

Progressive Brain Volume Changes and the Clinical Course of Schizophrenia in Men

A Longitudinal Magnetic Resonance Imaging Study

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Background: We sought to determine whether the brain dysmorphology previously observed cross-sectionally in people with schizophrenia progresses over time and whether such progression is related to the severity of the illness course.

Subjects and Methods: Men with chronic schizophrenia (n=24) and control men (n=25) received 2 brain magnetic resonance imaging scans, on average 4 years apart. Changes in brain volume were adjusted for head-repositioning error and expressed as slopes (cubic centimeters per year). Clinical course severity for the schizophrenic patients was assessed using the mean of time 1 and time 2 Brief Psychiatric Rating Scale (BPRS) scores and the percentage of time the patient was hospitalized during the interscan interval.

Results: Schizophrenic patients exhibited faster volume decline than control subjects in right frontal gray matter and bilateral posterior superior temporal gray matter, as well as faster cerebrospinal fluid volume expansion

in right frontal sulci, left lateral ventricle, and bilateral prefrontal and posterior superior temporal sulci. Faster rates of frontal sulcal expansion were related to greater BPRS total and positive symptom scores and longer time hospitalized. Prefrontal gray matter decline and sulcal expansion were associated with greater BPRS negative symptom scores and longer time hospitalized. Temporal lobe gray matter decline was associated with greater BPRS total and negative symptom scores.

Conclusions: This controlled study revealed that patients with chronic schizophrenia exhibited accelerated frontotemporal cortical gray matter decline and cortical sulcal and lateral ventricular expansion. Further, greater clinical severity was associated with faster rates of frontotemporal brain volume changes. These observations are consistent with a progressive pathophysiological process but need to be replicated in a larger sample.

Arch Gen Psychiatry. 2001;58:148-157

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NEUROIMAGING studies have established that schizophrenia is associated with brain dysmorphology, including increased ventricular and sulcal cerebrospinal fluid (CSF) volumes¹ and volume deficits in cortical gray matter (but not white matter), particularly in temporolimbic and frontal lobes.^{2,3} Absence of correlation between these brain volume abnormalities and illness duration,² as well as the presence of these abnormalities at illness onset,⁴⁻⁶ support the view that brain dysmorphology in schizophrenia reflects a neurodevelopmental insult and may not be progressive.⁷

A neurodevelopmental insult, however, does not preclude a neurodegenerative process. Whether schizophrenia produces progressive brain changes can be addressed definitively only with longitudinal imaging studies. Early computed to-

mography studies with a predominant focus on ventricular enlargement generally failed to show progression in schizophrenia,⁸⁻¹² with some exceptions.^{13,14} More recent longitudinal computed tomography and magnetic resonance imaging (MRI) studies of the lateral ventricles have yielded equivocal results, with some showing no progressive ventricular enlargement¹⁵⁻¹⁹ and others indicating trends²⁰ or significant progression,²¹ at least among subgroups of people with schizophrenia. These subgroups include patients with first-episode,^{22,23} chronic poor outcome,²⁴ and childhood-onset schizophrenia.²⁵⁻²⁷

Recent longitudinal MRI studies of schizophrenia have examined progression of total brain tissue^{15,18,22,23,25,28} or specific brain regions including temporal^{16,22,23,26,28,29} and frontal^{26,28} lobes, hippocampus/amygdala complex,^{22,23,27,29} and basal ganglia.^{20,22,23,25} In these stud-

SUBJECTS AND METHODS

SUBJECTS

All participants and/or legal guardians provided written informed consent. Subjects (**Table 1**) were drawn from a group of 71 men with schizophrenia and 73 control men described previously.³⁰ For patients, repeat scans were obtained 7 months to 7.5 years (mean=3.6 years; median=3 years) after initial MRI during subsequent rehospitalizations or outpatient visits; for control subjects, repeat scans were obtained 7 months to 6.7 years (mean=4.2 years; median=5 years) after initial MRI.³¹

Patients (n=24) were recruited from inpatient units of the VA Palo Alto Health Care System (VAPAHCS) in Palo Alto, Calif, screened, and diagnosed as previously described.³⁰ At the time of each scan, patients were taking antipsychotic medication and met *DSM-III-R* criteria for schizophrenia, determined by consensus of a psychiatrist or psychologist conducting a semistructured interview and a trained research assistant administering the Structured Clinical Interview for *DSM-III-R* (SCID).³⁹ Exclusion criteria were current alcohol or drug abuse or past history of dependence (determined by the *DSM-III-R*), of significant medical illness, or of head injury with loss of consciousness for more than 30 minutes. After scan 1, most patients continued treatment with the VAPAHCS, but neither clinical assessments nor medication dose or compliance data were systematically recorded. Illness duration and onset age were estimated from SCID interviews at each scan (Table 1).

