ORIGINAL ARTICLE

Hippocampal Volume in Patients With Alcohol Dependence

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Background: Smaller hippocampal volumes have been reported in the brains of alcoholic patients than in those of healthy subjects, although it is unclear if the hippocampus is disproportionally smaller than the brain as a whole. There is evidence that alcoholic women are more susceptible than alcoholic men to liver and cardiac damage from alcohol. It is not known whether the hippocampi of the female brain are more vulnerable to alcohol.

Methods: We compared the hippocampal volumes in 52 hospitalized alcoholic men and women with those of 36 healthy nonalcoholic men and women. All subjects were between 27 and 53 years of age. The hippocampal volumes were measured from sagittal T_1-weighted high-resolution magnetic resonance images.

Results: The alcoholic women had less lifetime drinking and a later age at onset of heavy drinking than alcoholic men. Both alcoholic men and women had significantly smaller right hippocampi and larger cerebrospinal fluid volumes than healthy subjects of the same sex. Only among women were the left hippocampus and the nonhippocampal brain volume also significantly smaller. The proportion of hippocampal volume relative to the rest of the brain volume was the same in alcoholic patients and healthy subjects, in both men and women. The right hippocampus was larger than the left among all subjects. Women demonstrated larger hippocampal volumes relative to total brain volume than men. Psychiatric comorbidity, including posttraumatic stress disorder, did not affect hippocampal volume.

Conclusions: In chronic alcoholism, the reduction of hippocampal volume is proportional to the reduction of the brain volume. Alcohol consumption should be accounted for in studies of hippocampal damage.

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IN PATIENTS with chronic alcoholism, brain volumes and brain weight are decreased.[1,2] Postmortem investigations show reduced white matter[3] as well as decreased neuronal density of the cortical gray matter[4] with selective neuronal loss in the superior frontal cortex.[4-6] Heavy drinking accelerates age-related myelin loss.[7] Neuronal loss in all hippocampal ammonic fields and the gyrus dentate has been reported.[8] Other investigators have found reductions of the hippocampal white matter only.[6]

Animal research has demonstrated neurodegeneration in the hippocampus with alcohol exposure.[9] With high peak doses, the damage is more substantial[10] and may be mediated by excitotoxicity.[11,12] During withdrawal, stress-induced corticosteroid elevation may act in concert with alterations in excitatory neurotransmission. The hippocampus is rich in glucocorticoid receptors and considered particularly vulnerable.[13] Thus, the human hippocampus may be more affected than other brain structures by alcohol's neurotoxic effects. By means of in vivo magnetic resonance (MR) imaging, hippocampal volume reduction has been reported in conditions associated with increased corticosteroid levels,[13,14] including Cushing syndrome,[15] posttraumatic stress disorder (PTSD) secondary to childhood sexual abuse[16,17] or combat,[18,19] and depression,[20] although in depression there have been studies with negative findings.[21] Neuronal reduction in hippocampal fields also occurs in postanoxic amnesia, temporal lobe epilepsy,[22,23] Alzheimer disease,[24,25] and schizophrenia.[26]

Hippocampal volume reductions on MR imaging have been reported in patients with chronic alcoholism[27] but not in those with alcoholic Korsakoff syndrome.[28] Reductions of whole-brain gray[29] and white[30] matter occur in alcoholism and increase with age.[31] These are most pronounced in the frontal lobe.[30] Recovery with abstinence appears greatest in the first weeks of sobriety.[32] Women achieve higher peak blood alcohol levels than men with the same alcohol dose.[33,34] A small number of imaging studies have investigated sex-specific vulnerability of the brain to alcohol[35-37] and have suggested that alcoholic women show the same degree of

SUBJECTS AND METHODS

SUBJECTS

As shown in **Table 1**, 26 alcoholic men, 26 alcoholic women, 17 healthy men, and 19 healthy women participated in the study. They were recruited by means of advertisements in a local newspaper's weekly health section as well as from area alcohol treatment programs. Age range was 27 to 53 years. They were studied at the Clinical Center of the National Institutes of Health, Bethesda, Md, from July 1992 through September 1997. All subjects were interviewed with the Structured Clinical Interview for *DSM-III-R*,[39,40] patient edition (with psychotic screen) for Axis I (clinical syndromes). The Structured Clinical Interview for *DSM-III-R* Personality Disorders was used to assess Axis II disorders. All subjects were administered the Michigan Alcoholism Screening Test.[41] Information on recent and long-term alcohol consumption, as well as alcohol-related behavior, was obtained from structured research questionnaires.[42] Alcohol intake in the past 6 months (recent alcohol intake) was corrected for alcohol distribution volume (total body water).[43] All subjects provided written informed consent to participate in the study.

