

# A Profile of Cortical Gray Matter Volume Deficits Characteristic of Schizophrenia

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**Quantitative magnetic resonance imaging (MRI) studies from our laboratory have reported that patients with schizophrenia show a widespread cortical gray matter volume deficit, which is especially pronounced in the prefrontal and anterior superior temporal cortices. The present study compared two separate samples of schizophrenic patients — 71 men from a Veterans Administration (VA) hospital and a sample of 57 severely ill men from a state hospital (SH) — in an effort to test whether the pattern of brain volume abnormalities previously observed in VA schizophrenic patients can be generalized to other groups of schizophrenic patients. MRI-derived brain volumes of gray matter, white matter and sulcal cerebrospinal fluid (CSF) in six cortical regions, and CSF in the lateral and third ventricles were computed. All MRI volumes were adjusted for normal variation in head size and age and were expressed as standardized Z-scores, which also permitted structures of different sizes to be compared directly. The two schizophrenic groups displayed similar patterns of volume abnormalities: cortical gray matter but not white matter volume deficits that were widespread but especially notable in the prefrontal and temporal regions. The regional gray matter deficits in the SH group were generally greater than those in the VA group, particularly in the prefrontal and posterior superior temporal regions. Both schizophrenic groups had abnormally large volumes of the cortical sulci and lateral and third ventricles; however, the SH group showed greater enlargements, the most prominent occurring in the ventricles and temporal sulci. The overlapping patterns of cortical gray matter deficits in the two groups provide evidence for generality of this pattern of regional brain volume abnormalities in schizophrenia.**

Quantitative *in vivo* neuroimaging studies based on magnetic resonance imaging (MRI) provide reasonably consistent evidence that patients with schizophrenia, as groups, have significant brain tissue volume deficits selectively affecting cortical gray matter and sparing white matter (Zipursky *et al.*, 1992b; Harvey *et al.*, 1993; Schlaepfer *et al.*, 1994; Lim *et al.*, 1995, 1996a,c; Sullivan *et al.*, 1997; for exceptions see Breier *et al.*, 1992; Wible *et al.*, 1995). A recent study from our laboratory reported that although a gray matter volume deficit was present throughout the cortex, the greatest volume deficits occurred in the prefrontal and anterior temporal cortices (Sullivan *et al.*, 1997). Furthermore, there is evidence for the specificity of this pattern of cortical gray matter deficits to schizophrenia because it was detectably different from the deficit pattern observed in a psychiatric comparison group – namely, patients with chronic alcoholism. In that study, both patient groups were recruited from a Veterans Affairs (VA) Health Care Center.

In the present analysis, we questioned whether the regional deficit pattern observed in the sample of VA schizophrenic patients was also present in a non-veteran sample of schizophrenic patients. Accordingly, we compared MRI-derived

volumes of gray matter from six cortical regions in two different groups of schizophrenic patients: those recruited from a VA hospital and those recruited from a state hospital (SH). MRI results from each group were included in separate previous reports (VA: Zipursky *et al.*, 1992a, 1994; Lim *et al.*, 1996c; Sullivan *et al.*, 1997; SH: Lim *et al.*, 1995, 1996a; Marsh *et al.*, 1997a), which established that, relative to controls, both groups showed significant gray but not white matter deficits widespread throughout the cortex when global volume measures were used, but white matter volume in the temporal lobes was abnormally small in the SH patients (Marsh *et al.*, 1997a). The present report describes a new analysis which provides support for a generalizable pattern of regional cortical volume abnormalities across these two samples of schizophrenic patients. As a group, the SH patients were more severely symptomatic than the VA patients, and, unlike the VA patients, who were hospitalized temporarily when symptoms had exacerbated, most SH patients were chronically hospitalized. Given the commonality of the diagnosis, we hypothesized that the schizophrenic groups would show the same pattern of cortical gray matter deficits. Given the difference in symptom severity and chronicity, we also hypothesized that the deficits in the SH group would be greater than those observed in the VA group. In addition, we examined the patterns of cortical sulcal and ventricular volumes in the two schizophrenic groups because our previous study (Sullivan *et al.*, 1997) also revealed different patterns and extents of CSF volume abnormalities that distinguished the schizophrenic and alcoholic groups.

## Materials and Methods

### Subjects

All study participants, legal guardians or both gave written informed consent for research participation. Clinical and demographic characteristics of the subject groups are presented below and summarized in Table 1. All subjects were men.

### Normal Healthy Control Subjects

The controls ( $n = 73$ ) were recruited from the community. Data from the full complement of 73 men (age 21–70 years) were used to derive the head size and age norms applied to the MRI data of the patients. Of this sample, 65 controls overlapped the patient groups in age range (21–63 years), and data from this subsample were used in the group analyses reported here. MRI data from the control group have been used in previous studies from our laboratory (e.g. Pfefferbaum *et al.*, 1994, 1997; Sullivan *et al.*, 1997). Subjects were excluded if they met research diagnostic criteria (Spitzer *et al.*, 1975) for any psychiatric disorder, partaken in substance abuse in the year prior to entry into the study or reported ever having consumed >54 g ethanol per day (equivalent of four 'drinks' containing an average of 13.6 gm ethanol) for a period exceeding 1 month. Data from physical examination and blood panel were reviewed

