

Compounded Brain Volume Deficits in Schizophrenia-Alcoholism Comorbidity

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Background: Schizophrenia and alcoholism are characterized by brain volume abnormalities. Despite the frequent comorbidity of these conditions, the potentially compounded effects of comorbidity on brain structure have seldom been rigorously assessed.

Methods: To determine the compounding effect of schizophrenia and alcoholism on regional brain volumes, we performed retrospective quantitative analysis of magnetic resonance images from men who participated in research protocols at the Veterans Affairs Palo Alto Health Care System, Palo Alto, Calif. Participants were selected on the basis of diagnostic criteria, yielding 4 comparison groups: 35 men comorbid for DSM-III-R schizophrenia or schizoaffective disorder and lifetime alcohol abuse or dependence; 64 men with DSM-III-R schizophrenia or schizoaffective disorder; 62 men with Research Diagnostic Criteria alcoholism; and 62 healthy men screened to exclude any Axis I diagnosis or heavy alcohol use. The comorbid group matched the schizophrenia group on age and illness se-

verity but was younger and drank 5 times less alcohol in their lifetimes than the alcoholism group. Gray and white matter volumes from 6 cortical regions were expressed as age- and head size-corrected z scores and were subjected to multivariate profile analyses.

Results: Gray matter volume deficits were present in all 3 patient groups but were greatest in the comorbid group. In the comorbid group, the most prominent volume deficits were in the prefrontal and anterior superior temporal regions.

Conclusions: Despite lower alcohol exposure than in pure alcoholism, the comorbidity of schizophrenia with alcoholism has a particularly profound effect on prefrontal gray matter volume, compounding the prominent prefrontal deficits present independently in schizophrenia and alcoholism.

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ESTIMATES OF the rate of alcohol abuse and dependence in patients with schizophrenia vary widely, ranging from 10% to 63%¹⁻⁴ depending on multiple factors, including how alcohol disorders are defined and assessed, whether current or lifetime problems are considered, and whether estimates are derived from specific clinical or community-based samples.^{4,5} With some exceptions,⁴ most studies converge in documenting an elevated risk of alcohol and other substance use disorders among schizophrenic patients.⁶ The Epidemiologic Catchment Area Study estimated that 24.0% of individuals with a lifetime diagnosis of schizophrenia or schizophreniform disorder met the criteria for lifetime alcohol dependence and that an additional 9.7% met the criteria for alcohol abuse, whereas only 14.6% met the criteria for lifetime abuse of other substances and 12.9% met the criteria for dependence on other substances.⁷

These rates converge with those of other studies^{1,3} in showing higher comorbidity of schizophrenia with alcoholism than with other substance use disorders, possibly reflecting the greater availability of alcohol but also consistent with hypothesized shared etiologic factors between schizophrenia and alcoholism.⁸

More generally, models proposed to account for comorbidity of schizophrenia with alcohol and drug disorders have been classified under the broad headings of (1) common etiologic factors, (2) unidirectional causation with either substance abuse or schizophrenia being primary, and (3) bidirectional causation.⁹ The existence of evidence supporting each model suggests that schizophrenia-alcoholism comorbidity arises for a variety of reasons, and, thus, any sample of comorbid patients will be heterogeneous.

Alcoholism and substance use disorders have an adverse impact on the clinical course of schizophrenia,^{6,10} including

greater symptom severity as suggested by many^{11,12} but not all¹³ studies. A multitude of adverse outcomes have been associated with comorbidity, including poor treatment compliance,¹¹ increased relapse rates with greater emergency and inpatient service use¹¹ and associated institutional costs,¹⁴ increased homelessness,¹⁵ greater risk of violent behavior and incarceration,⁷ higher suicide rates,¹⁶ and increased risk of tardive dyskinesia.²

Despite this extensive evidence documenting adverse outcomes in schizophrenia-alcoholism comorbidity, little is known about its impact on the brain. Although numerous quantitative volumetric magnetic resonance imaging (MRI) studies of schizophrenia and alcoholism exist, studies examining MRI brain dysmorphology in patients comorbid for both disorders are rare. Recently, Sullivan et al¹⁷ examined morphometric abnormalities of the cerebellum in schizophrenic, alcoholic, and comorbid patients. The comorbid patients showed greater hemispheric and vermal gray matter volume deficits and fourth ventricular enlargement than either the schizophrenic patients, who showed no cerebellar gray matter deficits, or the alcoholic patients, whose lifetime alcohol consumption was considerably greater than that of the comorbid patients. In the only other published study¹⁸ of which we are aware, uncalibrated raters made retrospective qualitative observations of clinical MRI scans and found that schizophrenic patients with a history of substance or alcohol abuse had a lower incidence of qualitative nonfocal abnormalities than schizophrenic patients without such a history. Thus, the impact of schizophrenia-alcoholism comorbidity on quantitative volumetric measures of cortical morphology remains essentially unknown.