The alcoholic patients met the *DSM-III-R* criteria for alcohol dependence. Patients who met the criteria for alcohol abuse but not alcohol dependence, who suffered from a somatic disease (including diseases associated with alcoholism), or who had a history of delirium tremens or psychotic disorders were excluded. In addition, patients who on neuropsychological testing had an IQ of less than 80 or demonstrated signs of dementia or Korsakoff disease were also excluded. No patients were thiamine deficient at admission. Subjects with a history of intravenous drug use at any time during their life or any substance abuse disorder, other than alcohol or tobacco abuse or dependence, in the 6 months preceding admission were excluded. The control group had no psychiatric disorder meeting *DSM-III-R* criteria.

On the basis of the subject's history, physical examination results, blood chemistry, and a negative urinary drug screen, all subjects were judged to be medically healthy. Weights were collected within 1 to 3 days from the MR imaging examination. The intracranial volume (ICV) was obtained as a volumetric measure calculated from MR images. Nutritional status was assessed by measuring the levels of total protein, albumin, transferrin, and mean corpuscular volume in serum at the time of admission and MR imaging. The values were all within the normal reference range. None of the subjects had a history of head injury requiring hospitalization. Seven of the alcoholic patients had a history of withdrawal seizures. Twenty-eight of the patients were actively drinking up to their hospitalization and were detoxified at the National Institutes of Health Clinical Center. Eleven of these required diazepam to control withdrawal symptoms. The mean amount of diazepam was 30 ± 10 mg, and the dose ranged between a total of 20 to 165 mg given over no more than 3 days. The remaining patients had initially been hospitalized at another facility or had stopped drinking several days to 1 week before admission. The alcoholic patients underwent MR imaging 3 weeks after admission.

MR IMAGE ACQUISITION AND ANALYSIS

The subjects were examined with 1.5-T MR imaging (GE Medical Systems, Milwaukee, Wis) by means of a fast spoiled gradient recalled acquisition in the steady state sequence. The brain was scanned in a gapless series of high-contrast, 2-mm-thick, T_1-weighted coronal images (repetition time, 25 milliseconds; inversion time, 5 milliseconds; and echo time, 16 milliseconds). The images were acquired by means of a 256×256 matrix with a 240×240-mm field of view. Each volumetric brain originally consisted of 124 coronal slices. The size of each voxel was $0.9375 \times 0.9375 \times 2.0\ mm^3$.

With the use of a hand-driven cursor, the intracranial tissue was deskulled on coronal sections. The ICV included the cerebrum and cerebrospinal fluid (CSF) spaces but excluded the cerebellum. The deskulled volume was automatically segmented into CSF and brain gray and white matter. The algorithm for the segmentation of intracranial tissues uses information from the histogram of pixel intensities of the intracranial image.[44]

With the current MR image contrast resolution, the hippocampus is practically isointense with some of the surrounding tissues and cannot be automatically segmented. Therefore, it must be manually outlined. We used sagittal

Continued on next page

brain damage as alcoholic men despite fewer years of heavy drinking.

Different imaging planes, section thickness, and arbitrary criteria to define hippocampal volume make the different MR imaging studies difficult to compare. Reported unilateral hippocampal volumes have ranged between 1.73 and 5.68 mL.[38] We used high-resolution volumetric MR imaging to study chronic alcoholic men and women who had abstained for at least 3 weeks. The hypotheses of the current study were as follows: (1) hippocampal volume is smaller in chronic alcoholic patients than in nonalcoholic patients and (2) the reduction in hippocampal volume among alcoholic patients is proportionally greater than the decrease in size of the rest of the brain volume. We made no specific prediction regarding sex differences in hippocampal volume among alcoholic patients but expected alcoholic women to have a lower estimated lifetime consumption than alcoholic men. We examined the effects of psychiatric comorbidity, particularly PTSD, on hippocampal volume.

RESULTS

SUBJECT CHARACTERISTICS

The alcoholic men and women and the healthy men and women did not differ with regard to handedness ($\chi^{23} = 4.719$, exact $P = .19$). Of the 36 controls, 2 (6%) were left-handed compared with 5 (10%) of the 52 alcoholics. As shown in Table 1, body mass index (BMI) was higher and ICV larger in men than in women. The num-

projections, because this approach allowed us to visualize the boundary between the hippocampus and the amygdala, thus ensuring that the entire hippocampal volume could be measured. The coronal sections were reformatted to a series of 1-mm-thick sagittal sections by means of a cubic spline interpolation.[45] The reformatted sagittal sections were contiguous. The 3-dimensional reconstruction was obtained by isosurface rendering.