Controls (n=25) were recruited from the community for cross-sectional normal aging⁴⁰ or clinical studies.^{30,41} Medical screening excluded subjects with conditions potentially affecting brain morphology. Psychiatric screening with the Schedule for Affective Disorders and Schizophrenia-Lifetime⁴² excluded subjects if they had ever met Research

Diagnostic Criteria⁴³ for any psychiatric disorder or for a substance abuse disorder in the year prior to study entry, had consumed over 54 g of ethanol per day (4 "drinks" containing an average of 13.6 g of ethanol) for more than 1 month, or scored less than 24 out of 30 on the Mini-Mental State Examination.⁴⁴ Original control subjects were retested after varying intervals for additional studies^{31,25}; men were selected to generate a control group comparable to the patient group in age, handedness,⁴⁵ and interscan interval. Patients and control subjects did not differ on premorbid IQ based on the National Adult Reading Test,⁴⁶ but the control subjects had more education (Table 1).

SEVERITY OF CLINICAL COURSE

Two trained raters administered the Brief Psychiatric Rating Scale (BPRS)⁴⁷ during a semistructured interview within 12 days of each scan, and their ratings were averaged. Total scores, as well as positive symptom (conceptual disorganization, unusual thought content, hallucinatory behavior) and negative symptom (emotional withdrawal, motor retardation, blunted affect) subscales,⁴⁸ were used in the present analysis. One patient did not have a BPRS rating at scan 2, so the closest rating (22 months after scan 1 and 15 months before scan 2) was substituted.

Clinical severity during the interscan interval was assessed using the mean of scan 1 and scan 2 BPRS ratings, as well as percentage of time the patient was hospitalized in Department of Veterans Affairs (VA) facilities during that interval. On average, patients were hospitalized 4 times (SD=3.1) for a total of 203 days (SD=172), representing 14.8% ± 8.3% of the interscan interval. One patient hospitalized throughout his interscan interval of 277 days (hospitalized 100% of the time) was excluded from this analysis as a statistical outlier.

Continued on next page

ies, progressive volume loss was observed for whole-brain measures in patients with first-episode schizophrenia,^{22,23} for temporal lobes and hippocampi in childhood-onset^{26,27,29} and first-episode^{22,28} schizophrenia, and for frontal lobes in childhood-onset,²⁶ first-episode, and chronic schizophrenia.²⁸

Clinical severity and course measures including time hospitalized,^{9,10,12,16,24} baseline and/or follow-up symptom ratings,^{10,16,18,19,24-26,28,29} and symptom change^{24,28} have been related to longitudinal brain volume changes in patients with schizophrenia, with mixed results. Longer time hospitalized during the interscan interval^{9,16,24} or since illness onset^{10,19} predicted slower ventricular enlargement in first-episode schizophrenia,¹⁶ faster ventricular enlargement in chronic schizophrenia,²⁴ or no significant brain changes.^{9,10,12} In first-episode schizophrenia, duration of initial untreated psychosis predicted right temporal lobe volume decline,²³ and an unremitting course predicted greater ventricular expansion and cortical tissue decline.¹⁸ In chronic schizophrenia, a poor functional outcome predicted faster ventricular enlargement.²⁴ In childhood-onset schizophrenia, greater severity at baseline and follow-up predicted greater ventricular enlargement²⁵ and right posterior superior temporal gy-

rus volume decline,²⁹ and greater baseline severity also predicted faster decline of frontal, temporal, and parietal gray matter.²⁶ Considering symptom changes between scans,²⁸ declines in frontal and temporal lobe volumes were associated with general symptom improvement in chronic patients, and with improvement in delusions and thought disorder but worsening of negative symptoms in first-episode schizophrenia. Thus, brain volume decline in schizophrenic patients may be directly related to both clinical severity and clinical improvement, underscoring the conceptual distinction between course severity and symptom change over time.

Limitations of prior longitudinal imaging studies of schizophrenia include small sample size; control groups that were absent,^{8-12,17} small,^{16,21,22} or not matched by age²⁴; use of difference scores rather than slopes when interscan intervals differed between subjects^{8,24,28}; and lack of control for head-repositioning error. Furthermore, few longitudinal MRI studies²⁶ have reported regional brain volume changes specific to gray matter.

Previously we reported both widespread cortical gray matter volume deficits, particularly in prefrontal and temporal regions, as well as sulcal and ventricular enlargement in patients with chronic schizophrenia as com-

MAGNETIC RESONANCE IMAGING

Acquisition and Analysis

Baseline and follow-up scans used the same MRI protocol⁴⁰ (1.5T General Electric Signa scanner, Milwaukee, Wis; axial spin echo, 5 mm thick, 2.5 mm skip; field of view = 24 cm; 256 × 256 matrix; TE = 20, 80 milliseconds; cardiac cycle gated effective TR > 2400 milliseconds; 256 phase encodes; oblique plane perpendicular to sagittal plane crossing through anterior and posterior commissures).