Morphometric brain imaging studies of patients with alcoholism^{19,20} or schizophrenia²¹⁻²³ alone have identified lateral ventricular enlargement and cortical gray matter volume deficits in each group, but cortical white matter deficits generally have been observed only in patients with alcoholism.²⁴ Studies of brain dysmorphology in schizophrenia have paid particular attention to the prefrontal cortex because of its hypothesized role in symptoms and cognitive impairment.^{23,25-27} Morphometric brain imaging studies have generally found frontal lobe volume deficits in schizophrenia,^{21,28-31} with some exceptions.³² In addition, magnetic resonance spectroscopic studies have shown reductions in *N*-acetylaspartate levels, a marker of neuronal integrity, in the prefrontal cortex of patients with schizophrenia.³³⁻³⁵ Moreover, impairment of executive control processes, known to be prefrontally mediated, is prominent among the cognitive deficits observed in schizophrenia.³⁶⁻³⁸ Functional brain imaging studies converge in showing hypoactivation of the prefrontal cortex when patients are engaged in executive function tasks.³⁹⁻⁴¹

Postmortem studies of alcoholic patients have shown gross frontal lobe atrophy, particularly in the prefrontal cortex,^{42,43} and reduced benzodiazepine⁴⁴ and cholinergic⁴⁵ receptor density and dysregulation of myelin-related gene expression⁴⁶ in the frontal cortex. In vivo MRI studies⁴⁷ reveal selective reduction of prefrontal cortical gray matter and frontal white matter in older relative to younger alcoholic men. Moreover, alcoholic patients exhibit executive dysfunction on cognitive tasks,^{38,48-50} consistent with frontal lobe dysfunction and

prefrontal volume deficits. Recently, the direct functional significance of these frontal cortical abnormalities has been demonstrated by functional MRI in alcoholic men⁵¹ and women.⁵²

Previously, we²⁴ compared regional cortical gray matter volume deficits in patients with schizophrenia and patients with alcoholism, finding that both groups showed comparable overall deficits relative to controls. However, the groups differed in their profiles of deficits across cortical regions. The alcoholic patients showed relatively uniform gray matter deficits across the cortex, with a tendency toward more prominent deficits prefrontally and relatively less involvement of the posterior superior temporal cortex. By contrast, the schizophrenic patients exhibited widespread regional deficits that were significantly more pronounced in the anterior superior temporal and prefrontal regions; only their temporal lobe volume deficits significantly exceeded those exhibited by the alcoholic patients. In the present study, we extend this previous analysis²⁴ of cortical gray matter volumes to include patients comorbid for schizophrenia and alcoholism, hypothesizing that they would show additive or compounded cortical gray matter volume deficits, particularly in the prefrontal cortex, where the volumetric gray matter deficits produced by both disorders are most prominent. Cortical white matter and ventricular volumes were also examined.

METHODS

PARTICIPANTS

All participants were men and gave written consent for study participation. Data from the controls,⁵³ alcoholic patients,^{20,54} and schizophrenic patients^{21,24} were reported previously and are included for comparison with data from the comorbid patients (**Table 1**).

Patients With Schizophrenia Comorbid for Alcoholism

The comorbid sample (CMB) (*n*=35) comprised patients diagnosed as having *DSM-III-R* schizophrenia or schizoaffective disorder who also had a history of either (1) *DSM-III-R* alcohol abuse or dependence or (2) alcoholism based on *Research Diagnostic Criteria* determined from the Schedule for Affective Disorders and Schizophrenia.⁵⁵ Patients were recruited from the inpatient units of the Mental Health Clinical Research Center at the Veterans Affairs Palo Alto Health Care System, Palo Alto, Calif, and they underwent medical screening and psychiatric assessment. Diagnosis was based on consensus between a research psychiatrist or psychologist conducting a clinical interview and a trained research assistant using the Structured Clinical Interview for *DSM-III-R*.⁵⁶ Patients were excluded for a diagnosis of lifetime nonalcohol substance dependence but not for a history of substance abuse. Otherwise, these patients met the same inclusion and exclusion criteria as the patients with schizophrenia alone.

Patients With Schizophrenia Only

The schizophrenia sample (SCZ) (*n*=64) comprised patients with *DSM-III-R* schizophrenia or schizoaffective disorder without current or lifetime alcohol abuse or dependence. Exclusion criteria were a history of significant medical or neurologic illness, head injury resulting in loss of consciousness for