**Table 1**  
Demographics of the three subject groups (means and standard deviations)

Group	Age (years)	Education (years)	IQ estimate	Illness duration (years)	BPRS		
					Positive	Negative	Total
Normal control (NC) ( <i>n</i> = 65)	41.3 (11.9)	16.6 (2.8)	111.5 (7.2)	–	–	–	–
VA Hospital SZ (VA) ( <i>n</i> = 71)	40.0 (8.6)	13.3** (1.9)	106.1** (8.9)	17.4 (8.8)	8.8 (3.3)	8.5 (2.6)	45.2 (8.8)
State Hospital SZ (SH) ( <i>n</i> = 57)	36* (8.2)	10.7** (2.1)	88.2† (19.4)	19.3 (7.9)	14.4** (4.5)	9.8** (2.9)	59.4** (13.2)
Significant paired differences:	NC = VA > SH	NC > VA > SH	NC > VA	n.s.	SH > VA	SH > VA	SH > VA

\* $P \leq 0.01$ , \*\* $P \leq 0.001$ .

†Only the control and VA groups could be compared statistically because IQ was estimated with the NART in the control and VA groups and with the WRAT in the SH group.

for evidence of medical conditions that might affect brain morphometry variables. Subjects 50 years and older were given the Mini-Mental State Examination (Folstein *et al.*, 1975) to screen for dementia and were excluded from this study if they achieved a score of 24 or less (maximum = 30).

#### VA Patients with Schizophrenia

Patients (*n* = 71, 23–63 years old) meeting DSM-III-R criteria for the diagnosis of schizophrenia were recruited from the unlocked voluntary ward of the Mental Health Clinical Research Center, as well as from a locked psychiatric ward at the VA Palo Alto Health Care System. Patients meeting criteria for current DSM-III-R alcohol abuse or having ever met criteria for DSM-III-R alcohol dependence were excluded. Other exclusion factors were a history of significant medical illness or head injury resulting in loss of consciousness for >30 min. DSM-III-R diagnoses were determined by clinical evaluation by a psychiatrist, clinical psychologist or psychiatric research fellow, and an independent structured interview by a trained research assistant using the Structured Clinical Interview for DSM-III (Spitzer *et al.*, 1992). Research diagnoses were based on a consensus of the two evaluations. All patients had been treated in the past with antipsychotic medications.

#### State Hospital (SH) Patients with Schizophrenia

The SH patients (*n* = 57; age 19–53 years old at MRI) were drawn from inpatient wards, met DSM-III-R criteria for schizophrenia, were severely ill and had a relatively early onset of illness [for complete description see Lim *et al.* (1996a) and Marsh *et al.* (1997a)]. Onset of the disease was age <30 years (symptom onset age = 7–29 years, mean age = 17 ± 4 years).

#### Measure of Symptom Severity

The clinical status of the patients was evaluated using the 18-item Brief Psychiatric Rating Scale (BPRS; Overall and Gorham, 1988) administered by two raters with established reliability. A negative symptom score was derived by summing scores for the following BPRS items: blunted affect, emotional withdrawal and motor retardation. A positive symptom score was derived by summing scores for the following BPRS items: hallucinatory behavior, unusual thought content and conceptual disorganization (Faustman, 1994).

#### Comparison of Group Demographics

The three groups differed in age, with the SH patients being the youngest and the VA patients not differing from the controls (see Table 1 for descriptive statistics and significance levels). Not surprisingly, the groups also differed in years of formal education, where the control group had significantly more years of education than the VA group, which had more education than the SH group. The control and VA groups undertook the National Adult Reading Test (Nelson, 1982), which provides an estimate of premorbid IQ; although the VA patients (range = 88–124) and the controls (range = 90–125) performed in the normal range, the VA group scored significantly lower than did the control group. The IQs of the SH patients were assessed with the Wide Range Achievement Test – Revised (Jastak and Wilkinson, 1984) reading subtest and ranged from 52 to 134. Relative to the VA group, the BPRS scores of the SH group were higher

(i.e. more severe symptoms) on the positive symptom score [ $t(126) = 8.178$ ,  $P = 0.0001$ ], negative symptom score [ $t(126) = 2.564$ ,  $P = 0.0001$ ] and total score [sum of the 18 items;  $t(126) = 7.254$ ,  $P = 0.0001$ ].

