A Controlled Study of Cortical Gray Matter and Ventricular Changes in Alcoholic Men Over a 5-Year Interval

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Background: We report on structural brain changes during a 5-year period in healthy control and alcoholic men.

Methods: Alcoholic patients (n = 16), from an initial group of 58 who underwent brain magnetic resonance imaging scanning while in treatment, were rescanned with the same acquisition sequence approximately 5 years later. Control subjects (n = 28) spanning the same age range also were scanned twice at a comparable interval. Changes in brain volume were corrected for error due to differences in head placement between scans and expressed as slopes (cubic centimeters per year), percentage of change over baseline for the control subjects, and standardized change for the alcoholic patients. The alcoholic patients varied considerably in the percentage of time that symptoms of alcohol dependence were present and in the amount of alcohol consumed during follow-up.

Results: The cortical gray matter diminished in volume over time in the control subjects, most prominently in the prefrontal cortex, while the lateral and third ventricles enlarged. The alcoholic patients showed similar age-related changes with a greater rate of gray matter volume loss than the control subjects in the anterior superior temporal lobe. The amount of alcohol consumed during follow-up predicted the rate of cortical gray matter volume loss, as well as sulcal expansion. The rate of ventricular enlargement in alcoholic patients who maintained virtual sobriety was comparable to that in the control subjects.

Conclusions: During a 5-year period, brain volume shrinkage is exaggerated in the prefrontal cortex in normal aging with additional loss in the anterior superior temporal cortex in alcoholism. The association of cortical gray matter volume reduction with alcohol consumption over time suggests that continued alcohol abuse results in progressive brain tissue volume shrinkage.

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IN VIVO NEUROIMAGING has shown that long-term consumers of large amounts of alcohol have increased cerebrospinal fluid (CSF) spaces and reduced cortical brain volume affecting gray and white matter compared with low alcohol consumers. Alcohol-related volume deficits are present in the frontal lobes, anterior hippocampus, mammillary bodies and cerebellum, and corpus callosum, particularly in older persons. Although alcohol consumption contributes to these group differences in brain structure, the progression of the disease must also be considered relative to normal aging changes. Studies comparing young and old groups of healthy people or applying regression analysis to samples representing a continuum of ages to estimate the rate of change over a given age span provide indirect evidence that the passage of time contributes to changes in brain structure.

Only longitudinal studies including patients and control subjects can provide direct information about disease progression relative to the normal changes of aging. To date, follow-up studies in alcoholic patients have included periods of treatment detoxification or 3 to 12 months after treatment. One study retested alcoholic patients after 5 years but did not retest control subjects. The potential interaction between normal aging and long-term excessive alcohol consumption on brain structure can be inferred from cross-sectional analysis showing that the older brain is more vulnerable to the effects of alcohol than the younger brain. Unlike Alzheimer disease, which progresses inexorably, albeit at variable rates, alcoholism typically involves periods of exacerbation, during which ex-
PATIENTS, SUBJECTS, AND METHODS

PATIENTS AND SUBJECTS

Alcoholic patients (group 1) and control subjects (group 2) (Table 1) gave written informed consent for participation in the study.

Alcoholic Patients

The patients, recruited from a Veterans Affairs inpatient alcohol rehabilitation program, had previously participated in cross-sectional and longitudinal neuroimaging studies. At baseline, they met the Research Diagnostic Criteria (RDC) for alcoholism but not for drug use disorder within the past year. They had no history of hospitalization for schizophrenia, major affective disorders, or medical or neurologic conditions affecting the central nervous system; seizure disorder unrelated to alcohol withdrawal; documented head injury with neurologic sequelae; or use of phenytoin or corticosteroids during the past month. The baseline scans were obtained 4 weeks (mean ± SD, 28.7 ± 5.5 days) after admission; 39 patients returned for a short-term follow-up study 2 to 12 months (mean ± SD, 28.7 ± 5.5 days) after discharge, and some participated in annual follow-up testing. Of the 16 patients in the present report, 15 were in the initial cross-sectional report, and 14 were also in the short-term follow-up report.

Efforts to recruit patients for a 5-year follow-up included an offer of overnight accommodation at the hospital and payment of $200 to complete 2 days of testing. Twenty-two alcoholic patients were no longer in active treatment in the Veterans Affairs program or did not respond to mail or telephone contact. Of the remaining 36 patients, 5 had died, and 5 had moved out of state, leaving a sample of 25 targeted for testing; 19 underwent scanning, but the data from 3 could not be used because technical errors in the baseline or follow-up scan precluded a valid assessment of change over time. Therefore, group 1 included 16 patients. The follow-up sample was demographically and clinically comparable with the patients lost to follow-up but showed slightly greater brain volume abnormalities; the difference was significant for cortical gray matter (Table 2).

Control Subjects

To determine the amount of change occurring during a comparable period in healthy control subjects, we recalled men whose ages matched those of group 1 patients from a group of healthy community members who had served in earlier studies of healthy aging and provided age norms for the initial cross-sectional studies of alcoholism. This sample of control subjects had been screened originally for psychiatric disorders by use of the Schedule for Affective Disorders and Schizophrenia–Lifetime version and for medical or neurologic conditions affecting the central nervous system, including head injury with documented loss of consciousness exceeding 30 minutes, by physical examination, medical history, and standard blood tests. Subjects were excluded if they had ever met the RDC for any psychiatric disorder, if they had experienced a drug use disorder during the year before entry into the study, or if they had ever consumed more than 54 g of ethanol per day (equivalent of 4 “drinks” containing an average of 13.6 g of ethanol) for a period exceeding 1 month as assessed through a semistructured interview used to measure alcoholic consumption history variables. Subjects 50 years and older were excluded if they scored 24 or less (maximum, 30) on the Mini-Mental State Examination. Group 2 included 28 subjects.

Follow-up

Group 1 and 2 participants underwent a physical examination, completed a questionnaire to identify illness during the intervening period, underwent standard medical laboratory tests, and participated in the Structured Clinical Interview for DSM-III-R (SCID) and a semistructured interview to quantify alcohol consumption since baseline. At baseline, the interviewer had already estimated alcohol consumption to that point, starting from the age at which the participant first drank on a regular basis (at least 1 drink per month) and eliciting the quantity (how many drinks per day) and the frequency (how many drinks on average during a month) of drinking over a series of “drinking stages,” differentiating between normal and maximum quantities and their frequencies. The types of alcoholic beverage (wine, beer, or spirit) were converted into “drink” equivalents, and each was given a value of 13.6 g of absolute alcohol. For follow-up assessment, the interviewer first reviewed the patient’s or subject’s alcohol use history, oriented the participant to the point in time at which the chronology was being resumed, and then elicited information about subsequent epochs of sobriety and drinking, using the same format as the original questionnaire.

MAGNETIC RESONANCE IMAGING

Acquisition and Analysis

The same magnetic resonance imaging protocol on a 1.5-T scanner (Signa, General Electric, Milwaukee, Wis) was used. The patients and control subjects were scanned on the same day at the same time of day, and scans were obtained at the same point in time at which the chronology was being resumed. The patients and control subjects had no known change in health status or alcohol consumption between baseline and follow-up. All scans were obtained in the axial plane, with T2-weighted scans from -120 to 240 mm and T1-weighted scans from -120 to 240 mm. The scans were obtained before and after inhaling oxygen, which increased the signal intensity of the gray matter.

The protocol was approved by the institutional review board, and written informed consent was obtained from all participants.
was used at baseline and at follow-up: axial spin echo, 5-mm thick, 2.5-mm skip; field of view, 24 cm; 256 × 256 matrix; echo times, 20, 80 milliseconds; cardiac cycle–gated effective repetition times, more than 2400 milliseconds; 256 phase encodes; and oblique plane perpendicular to sagittal plane crossing through anterior and posterior commissures.

Images were processed without knowledge of the participant's identity, age, diagnosis, or neuroradiologist's report. The most inferior slice above the level of the orbits, where anterior horns of the lateral ventricles could be seen bilaterally, was identified as the index slice. Index slices for baseline and follow-up scans were individually reviewed to ensure comparability across the 2 scans. Seven consecutive slices, including the index slice and six superior slices, sampled approximately half the total volume of the brain. Each slice from the magnetic resonance image, divided into an inner 55% and an outer 45%, was segmented into CSF, gray matter, and white matter compartments by using a semiautomated image analysis technique.32 This analysis yielded 3 global cortical measures (gray matter, white matter, and sulcal CSF) based on the outer 45%, a measure of lateral ventricles (CSF in the inner 55% of all slices on which they appeared), and the third ventricle measured on the index slice or the slice below it, wherever it appeared larger.

The images were further divided according to anatomical landmarks and a priori geometric rules into 6 standardized cortical regions of interest (ROIs), encompassing the outer 45% of each image and corresponding roughly to lobar anatomy: prefrontal, frontal, anterior superior temporal, posterior superior temporal, anterior superior parietal, and posterior parietal-occipital (Figure 1).

Volume Change
Regional volumes were expressed as cubic centimeters. The volume difference between scans provides the first estimate of change over time. The simple difference between scans represents the true biological change between scans plus measurement error due to differences in the position of a person's head in the scanner between imaging sessions.34 We used changes in head size (the sum of the volume of CSF and tissue on all 7 slices analyzed for this study) as an estimate of measurement error, because such change would not normally be expected in adults. To correct for measurement error, we regressed observed changes in CSF and gray and white matter volume for each region against the diagnostic group and differences in total head size between scans, assuming a common slope but different intercepts (if the groups differed in rate of change) for each group.17,34 We then added each person's residual score for each region and tissue type measure to the group intercept for that measure to calculate the adjusted change.

Because patients and subjects had varying interscan intervals, adjusted change scores were divided by the interscan interval, expressing the change as a slope or rate of change per year. To control for absolute baseline differences in structure size between persons and groups and differences between the sizes of regions, adjusted change values were expressed as the percentage of change ([adjusted change/baseline] × 100). An additional procedure standardizing each ROI against change in group 2 was used to compare change across regions within group 1 because the ROIs were of fundamentally different sizes. Finally, slopes were multiplied by a uniform 5-year interval for all participants, and the resulting estimate of 5-year volume change was added to the corresponding baseline measure to yield corrected follow-up volumes. These absolute baseline and adjusted follow-up measures are used in Figure 2 and Figure 3 to provide a direct representation of the nature and scale of change occurring during the follow-up interval.

STATISTICAL ANALYSIS
The effects of normal aging were assessed in group 2 by using the percentage of change per year. One-sample t tests were performed to detect differences from zero in the 3 global cortical and 2 ventricular brain measures. To determine whether gray matter changed at a greater rate in any 1 of the 6 cortical ROIs than the others, a 1-way repeated-measures analysis of variance (ANOVA) for cortical gray matter was performed and followed up with t test comparisons of each ROI against the others if an interaction was found.

To determine whether brain changes progressed at different rates in the 2 groups, the rates of change (cubic centimeters per year) for the 3 global cortical and 2 ventricular brain measures were compared by using t tests. To determine whether gray matter loss progressed at a greater rate at any 1 of the 6 cortical ROIs in group 1 than in group 2, a 2-way repeated-measures ANOVA for the 6 cortical ROIs was performed, using standardized scores. Follow-up t tests comparing individual ROIs were performed for significant interactions.

To determine whether age at study entry, drinking behavior, or symptom severity during the follow-up period predicted outcome within group 1, these predictors were correlated with the rate of change (slopes). In addition to assessing the effect of drinking behavior as a continuous variable among patients in group 1, we performed an exploratory analysis comparing drinking-defined subgroups with each other and with the control group.

at the Veterans Affairs Palo Alto Health Care System, Palo Alto, Calif, for alcohol dependence or other psychiatric (depression, posttraumatic stress disorder, anxiety disorders) and/or medical conditions. Four patients in group 1 maintained virtual sobriety during the follow-up period, and an additional 3 were within the control range of drinking. Cumulative but not necessarily continuous sober time during follow-up ranged from 5½ months to the entire period. Although the patients in group 1 differed widely among themselves, they also differed in age.

RESULTS

CLINICAL OUTCOME
The DSM-III-R diagnoses, SCID-based estimate of the amount of time patients had problems with alcohol, reports of the amount of alcohol consumed during the follow-up interval, and medical records indicated a wide range of outcomes (Table 3 and Table 4). In group 1, 8 of 16 patients received additional inpatient treatment during the follow-up period, and an additional 1 was within the control range of drinking. Cumulative but not necessarily continuous sober time during follow-up ranged from 5½ months to the entire period. Although the patients in group 1 differed widely among themselves, they also differed in age.

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aggregate from group 2 in the amount of alcohol consumed during follow-up (\(t_{27} = 2.46, P < .05\)). Laboratory tests, physical examinations, and medical histories for group 2 indicated normal health status for age without serious untreated medical illness, although the SCID detected the emergence of Axis I diagnoses in 2 subjects (Table 3).

EFFECTS OF NORMAL AGING ON BRAIN VOLUMES

The effects of normal aging were assessed by using the percentage of change per year as the dependent variable. One-sample \(t\) tests for group 2 alone revealed significant differences from the presumed population mean of 0 for global cortical gray matter (\(t_{27} = -3.37, P = .002\), mean = -0.008), third ventricle (\(t_{27} = 4.62, P < .001\), mean = 0.08), and lateral ventricles (\(t_{27} = 7.71, P < .001\), mean = 0.04) but not for the cortical sulci (\(t_{27} = 0.95, NS\)). Whether the overall cortical gray matter volume change varied by region was assessed by using a 1-way repeated-measures ANOVA, which yielded a significant region effect (\(F_{5,135} = 4.39, P = .001\)) (Figure 4, left). Follow-up 1-sample \(t\) tests revealed significant divergence from 0 for the prefrontal (\(t_{27} = -5.16, P < .001\)) and posterior parietal-occipital (\(t_{27} = -2.46, P = .02\)) gray matter volumes only. For 6 comparisons, with \(\alpha = .05\), 2-tailed, the conservative Bonferroni significance level was \(P = .008\).

<table>
<thead>
<tr>
<th>Table 1. Demographic Characteristic of Participants at Study Entry*</th>
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<tbody>
<tr>
<td>Group 1</td>
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<tr>
<td>--------</td>
</tr>
<tr>
<td>(n = 16)</td>
</tr>
<tr>
<td>Age, y</td>
</tr>
<tr>
<td>Education, † †</td>
</tr>
<tr>
<td>Lifetime alcohol consumption, kg ‡</td>
</tr>
<tr>
<td>NART-IQ 25</td>
</tr>
</tbody>
</table>

* Data are given as mean ± SD (range). Group 1 was alcoholic patients; group 2, control subjects. NART indicates National Adult Reading Test. † † P < .005, 2-tailed \(t\) test; ‡ P < .001, 2-tailed \(t\) test.

GROUP DIFFERENCES IN RATE OF CHANGE IN REGIONAL BRAIN VOLUMES

Group differences in the rate of change (cubic centimeters per year) for the global cortical and ventricular ROIs approached significance only for the lateral ventricles (\(t_{42} = 1.99, P = .053\)). To assess whether the cortical gray matter regions were differentially vulnerable to the passage of time in group 1, we standardized the rates of change for each ROI against the control values set to have a mean ± SD of 0 ± 1. Thus, deviations from 0 within group 1 indicated disease-related changes beyond those observed with normal aging. The 2-group ANOVA for these standardized scores yielded a significant interaction (\(F_{5,210} = 2.88, P = .02\)) (Figure 4, right). The follow-up analyses, using \(t\) tests to compare rates of change (cubic centimeters per year), showed that only the anterior superior temporal gray matter volume decreased significantly faster in group 1 than in group 2 (\(t_{42} = -2.88, P = .006\)).

Figures 2 and 3 plot the absolute brain volumes underlying the derived and standardized change measures.
described. Two-group (groups 1 and 2) repeated-measure (baseline and follow-up) ANOVAs for these raw data yielded essentially the same results.

**DRINKING BEHAVIOR AND BRAIN CHANGE OVER TIME**

Estimates of total alcohol consumption, the mean number of drinks per month when drinking, and the amount of time during past 5 years a patient had problems with alcohol dependence were correlated with rate of change (slope) in global measures (cortical gray matter and sulci, lateral and third ventricles) and regional cortical gray matter measures. A greater total alcohol consumption was significantly associated with greater decreases in total cortical gray matter (Spearman $r = -0.52$, $P = .04$) (Figure 5), particularly in the frontal region (Spearman $r = -0.57$, $P = .03$). Heavier drinking (number of drinks per month when drinking) was significantly associated with greater increases in cortical sulcal fluid (Spearman $r = 0.53$, $P = .04$) and greater decreases in the total cortical gray matter (Spearman $r = -0.49$, $P = .06$), particularly in the frontal region (Spearman $r = -0.51$, $P = .05$). The amount of time patients in group 1 experienced alcohol dependence symptoms was associated with a change in the total cortical gray matter volume (Spearman $r = -0.53$, $P = .04$), particularly in the prefrontal (Spearman $r = -0.47$, $P = .07$) gray matter.

In an exploratory analysis, the patients in group 1 were divided into those who maintained virtual sobriety during the follow-up period (n = 4, consumed <5 kg of alcohol) and those who resumed drinking (n = 12, consumed >5 kg of alcohol) (Table 4). The rate of change per year in the global ROIs in the sober and drinking subgroups of group 1 and group 2 was compared by using ANOVA. The group effect was significant for the lateral ventricles ($F_{2,43} = 5.425$, $P < .01$); the change in the sober subgroup was not different from group 2, while the sober subgroup and group 2 differed from the drinking subgroup (Figure 6).

**AGE AT BASELINE AND BRAIN CHANGE OVER TIME**

Group 1 showed no relationships between age at baseline and the rate of change over time, with the exception of the anterior superior temporal gray matter, in which younger alcoholic patients showed more negative slopes ($r = 0.50$, $P = .02$). Among group 2 subjects, the age at baseline tended to predict the rate of change in the overall cortical gray matter volume during the 5 years ($r = 0.36$, $P = .057$) with a significant effect only when drinking. 
at the prefrontal region ($r = 0.49$, $P = .009$). The direction of the association was that younger control subjects showed more negative slopes (ie, a greater loss of gray matter).

**COMMENT**

This naturalistic study reports on the change in the volume of cortical gray matter, cortical sulci, and ventricular CSF occurring during a 5-year period in men who met the RDC criteria for alcohol dependence at study entry and men specifically recruited and screened to serve as control subjects who consumed low amounts of alcohol. This study is unique in the length of its follow-up, the quantitative assessment of brain volume change with a correction for measurement error, and the availability of follow-up data for control subjects so that changes in alcoholic patients can be studied relative to ongoing normal aging changes. The study is limited in that behavior during the follow-up period was assessed retrospectively, and only 25% of the original sample of alcoholic patients was available for retesting. Nevertheless, the follow-up sample was demographically and clinically comparable with the patients lost to follow-up, although the alcoholic patients described herein had slightly greater brain volume abnormalities than did the alcoholic patients who were lost to follow-up.

This longitudinal analysis of healthy men confirms the widely held belief, based on cross-sectional studies (reviewed by Raz), that the prefrontal cortex undergoes greater normal age-related gray matter loss than other cortical regions. Raz et al, using a cross-sectional design, observed a gradient of age-related tissue volume decline greatest in the prefrontal gray matter, less in the primary motor and sensory cortex, and still less in the phylogenetically older brain regions, such as the limbic structures. As a later maturing and particularly plastic and malleable brain region, the prefrontal cortex may be especially susceptible to occult untoward events that accrue over a lifetime. The observations of magnetic resonance images are consistent with cognitive studies that commonly report age-related declines in tests assessing prefrontal cortical functions, including cognitive flexibility, working memory, and recall tasks requiring strategic search processes. The low correlation between ventricular enlargement and prefrontal volume loss ($r = -0.17$, $P = .37$) suggests that although the cortical and subcortical brain regions are susceptible to aging, these age-related effects proceed independently yet at similar rates. Indeed, a cortical-ventricular system independence has been noted in cross-sectional studies of aging.

Among the patients in group 1, alcohol consumption and health status during the follow-up period varied widely (Tables 3 and 4). Perhaps because of this variability, we found modest evidence, confined to the anterior superior temporal cortex, for accelerated brain deterioration over time in group 1 as a whole relative to group 2. However, among the patients in group 1, the amount

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**Table 3. Interval Between Scans and Diagnostic Status at Follow-up**

<table>
<thead>
<tr>
<th>Current DSM-III-R diagnosis, No. of participants</th>
<th>Group 1 (n = 16)</th>
<th>Group 2 (n = 28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol dependent</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Alcohol dependent (full remission)</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Major depression</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Posttraumatic stress disorder</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Obsessive-compulsive disorder</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Social phobia</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>No diagnosis</td>
<td>0</td>
<td>26</td>
</tr>
</tbody>
</table>

**Table 4. Amount of Alcohol Consumed During Follow-up**

<table>
<thead>
<tr>
<th>Amount, kg (No. of “Drinks”)</th>
<th>Group 1</th>
<th></th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total volume consumed, mean ± SD (range), kg</td>
<td>124 ± 233§ (970)</td>
<td></td>
<td>15.7 ± 19.71 (0-59)</td>
</tr>
</tbody>
</table>
of alcohol consumed predicted the amount of cortical gray matter loss, particularly in the prefrontal and frontal brain regions. From the early neuropathological observations of Courville38 through more recent neuropathological39 and in vivo neuroradiological studies,2,19,40 the frontal lobes seem particularly affected in persons with chronic alcoholism. While our study provides an in vivo neuropathological basis for the fairly consistent observation of frontal executive dysfunction in detoxified alcoholic patients,41-45 the small sample and the limited quantitative information about psychiatric and medical comorbid conditions during the follow-up period preclude a rigorous analysis of the relative contribution of these additional variables to the observed outcome. Similarly, the results of exploratory group analyses, which suggest that with essential sobriety over a 5-year period, the rates of change in ventricular volume become comparable to those seen in control subjects who consume low amounts of alcohol, call for replication in a larger sample.

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