Table 1. Characteristics (Mean ± SD) of the Study Participants

Variable	Healthy Controls (n = 62)	Alcoholic Patients (n = 62)	Schizophrenic Patients (n = 64)	Comorbid Patients (n = 35)	Overall Statistical Test	P Value	Post hoc Comparisons (P < .05, Familywise)*
Age, y	42.29 ± 11.2	44.6 ± 9.3	40.0 ± 8.6	38.5 ± 5.9	ANOVA	.02	ALC > CMB, HC = SCZ = CMB
Education, y	16.63 ± 2.7	13.45 ± 2.7	13.3 ± 2.0	12.7 ± 2.9	ANOVA	<.001	HC > ALC = SCZ = CMB
Handedness score†	26.1 ± 14.5	21.37 ± 10.9	20.54 ± 11.9	26.9 ± 17.7	ANOVA	.14	NA
NART IQ	111.5 ± 7.2	106.7 ± 7.9	106.1 ± 8.9	103.4 ± 7.5	ANOVA	<.001	HC > ALC = SCZ = CMB
Illness duration, y	NA	NA	17.67 ± 9.3	16.4 ± 7.0	<i>t</i>	.54	NA
BPRS score							
Total	NA	NA	45.6 ± 8.8	43.5 ± 7.6	<i>t</i>	.23	NA
Thinking disturbance	NA	NA	9.1 ± 3.2	7.7 ± 2.9	<i>t</i>	.03	NA
Hostility-suspiciousness	NA	NA	8.3 ± 3.0	8.1 ± 2.8	<i>t</i>	.76	NA
Withdrawal-retardation	NA	NA	8.5 ± 2.7	8.4 ± 2.3	<i>t</i>	.90	NA
Anxiety-depression	NA	NA	6.9 ± 2.4	7.6 ± 2.7	<i>t</i>	.14	NA
Lifetime alcohol intake, kg	51.31 ± 72.8	1278.0 ± 796.2	49.55 ± 95.4	262.8 ± 242.4	Kruskal-Wallis	<.001	ALC > CMB > SCZ = HC

Abbreviations: ALC, alcoholic patients; ANOVA, analysis of variance; BPRS, Brief Psychiatric Rating Scale; CMB, comorbid patients; HC, healthy controls; NA, not applicable; NART, National Adult Reading Test; SCZ, schizophrenic patients.

*Post hoc tests are Tukey Studentized Range tests, except for Bonferroni tests used for lifetime alcohol intake.

†Right-handedness, 14 to 32; left-handedness, 50 to 70.

longer than 30 minutes, *DSM-III-R*-defined substance abuse (eg, marijuana or cocaine) in the 3 months before the study, or a lifetime history of substance dependence.

Symptom severity for the SCZ and CMB groups at MRI was evaluated using the Brief Psychiatric Rating Scale⁵⁷ (Table 1) administered by 2 raters with established reliability. In addition to Brief Psychiatric Rating Scale total scores, subscale scores⁵⁸ reflecting thinking disturbance, hostility-suspiciousness, withdrawal-retardation, and anxiety-depression were examined. All SCZ patients had a history of treatment with antipsychotic medications.

Patients With Alcoholism Only

The alcohol-dependent sample (ALC) (n=62) was drawn from a larger group of patients receiving treatment at Veterans Affairs Palo Alto Health Care System alcohol rehabilitation programs.^{20,54} Patients met *Research Diagnostic Criteria* for alcoholism. Exclusion criteria were a lifetime history of *DSM-III-R* schizophrenia, schizoaffective disorder, or major affective disorder; a substance abuse disorder other than alcoholism within the past year; significant medical or neurologic illness (including a seizure disorder unrelated to alcohol withdrawal); and phenytoin or corticosteroid use in the past month. Patients underwent MRI at the end of their participation in a 28-day inpatient treatment program. The median time between their last drink and MRI was 33 days.

Healthy Control Subjects

Healthy control men recruited from the community (HC) (n=62) were screened by telephone and were further assessed by psychiatric interview using the Structured Clinical Interview for *DSM-III-R* or the Schedule for Affective Disorders and Schizophrenia, medical history, physical examination, and routine blood and serum studies. Participants were excluded for Axis I psychopathology, substance abuse in the year before study entry, alcohol consumption of more than 54 g/d (the equivalent of 4 "drinks" containing an average of 13.6 g of ethanol) for longer than 1 month, significant medical or neurologic illness, or head injury resulting in loss of consciousness for longer than 30 minutes. Control subjects 50 years and older were screened for dementia using the Mini-Mental State Examination⁵⁹ and were excluded for a score of 24 or less. A larger control sample (n=73)⁵³ provided the norms

used to adjust MRI regional brain volumes for normal variation in head size and age. The current subsample, drawn from this larger sample, encompassed a narrower age range to match the age distributions of the patient groups.

Assessment of Alcohol Consumption

To quantify exposure to alcohol, we used a semistructured interview based on one developed by Skinner^{60,61} and modified by us^{20,62} to derive estimates of total lifetime alcohol consumption. These estimates were not available for all participants.