### MRI Scanning

#### Acquisition Parameters

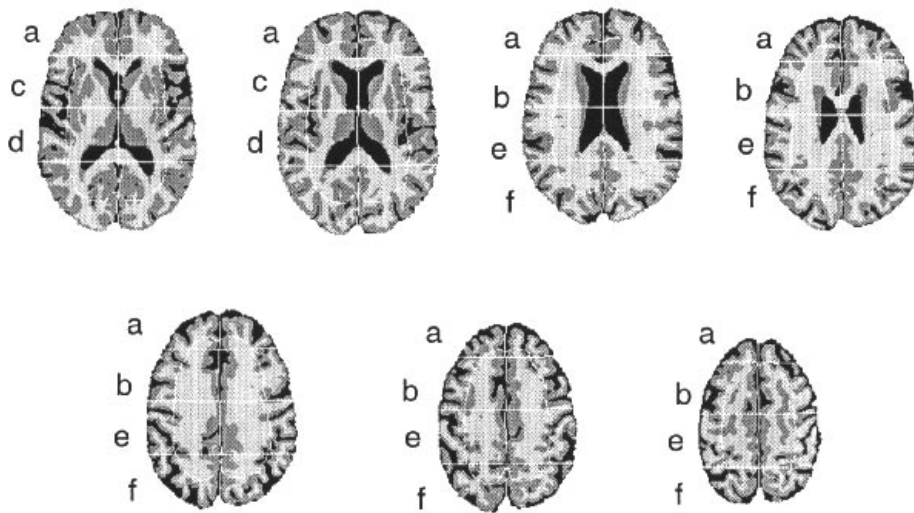
Subjects were scanned with 1.5T General Electric Signa MRI scanners. Image acquisition procedures and parameters have been detailed previously (Lim and Pfefferbaum, 1989; Pfefferbaum *et al.*, 1992, 1994). Axial MRI images were 5 mm thick (2.5 mm skip) and acquired in an oblique plane using a spin-echo sequence (20 and 80 m echoes) with a 24 cm field of view and a 256 × 256 matrix. Acquisition was gated to every other cardiac cycle for an effective TR of >2400 ms with one excitation for each of 256 phase encodes.

All images were stored on magnetic tape and transferred to optical disks for analysis. For each subject, the index slice was identified as the most inferior slice above the level of the orbits, where the anterior horns of the lateral ventricles could be seen bilaterally. Seven consecutive slices, beginning with the section inferior to the index slice and proceeding superiorly, were analyzed for each subject. The index slice or the slice below it was used for quantification of the third ventricle.

#### Regional Divisions and Segmentation of Images

Each MRI slice was segmented into cerebrospinal fluid (CSF), gray matter and white matter compartments, using a semi-automated image analysis technique (Lim and Pfefferbaum, 1989; Lim *et al.*, 1992). To separate the cerebral hemispheres, a midline was drawn manually on each slice. Additionally, each slice was divided into an inner 55% region (to facilitate quantification of central CSF, which arose primarily but not exclusively from the lateral ventricles) and an outer 45% (to facilitate quantification of the cortical tissue volumes and sulcal CSF) (Pfefferbaum *et al.*, 1986, 1992).

The images were divided according to anatomical landmarks and *a priori* geometric rules in an effort to achieve standardized regional divisions of the brain images. The cortical tissue measure (the outer 45% of each image) was divided into six geometrically defined regions of interest, which roughly corresponded to lobar anatomy. The regions did not fully correspond to the volumes of the cortical lobes after which they were named but provided a reliable basis for dividing the cortical sections (Zipursky *et al.*, 1992b). To form these divisions, each MRI slice was divided into four regions by three coronal planes, which 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 the two. The first plane established a boundary for the prefrontal region. From these quadrants and slices, we devised six cortical regions, defined as follows: *prefrontal* – the most anterior quadrant of all seven slices, which included most of the prefrontal cortex; *frontal* – the anterior middle quadrant of slices 3–7; *anterior superior temporal* – the anterior middle quadrant of slices 1 and 2, which included the anterior superior temporal gyrus and the most posterior extents of the frontal lobes at the level of the superior temporal gyrus; *posterior superior temporal* – the posterior middle quadrant of slices 1



**Figure 1.** Example of MR images, segmented into compartments of gray matter shown in dark gray, white matter shown in white and CSF shown in black. The curved white lines mark the division of each section into the outer 45% for cortical measures and the inner 55% for ventricular measures. The vertical and horizontal white lines delineate the four quadrants used to define the cortical regional measures: a = prefrontal; b = frontal; c = anterior superior temporal; d = posterior superior temporal; e = anterior parietal; and f = posterior parietal-occipital.

and 2, which included the posterior superior temporal gyrus and a small portion of the anterior extents of the parietal lobes just above the superior temporal gyrus; *anterior parietal* – the posterior middle quadrant of slices 3–7; and *posterior parietal-occipital* – the most posterior quadrant of slices 3–7, which also included much of the occipital lobes (Fig. 1).

#### Statistical Analysis

Pixel counts for gray matter, white matter and CSF in each brain region measured were transformed into cubic centimeters (cc) to provide estimates of the absolute volume encompassed by the total and regional cortical gray matter, white matter, and sulcal CSF and CSF in the lateral and third ventricles. These ‘raw’ estimates were then adjusted for normal variation in head size and age based on two successive regression models derived from the total sample of 73 normal control subjects. This two-step process, described previously (Mathalon *et al.*, 1993a,b; Pfefferbaum *et al.*, 1994) yields a head size- and age-corrected Z-score. Thus, for the total group of 73 control subjects, the expected mean Z-score is 0 with a SD of 1. For patients, Z-scores provide volume estimates relative to that which would be expected from normal subjects of a particular head size and age (Mathalon *et al.*, 1993b). Accordingly, a plot of means for each set of MRI regions, from the anterior to the posterior extents of the brain, in the controls produces a flat line; the shape of this line, a profile, in the patient groups, reflects regional variation in the extent of volume abnormalities. In addition, transformation of raw volumes into Z-scores, which are standardized scores, puts each brain region onto the same scale, regardless of its actual size. Consequently, use of age-corrected scores permits comparison of groups of different ages and of different head sizes, and also permits comparison of brain volumes of regions with fundamentally different sizes (e.g. lateral ventricular volume compared with third ventricular volume).