Images were processed blind to subject identity. The most inferior MRI slice used in quantification was identified as the index slice and was located above the orbits, where anterior horns of the lateral ventricles appeared bilaterally. Index slices for baseline and follow-up MRI were reviewed for comparability across scans. The index slice and the 6 consecutive slices superior to it sampled approximately half the brain and comprised our measure of intracranial volume (ICV). Each slice was segmented into CSF, gray matter, and white matter using a semiautomated segmentation algorithm.⁴⁹ The regions of interest (ROIs) were a measure of lateral ventricles (CSF in the inner 55% of all slices displaying ventricles) in addition to 2 frontal and 2 temporal lobe regions, defined by divisions of the outer 45% of each slice according to anatomical landmarks and a priori geometric rules: prefrontal, frontal, anterior superior temporal, and posterior superior temporal (**Figure 1**). These ROIs did not encompass the full volume of the lobes after which they were named but represented a large sample of those cortical regions.

Volume Change

Observed ROI volume differences (in cubic centimeters) between scans represents true biological change over time, plus measurement error primarily due to head-positioning

differences in the scanner. A change in ICV from scan 1 to scan 2 (Table 1) was considered an index of longitudinal measurement error because presumably an adult's head size does not change between scans. The range in correlations between ROI and ICV change scores was 0.08 to 0.47. We adjusted for this error using linear regression,^{31,50,51} in which each ROI change score is regressed on ICV change and a dummy variable coding group. Resulting residual scores represented ROI volume changes independent of ICV change and, after adding back the appropriate group intercept, provided an ROI volume change score adjusted for longitudinal measurement error. Adjusted ROI change scores were divided by interscan interval to control for interval variation between subjects, yielding adjusted slopes (cubic centimeters per year) as the units for all subsequent longitudinal MRI volume analyses.

STATISTICAL ANALYSIS

To determine whether brain changes progressed faster in patients with schizophrenia than in normal control subjects, left and right hemisphere-adjusted ROI slopes were analyzed using 2-way (group × hemisphere) repeated-measures analysis of variance (ANOVA). In addition, 2-way (group × hemisphere) analysis of covariance (ANCOVA) was performed for each ROI to control for potential confounding effects of age and National Adult Reading Test premorbid IQ. Pearson correlations assessed the relationships of clinical severity with ROI slopes. Between-group effect sizes for group differences are reported in the tabled results, and 2-tailed probability values are reported for the statistical tests ($\alpha = .05$) of our main hypotheses. In addition, because we had no a priori predictions about correlations emerging for ROIs in only 1 hemisphere, exploratory correlational analyses examined relationships between the clinical severity measures and the ROI slopes for each hemisphere separately (setting $\alpha = .01$).

pared with controls.³⁰ Here we report brain volume change rates in a subgroup of these patients, scanned twice over an average interval of 4 years, and compare them with the normal aging changes observed in controls rescanned at comparable intervals.³¹ A current theory holds that the pathophysiology of schizophrenia involves a progressive or neurodegenerative process.^{32,33} This position derives from observations of progressive changes in symptoms and decline in level of functioning during the illness course,³⁴ and longitudinal MRI data documenting accelerated brain volume changes in people with schizophrenia.^{33,35,36} Based on this theoretical perspective and accumulating supportive evidence, we hypothesized that patients with schizophrenia, relative to normal controls, would exhibit faster cortical gray matter volume decline and sulcal expansion in the frontal and temporal lobes as well as faster expansion of the lateral ventricles. In light of previous observations that the duration of untreated psychotic symptoms in schizophrenic patients predicts clinical deterioration and poor treatment response,^{37,38} we further hypothesized that patients with a more severe clinical course during the interscan interval, defined by higher positive, negative, and total symptom ratings at both scans and greater time hos-

pitalized, would exhibit faster frontotemporal brain volume decline.

RESULTS

Scans were acquired between 1989 and 1996. Scan 1 dates were distributed over a broader calendar range in patients than in control subjects, but scan 2 dates were similarly distributed across both groups. Interscan intervals were not significantly different between the groups ($t_{47} = 0.94$, $P = .35$). Intracranial volume decreased similarly in both groups between scan 1 and scan 2 (Table 1; controls by 1%, patients by 2%; $t_{47} = 1.22$, $P = .23$), reflecting both head-repositioning artifacts and uncontrolled aspects of the scanning procedure and providing an estimate of longitudinal method error used to statistically adjust the ROI change scores. Test-retest reliability of the ICV estimates across the 2 study scans, assessed with intraclass correlations³² of all scan 1 and scan 2 data, was 0.92 in the patients and 0.94 in the controls. Schizophrenic patients had significantly lower BPRS total scores at scan 2 than at scan 1 ($t_{23} = -2.99$, $P = .007$), reflecting the fact that all patients were hospitalized at scan 1, but many were outpatients at scan 2.