MRI SCANNING

MRI Acquisition

Participants were scanned with 1.5-T MRI scanners (Signa; General Electric, Milwaukee, Wis) beginning in 1988. As it took longer to accrue the full sample of patients with schizophrenia, recruitment and MRI scanning continued over a longer time span in the SCZ and CMB groups (1988-1994) than in the ALC (1988-1992) and HC (1988-1990) groups. Acquisition parameters, procedures, and reliability studies were previously described.^{53,63,64} Axial MRIs (5-mm thick, 2.5-mm interslice skip) were acquired using a spin-echo sequence (field of view, 24 cm; 256 × 256 matrix; cardiac gated for an effective repetition time >2400 milliseconds; 1 excitation for each of 256 phase encodes; echo time, 20, 80 milliseconds). Axial images were oriented in an oblique plane, perpendicular to the sagittal plane, and passing through the anterior and posterior commissures, identified from a midsagittal image. Intracranial volume (ICV) was estimated by modeling the intracranial vault as a sphere, with the intracranial height measured from a coronal acquisition series^{65,66} serving as the diameter and the area of the index slice (see the "MRI Analysis" subsection) serving as a plane passing through the sphere's center.⁶⁷

MRI Analysis

All images were processed blind to the participant's identity, age, and diagnosis and the neuroradiologist's report. An index slice was identified as the most inferior slice above the level of the orbits, where the anterior horns of the lateral ventricles appeared bilaterally. Seven consecutive slices, beginning at the

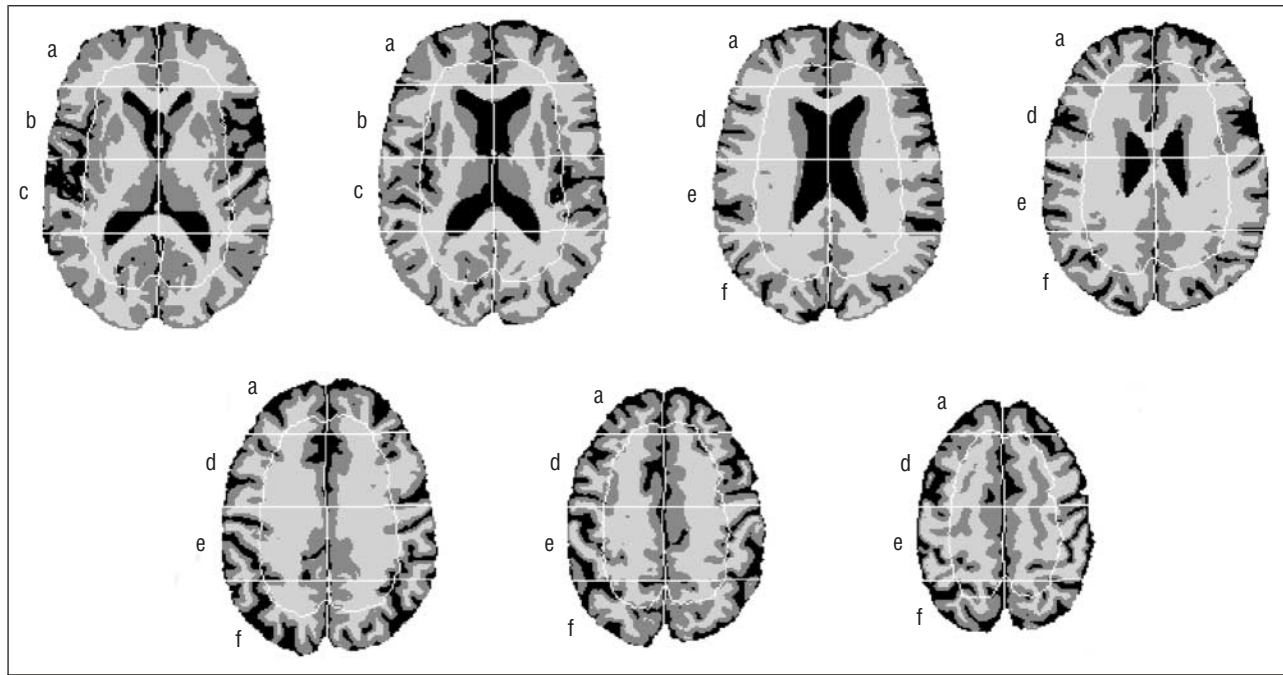


Figure 1. Example of the 7 axial MRI slices used to render the 6 cortical regional measures: a, prefrontal (the most anterior quadrant of all 7 slices composed the prefrontal region); b, anterior superior temporal (the anterior middle quadrant of slices 1 and 2 included mostly the anterior superior temporal lobe and a small amount of the motor cortex in some individuals); c, posterior superior temporal (the posterior middle quadrant of slices 1 and 2 included mostly the posterior superior temporal lobe and some of the inferior anterior parietal lobe); d, frontal (the anterior middle quadrant of slices 3-7 included the middle and more posterior extents of the frontal lobes); e, anterior parietal (the posterior middle quadrant of slices 3-7 included the middle to superior regions of the parietal lobes); and f, posterior parietal-occipital (the most posterior quadrant of slices 3-7 included the posterior parietal lobes and a large part of the occipital lobes).

index slice and proceeding superiorly, were analyzed for each participant; these slices sampled approximately half the total volume of the brain. Each MRI slice was segmented into cerebrospinal fluid, gray matter, and white matter compartments using a semiautomated image analysis technique.⁶³ Each slice was further divided into an inner 55% region (for quantification of central cerebrospinal fluid, arising primarily from the ventricles) and an outer 45% region (for quantification of cortical tissue volumes and sulcal cerebrospinal fluid).