Repeated measures analyses of variance (ANOVAs) were performed on whole cortex gray and white matter volumes to assess Group × Tissue Type interactions; on sulcal, lateral and third ventricular CSF to assess a Group × Cortical/Subcortical CSF volume interactions; and on gray matter, white matter and CSF volumes for each of the six cortical regional measures to assess Group × Region interactions. Follow-up *t*-tests were used to identify differences between group pairs.

#### Results

The main analyses were based on head size- and age-corrected Z-scores. Raw volumes, expressed in cc, are presented in

Table 2, but were not submitted to statistical tests of group differences.

#### Measures of Total Cortical Gray Matter and White Matter

A three group (VA patients, SH patients and controls) by two tissue type (cortical volumes of gray matter and white matter) repeated measures ANOVA revealed significant effects of group [ $F(2,190) = 5.902, P = 0.0033$ ], tissue [ $F(1,190) = 123.631, P = 0.0001$ ] and their interaction [ $F(2,190) = 34.157, P = 0.0001$ ]. Follow-up *t*-tests (Fig. 2A) indicated that both patient groups had cortical gray matter volume deficits, but neither patient group had a white matter volume deficit relative to the control group. A Bonferroni correction for three follow-up paired comparisons requires  $P \leq 0.02$  for statistical significance with  $\alpha = 0.05$ . The VA group had significantly smaller cortical gray matter volumes than the controls [ $t(134) = 5.512, P = 0.0001$ ] and a trend towards larger volumes than the SH group [ $t(126) = 2.163, P = 0.0325$ ].

#### Total Cortical Sulci, Lateral Ventricles and Third Ventricle Measures

The three group repeated measures ANOVA for these three CSF measures yielded significant effects of group [ $F(2,190) = 21.436, P = 0.0001$ ], region [ $F(2,380) = 3.831, P = 0.0225$ ] and interaction [ $F(4,380) = 2.897, P = 0.022$ ]. Significantly enlarged CSF volumes were present in all three regions in both schizophrenia groups relative to the control group ( $P < 0.004$ – $0.0001$ ) (Fig. 2B). Although the two patient groups did not differ in total cortical sulcal volume, the SH group had larger lateral ( $P = 0.0014$ ) and third ventricles ( $P = 0.0249$ ) than the VA group.

#### Regional Patterns of Volume Abnormalities

The non-regional analyses revealed significant volume abnormalities in both schizophrenic groups relative to the control group in cortical gray matter and sulcal CSF but not in cortical white matter. The following analyses examined the cortical gray matter and sulcal abnormalities across the six measured cortical regions.

**Table 2**  
Raw brain volumes (cc) for each MRI measure in each group (means, standard errors, percentage of control value)

MRI brain measure	Normal controls (n = 65)	VA schizophrenics (n = 71)	SH schizophrenics (n = 57)
<i>Global measures</i>			
Intracranial volume (cc)	1354.1 (15.2)	1332 (14.8)	1306.1 (18.20)
	–	98.4%	96.5%
Cortical gray matter	127.1 (1.76)	117.1 (1.97)	114.5 (1.9)
	–	92.1%	90.1%
Cortical white matter	75.1 (1.59)	75.4 (1.28)	74.5 (1.79)
	–	100.4%	99.2%
Cortical sulcal CSF	42 (1.5)	46.7 (1.83)	45.5 (1.57)
	–	111.2%	108.3%
Lateral ventricles	21.0 (1.17)	24.7 (1.05)	28.4 (1.87)
	–	117.6%	135.2%
Third ventricle	0.38 (0.02)	0.47 (0.02)	0.52 (0.04)
	–	123.7%	136.8%
<i>Regional measures</i>			
Cortical gray matter			
Prefrontal	30.6 (0.45)	27.7 (0.50)	26.8 (0.52)
	–	90.5%	87.6%
Frontal	16.4 (0.31)	15.1 (0.34)	15.2 (0.33)
	–	92.1%	92.7%
Anterior superior temporal	8.2 (0.14)	7.3 (0.15)	7.5 (0.18)
	–	89.0%	91.5%
Posterior superior temporal	8.2 (0.14)	7.5 (0.15)	7.4 (0.17)
	–	91.5%	90.2%
Anterior parietal	16.3 (0.32)	15.0 (0.37)	15.4 (0.46)
	–	92.0%	94.5%
Posterior parietal–occipital	30.8 (0.61)	29.1 (0.60)	27.6 (0.79)
	–	94.5%	89.6%

### Regional Cortical Gray Matter Volumes

A repeated measures ANOVA across the six cortical regions of the three groups revealed significant effects of group [ $F(2,190) = 23.924, P = 0.0001$ ], region [ $F(5,950) = 9.417, P = 0.0001$ ] and interaction [ $F(10,950) = 3.757, P = 0.0001$ ] (Fig. 3A). A follow-up ANOVA comparing the two schizophrenic groups to each other yielded no significant group effect [ $F(1,126) = 1.698, P = 0.1949$ ] but did show a trend towards an interaction [ $F(5,630) = 2.046, P = 0.0706$ ]. The only significant regional difference identified with *t*-tests showed that the SH group had a greater volume deficit in prefrontal gray matter than did the VA group [ $t(126) = 2.455, P = 0.0155$ ]. There were trends for the SH group to have smaller gray matter volumes in the posterior superior temporal region [ $t(126) = 1.696, P = 0.0923$ ] and the posterior parietal–occipital region [ $t(126) = 1.789, P = 0.076$ ].