OUTLINING THE HIPPOCAMPUS

The program developed to manually outline the hippocampus allows the operator to go back and forth between sections with the contours from the previous slice projected to the current slice. The contours are drawn at the pixel level by means of a hand-driven cursor and can be adjusted by 1-pixel-size vertexes. Vertexes can be moved, deleted, or added for editing. Images with higher contrast can be juxtaposed for anatomic clarity. Each contour is calculated as an individual volume (**Figure 1**). The volumes of each contour are summed to determine the entire hippocampal volume.

On T_1-weighted sagittal MR sections, the lateral part of the hippocampus appears sharply delineated from the CSF of the temporal horn and the parahippocampal gyrus. On more medial sections, the CSF from the most anterior part of the temporal horn separates the hippocampus from the amygdala. On a small number of sections, the amygdala and the hippocampus do not appear clearly separated by the CSF of the temporal horn. However, they can usually be separated by a fine white-matter lamina or by following the implicit curvature of the hippocampal head with previous contours used as guidelines. In the most medial sections, the hippocampal head can still be distinguished, but it is not possible to reliably determine the extension of the tail.[46] The posterior portion of the hippocampal tail is continuous with the indusium griseum, a thin strip of gray matter overlying the surface of the corpus callosum. A consensus was made with regard to the extent of the tail. We included it only as long as the hippocampal head could be identified. The number of sections used to complete a hemisphere was 17.7 ± 1.8 (mean ± SD; range, 13-22) on the right side and 17.4 ± 2.0 (range, 14-22) on the left side.

MEASUREMENT RELIABILITY

The intraclass correlation was determined by 2 operators who independently outlined the hippocampus in 10 randomly selected brains. The operators were blind to any subject information. The intraclass correlation was determined for the right ($r = 0.81$) and the left ($r = 0.89$) hippocampal volumes.

STATISTICAL ANALYSIS

Differences among groups were tested by either analysis of variance or Mann-Whitney *U* test. Two-tailed tests were used throughout. Basically, 2 types of analyses were performed. In the first analysis, diagnostic differences in regional brain volumes were tested in women and men separately. We analyzed the right hippocampal volume, the left hippocampal volume, the CSF volume, and the nonhippocampal brain volume (NHB, the brain volume minus right and left hippocampal volumes). Together these compartments compose the ICV. Since the ICV differed significantly between men and women (Table 1), a within-sex analysis omits the need to correct for individual differences in ICV. Thus, we could unambiguously compare the absolute hippocampal values for alcoholic patients and healthy subjects for each sex.

In the second analysis, we investigated the proportion of the hippocampal volume to the rest of the brain volume in the alcoholic patients and the healthy subjects, men and women together. This was performed by creating ratios between the hippocampal volume and the rest of the brain volume. The ratios were log transformed to normalize the data.[47] The log ratios of right hippocampal/NHB, left hippocampal/NHB, and CSF/NHB volumes were investigated for the comparison of men and women. This type of analysis is necessary for a rigorous statistical analysis of compositional data,[47,48] such as the component volumes of the inside of the skull where by definition the sum of the volumes must equal the ICV.

Multiple regression analysis was used to determine the influence of drinking measures and age on differences in brain volumes. Because of the number of tests performed, a conservative α level of .01 was used (ie, rounded to .01).

ber of years of education was higher in the healthy subjects. The alcoholic women and men differed with respect to age at onset, number of years of heavy drinking, and lifetime drinking (Table 1).

Table 2 demonstrates the number of *DSM-III-R* Axis I and Axis II diagnoses among the alcoholics excluding alcohol dependence. The number of Axis I diagnoses ranged between 0 and 11 (0 to 11 in men and 0 to 7 in women). The number of Axis II diagnoses ranged from 0 to 6. Average total numbers of Axis I and Axis II diagnoses among men were 2.7 ± 2.8 and 1.8 ± 1.9, respectively, and among women, 2.9 ± 2.2 and 1.7 ± 1.8, respectively. The mood disorders were almost all organic mood disorder, indicating that the mood disorder occurred in the presence of heavy alcohol consumption.