Regional Divisions of Segmented Images

The images were divided according to anatomical landmarks and a priori rules in an effort to achieve standardized regional divisions of the brain images (**Figure 1**). The cortical measure (the outer 45% of each image) was divided into 6 geometrically defined regions of interest (ROIs) that roughly corresponded to lobar anatomy. The ROIs did not fully encompass the cortical lobes after which they were named but did represent a large sample of those cortical regions. These divisions were based on anatomical landmarks as follows: each MRI slice was divided into 4 regions by 3 coronal planes that passed through the most anterior extreme of the genu of the corpus callosum, the most posterior extreme of the splenium of the corpus callosum, and midway between them. The first plane established a boundary for the prefrontal region. The latter planes, although arbitrary, provided a more reliable basis for dividing cortical slices than specific cortical sulcal landmarks, which were otherwise difficult to establish reliably on axial images. These planes were projected through each slice, perpendicular to the orientation of the axial slices and the midline. Six cortical regional measures resulted: prefrontal, frontal, anterior superior temporal, posterior superior temporal, anterior parietal, and posterior parietal-occipital (Figure 1).

STATISTICAL ANALYSIS

Two consecutively calculated regression analyses adjusted “raw” ROI volumes for normal variation in ICV and age based on observed relationships of the ROIs with ICV and age in a sample of 73 control men aged 21 to 70 years.⁵³ This 2-step analysis^{20,53} yielded an ICV- and age-corrected *z* score for each participant based on the normative data. By definition, the mean \pm SD ROI *z* scores for the 73 controls equal 0 ± 1 . For patients, *z* scores provide volume estimates relative to that which would be expected from healthy individuals of a particular ICV and age.²⁰ For all groups, *z* scores express deviations of ROI volumes from the normative ROI volume estimates in standardized units. Accordingly, the profile of ROI *z* score means for the 62 HCs used herein in group comparisons was nearly flat, and the profiles of the patient groups reflect regional variation in the extent of volume abnormalities. Use of *z* scores enabled comparison of MRI data across groups with different mean ages and across brain regions of fundamentally different sizes.

Multivariate profile analyses⁶⁸ evaluated group differences in the extent and regional profiles of cortical gray and white matter *z* scores. Profile analysis involves group comparisons on 2 aspects of regional profiles: elevation and parallelism.⁶⁸ Group differences in overall profile elevation were assessed with the group effect from a 2-way (group \times region) univariate repeated-measures analysis of variance (ANOVA). Group differences in the configuration or pattern of regional involvement, independent of differences in profile elevation, were assessed using multivariate ANOVA (MANOVA) tests of parallelism of the profiles across the 4 comparison groups, the multivariate equivalent of the group \times region interaction effect in a univariate repeated-measures design. Significant nonparallelism of the profiles across the 4 groups was followed up with 2-group parallelism tests (ie, MANOVAs) to compare the CMB group profile with those of the other 3 groups. Profile com-

Table 2. Volumes of Gray Matter and White Matter in 6 Cortical Regions of Interest and of Cerebrospinal Fluid in the Lateral and Third Ventricles*

	Healthy Controls (n = 62)	Alcoholic Patients (n = 62)	Schizophrenic Patients (n = 64)	Comorbid Patients (n = 35)
Cortical gray matter				
Prefrontal	30.48 ± 3.70	27.41 ± 4.95	27.73 ± 4.04	25.81 ± 3.95
Frontal	16.23 ± 2.56	14.60 ± 2.53	15.17 ± 2.93	14.63 ± 2.36
Anterior superior temporal	8.15 ± 1.10	7.48 ± 1.24	7.32 ± 1.27	7.29 ± 1.21
Posterior superior temporal	8.16 ± 1.10	7.83 ± 1.13	7.54 ± 1.22	7.49 ± 1.14
Anterior parietal	16.18 ± 2.60	14.72 ± 2.64	15.14 ± 3.05	14.20 ± 2.74
Posterior parietal-occipital	30.70 ± 4.98	27.71 ± 5.24	29.27 ± 5.03	27.07 ± 5.78
Cortical white matter				
Prefrontal	15.79 ± 3.08	13.73 ± 3.32	15.19 ± 3.09	14.06 ± 3.57
Frontal	10.69 ± 1.99	9.99 ± 1.99	10.67 ± 2.09	10.30 ± 2.11
Anterior superior temporal	3.79 ± 1.17	3.87 ± 1.13	3.96 ± 1.25	4.16 ± 1.03
Posterior superior temporal	4.94 ± 0.93	4.44 ± 0.85	4.79 ± 0.90	4.70 ± 0.85
Anterior parietal	11.66 ± 1.96	11.12 ± 1.57	11.70 ± 1.73	11.43 ± 1.60
Posterior parietal-occipital	17.09 ± 5.09	15.79 ± 4.27	17.71 ± 3.73	16.61 ± 3.99
Lateral ventricles	21.03 ± 9.45	28.62 ± 15.52	25.25 ± 8.97	23.34 ± 11.33
Third ventricle	0.39 ± 0.18	0.57 ± 0.33	0.49 ± 0.21	0.46 ± 0.20