Next, we used *t*-tests to examine the differences in regional gray matter volumes within each schizophrenic group. Within the VA group, prefrontal gray matter volume was smaller than volumes in the frontal ( $P = 0.0645$ ), anterior parietal ( $P = 0.0143$ ) and posterior parietal–occipital ( $P < 0.0001$ ) regions. The anterior superior temporal gray matter volume was significantly smaller than volumes in all regions ( $P = 0.0017$ – $0.0001$ ) except the prefrontal cortex. In addition, the posterior superior

**Table 2** continued

Cortical white matter			
Prefrontal	15.7 (0.40)	15.2 (0.38)	14.8 (0.41)
	–	96.8%	94.3%
Frontal	10.7 (0.26)	10.6 (0.24)	10.7 (0.37)
	–	99.1%	100.0%
Anterior superior temporal	3.8 (0.14)	4.0 (0.15)	3.6 (0.16)
	–	105.3%	94.7%
Posterior superior temporal	4.9 (0.12)	4.8 (0.11)	4.9 (0.16)
	–	98.0%	100.0%
Anterior parietal	11.7 (0.25)	11.7 (0.20)	11.7 (0.34)
	–	100.0%	100.0%
Posterior parietal–occipital	16.9 (0.64)	17.6 (0.45)	16.9 (0.69)
	–	104.1%	100.0%
Cortical sulcal CSF			
Prefrontal	13.8 (0.51)	15.6 (0.63)	14.8 (0.59)
	–	113.0%	107.2%
Frontal	6.0 (0.27)	6.8 (0.30)	6.7 (0.27)
	–	113.3%	111.7%
Anterior superior temporal	2.3 (0.13)	2.8 (0.14)	3.0 (0.17)
	–	121.7%	130.4%
Posterior superior temporal	1.4 (0.084)	1.9 (0.11)	2.0 (0.12)
	–	135.7%	142.9%
Anterior parietal	5.3 (0.24)	5.8 (0.25)	5.9 (0.24)
	–	109.4%	111.3%
Posterior parietal–occipital	11.9 (0.50)	12.1 (0.61)	11.6 (0.54)
	–	101.7%	97.5%

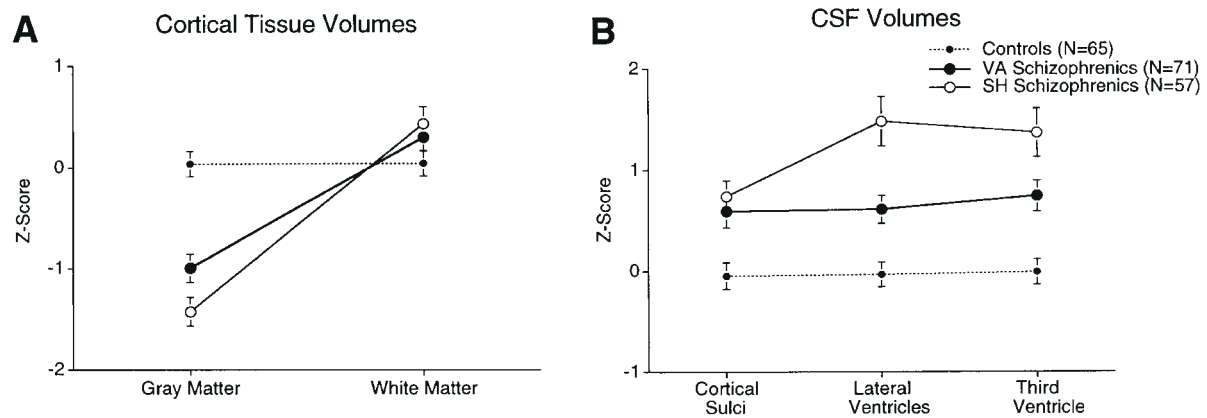
temporal gray matter volume was smaller than the anterior parietal ( $P = 0.0617$ ) and posterior parietal–occipital ( $P = 0.0127$ ) volumes.

The pattern of volume differences observed within the SH group was similar to, and in some cases more robust than, that observed in the VA group. Within the SH group, prefrontal gray matter volume was smaller than volumes in the frontal ( $P < 0.0001$ ), anterior parietal ( $P < 0.0001$ ) and posterior parietal–occipital ( $P < 0.0001$ ) regions. The anterior superior temporal gray matter volume was significantly smaller than volumes in the frontal ( $P = 0.0022$ ) and anterior parietal ( $P < 0.0001$ ) regions. The posterior superior temporal gray matter volume was smaller than the frontal ( $P = 0.0034$ ) and anterior parietal ( $P < 0.0001$ ) volumes.