VOLUME DIFFERENCES IN MEN AND WOMEN

As demonstrated in **Table 3**, right and left hippocampal volume and NHB volume were smaller and the CSF volume was larger in the alcoholic women than in the nonalcoholic women. Among men, only the right hippocampal volume was smaller, and the CSF volume was larger in alcoholic men than in nonalcoholic men.

LATERALITY DIFFERENCES

The right and the left hippocampal volume differences did not differ significantly between the alcoholic and healthy women (ie, no laterality × diagnosis interaction). Therefore, the laterality main effect was tested

Table 1. Differences in Descriptive Variables of Alcoholic and Healthy Subjects*

Variables	Alcoholic Men		Alcoholic Women		Healthy Men		Healthy Women	
	Mean ± SD	No.	Mean ± SD	No.	Mean ± SD	No.	Mean ± SD	No.
Age, y	36.9 ± 6.2	26	37.4 ± 5.6	26	35.7 ± 8.2	17	35.6 ± 7.9	19
Education, y†	13.9 ± 2.5	26	15.0 ± 2.1	25	16.4 ± 2.4	15	17.3 ± 1.9	15
Height, cm‡	174.9 ± 6.6	26	167.9 ± 7.4	26	176.7 ± 6.3	17	165.4 ± 8.4	19
Weight, kg‡	80.0 ± 10.9	26	62.2 ± 7.8	23	80.2 ± 10.5	15	69.8 ± 15.8	18
BMI, kg/m^2‡	26.16 ± 3.48	26	22.32 ± 2.43	23	25.91 ± 2.69	15	25.51 ± 5.24	18
Intracranial volume, mL‡	1357.3 ± 122.0	26	1189.6 ± 81.8	23	1368.1 ± 87.6	17	1248.4 ± 113.1	19
Recent drinking, kg	2.223 ± 1.457	26	2.060 ± 1.606	25	. . .§	. . .	. . .	. . .
Recent drinking/TBW, kg/L	0.51 ± 0.33	26	0.68 ± 0.57	22	. . .	. . .	. . .	. . .
Years of heavy drinking‖	13.6 ± 7.6	26	6.9 ± 5.1	25	. . .	. . .	. . .	. . .
Age at onset, y‖	23.3 ± 6.0	26	26.2 ± 12.2	25	. . .	. . .	. . .	. . .
Lifetime drinking, kg‖	624.7 ± 555.2	26	360.3 ± 476.9	25	. . .	. . .	. . .	. . .
MAST score	59.9 ± 72.9	25	41.7 ± 16.6	25	. . .	. . .	. . .	. . .

*BMI indicates body mass index; recent drinking, total number of days drinking in the last 6 months multiplied by number of drinks in a day in the last 6 months multiplied by type of drink in grams; TBW, total body water (used to correct for individual differences in alcohol distribution[43]); years of heavy drinking, if the number of days of drinking in the last month multiplied by the number of drinks in a day in the last 6 months multiplied by type of drink in grams is greater than 90, then sum those years; age at onset, current age minus the number of years of heavy drinking; lifetime drinking, number of years of drinking multiplied by 12 multiplied by number of days per month multiplied by average number of drinks multiplied by type of drink in grams; and MAST, Michigan Alcoholism Screening Test.[35]

†*Diagnosis effect at* $P<.01$, *analysis of variance.*

‡*Sex effect at* $P<.01$, *analysis of variance.*

§*Ellipses indicate not applicable.*

‖*Among drinking variables in alcoholic subjects, lifetime drinking and heavy drinking differed at* $P<.01$, *age at onset differed at* $P<.05$, *Mann-Whitney* U *test.*

($F_{1,43} = 9.90$, $P = .003$). The right hippocampus was significantly larger than the left (**Figure 2**, left).

Left and right hippocampal volume differences between the alcoholic and nonalcoholic men were not significant (ie, no laterality × diagnosis interaction). Therefore, the laterality main effect was tested ($F_{1,41} = 21.01$, $P<.001$). In men, the right hippocampus was significantly larger than the left (Figure 2, right). Thus, the right hippocampal volume was larger than the left in both men and women irrespective of the diagnosis of alcoholism.

DIFFERENCES IN LOG RATIOS

The univariate tests investigating the effect of diagnosis on differences in the log ratios demonstrated that only the log ratio of CSF to NHB significantly differed between alcoholic patients and healthy subjects, with a larger proportion of CSF relative to brain volume in the alcoholic men and women (**Table 4**). The univariate test investigating the effect of sex on differences in the log ratios demonstrated a significantly larger left hippocampus to NHB volume log ratio in women than in men (Table 4). There were no significant interaction effects between diagnosis and sex.