Table 1. Mean Demographic, Clinical, and Intracranial Volume Measures in Controls and Schizophrenic Patients*

Variable	Healthy Controls (n = 25)			Schizophrenic Patients (n = 24)			Group Differences†		
	Mean	SD	Range	Mean	SD	Range	t	df	P
Age at scan 1, y	40.7	8.5	22-54	39.4	6.4	24-51	0.63	47	.53
Interscan interval, y	4.2	1.9	0.6-6.7	3.6	2.2	0.6-7.5	0.94	47	.35
Years of education	16.2	2.6	11.5-20	13.3	2.1	9-17	4.45	47	<.001
Handedness‡	25.2	15	14-66	22.6	16	14-67	0.57	44	.57
NART premorbid IQ§	111.2	7.8	90-124	107.7	7.5	96-124	1.53	43	.13
Intracranial volume									
Scan 1 (cm ³)	524.5	42	440-612	501.0	47	391-580	1.86	47	.07
Scan 2 (cm ³)	519.2	41	461-616	490.8	45	360-553	2.31	47	.03
BPRS total at scan 1	45.3	7.6	31-54
BPRS total at scan 2	39.5	7.5	27.5-53
Age at illness onset, y	24.0	3.8	18-32
Illness duration, y	15.3	6.4	2.2-26.5

*NART indicates National Adult Reading Test; BPRS, Brief Psychiatric Rating Scale.

† t indicates student's t test for independent groups. Probability values are 2-tailed.

‡ A range of 14-32 indicates right-handedness.

§NART scores were not available for 2 patients and 2 controls.