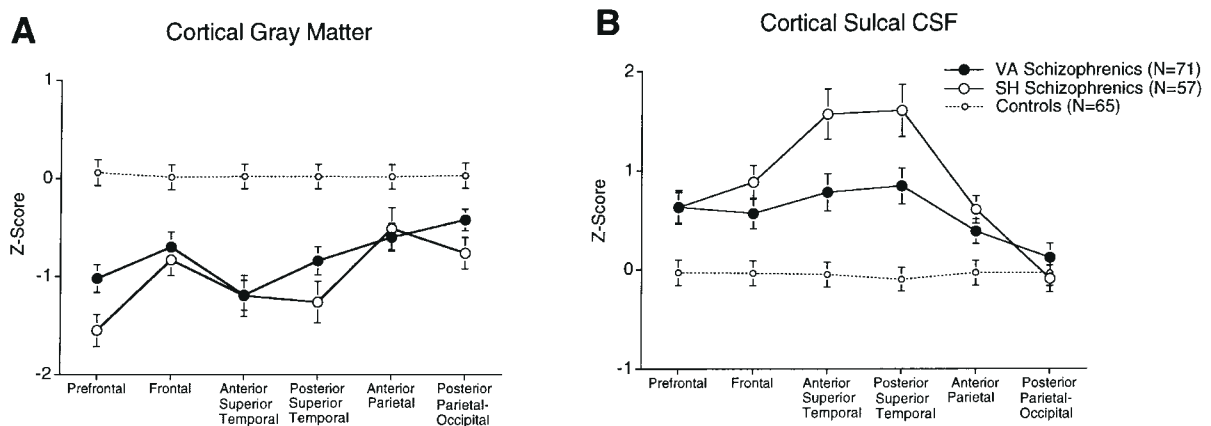
### Regional Cortical Sulcal Volumes

The three group  $\times$  six region ANOVA yielded significant effects of group [ $F(2,190) = 14.53, P = 0.0001$ ], region [ $F(5,950) = 16.207, P = 0.0001$ ] and interaction [ $F(10,950) = 7.202, P = 0.0001$ ; Fig. 3B]. The sulcal volumes of the two temporal regions (i.e. anterior and posterior superior temporal) were significantly larger ( $P < 0.02$  for each comparison) in the SH group than in the VA group.

As with the gray matter volumes, we used *t*-tests to examine the differences in regional cortical sulcal volumes within each schizophrenic group. In general, for the VA group, the sulci in the four anterior regions were significantly larger than the sulci in the two most posterior regions ( $P < 0.05$ – $0.0001$ ); although



**Figure 2.** Head size- and age-corrected Z-scores for each subject group for the five global measures. (A) The tissue volume deficits of the two schizophrenic groups were limited to cortical gray matter. (B) In addition, both patient groups showed significant cortical sulcal and ventricular enlargement relative to the control group.



**Figure 3.** Volume profiles of (A) cortical gray matter and (B) cortical sulcal CSF of the VA and SH schizophrenic groups. The two groups showed similar patterns of cortical gray matter volume deficits. The cortical sulcal volumes of the SH group were largest in the temporal lobes, whereas the pattern of sulcal enlargement in the VA group was relatively flat.

the prefrontal sulci were larger than the anterior parietal sulci, this difference was not significant ( $P = 0.1088$ ). In addition, the posterior superior temporal sulci were larger than the frontal sulci ( $P = 0.0481$ ). Within the SH group, the sulci in the two temporal lobe regions were significantly larger than those in any other region ( $P = 0.0039-0.0001$ ). Next in size were the sulci of the frontal region, which were significantly larger than the anterior parietal ( $P = 0.0134$ ) and posterior parietal-occipital sulci ( $P < 0.0001$ ).

#### Analysis of Covariance with Age as the Covariate

In order to verify the results obtained with the head size- and age-corrected Z-scores, we retested the group differences with analysis of covariance (ANCOVA), using age as the covariate. The volume measures used in the ANCOVAs were adjusted through regression analysis for variation in head size based on the full complement of 73 controls. Two ANCOVAs were calculated for each brain measure: the first compared all three groups and the second compared the two schizophrenic groups. These ANCOVAs yielded the same results as did the ANOVAs based on head size- and age-corrected Z-scores. Specifically, the three group ANCOVAs were significant for both ventricular measures and all cortical regions of gray matter (but not white matter) and sulcal CSF ( $P \leq 0.013-0.0001$ ) except the posterior parietal-

occipital sulcal CSF. The ANCOVAs comparing the two patient groups yielded significant differences ( $P < 0.02-0.002$ ) for the lateral and third ventricles and total cortical gray matter, where the SH group had greater abnormalities than did the VA group. The only regional cortical measure to reach significance was posterior parietal-occipital gray matter; relative to the VA group, the SH group showed a trend towards greater volume deficits in prefrontal cortical gray matter ( $P = 0.0323$ ) and larger volumes in the anterior and posterior superior temporal sulci ( $P = 0.0370$  for both).

#### Discussion

The present study provides confirmation of the replicability of a specific pattern of cortical gray matter volume deficits in schizophrenia. Two schizophrenia groups – one recruited from a VA facility and the other from a state hospital – displayed similar patterns of brain volume abnormalities. In particular, both groups had cortical gray matter but not white matter volume deficits that were widespread and relatively more pronounced in the prefrontal and temporal regions. The regional gray matter deficits in the SH group were generally greater than those in the VA group. In addition, both schizophrenic groups had abnormally large volumes of the cortical sulci and lateral and

third ventricles. However, the SH group, which was more severely ill than the VA group, showed greater CSF volume enlargements, most prominently in the ventricles and temporal sulci.