DRINKING SEVERITY, BMI, AND PSYCHIATRIC COMORBIDITY

When we corrected for differences in age among the alcoholics, we did not find statistically significant evidence that recent drinking or lifetime drinking contributed to differences in hippocampal volumes. The BMI was not a significant covariate in the statistical analyses. Psychiatric comorbidity did not predict outcome of the volumetric measures, nor did the number of diagnoses. There were no differences in regional brain volumes or drinking measures between the alcoholic women with and without PTSD. Mean values and SDs of the right and left hippocampal volumes in the alcoholic women who also had PTSD (n = 12) were 3.325 ± 0.331 and 3.195 ± 0.345 mL, respectively. The corresponding values for the alcoholic women who did not have PTSD (n = 14) were 3.325 ± 0.470 and 3.236 ± 0.404 mL.

COMMENT

The use of sagittal sections allowed us to distinguish between the hippocampus and the amygdala and measure the entire hippocampus without the exclusion of the anterior portion. The mean values and SDs for the hippocampal volumes were in agreement with previous studies.[38]

When we studied the sexes separately, we found that both alcoholic men and women had significantly smaller right hippocampi than healthy subjects of the same sex, but only in women were the left hippocampus and the NHB volume also significantly smaller among the alcoholic patients. In this analysis, the alcoholic men and women were not directly compared. It is noteworthy that the alcoholic women in comparison with the healthy women demonstrated significant volume differences in all 4 volumes we studied, whereas in alcoholic men only the right hippocampus and the CSF volume differed significantly from those of the healthy men. This occurred despite less lifetime drinking, fewer years of heavy drinking, and a later age at onset of heavy drinking among the alcoholic women than among the alcoholic men. However, the alcoholic women and men did report similar alcohol intake during the 6 months preceding admission.

The alcoholic women in our study had a lower-than-expected mean BMI. The average BMI of the alco-