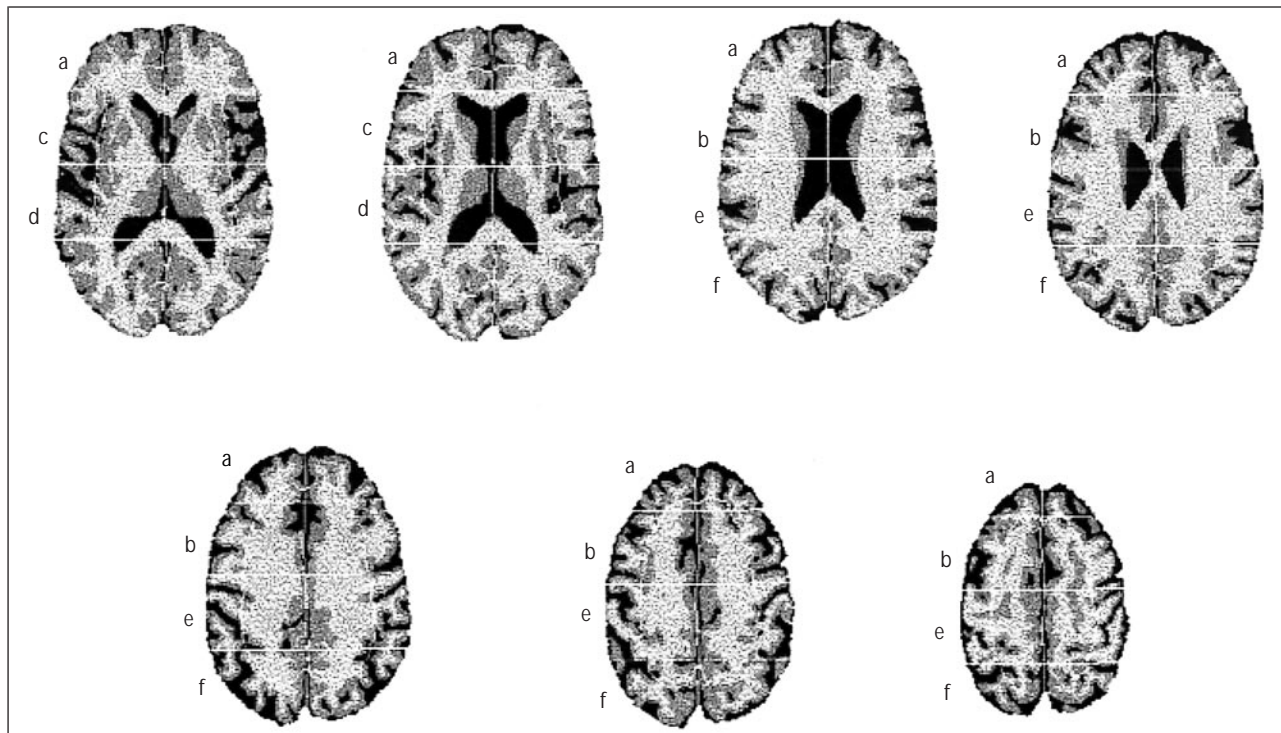


Figure 1. Seven axial magnetic resonance images segmented into gray matter (dark gray), white matter (white), and cerebrospinal fluid (black). The curved white lines mark the division of each section into the outer 45% for cortical measures and inner 55% for ventricular measures. Horizontal white lines mark 3 coronal planes used to delineate 4 quadrants for defining cortical regions of interest. These planes pass 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. Six cortical regional measures are defined by summing quadrants across slices as follows: a=prefrontal; b=frontal; c=anterior superior temporal; d=posterior superior temporal; e=anterior superior parietal; and f=posterior parietal-occipital. The present study employs only the prefrontal, frontal, and anterior and posterior temporal cortical regions, and the lateral ventricles.

GROUP DIFFERENCES IN RATES OF CHANGE OF REGIONAL BRAIN VOLUMES

Analysis of mean MRI slopes for the 9 ROIs (**Table 2**), based on 2-way (group × hemisphere) repeated-measures ANOVA, showed a significant group effect for posterior temporal sulci and group trends for posterior temporal gray matter and prefrontal sulci (**Figure 2**). Mean

between-group effect sizes across hemispheres were in the range of 0.42 to 0.51 (Table 2), all indicating faster progression in the schizophrenic patients than in control subjects. Additional group differences in ROI slopes depended on hemisphere, with significant group × hemisphere interactions emerging for frontal sulci and gray matter and for the lateral ventricles. For the frontal region, relative to the control subjects, schizophrenic patients

Table 2. Adjusted Magnetic Resonance Imaging Slopes for Normal Controls and Schizophrenic Patients: Means, Percent Change per Year, and Effect Sizes*

Region of Interest	Left Hemisphere					Right Hemisphere					ANOVA Effects†					
	Controls		Patients		Effect Size‡	Controls		Patients		Effect Size‡	G		H		G × H	
	Mean ± SD	Percent Change/y	Mean ± SD	Percent Change/y		Mean ± SD	Percent Change/y	Mean ± SD	Percent Change/y		F	P	F	P	F	P
Cerebrospinal fluid																
Prefrontal	.19 ± .28	3.63	.45 ± .60	6.63	.57	.05 ± .32	1.55	.19 ± .56	4.68	.31	2.97	.09	11.5	.001	1.1	.29
Frontal	.10 ± .22	6.01	.03 ± .34	2.75	-.22	-.06 ± .24	2.19	.10 ± .32	2.71	.58	0.65	.42	0.77	.38	4.47	.04
Anterior superior temporal	.07 ± .13	10.95	.11 ± .19	14.83	.23	.01 ± .15	1.37	.01 ± .19	7.38	.00	0.28	.60	5.83	.02	0.3	.585
Posterior superior temporal	.03 ± .10	4.47	.05 ± .17	9.65	.15	-.04 ± .12	3.66	.05 ± .12	8.10	.68	4.00	.05	1.12	.295	1.43	.24
Lateral ventricles	.39 ± .73	4.80	1.00 ± 1.52	12.96	.51	.33 ± .67	4.15	.60 ± 1.09	7.83	.30	2.27	.14	9.86	.003	5.15	.03
Gray matter																
Prefrontal	-.59 ± .93	3.82	-.26 ± .69	1.81	.40	-.23 ± .57	1.51	-.30 ± 1.02	2.12	-.08	0.38	.54	2.47	.12	3.89	.055
Frontal	.02 ± .51	0.19	-.07 ± .34	0.97	-.20	.19 ± .66	2.25	-.13 ± .32	1.72	-.60	2.47	.12	1.23	.27	5.22	.03
Anterior superior temporal	-.07 ± .23	1.51	-.11 ± .23	3.31	-.19	-.05 ± .23	1.11	-.04 ± .17	0.77	.06	0.11	.745	1.49	.23	0.46	.50
Posterior superior temporal	.04 ± .43	1.61	-.11 ± .19	2.68	-.44	-.01 ± .20	0.19	-.13 ± .23	3.35	-.57	3.87	.055	0.67	.42	0.08	.77

*Negative slopes indicate volume decline, and positive slopes indicate volume expansion. Percent change is slope (cubic centimeters per year) divided by scan 1 volume for each region of interest. Negative effect sizes for tissue regions of interest and positive effect sizes for cerebrospinal fluid regions of interest indicate faster rates of progression in the schizophrenic patients.

