We have previously demonstrated relatively intact cognitive function (with the exception of suggestive evidence for persistent deficits in spatial information processing) in middle-aged long-term abstinent alcoholics (LTAA, abstinent 6 months to 14 years) compared to age and gender comparable non-alcoholic controls (NAC) (Fein et al., 2006). Although our data in that study was cross-sectional rather than longitudinal, we interpreted the results as indicating that long-term abstinence is associated with relatively complete recovery from the neurocognitive morbidity of chronic alcohol dependence.

   Parietal lobe function has been previously linked to spatial domain performance, including object recognition, guidance of movement, sensorimotor transformation, and spatial navigation (Kolb and Whishaw, 2009). For example, event-related potentials (ERPs) within the posterior parietal lobe have been found to precede eye movements in response to visual stimuli (Hillyard and Anllo-Vento, 1998), and blood flow to the region increases when subjects direct their attention to visual targets (Roland, 1993). Studies have also shown sex differences in the relationship between parietal lobe morphology and spatial processing abilities. Koscik et al. (Koscik et al., 2009) found in normal subjects, that larger parietal lobe volumes were correlated with increased mental rotation abilities in men, whereas parietal lobe surface area, not volume, was related to improved performance in women.

   Decreased spatial domain performance by alcoholics has been reported on a wide variety of tasks for over twenty years. These include visuospatial construction (Beatty et al., 1996,
Stringer and Goldman, 1988, Wechsler, 1981, Yohman et al., 1985), copying complex designs (Sullivan et al., 1992, Wilson et al., 1987), mental rotation (Brandt et al., 1983, Glenn and Parsons, 1991, Beatty et al., 1996), and visuospatial learning (Ryan and Butters, 1980, Sullivan et al., 1992, Wilson et al., 1987). In the current study, we examined cortical gray matter volumes in the same middle-aged LTAA and NAC samples as in our cognitive study (Fein et al., 2006) to determine whether there are cortical gray matter volume reductions in LTAA consistent with the cognitive results – i.e., exhibiting gray matter volumes comparable to NAC in brain regions subserving intact cognitive functions (e.g., abstraction, cognitive flexibility and memory), with indications of persistent shrinkage in the regions subserving spatial information processing.

Many recent studies have addressed the effects of short-term abstinence on recovery of alcohol-related brain shrinkage. Longitudinal studies have found that overall brain volume increases can occur within the first 5-6 weeks of abstinence (Mann et al., 2005), with spatially significant recovery occurring within the deeper brain structures, including the cerebellar vermis and the periventricular edges (Bartsch et al., 2007). Studies covering longer periods of abstinence (6-8 months) have shown continued tissue volume recovery over time, although abstinent samples continued to exhibit significant shrinkage compared to light/non-drinking controls within the frontal lobe, anterior parietal lobe, temporal lobe, lingual lobe, cingulate gyrus, insula, thalamus, and cerebellum (Cardenas et al., 2007, Chanraud et al., 2007).

Studies of the effects of chronic alcohol abuse and dependence on regional cortical atrophy have used atlas-based identification of regions of interest (ROIs) (Cardenas et al., 2005, Gazdzinski et al., 2008a, Gazdzinski et al., 2008b, Cardenas et al., 2007, Makris et al., 2008) or voxel-based morphometry (VBM) techniques (Bartsch et al., 2007, Chanraud et al., 2007, Mechtcheriakov et al., 2007, Jang et al., 2007, Sachdev et al., 2008). We used a region-based
method of measuring tissue volumes to focus our analyses on areas of the brain that are associated with the psychological and cognitive measures that we previously examined.

2. Methods and Materials

Participants

A total of 100 participants were recruited from the community by postings at AA meeting sites, mailings, newspaper advertisements, a local Internet site, and subject referrals. The study consisted of two subject groups: LTAA and NAC. The LTAA group comprised 24 women and 28 men, ranging from 35 to 58 years of age (mean = 46.6 years), who were abstinent from alcohol and drugs (except nicotine and caffeine) for 6 months to 21 years (mean = 6.3 years). Table 1 lists demographic and alcohol use information by group. The inclusion criteria for the LTAA group were: 1) met DSM - IV (American Psychiatric Association, 2000) criteria for lifetime alcohol dependence, 2) were abstinent for at least 6 months. A standard drink was defined as 12 oz. beer, 5 oz. wine, or 1.5 oz. liquor. The NAC consisted of 23 women and 25 men, ranging from 34 to 60 years of age (mean = 45.6 years). The inclusion criterion for the NAC group was a lifetime drinking average of less than 30 standard drinks per month, with no periods of drinking more than 60 drinks per month.