*Data are given as mean ± SD cubic centimeters.

parisons among the HCs and the 2 single-diagnosis groups (ie, SCZ or ALC) have been previously reported²⁴ and are summarized at the beginning of this article. All multivariate F tests were based on Wilks' λ ,⁶⁸ with $\alpha = .05$.

Post hoc comparisons of the CMB group and the 3 remaining groups on individual ROI volumes were assessed using Dunnett *t* tests. These post hoc tests used the mean square error terms from the 4 group analyses and maintained family-wise type I error rates to $\alpha = .05$ across the multiple group comparisons for each ROI.⁶⁹ In light of the multiple ROIs examined, a more conservative $\alpha = .01$ was also applied, and post hoc comparisons significant at this level are so indicated. Post hoc Tukey tests⁶⁹ controlling for all pairwise group comparisons were used to follow up significant ANOVAs conducted on the demographic data. Owing to large group differences in variance, lifetime alcohol consumption was compared across groups using a nonparametric Kruskal-Wallis 1-way ANOVA, with Bonferroni-corrected follow-up comparisons.⁷⁰ Pairwise differences between ROIs were assessed in the CMB group using paired *t* tests with Bonferroni correction. Relationships between clinical variables and regional brain volumes were assessed using Pearson correlation coefficients with Bonferroni correction for the number of correlations examined. Familywise $\alpha = .05$ was used for all post hoc tests and Bonferroni corrections, except for the Dunnett tests, where $\alpha = .01$ was also considered. Two-tailed probability values are reported for all statistical tests.

RESULTS

DEMOGRAPHIC DATA

One-way ANOVAs of the demographic variables (Table 1) across the 4 groups yielded significant differences in age ($F_{3,219} = 3.44$; $P = .02$), education ($F_{3,218} = 26.29$; $P < .001$), and IQ estimated using the National Adult Reading Test⁷¹ ($F_{3,192} = 9.44$; $P < .001$) but not in handedness as measured using a quantitative test ($F_{3,204} = 1.83$; $P = .14$).⁷² Follow-up Tukey test results indicated that the ALC group was significantly older than the CMB group ($P < .05$), with none of the remaining pairwise group comparisons reaching significance (Table 1). The 3 patient groups had less education and lower National Adult Reading Test IQ scores

($P < .01$ for both) than the HC group, but there were no significant differences between the patient groups on these measures. Lifetime alcohol consumption significantly differed among the 4 groups (Kruskal-Wallis $\chi^2 = 134.31$; $P < .001$): it was greater in the ALC group than in any of the other groups ($P < .01$) and in the CMB group than in the SCZ and HC groups ($P < .01$). The CMB group did not differ from the SCZ group in age at illness onset ($t_{92} = 1.04$; $P = .30$), illness duration ($t_{92} = 0.61$; $P = .54$), or Brief Psychiatric Rating Scale total ($t_{97} = 1.22$; $P = .23$), hostility-suspiciousness ($t_{97} = 0.31$; $P = .76$), withdrawal-retardation ($t_{97} = 0.12$; $P = .90$), or anxiety-depression ($t_{97} = -1.48$; $P = .14$) scores, but they did have less severe thinking disturbance scores ($t_{97} = 2.14$; $P = .03$).

REGIONAL BRAIN VOLUME DIFFERENCES

Cortical Gray Matter

Volumetric analysis was conducted on head size- and age-corrected *z* scores. Group means for the cortical gray matter ROI raw volumes, although not analyzed statistically, are presented in **Table 2**. The profiles of the 6 cortical ROIs (**Figure 2**) showed significant group differences in elevation ($F_{3,219} = 15.79$) and parallelism ($F_{15,594} = 2.98$) ($P < .001$ for both). Comparison of the CMB profile with the essentially flat HC profile revealed a significant elevation difference ($F_{1,95} = 46.05$; $P < .001$), with the CMB group exhibiting cortical gray matter volume deficits in all of the cortical regions (all post hoc test results were significant at $P < .01$), and significant nonparallelism of the profiles ($F_{3,91} = 4.05$; $P = .002$), reflecting the relative prominence of these deficits in the prefrontal and, to a lesser extent, anterior superior temporal regions. In the CMB group, results of paired *t* tests indicated that volume deficits in the prefrontal cortex were significantly greater than those in 4 of the 5 remaining ROIs (Bonferroni-corrected $P = .05$); the exception was the anterior superior temporal lobe, where the difference did not reach significance.