†For all F tests, df = 1.47. P values are 2-tailed. ANOVA indicates analysis of variance; G, group; and H, hemisphere.

‡Between-group effect size = (schizophrenia group mean - control group mean)/pooled standard deviation.

showed faster sulcal expansion and gray matter decline in the right but not the left hemisphere (Figure 2). Between-group effect sizes for the right frontal region were 0.58 for sulci and 0.60 for gray matter (Table 2). Lateral ventricular expansion was faster in schizophrenic patients than in control subjects, and this expansion was significantly faster in the left than in the right hemisphere (Figure 2). A trend toward a group × hemisphere interaction for prefrontal gray matter indicated that schizophrenic patients have faster gray matter decline on the right side than control subjects but, contrary to our directional hypothesis, that controls have faster decline on the left than the patients.

Neither age at scan 1 nor National Adult Reading Test IQ significantly differed between the groups (Table 1), nor did these variables significantly correlate with any ROI slopes within each group. Two-way ANCOVA, separately controlling for each of these variables, yielded essentially the same ROI results as the ANOVA. In addition, significant group differences in ROI slopes persisted after controlling for baseline ROI volumes using ANCOVA. These group differences emerged despite considerable overlap between the group distributions of ROI slopes and evidence of greater variability in the patients than in control subjects (Figure 2).

RELATIONSHIPS OF ROI SLOPES WITH CLINICAL SEVERITY MEASURES

Clinical symptom severity, as reflected by time-averaged BPRS ratings and percentage of time hospitalized during the interscan interval, was significantly cor-

related with the rate of progressive volume changes in frontotemporal regions of schizophrenic patients (Table 3 and Figure 3). In terms of global measures of severity, higher BPRS total scores were related to faster frontal sulcal expansion and anterior temporal lobe gray matter decline, accounting for 35% and 21% of the variance in these ROI slopes, respectively. Percentage of time hospitalized accounted for 27% of the variance in prefrontal sulcal expansion and gray matter decline, and 23% of the variance in frontal sulcal expansion. In terms of specific symptom domains, higher BPRS positive symptom scores were associated with faster frontal sulcal expansion, accounting for 36% of the variance. Higher negative symptom scores were associated with faster prefrontal sulcal expansion and gray matter decline, accounting for 14% and 25% of their variances, respectively, and also accounted for 18% of the variance in posterior temporal lobe gray matter decline. Percentage of time hospitalized and time-averaged BPRS scores were not significantly correlated, indicating their sensitivity to distinct aspects of clinical severity.

Supplementing the correlations based on bilateral ROI slopes, analyses of the separate left and right hemisphere ROIs identified 2 additional correlations. Higher BPRS positive symptom scores correlated with faster decline of left frontal gray matter ($r = -0.50, P = .01$), consistent with their association with faster bilateral frontal sulcal expansion. Higher BPRS negative symptom scores correlated with faster right frontal sulcal expansion ($r = 0.54, P = .006$).

