Published in final edited form as:

Alcohol Clin Exp Res. 1995 October ; 19(5): 1121–1126.

Brain Atrophy and Cognitive Function in Older Abstinent Alcoholic Men

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Abstract

We used computer-aided magnetic resonance image analysis and an age-normed battery of neuropsychological tests to measure brain atrophy and cognitive function in 14 older abstinent alcoholic men and 11 older controls in the expectation that these subject groups would show the greatest and most persistent cerebral effects consequent to chronic alcoholism. The abstinent alcoholics exhibited cognitive impairments (primarily in memory and visual-spatial-motor skills) compared with the controls. In contrast, we found no difference in global cerebral atrophy between the groups, although two alcoholics had extensive atrophy compared with all other subjects. However, there was a stronger association between age and ventricular dilation in the alcoholic sample compared with controls. We conclude that a substrate other than magnetic resonance imaging-detectable global atrophy must underlie the persistent cognitive impairments evident in the sampled alcoholics. Furthermore, if there are global atrophic changes in the brain associated with chronic alcoholism, these effects are not ubiquitous and/or may be reversible in most patients with sufficient abstinence.

Keywords

Cerebral Atrophy; Alcoholism; Magnetic Resonance Imaging (MRI); Neuropsychological Assessment; Reversibility

NUMEROUS INVESTIGATORS have found an association between global cerebral atrophy and chronic alcoholism using x-ray computed tomography (CT) or magnetic resonance imaging (MRI) measures of sulcal and ventricular cerebrospinal fluid (CSF) volume.¹⁻⁹ Many studies of brain atrophy in alcoholics have identified age as a critical modulating factor, with greater magnitude and increased persistence of atrophy evident in the brains of older alcoholics.^{1,4,10-12} Pfefferbaum (1992) used MRI to focus on brain volume in younger and older abstinent alcoholics with comparable drinking histories. In this unique sample, age was not associated with either length of illness or total alcohol consumption. Even after controlling for normal age-related brain atrophy, the strong positive correlation between alcoholic brain shrinkage and age was still evident. In addition to the association of age with alcohol abuse-related atrophy, both Jacobson¹³ and Bergman¹⁴ suggested that the atrophic changes to the cerebrum consequent to alcoholism may be more persistent in men.

Chronic alcoholism also has a highly detrimental effect on cognitive function. Among patients hospitalized for the investigation of dementia, alcohol abuse is often the primary or a contributing factor, cited as often as multiinfarct dementia.¹² Cognitive dysfunction in alcoholics seems to be associated with age in much the same manner as is cerebral atrophy, in that at least some of the cognitive deficits found in long-term alcoholics are distinguishable from those associated with normal aging (i.e., alcoholism induces an “independent decrement” in cognitive function).¹⁵ Goldman et al.¹⁶ reported that age was the critical factor in the persistence of cognitive deficits associated with chronic alcoholism. In their study of abstinent alcoholics, the younger alcoholics improved to the level of the control groups in the area of visual-spatial functions (which are among those most sensitive to the effects of chronic alcohol abuse), whereas the oldest alcoholics continued to show deficits.

We recruited 14 older alcoholic men abstinent 3 months or more (i.e., beyond acute ethanol withdrawal) and 11 age-matched controls in the expectation that this alcoholic group would show the greatest nontransient cerebral effects consequent to alcoholism. We elsewhere reported measures of neuronal loss as assessed by proton spectroscopy for these samples.¹⁷ Herein, we submit the results of computer-aided MRI analysis and age-normed neuropsychological testing for the same samples. We asked the following questions: (1) Did global atrophy exist in these chronic older male alcoholics after 3 months–2 years of abstinence? (2) Did cognitive deficits exist in these chronic older male alcoholics after 3 months–2 years of abstinence? (3) Was the presence and severity of global atrophy and/or cognitive deficits associated with the duration of abstinence in the alcoholic sample? (4) Was the presence and severity of global atrophy associated with the presence and severity of cognitive deficits in the abstinent alcoholic sample?

METHODS

Subjects

Twenty-five subjects participated in the MRI study. The abstinent alcoholics were recruited from residential and outpatient treatment centers that specialize in the treatment of the older alcoholic. We studied 14 recovering alcoholic men (age: 59.7 ± 6.3 years; range: 49–72 years; years of education: 15.0 ± 2.5) and 11 male healthy controls (age: 63.0 ± 10.2 years; range: 45–75 years; education: 16.7 ± 2.4 years) recruited from the community. All subjects were screened to exclude those with histories of significant drug use other than alcohol, or a major psychiatric or neurological disorder other than those secondary to chronic alcohol abuse (e.g., a history of alcohol withdrawal seizures), or those on medications with central nervous system side effects. Subjects were not excluded for episodes of alcohol-associated head trauma with loss of consciousness, if these episodes were not serious enough to require hospitalization.