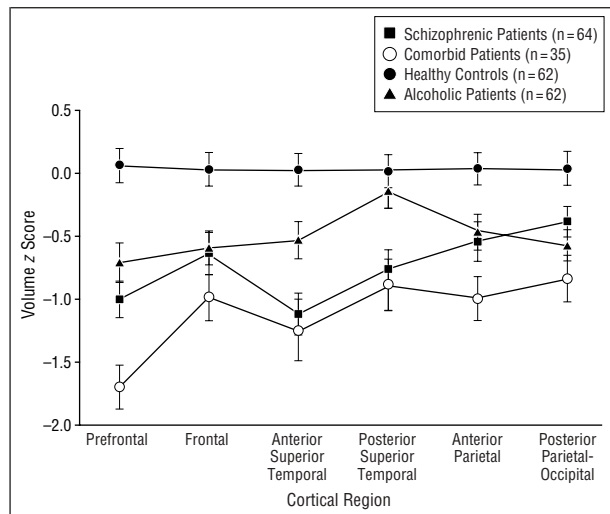


Figure 2. Profile of regional cortical gray matter volumes expressed as head size- and age-corrected mean \pm SEM z scores for the 4 comparison groups.

Compared with the ALC profile, the CMB profile was significantly lower (elevation: $F_{1,95}=11.65$; $P<.001$), reflecting greater volume deficits overall, and showed a significantly different pattern of regional deficits (parallelism: $F_{5,91}=2.77$; $P=.02$). In particular, post hoc tests showed the CMB group to have significantly greater deficits than the ALC group in the prefrontal ($P<.01$), anterior superior temporal ($P<.05$), and posterior superior temporal ($P<.01$) regions but not in the frontal, anterior parietal, or posterior parietal-occipital regions.

Compared with the SCZ profile, the CMB profile showed a trend toward smaller overall volumes (elevation: $F_{1,97}=3.49$; $P=.06$) but no significant difference in parallelism ($F_{5,93}=1.20$; $P=.32$). However, in support of our hypothesis about the vulnerability of the prefrontal cortex to the deleterious effects of alcohol, Figure 2 indicates significantly greater deficits in the CMB group than in the SCZ group in the prefrontal region ($P<.05$), an effect that was notably absent from the other region of prominent gray matter deficit in schizophrenia—the anterior superior temporal cortex.

Cortical White Matter

Profile analysis of the 6 regional white matter volume z scores across the 4 groups (Figure 3) showed group differences in profile elevations ($F_{3,219}=2.58$; $P=.05$) and a trend toward nonparallelism of the group profiles ($F_{15,594}=1.58$; $P=.07$). Compared with the relatively flat HC profile, the CMB profile was not reduced overall (elevation: $F_{1,95}=0.18$; $P=.67$) but did show selective involvement of some cortical regions (parallelism: $F_{5,91}=2.66$; $P=.03$). Inspection of the CMB white matter profile in Figure 3 suggests selective volume reduction in the prefrontal cortex, although none of the results of the post hoc tests comparing the CMB and HC groups was significant.

Compared with the ALC profile, the CMB profile showed less white matter reduction overall (elevation: $F_{1,95}=3.77$; $P=.055$) but no significant difference in the regional pattern of deficits (parallelism: $F_{5,91}=0.53$;

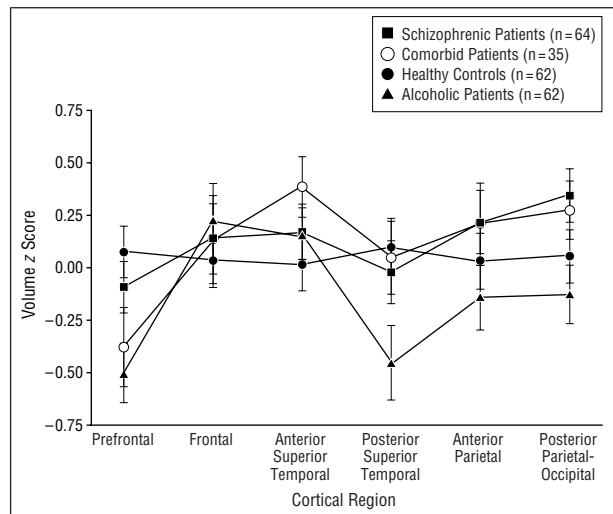


Figure 3. Profile of regional cortical white matter volumes expressed as head size- and age-corrected mean \pm SEM z scores for the 4 comparison groups.

$P=.75$). None of the post hoc test results comparing the ALC and CMB groups on individual cortical ROIs was significant.

Compared with the SCZ profile, the CMB profile showed no significant differences in profile elevation ($F_{1,97}=0.01$; $P=.93$) or parallelism ($F_{5,93}=0.60$; $P=.70$). Despite the suggestion of some white matter volume loss in the prefrontal cortex of the CMB patients, none of the results of post hoc comparisons between the CMB and SCZ groups for individual cortical regions was significant.