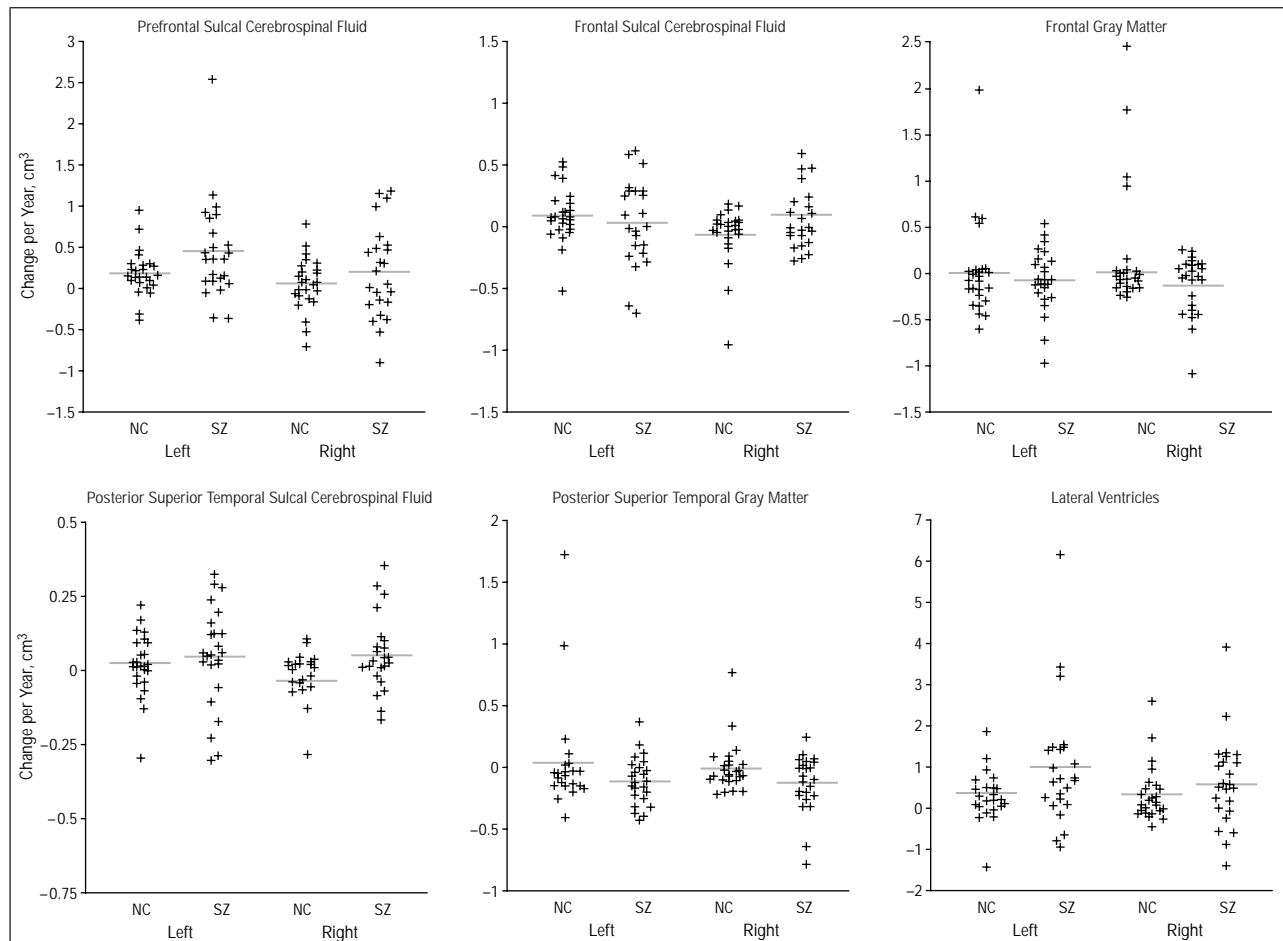


Figure 2. Means and distributions of left and right hemisphere magnetic resonance imaging slopes (cubic centimeters per year) for regions of interest in which patients with schizophrenia (SZ) exhibited significant bilateral or unilateral progression relative to normal control men (NC). Means are represented by solid horizontal lines drawn on each group's distribution. In the right (but not the left) hemisphere, frontal gray matter volume declined, and frontal sulcal cerebrospinal fluid expanded faster in the schizophrenic patients than in the control subjects. On the left (but not the right), lateral ventricular volume increased faster in the schizophrenic patients than in controls. Prefrontal and posterior superior temporal sulcal cerebrospinal fluid volume expanded faster and posterior superior temporal gray matter declined faster in the schizophrenic patients than in controls, bilaterally.

COMMENT

These longitudinal MRI data, obtained over an average interval of 4 years, provide support for progressive brain volume changes in patients with chronic schizophrenia that exceed the normal aging changes observed in healthy control subjects. Although some differences were small, 14 of the 18 regions examined showed faster progression in the patients than in controls. Further, when significant group differences did emerge, they were generally in the predicted direction, with schizophrenic patients progressing faster than normal control subjects. The faster brain volume changes in the patients with schizophrenia were not always evident bilaterally, nor was a single hemisphere consistently implicated. Rather, a pattern of volume progression was evident in right frontal gray matter and sulci, bilateral posterior temporal sulci, and the left lateral ventricle, with trends in the bilateral posterior temporal gray matter and prefrontal sulci. This pattern corroborated results from a previous longitudinal study of first-episode schizophrenia,²² in which patients showed faster bilateral temporal lobe volume loss and left lateral ventricular expansion than control subjects during a 4-year

interval. Moreover, our finding that patients exhibited faster left ventricular expansion is consistent with several previous longitudinal reports based on first-episode,^{22,23} childhood-onset,²⁵ and chronic poor outcome²⁴ schizophrenia as well as with prior cross-sectional studies,^{53,54} suggesting that a progressive process may disproportionately affect left subcortical structures.