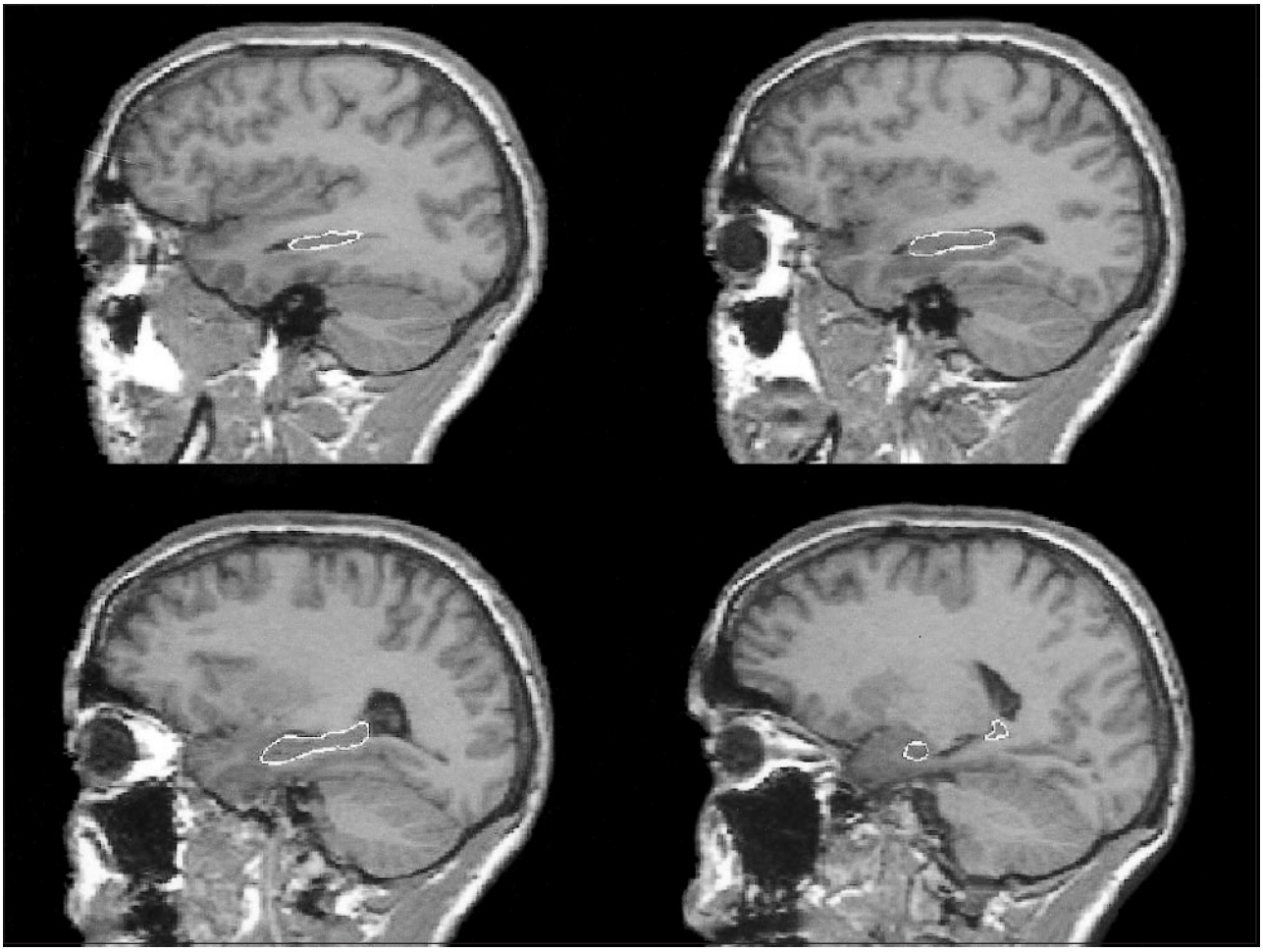

Figure 1. *Images demonstrating the outlined hippocampal contours in the sagittal plane beginning from lateral (upper left) to the most medial (lower right) aspects of the hippocampus.*

holic women in our study was 3.2 kg/m^2 less than the average BMI for the women controls and 4.1 kg/m^2 less than the average of the age group according to the National Health and Nutrition Examination Survey III, phase 1 study.[49] The alcoholic women weighed on average 7.6 kg less than the women controls and were 1.6 cm taller. The BMI of the alcoholic and healthy men in our sample was closer to the expected means,[49] and average weight was the same. With a lower-than-expected BMI, malnutrition in women alcoholics could offer an explanation for the current findings. However, serum albumin, protein, mean corpuscular volume, and transferrin levels were within the normal reference range. Also, in the statistical analyses, differences in BMI were not significantly related to differences in hippocampal volumes or to the proportional relationships between brain structures. In adult drinkers, there is a substantial inverse relationship between body mass and alcohol intake in women but not in men.[50-53] We also cannot exclude that there are sex differences in the self-report on drinking habits. For instance, from obesity studies, it is known that women tend to underestimate weight and men tend to overestimate height.[54]

The reason for women's apparent greater sensitivity to alcohol is uncertain. Identical doses of alcohol per kilogram of body weight produce significantly higher blood alcohol concentrations in women than in men.[33,34] Proportional to body mass, women have a smaller alcohol distribution volume (body water), which may also vary with the menstrual cycle. Peak blood alcohol levels might have been higher in the alcoholic women during the 6 months preceding admission, and this may have affected hippocampal and brain volumes. Previous studies have shown that women who consume less than half the amount of alcohol per day that men do are at comparable risk for the development of hepatic complications of alcoholism.[35] A similar relationship may hold for alcohol-induced brain damage. This would be consistent with computed tomographic studies that found similar increases in intracranial CSF spaces in alcoholic women and men despite a shorter duration of excessive drinking and smaller average amount of daily alcohol consumption by the alcoholic women.[35,36] Greater structural changes in the brains of alcoholic women than of alcoholic men have not been reported[37] except in a study of the corpus callosum.[55] Although, in the first analysis, we did not provide a direct measure of the differences between alcoholic men and women with regard to hippocampal size, our results underline the importance of sex differences in the biological effects of alcoholism.

The proportional relationship between regional brain volumes can only be investigated in terms of con-

Table 2. Psychiatric Comorbidity in Alcoholic Subjects Defined by *DSM-III-R

	All (N = 52)	Men (n = 26)	Women (n = 26)
Axis I†			
Mood disorders	**19** (1); 13 (2); 3 (3)	10 (1); 4 (2); 1 (3)	9 (1); 9 (2); 2 (3)
Substance dependence or abuse	**16** (1); 6 (2); 3 (3); 1 (4)	9 (1); 4 (2); 2 (3); 1 (4)	7 (1); 2 (2); 1 (3)
Anxiety disorders	**12** (1); 4 (2); 1 (3); 1 (4)	5 (1); 2 (2); 1 (3); 1 (4)	7 (1); 2 (2)
Posttraumatic stress disorder	**16**	4	12
Other Axis I diagnoses	**8**	5	3
Total	**103**	**49**	**54**
Axis II‡			
Personality disorder not otherwise specified	**20**	12	8
Avoidant	**16**	7	9
No Axis II diagnosis (V71.09)	**15**	7	8
Borderline	**15**	5	10
Obsessive-compulsive	**10**	4	6
Narcissistic	**7**	3	4
Passive-aggressive	**7**	4	3
Antisocial	**6**	6	0
Schizoid and/or schizotypal	**6**	4	2
Dependent	**4**	2	2
Total	**106**	**54**	**52**