In both patient groups, the gray matter deficits in cortical volume of the prefrontal and temporal regions were relatively greater than those in the rest of the cortex, although the remaining regions also had abnormally small volumes. These results are consistent with other MRI studies of schizophrenia that distinguished gray matter and white matter, and that surveyed the anterior to posterior limits of the brain (Zipursky *et al.*, 1992b; Harvey *et al.*, 1993; Andreasen *et al.*, 1994; Schlaepfer *et al.*, 1994; Lim *et al.*, 1995, 1996a,c; Sullivan *et al.*, 1997) and also with many studies that examined selective cortical regions (e.g. frontal lobe: Andreasen *et al.*, 1986; Jernigan *et al.*, 1991; Raine *et al.*, 1992; Turetsky *et al.*, 1995; Woods *et al.*, 1995, but see Wible *et al.*, 1995; temporal lobe: Barta *et al.*, 1990; Shenton *et al.*, 1992; McCarley *et al.*, 1993; Zipursky *et al.*, 1994; Menon *et al.*, 1995; Turetsky *et al.*, 1995; Woods *et al.*, 1995; Marsh *et al.*, 1997a)].

The prefrontal volume deficit in the context of the widespread cortical gray matter volume deficit observed in this *in vivo* study is consistent with the neuropathological study of Selemon *et al.* (1995). In that study, schizophrenic patients had an increased neuronal density and thinning of the neuropil not only in Brodmann's area 9 of prefrontal cortex, an area of expected abnormalities, but also in area 17, the primary visual cortex, a comparison region in which no structural abnormalities were expected. The extent of the prefrontal cortical abnormalities, however, was greater than that observed in the visual cortex. Similarly, in the present study, although both cortical areas were affected, the magnitude of the abnormalities observed in prefrontal cortex was greater than that observed in the occipital cortex.

In addition to the prefrontal abnormalities, both patient groups showed severe superior temporal gray matter volume deficits, which were more extensive in the SH than VA patients. These results were confirmed in separate studies in subsets of these patient groups, where virtually the entire temporal lobe and subregions were delineated using anatomical landmarks (Zipursky *et al.*, 1994; Marsh *et al.*, 1997a,b). Similar to the observation of the present study, which used geometrically based cortical divisions, those studies observed gray matter volume deficits in the superior temporal gyrus bilaterally in both the patients groups, and this deficit was greater in the SH than VA patients; by contrast, neither patient group had volume deficits in either hippocampus. This salient temporal cortical volume deficit is widely documented and has been reported to be related to severity of psychotic symptoms (Shenton *et al.*, 1992; Menon *et al.*, 1995; Marsh *et al.*, 1997a) and auditory hallucinations (Barta *et al.*, 1990).

The SH group showed a pattern of gray matter volume deficits similar to, but which tended to be greater than, that observed in the VA group, despite the fact that the VA patients were, on average, older than the SH patients. This difference was especially prominent in the prefrontal and posterior superior temporal cortices. We assume that the effects of normal aging on brain morphology were minimized because such effects were taken into account with the head size- and age-corrected Z-scores used in the analyses (Mathalon *et al.*, 1993a,b). The SH patients, however, were symptomatic for a significantly greater proportion of their lives than were the VA patients (52 vs. 41%,  $P = 0.0001$ ). The greater length and degree of symptoms in the SH

group were also undoubtedly accompanied by a higher lifetime dose of antipsychotic medication, all of which may have influenced the greater brain volume abnormalities in the SH group relative to the VA group (cf. Wyatt, 1991; Andreasen and Carpenter, 1993). A recent study in an animal model lends indirect support to this hypothesis. Selemon *et al.* (1997) have demonstrated that typical and atypical neuroleptics given chronically for 6 months to rhesus monkeys can cause increased cortical glial density in prefrontal cortex. This increased density could translate into smaller gray matter volumes because MRI is incapable of distinguishing glial from neuronal cells in its gray matter measure. *In vivo* MRI combined with MR proton spectroscopic imaging of *N*-acetyl aspartate, a neuronal marker, may aid in making this distinction between cell type volumes (cf. Lim *et al.*, 1997).

The constellation of brain volume abnormalities shared by these two different groups of schizophrenic patients was also observed in a group of state hospital patients with congenital rubella plus schizophrenia-like symptoms (Lim *et al.*, 1995). The near microcephaly characterizing the rubella patients was attributable to a severe gray matter volume deficit, which was present throughout the cortex and maximal in the prefrontal and superior temporal regions. This pattern shared by the schizophrenic groups was distinct from that observed in a group of VA alcoholic patients. The alcoholic group had significant tissue volume deficits in both cortical gray matter and white matter, and also had greater sulcal and ventricular enlargement than the VA schizophrenic group (Sullivan *et al.*, 1997). Despite the presence of a tissue volume deficit extending to cortical gray and white matter in the alcoholics, the cortical gray matter volume deficit in the VA schizophrenic group was greater than that observed in the VA alcoholic group. These differences suggest that patterns of brain volume abnormalities can be disease-specific in psychiatric diseases without clear lesions. These results complement those of Schlaepfer *et al.* (1994) and Woods *et al.* (1995), who contrasted patterns of brain morphology in patients with schizophrenia versus bipolar disorder and observed different patterns of volume deficits in the two diseases. Those studies, too, reported prominent volume deficits in prefrontal and temporal cortex in the schizophrenics, and the Schlaepfer study identified a third affected region, the inferior parietal cortex.