Exclusion criteria for both groups were: 1) lifetime or current diagnosis of schizophrenia or schizophreniform disorder using the computerized Diagnostic Interview Schedule (Bucholz et al., 1991, Erdman et al., 1992, Levitan et al., 1991, Robins et al., 1998), 2) history of lifetime or current drug abuse or dependence (other than nicotine or caffeine), 3) significant history of head trauma or cranial surgery, 4) history of significant neurological disease, 5) history of diabetes, stroke, or hypertension that required an emergent medical intervention, 6) laboratory evidence of hepatic disease, or 7) clinical evidence of Wernicke-Korsakoff syndrome.
All individuals participated in the following assessments: 1) psychiatric diagnoses and symptom counts were gathered using the c-DIS (Robins et al., 1998), 2) participants were interviewed on their lifetime drug and alcohol use using the timeline follow-back methodology (Skinner and Allen, 1982, Skinner and Sheu, 1982, Sobell and Sobell, 1990, Sobell et al., 1988), 3) medical histories were reviewed in an interview by a trained research associate, 4) blood was drawn to test liver functions, and 5) the Family Drinking Questionnaire was administered based on the methodology of Mann et al. (Mann et al., 1985, Stoltenberg et al., 1998). The Family Drinking Questionnaire asked participants to rate the members of their family as being alcohol abstainers, alcohol users with no problem, or problem drinkers. Family History Density (FHD) was defined as the proportion of 1st degree relatives that were problem drinkers. Approval for the study was obtained from a free-standing independent human subjects research review committee [Independent Review Consulting, Corte Madera, CA], and written informed consent was obtained from all research participants.

*Insert Table 1 Here*

**Neuropsychological and Psychiatric Assessments**

A number of neuropsychological assessments were administered in one session to assess the cognitive abilities of the subjects. The computerized Diagnostic Interview Schedule (c-DIS (Robins et al., 1998)) was administered to all participants by a research associate. The c-DIS generates a list of endorsed lifetime symptoms, determining whether individuals met criteria for a lifetime psychiatric diagnosis. Eighty-seven percent of LTAA were found to have at least one lifetime psychiatric diagnosis (including mood, anxiety, and externalizing disorders), compared to 58% of NAC. Thirty-five percent of LTAA with at least 18 months of abstinence (so that only periods after six months of abstinence are counted) had a current psychiatric diagnosis, compared to 6% of NAC. Spatial processing abilities were assessed using the MicroCog software package
(Powell et al., 1993) and WAIS (Wechsler, 1981). Overall spatial processing scores were computed by averaging scores from the Clocks and Tic Tac (MicroCog), and Block Design (WAIS-R) tests. In the Clocks test, subjects were presented with seven numberless clock faces and were asked to choose the correct time. In the Tic Tac test, the subject was presented with a pattern on a 3 x 3 matrix for one second and was asked to replicate the pattern. The block design test required the subject to arrange blocks with different colors on each side to match a template pattern. Verbal abilities were assessed using the American version of the Nelson Adult Reading Test (AMNART)(Grober and Sliwinski, 1991) and the Controlled Oral Word Association Test (COWAT)(Benton and Hamsher, 1983). Details of the administration of the other neuropsychological tests and the c-DIS for this sample have been described in our previous papers (Fein and McGillivray, 2007, Fein et al., 2006).

Image Acquisition

All MRIs were collected on a 1.5T GE Signa Infinity with the LX platform (GE Medical Systems, Waukesha, WI) located at the Pacific Campus of the California Pacific Medical Center in San Francisco. For each subject, we acquired a transaxial T1-weighted Spoiled Gradient image (TR = 35 ms, TE = 5 ms, acquisition matrix = 256 x 192) at 1.3 mm thickness and a Fluid Attenuated Inversion Recovery (FLAIR) image (TR = 8800 ms, TE = 144.7 ms, inversion time = 2200 ms, acquisition matrix = 256 x 256) at 5 mm thickness. A neuroradiologist read all MRI scans. All scans were free from abnormalities other than white matter signal hyperintensities (WMSH).

Image Processing

Image preprocessing was performed using FSL, version 3.3 (Oxford, UK). Preprocessing steps included brain extraction, registration, segmentation and cranium size estimation (an
estimate of premorbid brain size) (Fein et al., 2004). After preprocessing, we corrected areas of misclassified white matter within the segmentations due to white matter signal hyperintensities using in-house image processing software.