Self-report of family history of alcoholism was based on the following classification: definite family history positive (FHP)—alcoholic father, with or without alcoholism in other first- or second-degree relatives; definite family history negative (FHN)—no alcoholism in first- or second-degree relatives; and an intermediate group (FHI)—alcoholism in first- or second-degree relatives, but not in the father. There was greater genetic loading for alcoholism in the alcoholics compared with the controls: FHP—6 alcoholics, 2 controls; FHI—6 alcoholics, 3 controls; FHN—2 alcoholics, 6 controls (Bartholomew's χ^2 test = 4.71, $p = 0.05$).

The self-report measure of alcohol consumption was an estimate of current and past intake. One drink was considered a glass of wine, beer, or a shot of hard liquor, all averaging ~10 g ethanol. According to this self-report, two of the recovering alcoholics had been binge drinkers for the last 30 and 32 years (drinking to blackout more than once/month); the rest had abused alcohol continuously and heavily (22 ± 3 drinks/day; range: 8–40 drinks/day) for 10–40 years before cessation (years of abuse: 26.6 ± 8.7 years). At the time of study, 10 of 14 alcoholics

had been abstinent for a period of 3-11 months (6.1 ± 2.9 months); the other four had been abstinent for 17-24 months (entire patient cohort; duration of abstinence: 10.3 ± 7.5 months). All 11 controls reported having always drunk <60 drinks/month, with 8 of 11 controls having drunk between 0 and 8 drinks/month.

All subjects underwent 40 min of neuropsychological testing. In this battery, attention and concentration were measured by the Trails A Test¹⁸; verbal skills with and without a memory component were measured by the Wechsler Memory Scales Logical Memory Subtests;¹⁹ visual-spatial-motor processing with and without memory was measured by the Visual Functions Scale of the Luria-Nebraska Neuropsychological Battery,²⁰ Wechsler Memory Scales Design Reproduction Subtests,¹⁹ and Rey Complex Figure Test;²¹ and prefrontal processing was measured by the Trails B Test and the Hooper Visual Organization Test.^{18,22} The Shipley Vocabulary Subtest was included as an indicator of premorbid intelligence, and the Shipley Abstract Reasoning Subtest was used to measure current reasoning ability.²³

Each test score was ranked on a scale from 0 to 2 (the higher the score, the more severe the impairment) and used to compute a composite score. A subject received a 0 if he scored above the 15th percentile for the test, a 1 if he scored from the 5th through the 15th percentile, and a 2 if he scored below the 5th percentile. Memory retention on the Wechsler Scales was ranked as 1 if retention was 51-70%, and 2 if retention was $<51\%$. Subjects were also given 1 point if the difference between Vocabulary and Abstract Reasoning Subtest T-scores on the Shipley was 1 or more standard deviations, with Vocabulary (as an estimate of premorbid IQ) being higher. Points earned on all tests were then summed to yield a global impairment rating (GIR).

MRI Measurement of Brain Atrophy

MRI studies of 11 of the alcoholics and 9 of the controls were performed on a whole-body Phillips 2 Tesla MRI/MRS system. A sagittal T₁-weighted study (TR/TE = 450/30) was used for determination of the cantho-meatal plane. This was followed by a spin-echo sequence (TR/TE = 3000/30/80 msec) performed parallel to the cantho-meatal plane and covering the entire brain from the cerebellum to the vertex. The spin-echo sequence yielded a set of 19-23 proton density (the 30-msec echo) and T₂-weighted (the 80-msec echo) 5.1-mm-thick (with a 0.5 mm interslice gap) axial images. One subject had difficulty tolerating the procedure and, to shorten the acquisition time, the TR was shortened to 2068 msec, and only 13 slices were acquired (which included all of the slices needed for the analyses presented herein). Because of the removal of the Phillips magnet during a systems upgrade, the remaining three alcoholics and one control were scanned on a 1.5 Tesla Siemens system. The T₁-weighted sagittal scout image (TR/TE = 350/15) and the subsequent spin-echo sequence (TR/TE = 2700/22/90) were the same in their orientation and coverage; however, the spin-echo slice thickness was reduced to 4 mm (no slice gap), yielding 41 slices in all four subjects.

Computer-assisted segmentation of the MRI into tissue, ventricular, and sulcal CSF volumes was conducted for all subjects. A further segmentation of the tissue compartment into gray and white matter was performed only on the larger subset of 11 alcoholics and 10 controls scanned on the Phillips MRI system, because the gray versus white matter discrimination is much more sensitive to the differing MRI systems and sequences than the extremely robust CSF versus tissue discrimination. The tissue versus CSF segmentation was performed on sequential slices, beginning with the slice on which the red nucleus appeared and ending one slice above the lateral ventricles. The gray versus white matter segmentation was performed on a subset of these slices, beginning with the appearance of the fully volumed lateral ventricles and ending with the last appearance of partially volumed lateral ventricles. Figure 1 displays a representative subject's MRI data, together with the segmentation results for a slice through the lateral ventricles.

Preprocessing involved two steps. The skull was first stripped off the image using a modification of the algorithm developed by Lim and Pfefferbaum.²⁴ The resulting image, which was subject to all remaining analyses, was limited to the boundaries of the intracranial vault. This was followed by estimation and removal of RF field inhomogeneity via digital filtering. The inhomogeneity-corrected images were then processed independently by two operators, both blind to subject identity.

On a slice-by-slice basis, the operators thresholded subtraction images (i.e., the difference image between the T_2 and proton density-weighted images) to specify conservative CSF and non-CSF samples. These samples were chosen to represent tissue that definitely belonged to the correct (i.e., CSF or non-CSF) classification and left a sizable amount of tissue unclassified. For each slice, the conservative CSF and non-CSF samples were then used as training sets for a discriminant analysis that used both the proton density-weighted and the T_2 -weighted image pixel intensities to classify each pixel as either CSF or non-CSF. Each operator then separated ventricular from sulcal CSF by delineating the anatomical boundaries of the ventricular system on each slice. Ventricular and sulcal CSF volumes aggregated on the slices analyzed were then computed as a percentage of total intracranial vault volume to correct for variation in head size. There was excellent agreement between the operators, with the between operator correlation >0.99 for both percentage ventricular CSF and percentage sulcal CSF.

The gray versus white matter discrimination was accomplished in a similar manner to the CSF versus non-CSF discrimination. On a slice-by-slice basis, the operators thresholded the addition image (i.e., the sum of the proton density-weighted and T_2 -weighted images) to specify conservative white matter and gray matter samples. These samples were chosen to represent tissue that definitely belonged to the correct (i.e., white versus gray) classification and left a sizable amount of tissue unclassified. For each slice, the conservative tissue samples were then used as training sets for a discriminant analysis that used both the proton density-weighted and the T_2 -weighted pixel intensities to classify all non-CSF pixels as either gray or white matter. Pixels that were classified by the discriminant analysis as gray matter, but which must be white matter by anatomical location, were manually changed to hyperintense white matter signal classification. The white matter and gray matter volumes aggregated over the slices analyzed were then computed as a percentage of total intracranial vault volume. The hyperintense white matter signal category was computed as a percentage of total white matter on the slices analyzed. The between operator correlations for percentage white, percentage hyperintense white matter signal, and percentage gray matter were 0.82, 0.87, and 0.66, respectively.

RESULTS

Only one subject, an alcoholic, did not score within one standard deviation of the norm on the Shipley Institute of Living Scale Recognition Vocabulary Test that provides an estimate of premorbid cognitive function. Lack of education was the most likely explanation for his low performance on this test; on the abstract reasoning portion of the test (which does not depend on education), he scored within the normal range. There was a trend for the Shipley Recognition Vocabulary Test estimate of premorbid IQ to be lower in alcoholics (58.6 ± 9.5) compared with controls (63.7 ± 5.0) ($t_{20,5} = 1.74$, $p = 0.097$).

Neuropsychological Assessments

As displayed in Fig. 2, the recovering abstinent alcoholics were cognitively impaired (i.e., had higher GIR's, 4.6 ± 3.2 ; range: 1-14) compared with the control sample (1.5 ± 2.0 ; range: 0-6) ($t_{23} = 2.78$, $p = 0.011$). Tests involving visual-spatial-motor skills and/or delayed memory were more likely to show impairment than those depending on verbal skills (Table 1). When the Shipley Recognition Vocabulary Test premorbid IQ estimate was used as a covariate, the alcoholics still evinced a greater level of cognitive impairment than the controls ($F_{1,22} = 4.72$,

$p = 0.041$). The validity of the analysis of covariance was established by the lack of significance in the test of equality of regression slopes between groups ($F_{1,21} = 1.27, p = 0.27$). The mean GIR adjusted for the difference between groups in the premorbid IQ estimate was 4.35 for the alcoholics versus 1.92 for the controls. In the alcoholic sample, there was no association between FHP and GIR, with FHP alcoholics having an average GIR of 5.0 ± 4.5 , just slightly higher than the average GIR of all alcoholics (4.6 ± 3.2). There was only a weak trend for a GIR - age correlation across groups ($r = 0.30, p = 0.15$), with a nonsignificant difference between groups in the correlation (age $\times$ group interaction: $F_{1,24} = 0.66, p = 0.43$).