Ventricular Cerebrospinal Fluid

One-way ANOVAs showed significant group differences in the volumes of the lateral ($F_{3,219}=6.40$; $P<.001$) and third ($F_{3,219}=7.55$; $P<.001$) ventricles. The CMB group showed significant enlargement of the lateral ($P<.05$) and third ($P<.01$) ventricles relative to the HC group but did not differ significantly from the other 2 patient groups.

Correlations With Alcohol History Variables

In the CMB group, none of the volume z scores was significantly correlated with lifetime alcohol consumption after Bonferroni correction.

Effects of Nonalcohol Substance Abuse History

Eleven of the CMB patients also had a history of abuse of other drugs (cannabis [$n=8$], cocaine [$n=2$], and benzodiazepine [$n=1$]). When these patients were compared with the remaining CMB patients, no significant differences were observed on any demographic, clinical, or MRI measures.

COMMENT

These results indicate that schizophrenia and alcoholism, although characterized by different patterns of cortical volume deficits,²⁴ produce compounded cortical deficits in patients comorbid for both disorders, particularly

in the prefrontal cortex. The comorbid patients had a significantly greater prefrontal gray matter deficit than either the patients with schizophrenia or alcoholism alone, and it was clearly the most prominent deficit in their regional profile of gray matter deficits. Moreover, the regional cortical volume deficits present in schizophrenia were not equally susceptible to exacerbation by alcoholism in comorbid patients. This was demonstrated in a striking dissociation between the prefrontal and temporal gray matter, the 2 cortical regions where volume deficits due to schizophrenia are most prominent: the prefrontal deficits were far greater in the comorbid patients than in the schizophrenic patients, but the temporal lobe deficits were equivalent. In addition, inspection of the cortical gray matter volume profiles (Figure 2) reveals a second region where the effects of alcoholism and schizophrenia seemed to be compounded—the anterior parietal cortex—which is not surprising given the dense connections between the prefrontal and parietal cortical regions.⁷³ These compounded deficits occurred despite a lack of difference between the comorbid and schizophrenic patients in current illness severity, onset age, or duration of illness and despite substantially lower lifetime alcohol consumption in the comorbid patients than in the alcoholic patients.

Our a priori focus on the prefrontal cortex was based on the assumption that the pathophysiologies of both disorders would converge on this region in comorbid patients and reflect additive or interactive effects. In fact, the prefrontal gray matter volume deficit of the comorbid patients (mean $z = -1.70$) was equivalent to the additive effects of alcoholism (mean $z = -0.71$) and schizophrenia (mean $z = -1.00$). Alternatively, this compounded effect of schizophrenia and alcoholism could be characterized as interactive when considering lifetime alcohol consumption, which was nearly 5 times less in the comorbid patients than in the alcoholic patients (263 vs 1278 kg). In other words, comorbid patients exhibited the full detrimental effect of alcoholism on prefrontal (and anterior parietal) gray matter volume, despite significantly less lifetime alcohol intake than the alcoholic patients. Although we did not observe a direct correlation between lifetime alcohol consumption and regional brain volumes in the comorbid group, the absence of correlation may have resulted from a threshold effect, which this group met or exceeded. Whether additive or interactive, the vulnerability of the prefrontal cortex in schizophrenia clearly combines with alcohol's tendency to produce pathologic changes selective to the prefrontal cortex.^{42,43}

Comorbid patients tended to exhibit a white matter volume deficit selective to the prefrontal cortex that was comparable to the deficit observed in the alcoholic patients. That the remaining cortical white matter was not similarly affected lends further support to the hypothesis that deleterious effects of schizophrenia and alcoholism converge in the prefrontal cortex. The schizophrenic patients showed a slight reduction in prefrontal white matter that did not differ significantly from that of the control group or the comorbid group. However, most previous studies,^{22,24} but not all,²⁸ report that schizophrenia per se does not affect white matter volume (although white matter microstructural integrity may be compromised^{74,75}), strongly supporting the contention that

the observed prefrontal white matter macrostructural deficit in the comorbid patients is a consequence of their alcoholism.

The present analysis provides biological evidence consistent with clinical observations of heightened vulnerability to adverse outcomes among comorbid patients.⁹ Moreover, together with the results of a previous study,¹⁷ our neuroimaging data indicate that particular brain regions, including the prefrontal cortex and its underlying white matter, the cerebellum, and possibly the anterior parietal cortex, are susceptible to the compounding effects of schizophrenia and alcoholism in patients comorbid for both disorders. One implication of these results is that disruption of frontoparietal and frontocerebellar circuitry is a critical neural substrate of the clinical, cognitive, and motor dysfunctions associated with this comorbidity. Although the pathophysiologic mechanisms by which alcoholism and schizophrenia interact to produce these regionally specific brain volume abnormalities are unknown, the demonstration of these abnormalities underscores the need for further research on the neurobiologic causes and consequences of alcoholism-schizophrenia comorbidity.

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