We performed a ROI-based analysis to aggregate gray matter within the cerebral lobes (see Figure 1) and sub-lobar areas using lobar and Brodmann area definitions from the Talairach atlas (Talairach and Tournoux, 1988). A challenge posed by using ROIs defined in a standard space and transforming them to fit individual subjects’ brains is that individual differences in brain morphology and inaccuracies in the image registration process can result in the ROIs missing part of the region or capturing parts of an adjacent region. In addition, the Talairach definitions of the Brodmann areas are thin strips that must be dilated in order to ensure that the ROI covers most of the gray matter in subject space. Simple dilation causes the boundaries of the ROI to extend into the adjacent Brodmann areas. For small ROIs consisting of one or two Brodmann areas, the amount of overlap can be significant in comparison to the size of the undilated ROI.

We created our ROIs by dilating a Brodmann area atlas in MNI 152 standard space using nearest neighbor interpolation. This had a distinct advantage over conventional dilation of individual ROIs, where overlap between adjacent regions is a problem (see Figure 2). ROIs were then created by aggregating functionally related Brodmann areas and constraining them within their respective cerebral lobes. Finally, the ROI masks were overlaid onto each subject’s gray matter segmentation and corrected using software that we developed to selectively include and exclude gray matter gyri near the ROI boundaries based on connectivity. A list of all of the ROIs used in our analyses is presented in table 2.

Insert Figures 1 & 2 here
Statistical Analyses

Statistical analyses were performed using the General Linear Model implementation of analysis of covariance within the Statistical Analysis Software (SAS), version 9.1.3. Since we are interested in inferring shrinkage (i.e., loss of gray matter) from our gray matter volumes, we first used linear regression analysis to adjust each gray matter volumes for premorbid brain size using the cranium size index from FSL’s SIENAX program. We have previously shown that the cranium size index has an almost perfect correlation with intracranial vault volume (Fein et al., 2004). To have a more sensitive test of the atrophic effects of alcohol dependence given that gray matter volumes are known to decrease with increasing age beginning in middle age, we included age as a covariate and group and gender as between subject effects. The analysis was first run with age by group and age by gender interaction effects to test for the appropriateness of using age as a covariate (i.e., no significant age by group or age by gender interactions). Since there were no significant age by group or age by gender interactions for any dependent variable, we then proceeded with the ANCOVA proper, (i.e., without the age interaction effects).

3. Results

Cranium Size

Men had craniums 12.1% larger than women, with gender accounting for 34.8% of the variance of the cranium size index ($F_{1,96} = 51.18, p < 0.0001$). In contrast to the cranium size difference by gender, we found no cranium size difference between groups, with group accounting for only 0.5% of the variance of the cranium size index ($F_{1,96} = 0.49, p > 0.48$), and no group by gender cranium size interaction effect (effect size 0.2% of the variance, $F_{1,96} = 0.22, p > 0.63$). Linear regression analysis was used to generate cranium size adjusted values for all gray matter volume measures, and the adjusted values were used in all subsequent analyses.
**Gray Matter Volumes**

Table 2 presents the gray matter volumes adjusted for cranium size and age for male and female LTAA and NAC samples. LTAA had less total cortical gray matter than NAC, with group accounting for 7.0% of the variance of total cortical gray matter. No significant group differences were found for the frontal, limbic, and temporal lobes (p’s > 0.12, effect sizes less than 2.5% of variance), whereas the LTAA had significantly lower gray matter volumes than NAC for the occipital (p = 0.001, effect size 12.5% of variance) and parietal (p = 0.002, effect size 10.0% of variance) lobes and the insula (p = 0.039, effect size 4.4% of variance). The largest between group effect sizes were in the visual association area, followed by the lateral parietal, primary somatosensory and primary motor cortices. Within the occipital lobe, the visual association area (p < 0.001) and to a lesser extent, the primary visual cortex (p = 0.008), LTAA had less gray matter than NAC. Within the parietal lobe, the lateral parietal (p < 0.002) and the mesial parietal (p = 0.010) areas exhibited reduced gray matter volumes in the LTAA. Other areas with significantly lower gray matter volumes in LTAA compared to NAC were the primary somatosensory cortex (p = 0.003), primary motor cortex (p = 0.004), and the anterior cingulate (p = 0.019). In the orbital frontal, primary visual, and primary somatosensory cortices, there were group by gender interactions, wherein reduced gray matter was present either only, or primarily, in male LTAA. The LTAA were found to have greater gray matter volumes than NAC in the inferior temporal region (p = 0.009). Each of these effects was followed up with nonparametric Mann-Whitney U-Tests, and each effect remained statistically significant when analyzed nonparametrically.

**Insert Table 2 here**

*Correlations Between ROI Volumes and Subject Variables*
The first analysis we carried out was an *a priori* partial correlation analysis within each group controlling for age, between the neuropsychological assessment spatial processing domain score (the only domain in which LTAA demonstrated deficits vs. NAC), and parietal lobe cranium size adjusted gray matter volumes. Within NAC, there were no associations; however, within LTAA, there were significant positive associations between the spatial processing domain score and the parietal lobe brain size adjusted gray matter volumes (r = 0.26 for the parietal lobe, r = 0.028 for the lateral parietal, and r = 0.26 for the mesial parietal lobe, all significant at p < 0.03, 1-tail). However, this association was entirely carried by men (r = 0.420 for the entire parietal lobe, r = 0.378 for the lateral parietal, and r = 0.413 for the mesial parietal lobe, all significant at p < 0.03, 1-tail), but not in women (r’s < 0.132, p’s > 0.28). This association was specific to the spatial processing domain; for example, there were no significant correlations within LTAA between parietal lobe gray matter volumes and neuropsychological scores in the verbal domain (computed as the average of the COWAT and AMNART scores) in either gender. The partial correlation of cranium size adjusted total cortical gray matter (less parietal lobe gray matter) with the spatial processing domain score was not significant (r = 0.286, p = 0.15 in men; r = 0.045, p = 0.837 in women). Figure 3 displays the association between the cranium size adjusted parietal lobe gray matter volumes and the spatial processing domain scores separately for LTAA and NAC. For the LTAA, Figure 4 shows this effect separated for males and females.

To examine the effect of the level of alcohol use on regional gray matter volumes, we examined the correlations between the alcohol use variables (average lifetime and peak dose, total lifetime and peak consumption, and abstinence duration) and the cranium size adjusted gray matter volumes separately in men and women. Because some of the alcohol use variables were
highly correlated with age, we also performed analogous partial correlations, controlling for age.

In LTAA women, there were no significant correlations between regional gray matter volumes and average lifetime alcohol dose. In LTAA men, there were significant inverse relationships between the cranium size adjusted ROI volumes and average lifetime alcohol dose (in standard drinks per month) for total cortical gray matter \((r = -0.592, p < 0.001)\), in the frontal (frontal lobe \((r = -0.641, p < 0.001)\), dorsolateral prefrontal \((r = -0.639, p < 0.001)\), lateral prefrontal \((r = -0.425, p = 0.024)\), posterior prefrontal \((r = -0.591, p < 0.001)\), prefrontal \((r = -0.623, p < 0.001)\)), parietal (parietal lobe \((r = -0.456, p = 0.015)\), lateral parietal \((r = -0.513, p = 0.005)\), mesial parietal \((r = -0.505, p = 0.006)\)), and temporal (temporal lobe \((r = -0.690, p < 0.001)\), superior temporal \((r = -0.716, p < 0.001)\)) regions. Correlations between lifetime dose and total cortical gray matter remained significant when the parietal lobe was excluded from the analysis \((r = -0.539, p = 0.004)\). Total lifetime consumption (std. drinks), peak alcohol consumption (total amount consumed during periods of peak drinking, measured in std. drinks), and peak alcohol dose (std. drinks/month) were also negatively correlated with cranium size adjusted gray matter volumes in these areas, with associations of comparable size. After partialling out age, these negative associations between alcohol load and cranium size adjusted gray matter volume remained, although they were somewhat reduced in magnitude (e.g., for total cortical gray matter, the age adjusted correlation was \((r = -0.515, p = 0.006)\)). The negative association of alcohol dose with cranium size adjusted parietal gray matter and with total cortical gray matter excluding the parietal lobe in LTAA is presented in Figure 5. These relationships were not found in the NAC. No significant correlations between alcohol use and gray matter volumes were found within the occipital and limbic lobes. Some significant correlations between gray matter
volumes and abstinence duration were found within LTAA men, but these appeared to be a function of decreased alcohol consumption in those who were abstinent the longest.

Given our finding of a greater WMSH load in LTAA vs. NAC, we computed within group correlations between total white matter adjusted periventricular and deep WMSH volumes and the cranium size adjusted gray matter volume measures. No association was apparent within the LTAA as a group, but greater deep WMSH loads were associated with smaller gray matter volumes in men within the frontal lobe (r = -0.464, p = 0.015), insula (r = -0.455, p = 0.017), and overall cortical gray matter (r = -0.383, p = 0.049), and periventricular WMSH was significantly correlated with smaller gray matter within the limbic lobe (r = -0.418, p = 0.030). No such relationships were found in women.

Finally, we examined whether psychiatric illness was associated with cranium size adjusted gray matter volumes. Twenty of the fifty-two LTAA had a current psychiatric diagnosis. LTAA with vs. without a current psychiatric diagnosis did not differ on any cranium size adjusted gray matter volume measure (all p’s > 0.35). Analyzing the data separately by gender did not reveal any significant correlations.

4. Discussion

We examined regional gray matter volume loss in middle-aged alcoholic men and women abstinent an average of 6.3 years using an atlas-based ROI identification method. Our main finding was of regionally specific persistent gray matter deficits in LTAA. In particular, we found parietal lobe shrinkage consistent with our prior report of suggestive evidence of spatial processing deficits in this sample of LTAA (Fein et al., 2006). More compelling, the magnitude of parietal gray matter loss in LTAA men was negatively associated with spatial processing
domain performance and positively associated with alcohol dose. Taken together, the cognitive and structural imaging data provide compelling evidence that chronic alcohol abuse results in shrinkage of the parietal cortex with associated deficits in spatial information processing, and that this effect is not resolved with even multi-year abstinence.

The data also suggest that region-specific recovery of alcohol-related gray matter damage occurs with very long-term abstinence. The absence of persistent shrinkage in the pre-frontal and temporal lobes, which have previously been found to undergo atrophic changes due to alcohol dependence (Fein et al., 2002, Cardenas et al., 2005), is consistent with intact memory and executive function in this sample. However, there were strong negative correlations between levels of alcohol consumption and regional gray matter volume within the frontal and temporal regions in LTAA men, suggesting that alcohol-related damage (much of which has recovered) was more present in men than women. The evidence of persistent gray matter deficits within the parietal lobe, the spatial processing deficiencies, and the otherwise intact cognitive functioning are strong indicators that alcohol-related damage may be at least partially reversible in the frontal and temporal lobes, but not in the parietal lobe.

The results are consistent with men being more vulnerable to the detrimental effects of chronic alcohol abuse, having less recovery from the atrophic effects of chronic abuse, or some combination of the two phenomena. Neither these results, nor the results in other brain regions, are consistent with suggestions that women are more vulnerable to the atrophic effects of chronic alcohol abuse.

We did not find any significant relationships within the LTAA between lifetime or current psychiatric diagnoses and regional cortical gray matter volumes. These data suggest that
the reduced gray matter volumes within the LTAA reflect the effects of heavy alcohol use rather than psychiatric comorbid factors.

Finally, our results disagree with those of Gilman et al (Gilman et al., 2007) regarding reduced intracranial vault size (i.e., cranium size) in early onset alcoholics. Thirty-nine of the 52 LTAA were early-onset alcoholics, yet there was no difference in cranium size between LTAA and NAC (the cranium size did not differ between early- and late-onset LTAA, and in fact the cranium size index was numerically larger in early-onset alcoholics). Our failure to replicate their findings suggests that more research is needed. One possibility is that larger cranium sizes (a marker of larger premorbid brain size and greater brain functional reserve capacity) may be a predictor of obtaining long-term abstinence.

An important limitation of this study is its cross-sectional nature. We need to emphasize that we do not have longitudinal data, and can only infer recovery from chronic alcohol abuse induced brain shrinkage from the literature and the association of cranium size adjusted gray matter volumes with alcohol dose. In this regard, we note that there were no associations of cranium size adjusted gray matter volumes with alcohol dose in the occipital and limbic lobes. Therefore the inference that the reduced cranium size adjusted gray matter volumes in these regions are a result of chronic alcohol abuse is more tenuous. It is also possible that such findings may reflect phenomena that existed prior to chronic alcohol abuse (i.e., they may reflect phenomena associated with risk factors for chronic alcohol abuse).
References


Figure Legends

**Figure 1.** The cerebral lobe definitions used in our analyses. The frontal lobe (blue), parietal lobe (yellow), temporal lobe (red), and occipital lobe (green) are visible from the surface of the brain. The limbic lobe, containing the cingulate gyrus, cannot be seen from this viewpoint.

**Figure 2.** Comparison of ROI creation techniques in standard MNI space. (a-b) Neighboring ROIs consisting of adjacent Brodmann areas: Orbital frontal cortex (red), dorsolateral prefrontal cortex (green). (c-d) The boundaries of the same ROIs created using a three-voxel dilation in MNI space. Notice the significant overlap between nearby ROIs, which was caused in part by dilation from inferior and superior axial slices. (e-f) Nearest neighbor interpolation captures the cortical sheet while preserving boundaries between neighboring ROIs.

**Figure 3.** There was no significant correlation between parietal lobe volumes and spatial processing scores within the controls (left), but there was a strong trend within the LTAA (right). The dotted lines represent the 95% confidence interval.

**Figure 4.** In the LTAA women, there was no relationship between parietal lobe volumes and spatial processing scores. The relationship between spatial processing scores and parietal lobe volumes within the LTAA was entirely carried by men (right). The dotted lines represent the 95% confidence interval.

**Figure 5.** The LTAA men exhibit a significant negative relationship between average lifetime alcohol dose and parietal lobe volume (left) and total gray matter volumes excluding the parietal
lobe (right), where increased alcohol consumption is related to lower gray matter volumes within the parietal lobe and other areas of the brain. This relationship between alcohol and volume was not present within LTAA women or the NAC.
Figure 4: Parietal Lobe Volume vs. Spatial Processing Score (LTA3A Men)

$r = 0.42, p = 0.02$

Figure 5: Parietal Lobe Volume vs. Spatial Processing Score (LTA3A Women)

$r = 0.04, p = 0.87$
### Table 1. Sample demographics.

<table>
<thead>
<tr>
<th>Demographic Variables</th>
<th>Middle-Aged Normal Controls</th>
<th>Middle-Aged Abstinent Alcoholics</th>
<th>Effect Size (%)</th>
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<tr>
<td></td>
<td>Male (n=25)</td>
<td>Female (n=23)</td>
<td>Male (n=28)</td>
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<tr>
<td>Age (Years)</td>
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<td>48.0 ± 6.6</td>
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<td>Family Drinking Density(^1)</td>
<td>0.14 ± 0.22</td>
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<td>Years Education</td>
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<td>AMNART (Estimated Premorbid Verbal IQ)</td>
<td>1.20 ± 0.46</td>
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**Alcohol Use Variables**

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<th></th>
<th>Duration of Active Drinking (months)</th>
<th>Average Lifetime Drinking Dose (std. drinks/month)</th>
<th>Lifetime Alcohol Use (std. drinks)</th>
<th>Duration of Peak Drinking (months)</th>
<th>Average Peak Drinking Dose (std. drinks/month)</th>
<th>Peak Alcohol Use (std. drinks)</th>
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<td></td>
<td>230 ± 130</td>
<td>7 ± 8</td>
<td>1,800 ± 2,200</td>
<td>70 ± 81</td>
<td>15 ± 14</td>
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<td></td>
<td>290 ± 130</td>
<td>7 ± 8</td>
<td>2,000 ± 2,300</td>
<td>114 ± 113</td>
<td>17 ± 22</td>
<td>1,000 ± 1,500</td>
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<td>260 ± 90</td>
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<td>54,000 ± 59,000</td>
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<td>41.0(^2)</td>
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<td>0.6(^2)</td>
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\(^1\) Family drinking density is the proportion of first-degree relatives who were problem drinkers; statistical comparisons (and estimates of effect size for family drinking density were performed after normalizing the proportions via the arcsine transformation.

\(^2\) Statistical comparisons between groups are not valid since the group definitions are a function of the variable. Effect is significant: * p ≤ 0.05, ** p ≤ 0.01, *** p ≤ 0.001.
Table 2. Average gray matter volumes in regions of interest, adjusted for variations in head size with age as a covariate.

<table>
<thead>
<tr>
<th>Region</th>
<th>Middle-Aged Normal Controls</th>
<th>Middle-Aged Abstinent Alcoholics</th>
<th>Effect Size (%)</th>
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</thead>
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<td></td>
<td>Male (n=25)</td>
<td>Female (n=23)</td>
<td>Male (n=28)</td>
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<td>TOTAL GRAY MATTER</td>
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<td>422</td>
<td>414</td>
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<tr>
<td>Frontal Lobe</td>
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<td>142</td>
<td>139</td>
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All volumes are reported in cubic centimeters.
Effect is significant: * p ≤ 0.05, ** p ≤ 0.01, *** p ≤ 0.001.