We may speculate that overall disease severity and quality of life is related to prefrontal cortical integrity and may be further compromised by reduced functioning associated with additional widespread cortical volume deficits. Previously, we observed significant relationships between performance on tests assessing different cognitive and motor processes and cortical gray matter volumes in a subgroup of the VA patients (Sullivan *et al.*, 1996b). Although we did not detect relationships between specific processes and regional brain volumes, relationships between total cortical gray matter volume and test scores indicate functional significance of cortical volume deficits in schizophrenia. The present results identified even smaller cortical volumes in the more severely symptomatic SH group than in the VA group. These marked cortical volume deficits may well contribute to the compromised quality of life and ability to engage in independent living, especially notable in the SH patients.

For the most part, our series of MRI studies have used a common control group to establish abnormalities in regional brain volumes in schizophrenia and other diagnoses (e.g. Pfefferbaum *et al.*, 1992, 1995, 1997; Zipursky *et al.*, 1992b; Lim

*et al.*, 1995, 1996a; Sullivan *et al.*, 1997). The possibility remains, therefore, that the abnormalities observed between the pathological groups and the control group, as well as differences between the two pathological groups, are attributable to an inaccurate representation of the condition of the brain of the normal population by the selected control sample. We have several reasons to believe, however, that the observed pattern of brain volume abnormalities in schizophrenia is not necessarily linked to control sample bias. Firstly, we used non-overlapping controls in our CT and MRI studies, which have produced comparable results on similar measures of sulcal and ventricular volumes. Secondly, in our MRI replication study (Lim *et al.*, 1996c), we compared the results derived from the originally published groups of 22 schizophrenic patients and 20 age- and sex-matched controls with results based on new samples of schizophrenic and control subjects. We obtained the same pattern of results, i.e. gray matter volume deficits widespread throughout the cortex and no white matter volume deficit. Thirdly, Lim *et al.* (1996b), through the Stony Brook First Episode Study in New York, acquired MRI in patients hospitalized for their first psychotic episode. MRI analysis used a fully automated segmentation approach for quantifying cortical gray matter, white matter, and sulcal and ventricular CSF volumes; the comparison group comprised normal subjects recruited from the same geographical location as the patients. That study, too, observed widespread cortical gray but not white matter volume deficits. Lastly, the control group on which we based our head size and age correction is relatively large ( $n = 73$ ) and spans the adult age range (21–70 years), with ~12 subjects per decade. These subjects were recruited from the community at large, and we did not use scans collected through clinics and read as normal. We believe that these characteristics of our control sample reduce the chances of obtaining false group differences arising from control sample bias.

Because image analysis requires that the data be collected with the same acquisition protocol over the course of the study, it is impossible to initiate later, any improved acquisition techniques that become available the study progresses. Accordingly, we used the same MRI protocol throughout this study. Clearly, current imaging capabilities allow for higher resolution, with smaller voxels, less partial voluming and more segmentation precision. Even at the highest resolution of MRI, however, partial voluming occurs and affects segmentation. Thus, while it is true that smaller voxels would produce more precise measurement, the approach used here has been sufficiently sensitive to detect the decline in cortical gray matter volume associated with normal aging as well as that in several disease-states [e.g. alcoholism (Pfefferbaum *et al.*, 1995), Alzheimer's disease (Fama *et al.*, 1997) and epilepsy (Marsh *et al.*, 1997c)] confirmed by the neuropathological literature. Nonetheless, the results of our series of studies must withstand further replication in future studies using high resolution three dimensional imaging techniques in new samples of schizophrenic patients and control subjects.

In conclusion, the overlap of deficit pattern in cortical gray matter volume across the two schizophrenic groups, which differed greatly in severity, chronicity and onset age, provides evidence that it is generalizable within schizophrenia. The cortical regions of maximal abnormality may be selectively affected with greater illness severity. These brain regions include some loci, albeit not all, of heteromodal cortex (Mesulam, 1985), which is highly interconnected (Selemon and Goldman-Rakic, 1988), serves to integrate polysensory input, and undergoes

relatively late maturation; these loci have been shown by others as well to be selectively involved in schizophrenia (Schlaepfer *et al.*, 1994). The patterns of functional interactions between prefrontal and superior temporal regions observed in regional cerebral blood flow studies were different in healthy controls and in schizophrenics, who have been described as exhibiting a disconnection syndrome when they attempt to integrate intrinsically generated responses vs. extrinsically generated stimuli (Friston and Frith, 1995). Given the wide range of symptom type and severity in the two patient samples presented here, the converging evidence points to a characteristic pattern of cortical brain dysmorphology in schizophrenia, involving the prefrontal and temporal regions as areas of maximal involvement that occur within the context of milder yet significant gray matter volume deficits present throughout the cortex.

## Notes

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