**The number of alcoholic subjects who received one or several diagnoses are presented in order of frequency. The number of diagnoses within the category that a certain number of subjects received are given within parentheses.*

†*Axis I diagnoses were combined according to* DSM-III-R[39] *categories except organic mood disorder, which was categorized as a mood disorder, and posttraumatic stress disorder, which was presented separately from the anxiety disorders.*

‡*Of Axis II disorders, schizoid and schizotypal personality disorder were combined.*

Table 3. Right Hippocampal (RH), Left Hippocampal (LH), Nonhippocampal Brain (NHB), and Cerebrospinal Fluid (CSF) Volumes in Alcoholic and Healthy Subjects

	Volume, mL		Effect of Diagnosis*	
	Alcoholic Subjects, Mean ± SD (Range)	Healthy Subjects, Mean ± SD (Range)	$F_{1,2}$	*P*
	Women†			
RH	3.325 ± 0.403 (2.537-4.090)	3.729 ± 0.471 (2.821-4.450)	9.52	.004
LH	3.217 ± 0.371 (2.489-4.035)	3.529 ± 0.405 (2.668-4.135)	7.20	.01
NHB	915.7 ± 78.4 (773.9-1090.8)	1010.9 ± 90.9 (842.2-1218.3)	14.13	<.001
CSF	267.3 ± 44.4 (177.3-342.7)	230.3 ± 47.9 (155.2-298.3)	7.13	.01
	Men‡			
RH	3.596 ± 0.409 (2.983-4.600)	3.938 ± 0.362 (3.304-4.391)	7.82	.008
LH	3.454 ± 0.385 (2.587-4.279)	3.613 ± 0.462 (2.785-4.549)	1.49	.23
NHB	1060.6 ± 104.1 (851.3-1267.7)	1105.5 ± 87.5 (958.0-1260.8)	2.16	.15
CSF	289.6 ± 48.7 (191.8-379.4)	255.0 ± 28.5 (217.8-309.7)	6.98	.01

**Analysis of variance, univariate tests.*

†*N = 26 alcoholic women and 19 healthy women (*df *= 1,43).*

‡*N = 26 alcoholic men and 17 healthy men (*df *= 1,41).*

trast.[47,48] The log ratio analysis used for this purpose demonstrated that the proportion between the hippocampal volume and the rest of the brain volume did not differ between the alcoholic patients and the healthy subjects. This does not exclude the possibility that certain structures within the hippocampus are more adversely affected by different drinking practices and that others are more spared. Animal studies have shown that a pattern of alcohol administration resembling binge drinking with intermittently high peak blood alcohol levels may cause specific damage of selective parts of the hippocampus,[10,56] but this remains to be determined in human populations.

The log ratio of the left hippocampus to the rest of the brain was higher in women than in men, reflecting proportionally larger left hippocampi in women. However, women did not have significantly larger right hippocampi relative to the rest of the brain volume than men. Larger right and left hippocampal volumes in women when corrected for intracranial volume have been reported[57,58] but may only be present in younger subjects (aged 20-35 years). The size of brain structures in men and women change differently during the life span, which may be caused by the influence of gonadal hormones.[58,59] In our sample, the alcoholic patients demonstrated greater CSF volumes relative to the rest of the brain