The progressive volume changes in temporal and frontal lobes observed in the schizophrenic patients are striking in light of cross-sectional MRI studies showing particularly prominent volume deficits in these regions.³⁰ Decline in temporal lobe tissue or gray matter was observed in patients with childhood-onset^{26,29} and first-episode²² schizophrenia. A recent MRI study²⁸ did not find faster temporal volume decline in chronic or first-episode patients; however, measurement of undifferentiated tissue may have obscured volume decline specific to gray matter. The frontal gray matter decline and sulcal expansion are consistent with previous longitudinal observations of frontal tissue decline in people with schizophrenia,²⁸ including patients with childhood-onset schizophrenia.²⁶ Assuming an *ex vacuo* process, we would have expected the observed prefrontal sulcal expansion in pa-

Table 3. Pearson Correlations of MRI Slopes With Clinical Severity Measures in Schizophrenic Patients*

MRI Slope (cm ³ /y) Region of Interest	Time-Averaged BPRS Scores†			Percentage of Time Hospitalized
	Total	Positive Symptoms	Negative Symptoms	
Cerebrospinal fluid				
Prefrontal	0.25	0.33	0.37‡	0.52
Frontal	0.59¶	0.60¶	0.25	0.48§
Anterior superior temporal	-0.23	0.09	-0.27	0.01
Posterior superior temporal	0.08	-0.01	-0.14	0.04
Lateral ventricles	0.07	0.26	0.20	0.27
Gray matter				
Prefrontal	-0.24	-0.20	-0.50	-0.52
Frontal	0.31	-0.32	-0.03	-0.17
Anterior superior temporal	-0.46§	-0.31	-0.21	-0.31
Posterior superior temporal	-0.23	0.06	-0.42§	-0.32

*n = 24. MRI indicates magnetic resonance imaging; BPRS, Brief Psychiatric Rating Scale. For cerebrospinal fluid region of interest measures, larger slopes indicate faster rates of sulcal or ventricular expansion.

†Time-averaged BPRS = (BPRS 1 + BPRS 2) ÷ 2; higher scores indicate faster rates of tissue volume loss.

‡P ≤ .10.

§P ≤ .05.

||P ≤ .01.

¶P ≤ .005.

tients to be accompanied by prefrontal gray matter decline. Perhaps sulcal CSF volume is more sensitive to diffuse tissue loss than to tissue volume itself because additive *ex vacuo* effects of small distributed tissue losses may accumulate in sulcal CSF. Whether underlying white matter changes contribute to prefrontal sulcal expansion over time is unclear, but previously we have not found white matter volume deficits in patients with schizophrenia.^{30,55} However, other aspects of white matter integrity may be compromised in schizophrenia.^{56,57}

A more severe clinical course, as measured by time-averaged BPRS total, positive, and negative symptom scores as well as percentage of time hospitalized, was associated with faster frontal and temporal lobe rates of progression, further corroborating the pathophysiological significance of accelerated progressive changes observed in the patients. Moreover, the correlations are consistent with models linking positive and negative symptoms to dysfunctional frontotemporal circuitry.⁵⁸⁻⁶⁵ Positive symptom severity correlated with indicants of faster deterioration in the frontal lobes, whereas negative symptom severity correlated with indicants of faster deterioration in the prefrontal, frontal, and posterior temporal lobes, particularly in terms of cortical gray matter volume decline. The more global measures of clinical severity were also associated with faster progressive brain changes, with higher BPRS total scores correlated with faster frontal sulcal expansion and anterior temporal lobe gray matter decline, and percentage of time hospitalized correlated with faster prefrontal and frontal sulcal expansion and faster prefrontal gray matter decline. Similar brain volume change relationships with clinical severity were reported based on time hospitalized,²⁴ clinical ratings,^{25,29} or other measures.^{18,23,24} Overall, the results of the present study indicated that progressive brain volume changes were greater in schizophrenic patients with more severe symptoms at both scans, suggesting that persistent or cumulative clinical severity reflects progressive pathophysiological processes.

Brain changes associated with greater severity could reflect medication-induced neurotoxicity, because patients with more severe symptoms tend to receive higher doses of antipsychotic medication. Alternatively, psychosis itself may be neurotoxic,^{37,66} such that noncompliance with or nonresponsiveness to neuroleptics may contribute to faster brain volume decline in symptomatic patients. Unfortunately, medication history and compliance data were not systematically recorded, precluding resolution of this issue in our study. Evidence that antipsychotic medication may be “neuroprotective” derives from longitudinal imaging studies (medication compliance is associated with less ventricular expansion^{21,23} and less temporal lobe volume decline²³), first-episode follow-up studies (early antipsychotic treatment improves clinical outcome^{67,68}), and animal studies (certain antipsychotics block neurotoxic effects of psychotogenic N-methyl D-aspartate antagonists⁶⁹). However, higher medication doses in patients with first-episode schizophrenia have been associated with greater frontal and temporal lobe volume decline,²⁸ which could have resulted from medication- or psychosis-related neurotoxicity. Several studies found no correlation between medication and brain changes over time.^{10,19,22} