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Volumetric Magnetic Resonance Imaging Quantification of Longitudinal Brain Changes in Abstinent Alcoholics

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Magnetic resonance imaging (MRI) of the brain was performed on a group of 24 recently detoxified, male alcoholics approximately 1 month after their date of last drink. The imaging was repeated 3 months later, at which point 9 subjects had resumed drinking and 15 had maintained abstinence. Contrasts between these two drinking groups revealed that, despite comparable baseline values, the Abstainers exhibited volumetric white matter increases and cerebrospinal fluid reductions over the follow-up interval, whereas the Drinkers did not show significant change on either of these MRI indices. These results provide the first evidence suggestive of significant volumetric white matter increase with abstinence.

Key Words: Alcohol, MRI, Longitudinal, White Matter.

NEUROIMAGING STUDIES of recently detoxified chronic alcoholics have consistently documented abnormal brain cerebrospinal fluid (CSF) volume elevations in this population.[1-7] In addition, two studies have used volumetric magnetic resonance imaging (MRI) quantification to examine alcohol-related abnormalities in specific brain tissue regions. Jernigan et al.[6] reported the presence of widespread volume loss across multiple cortical and subcortical grey matter regions in a group of chronic alcoholics, the degree of which was significantly associated with the observed CSF volume elevation. This study did not examine the total white matter volume, although the authors did report that the alcoholic group showed a significant increase in the prevalence of white matter pixels that were slightly hyperintense (i.e., pixels that were potentially abnormal in that they had the signal intensity most characteristic of grey matter). Pfefferbaum et al.[7] replicated the finding of widespread grey matter loss, but also found volumetric white matter abnormality that was of a similar severity to the measured grey matter deficit. These in vivo findings are consistent with neuropathological data showing reduced brain weights in alcoholic subjects,[8] as well as pronounced cerebral white matter loss that may be even more prominent on autopsy than are the grey matter changes.[9-12]

As a group, alcoholics who maintain abstinence exhibit at least partial reversal of CSF volume elevations on serial neuroimaging assessments.[13-18] Although this fluid reduction is a putative marker for volumetric cerebral tissue increases, consideration to date of which affected brain regions may recover with sobriety has been only speculative. A portion of this CSF volume reduction may be reflective of acute tissue rehydration and electrolytic changes that occur early in abstinence; however, there is also evidence of continued improvement that extends beyond this acute period.[13]

Because there appear to be individual differences among alcoholics in the magnitude of recovery with abstinence, investigators have examined factors that may covary with imaging changes. Carlen et al.[15] found that the degree of CSF volume reduction was greatest in subjects who had a brief interval between their date of last drink and baseline CT examination. Further, after accounting statistically for both age and the interval between last drink and baseline CT, the alcoholics in that sample who remained abstinent did not differ in degree of CSF change from those patients who continued to drink. Age is known to be an important cross-sectional predictor of brain abnormality in alcoholics, with older patients demonstrating greater impairment than younger patients, relative to their healthy agemates.[5,7,19] The relationship between age and neuropathological recovery, however, has not been well documented.

In the present study, longitudinal change in MRI brain measures for a sample of recently detoxified, abstinent alcoholics are contrasted with results from a comparison group that resumed drinking during the follow-up interval. To our knowledge, this is the first investigation to use volumetric, MRI-derived indices to examine abstinence-related changes not only in CSF, but also in the grey and white matter tissue compartments. In addition, we report the correlations between MRI change scores and descriptive variables such as age and drinking history.

METHODS

Subjects and Procedure

Twenty-four chronic alcoholic men participated in the study. All subjects were drawn from the inpatient Alcohol Treatment Program at

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the Department of Veterans Affairs Medical Center, San Diego. The majority of these patients had undergone detoxification shortly before admission to the hospital. All subjects were administered the Alcohol Research Center Intake Interview,[20] and a resource person (family member or friend) was interviewed for corroborative diagnostic information. Subjects were accepted into the study only if these interview data supported a DSM-III diagnosis of alcohol abuse or dependence. In cases where the resource person and the patient provided discrepant information, the more severe of the two histories was coded (e.g., the more recent date of last drink or the more protracted disease course).

Prospective subjects were excluded for history of polysubstance abuse, primary psychiatric disorders other than alcohol abuse, Antisocial Personality Disorder, history of serious neurologic insult or injury, liver disease, or metabolic disturbance. In addition, they were excluded for conditions that would preclude the completion of an MRI brain scan (e.g., claustrophobia, pacemaker placement, metal pins or clips in the upper body, or a history of metal fragments in the eye). All participants provided informed consent.

The MRI examinations were first performed during approximately the 3rd week of hospitalization (mean = 28.7 days since last drink, SD = 5.9) and again at ~3 months following discharge from the hospital (mean follow-up interval = 107 days, SD = 19.4). Patients were included in the present study only if both baseline and follow-up MRI examinations were completed and the data were technically adequate for the image analysis procedure. Baseline MRI and cognitive data for a subset of these subjects have appeared in previous reports.[6,21,22]

At the follow-up assessment, 9 of the 24 subjects had returned to drinking (i.e., had consumed at least one alcoholic beverage during the follow-up interval); the other 15 individuals remained abstinent. Descriptive information for the Drinkers and Abstainers is presented in Table 1. One-way ANOVAs indicated that the subjects in the two drinking groups were not statistically different in age, years of education, interval between imaging sessions, years of problem drinking, or the average number of drinks consumed in the 3 months prior to their admission to the hospital.

The MRI was performed according to a standard protocol with a 1.5 Tesla superconducting magnet (Signa; General Electric, Milwaukee) at the UCSD/AMI Magnetic Resonance Institute, and data were analyzed at the Brain Image Analysis Laboratory of the Department of Psychiatry, UCSD. Proton-density weighted and T2-weighted images were obtained simultaneously for each section, using an asymmetrical, multiple echo sequence (TR = 2000 msec, TE = 25, 70 msec) to obtain images of the entire brain in the axial plane. Section thicknesses were 5 mm with a 2.5 mm gap; a 256 × 256 matrix was selected, with a 24 cm field of view.

The image analysis procedure has been described in detail previously.[6,23–25] Briefly, each axial image was first digitally filtered to reduce signal drift due to magnetic field and gradient inhomogeneities. Trained operators, who were blind to subject diagnosis, then applied a semiautomated procedure to classify each pixel location within a section of the imaged brain on the basis of its signal value in both original images (TE = 25, TE = 70) as most resembling CSF, grey matter, white matter, or signal hyperintensity (tissue abnormality). This procedure was accomplished in two steps. First, two new linear combinations of the pixel values were computed to optimize tissue contrast (CSF vs. brain and grey matter vs. white matter). Classification criteria that were adjusted separately for each section were then applied to these computed values. The full series of axial images was analyzed, beginning at the bottom of the cerebellar hemispheres and extending through the vertex, after which a stylus-controlled cursor was used to separate manually infratentorial (cerebellar) from supratentorial regions. Three summary indices were created by totaling supratentorial pixels that had been classified as grey matter, white matter, and CSF. Each of these summary indices was expressed as a proportion of the total supratentorial cranial volume, to adjust the raw pixel values for individual differences in head size.

Table 1. Means and Standard Deviations for Demographic and Descriptive Variables

	Drinkers (n = 9)	Abstainers (n = 15)
Age	48.6 (10.9)	48.8 (9.6)
Education	13.9 (1.7)	14.4 (1.9)
Years of problem drinking	15.9 (11.8)	14.5 (10.2)
Average no. of drinks/day in 3 months prior to admission	11.6 (6.2)	13.5 (8.9)
Days of sobriety at baseline session	30.4 (6.0)	27.7 (5.7)
Interval between imaging sessions (days)	111.3 (29.42)	104.9 (10.4)
Average no. of drinks/day in 3 months following discharge	1.1 (1.7)	0.0 (0.0)

RESULTS

The grey matter, white matter, and CSF proportion scores for the two drinking groups at baseline and follow-up are summarized in Table 2. These three proportions do not sum to exactly 100%, because cortical pixels classified as signal hyperintensity were excluded from the analysis.

Change in each proportion score (grey, white, and CSF) across the two imaging sessions was investigated with a series of three repeated-measures ANOVAs, in which drinking group (Drinkers vs. Abstainers) served as the between-subjects measure. Two cases appeared as outlying values in terms of change across images; the results of analyses with and without these individuals, however, were comparable. Results revealed significant interactions between drinking status and change over time (baseline vs. follow-up) for both the CSF [$F(1,22) = 9.88$, $p < 0.01$] and white matter [$F(1,22) = 4.95$, $p < 0.04$] indices. There were no significant main effects or interactions in the grey matter analysis.

Post-hoc pairwise comparisons indicated that the Drinkers and Abstainers did not differ significantly in their baseline CSF or their baseline white matter proportions. In terms of change across time, the Abstainers demonstrated significant CSF volume reduction ($p < 0.01$) and white matter volume elevation ($p < 0.05$) across the follow-up interval. In contrast, the Drinkers did not evidence significant change on either measure, although it is interesting to note that the relative mean differences in this group were in the direction of *increased* CSF and white matter abnormality over time. Figure 1 illustrates the change in white matter, grey matter, and CSF proportions for each of the 24 individual subjects across the follow-up interval.

Although the Drinkers and Abstainers did not differ significantly in their baseline MRI values, we performed analyses of covariance to confirm that the obtained group

Table 2. MRI Indices Expressed as Proportions of the Total Supratentorial Cranial Volume

	Drinkers (n = 9)		Abstainers (n = 15)	
	Baseline	Follow-up	Baseline	Follow-up
Fluid	0.162 (0.062)	0.172 (0.059)	0.153 (0.051)	0.134 (0.045)
White matter	0.422 (0.025)	0.406 (0.048)	0.401 (0.038)	0.417 (0.049)
Grey matter	0.411 (0.049)	0.418 (0.046)	0.440 (0.037)	0.443 (0.041)

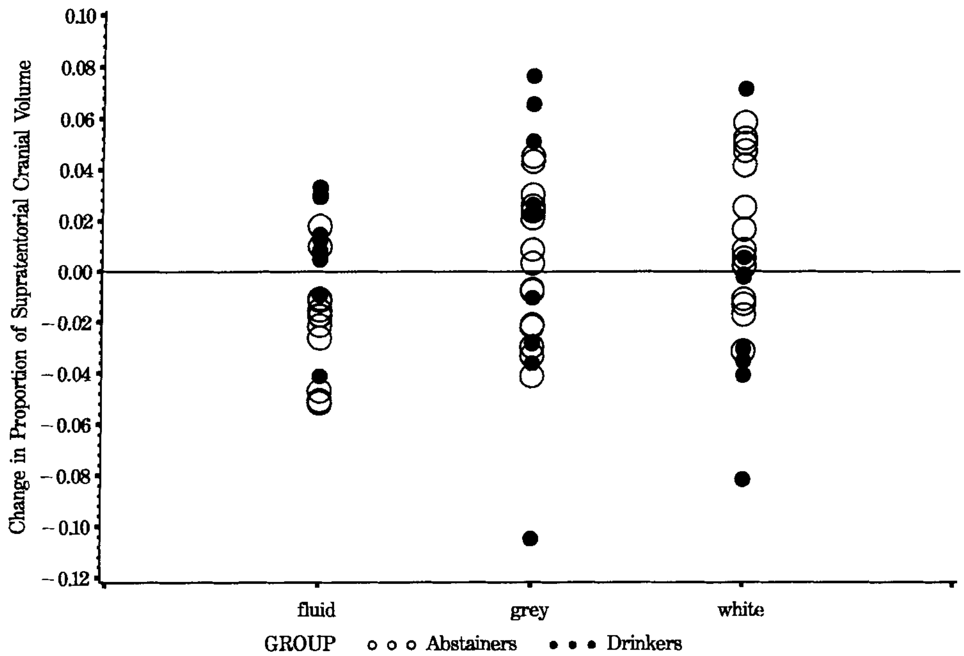

Fig. 1. Change in proportion scores for individual subjects. Positive values reflect increases in the proportion score for a given MRI index across the two examinations; negative values reflect decreases.

effects would endure after adjusting for individual differences present at the first imaging session. These analyses revealed that, even when baseline CSF proportions were accounted for, there remained a highly significant elevation in the CSF values of the Drinkers at follow-up, relative to the Abstainers [$F(1,21) = 9.88$, $p < 0.01$]. Similarly, taking baseline into account, the follow-up white matter proportion was significantly higher in the Abstainers than in the Drinkers [$F(1,21) = 4.39$, $p < 0.05$]. Furthermore, an ANCOVA with white matter change as the dependent measure and grey matter change as the covariate still revealed a group effect [$F(1,21) = 14.96$, $p < 0.001$], reflecting a significant volumetric increase in white matter associated with abstinence, which is statistically independent of changes occurring in the grey matter. A repeated-measures ANOVA with tissue type (change in white matter vs. change in grey matter) as the within-subjects measure did not show a significant main effect for tissue type or interaction between drinking group and tissue type. Therefore, although there is significant white matter change in the Abstainers that is independent of the grey matter change, the magnitude of the white matter increase does not differ significantly from that in the grey matter.

Pearson correlations revealed that, in the full sample of 24 subjects, age was significantly associated with cross-sectional proportion scores for CSF ($r = 0.55$ at baseline; $r = 0.46$ at follow-up) and for grey matter ($r = -0.65$ at baseline; $r = -0.42$ at follow-up), but not with white matter ($r = -0.04$ and $r = -0.12$, respectively). These findings are consistent with other reports of greater brain abnormality in older than younger alcoholics.[5,7,19] There was no significant association in our data, however, between age and the degree of change over time in white matter ($r = -0.115$), grey matter ($r = 0.247$), or CSF ($r = -0.234$). Subjects who consumed more alcohol in the 3 months prior to admission had significantly lower grey matter proportion scores at baseline ($r = -0.41$) and showed greater CSF reversibility ($r = -0.45$). The length of the follow-up interval was not significantly correlated with any cross-sectional proportion scores or longitudinal change scores.

Finally, we tested the Carlen et al.[15] finding that the duration of the interval between last drink and baseline CT was an important predictor of subsequent CSF volume reductions in their sample. Following these authors' analyses, we used ANCOVAs to test the effect of drinking group after removing the contributions of age and days of sobriety at baseline assessment. In contrast to Carlen et al., these analyses revealed a significant effect of group (after accounting for age and duration of sobriety at baseline) for both CSF [$F(1,23) = 9.15$, $p < 0.01$] and white matter change [$F(1,23) = 5.34$, $p < 0.04$].

DISCUSSION

The present findings are consistent with the existing literature on CSF abnormalities in alcoholics in confirming the presence of significant volumetric CSF reductions in the brains of patients who maintain sobriety. In addition, our data suggest that abstinence is associated with small but statistically significant white matter volume increases. No significant grey matter change was identified, although we cannot rule out the possibility that our sample size was insufficient to detect small grey matter effects or, alternatively, that grey matter regions show volumetric increases across a time period that exceeds our sampled follow-up interval. Although our results do not imply that tissue changes occur exclusively in the white matter rather than the grey matter, we were able to identify a significant change within the white matter compartment that was associated with abstinence and was independent of any corresponding grey matter change. Both the CSF and white matter changes in the Abstainers differed significantly from the (nonsignificant) changes observed in the Drinkers. This group difference is particularly important, because it suggests that the measured changes in the Abstainers are unlikely to be due to random measurement error or methodological factors (e.g., differences in head positioning across the two imaging sessions) that would be expected to affect both groups equally.

In terms of change within individual subjects, 13 of the 15 Abstainers (86.7%) showed CSF volume reductions across the follow-up interval, whereas only 2 of 9 Drinkers (22.2%) improved. In the white matter compartment, 11 of the Abstainers (73.3%) and 2 of the Drinkers (22.2%) showed volumetric increases. The magnitudes of the three change scores were not significantly correlated with age, although subjects with higher alcohol consumption in the 3 months prior to admission were found to show greater CSF volume reduction across imaging session.

We did not replicate the Carlen et al.[15] finding that the statistical control of age and date of last drink-ameliorated group differences between Drinkers and Abstainers. There are several methodological issues that may contribute to these differing results. Carlen and colleagues performed baseline CT scans across a wide range of abstinence durations, which encompassed both acute and potentially more gradual recovery processes. In contrast, our subjects received MRI examinations a minimum of 19 days after last drink, which likely postdated any acute withdrawal effects. It is noteworthy that we were able to identify significant CSF and white matter volumetric changes that are unlikely to be due to acute withdrawal or rehydration effects.

The specific mechanisms that mediate the neurotoxic effects of alcohol and the reversibility of these effects with abstinence are as yet poorly understood. Postnatal exposure to alcohol is known to interfere with myelination in laboratory animals[26] and, in the peripheral nervous system, alcohol has been shown to inhibit the in vitro regeneration of Schwann cells and myelin.[27] Although there are no reports of frank demyelinization in autopsy studies of alcoholics, multiple investigations that have documented substantial white matter volume loss in this population in vivo[7] and postmortem,[10–12] and there has been speculation that the observed white matter shrinkage may be reversible with abstinence.[9,12] To our knowledge, the present study provides the first empirical evidence that abstinence may be associated with a white matter volume increase. It will be important for future work to confirm the presence of tissue volume increases in specific cerebral regions and to examine with a larger sample size the relationship between brain tissue changes and the well-documented cognitive recovery exhibited by many abstinent alcoholics.

There are several aspects of our study design that have implications for the generalizability of the findings. The subjects were required to meet rigorous medical and psychiatric inclusionary and exclusionary criteria, which allowed us to study changes associated with abstinence that were not confounded with these other conditions. It is probable, however, that this carefully selected sample may not be representative of individuals in the larger alcoholic population, who may demonstrate differing courses of recovery. In addition, this study, as well as the majority of other investigations of alcohol-related brain changes, focused on male patients exclusively. Although female alcoholics may show similar neuropathological changes to those identified in males,[28] there is evidence that the relationships between structural brain abnormalities and demographic and alcohol consumption measures may differ with gender.[29] One longitudinal MRI study failed to find significant CSF reversibility in a small group of alcohol-dependent women, although these patients also tended to be young and were not clearly abnormal at baseline.[30] At present, then, there is not sufficient information to speculate about the generalizability of the present findings to samples of alcoholic women.

The obtained differences between alcoholics who resume drinking and those who abstain may potentially be reflective of a regenerative process following drinking cessation that is inhibited by relapse. Consideration must be given, however, to the fact that the Drinkers in the present sample had only a low alcohol intake during the follow-up interval. It is plausible, therefore, that factors in addition to alcohol intake per se contributed to the magnitude of the group differences. Although we did not find significant group differences at baseline on any of the demographic, drinking, or MRI measures, the small sample size may have precluded detection of subtle differences present at the initial assessment. Additionally, because group membership was determined only at the end of the follow-up interval, events occurring during that 3-month period (e.g., metabolic or nutritional changes) may have mediated both the MRI results and drinking status. Finally, it is plausible that abstinence may have been facilitated somewhat in individuals who experienced greater neuropathological recovery; therefore, we cannot rule out the possibility that the measured cerebral changes may have themselves influenced the group classification.

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