MRI Measures of Brain Atrophy

The CSF versus tissue segmentation (which was performed on all subjects) showed no significant differences between groups for either the percentage ventricular ($t_{19,1} = 1.00, p = 0.33$) or the percentage sulcal ($t_{23} = 0.05, p = 0.96$) CSF measure. These data are presented in Fig. 3. Although there is substantial overlap between groups, there were four recovering older alcoholic patients who had larger ventricles than any of the controls, with two of these having ventricular percentages 40% (abstinent 11 months) and 80% larger (abstinent 3 months) than the largest ventricular percentages in the control group. These two recovering older alcoholics also had the largest sulci, although the overlap between alcoholics and controls was greater for the percentage of sulcal CSF compared with the percentage of ventricular CSF measure. This pattern of results was the same whether the data were analyzed as ventricular and sulcal CSF volume, ventricular and sulcal CSF volume as a percentage of intracranial vault volume, or ventricular and sulcal CSF volume after covarying out the effect of intracranial vault volume.

In the alcoholic group, there were significant age-related increases for both ventricular and sulcal percentage ($r = 0.63, p = 0.02$; $r = 0.60, p = 0.03$, respectively). For the controls, there was a significant age-related increase in sulcal percentage ($r = 0.76, p = 0.006$), but the age-related increase in ventricular percentage did not reach significance ($r = 0.42, p = 0.20$). In an analysis of covariance for ventricular percentage (but not for sulcal percentage), the age $\times$ group interaction was statistically significant ($F_{1,21} = 5.02, p = 0.036$), reflecting the stronger association between age and ventricular dilation in the abstinent alcoholics compared with the controls. Figure 4 displays the ventricular dilation data for both groups as a function of age. When data for all subjects were transformed to residuals from the control group age regression curves, the difference between the groups on percentage of ventricular CSF was slightly enhanced, but still did not reach statistical significance ($t_{18,9} = 1.31, p = 0.21$).

There was no significant difference between the groups on the percentage of gray matter ($t_{18} = 0.58, p = 0.57$), percentage of white matter ($t_{18} = 0.59, p = 0.56$), or percentage of white matter displaying a hyperintense magnetic resonance signal ($t_{18} = 0.78, p = 0.45$). There were negative correlations (all of magnitude > -0.35) of the percentage of gray matter and percentage of white matter with age in both groups, with only the age-related reduction in white matter percentage in the controls reaching significance ($r = -0.74, p = 0.02$).

Although not statistically significant because of the very small n 's in the subgroups, the mean sulcal and ventricular percentages were higher in FHP versus combined FHI and FHN alcoholics (13.5% vs. 9.9% for sulcal CSF; 5.5% vs. 4.2% for ventricular CSF), with only the difference in sulcal CSF evidencing a trend toward significance ($t_{11} = 1.90, p = 0.08$). No association was apparent between any of the MRI measures and duration of alcohol abuse. There was a trend for increased duration of abstinence to be associated with smaller ventricles ($r = -0.47, p = 0.09$). Finally, there were no associations apparent between GIR and the MRI measures. The lack of association between global atrophy on MRI and the persistence and severity of cognitive deficits is illustrated by the abstinent older alcoholics with the largest and smallest ventricular volumes. The alcoholic with the largest ventricles (82% larger than any

control) had a GIR of 3, whereas the alcoholic with the smallest ventricles (smaller than any control) had a GIR of 6 (both in comparison with a control mean GIR of 1.50).

DISCUSSION

This study found large and persistent cognitive impairments in older alcoholic men abstinent 3 months-2 years. The deficits were primarily in visual-spatial-motor skills and in delayed memory abilities, a pattern similar to that cited by other alcohol researchers. In contrast, we did not find a statistically significant increase in global brain atrophy on MRI (as measured by ventricular or sulcal CSF percentage), even though older males are the group most likely to have the largest and most persistent atrophic effects consequent to chronic alcoholism. These results do not support a simple model, wherein global atrophy and cognitive impairments in chronic alcoholics reflect the same underlying reversible process. Rather, these results suggest that global atrophy may be less of a protracted effect than are cognitive impairments, which may persist for much greater periods of abstinence, especially in the older male chronic alcoholic.