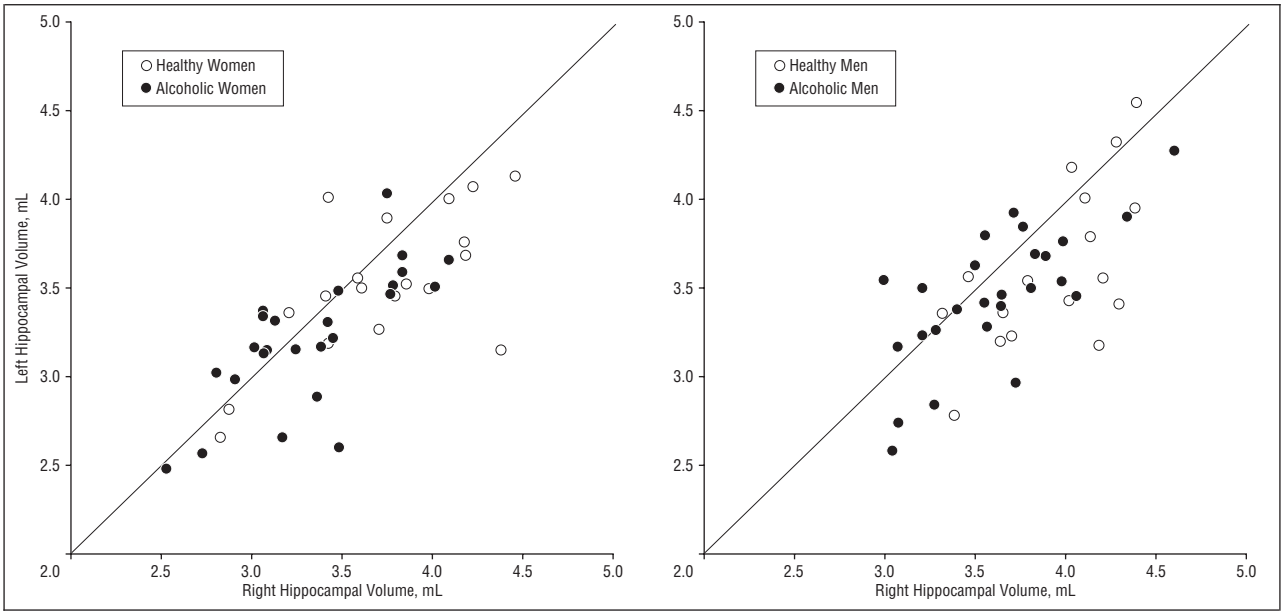

Figure 2. *The distribution of right and left hippocampal volumes in alcoholic women (n = 26) and healthy women (n = 19) (left) and alcoholic men (n = 26) and healthy men (n = 17) (right). Values that fall on the diagonal line have equal right and left hippocampal volumes. Values on the right side of the diagonal line indicate larger right hippocampal volumes. The right hippocampal volume was larger than the left in all subjects.*

Table 4. Effect of Sex and Diagnosis on Differences in Log Ratios of Right Hippocampal (RH), Left Hippocampal (LH), and Cerebrospinal Fluid (CSF) Volumes to Nonhippocampal Brain (NHB) Volumes in Alcoholic and Healthy Subjects*

	Mean ± SD Log Ratio				Effect of Sex		Effect of Diagnosis	
	Alcoholic Women (n = 26)	Healthy Women (n = 19)	Alcoholic Men (n = 26)	Healthy Men (n = 17)	$F_{1,84}$	*P*	$F_{1,84}$	*P*
RH/NHB	–5.621 ± 0.115	–5.607 ± 0.0793	–5.688 ± 0.084	–5.639 ± 0.099	5.54	.02	2.40	.13
LH/NHB	–5.654 ± 0.117	–5.660 ± 0.109	–5.729 ± 0.102	–5.728 ± 0.150	7.64	.007	0.01	.92
CSF/NHB	–1.242 ± 0.214	–1.497 ± 0.208	–1.307 ± 0.188	–1.470 ± 0.147	0.20	.66	24.52	<.001

**Analyzed by analysis of variance, univariate tests; no significant interaction effects.*

volume. This reflects the overall reduction in brain volume found in chronic heavy drinkers.

The hippocampal volumes in the alcoholic women who had PTSD did not differ from those of the alcoholic women who did not have PTSD. It has been reported that in women and men, the occurrence of PTSD contributed more to the decrease in hippocampal volume than alcohol abuse.[16-19] The current study shows that among alcohol-dependent women the effects of alcohol on brain volumes are greater than any effect of PTSD. Although it is possible that the patients in our study suffered from more severe alcoholism than subjects in the PTSD studies, our findings demonstrate the need to carefully control for alcohol consumption in human studies of the hippocampus.

Because of the current limitations in MR image resolution, we were not able to assess the relative damage of the different anatomical parts of the hippocampus. Self-reported drinking measures should be considered to be only estimates. Their ultimate validity cannot be known. Although it is likely that the recovery of the brain tissue with abstinence is greatest in the first few weeks of sobriety, it is possible that if we had studied alcoholics who had successfully abstained from alcohol for several months, the difference in brain volumes between alcoholic patients and healthy subjects may have been smaller.

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