Failure to demonstrate a statistically significant difference in mean cerebral atrophy between the older abstinent male alcoholics and the matched controls must be viewed in the context of the relatively small sample size and the resultant limited power of the study. Both the presence of outliers on ventricular size in the alcoholic group and the results of the covariate analyses of age and ventricular size suggest the possibility that there may be some difference in brain volume between the groups that the sample size is insufficient to detect. The age covariate analyses revealed a greater increase in ventricular dilation with age in the alcoholics compared with the controls—a pattern consistent with the aforementioned study of Pfefferbaum (1992). The presence of outliers with significant brain atrophy in the alcoholic group suggests that a subset of older alcoholic men may evince severe and persistent cerebral atrophy well into abstinence. The power of the current study *was* adequate to detect significant correlations of age and atrophy in both groups, and to detect robust differences between the groups in measures of cognitive functioning. Therefore, it is likely that, if a difference in brain volume caused by alcoholism does exist between the groups, this effect is small in comparison with the decrease in brain volume caused by age in both groups and in comparison with the decreased cognitive function in the alcoholic group.

There may be a number of factors contributing to our failure to demonstrate statistically significant brain shrinkage in older abstinent alcoholic men. Our study is the first to focus on brain atrophy in older men with abstinence of significant duration. It may be that 3-24 months of abstinence is a sufficient time period for resolution of atrophic changes in most older alcoholic men. Other studies that find increased MRI/CT measures of cerebral atrophy in alcoholics (with the effect larger in older alcoholics) have examined subjects with considerably less abstinence than our study cohort. It is also possible that choosing alcoholics with relatively long-term abstinence may result in a biased sample of alcoholics, favoring those with relatively less brain shrinkage. This would be the case if either the extent and/or potential reversibility of cerebral atrophy consequent to alcoholism was associated with the ability to remain abstinent. If this is true, then measures of atrophy in older alcoholics may have some utility for treatment planning.

The clearest finding of this study is the strong detrimental effect of chronic alcoholism on cognitive functioning, an affect that persists well into abstinence. The second finding of this study, that there is no difference in brain volume, must be qualified by the possibility that a larger sample size may demonstrate a difference in brain volume. However, even if a larger sample size did detect a decrease in brain volume in the alcoholics, it is unlikely that global atrophy would emerge as the physical substrate of the cognitive impairment in the alcoholics,

because there was no association between any of the MRI measures and GIR in this sample. Given the specificity of function in the human brain, it is more likely that the effect of alcohol on specific brain structures (such as the hippocampus) is the physical substrate for the persistent cognitive impairments exhibited by this sample of older abstinent alcoholic men.

Acknowledgments

We thank Nancy Poole for administering the cognitive battery to these samples.

This study was supported by the National Institute on Alcohol Abuse and Alcoholism Grant R01 AA08968 (to G.F.), by general medical research funds to the Department of Veterans Affairs, and by a Department of Veterans Career Research Scientist Award (to G. F.).

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Fig. 1. Segmentation of magnetic resonance images. Segmented image shows white matter with an abnormally high signal in the areas below the occipital horns of the lateral ventricles.

Fig. 2.
GIR scores from controls and alcoholics. Alcoholics have much higher GIR scores than controls.

Fig. 3.

Ventricular and sulcal CSF volumes as a percentage of total brain volume for controls and alcoholics. There is no significant difference in ventricular or sulcal volumes between groups. Two alcoholics have ventricular atrophy 40% and 82% greater than any control.

Fig. 4. Ventricular volume (as a percentage of total brain volume) versus age. The association between age and ventricular dilation is stronger in alcoholics than in controls. ○, older alcoholics; ●, controls.

Table 1

Neuropsychological Test Performance

Test	Alcoholics (<i>n</i> = 14)		Controls (<i>n</i> = 11)	
	Mean	SD	Mean	SD
Shipley Verbal	58.6	9.5	63.7	5.0
Shipley Abstract	56.9	10.3	63.5	4.7
Luria 99	6.1	1.9	6.8	1.5
Rey	9.5	2.8	10.4	1.8
WMS—Verbal im	37.4	29.0	53.5	30.7
WMS—Verbal del	36.2 [*]	30.1	59.3	24.4
WMS—Design im	28.4 ^{***}	18.5	59.5	16.4
WMS—Design del	14.2 ^{**}	11.9	53.3	31.1
Trails A	53.5	25.5	63.8	23.8
Trails B	49.0 ^{**}	25.0	76.5	19.8
Hooper	60.9 [*]	9.0	53.7	6.6

Different from controls:

WMS, Wechsler Memory Scale; im, impairment; del, delayed memory.

*
 $p < 0.05$

**
 $p < 0.01$

 $p < 0.0001$.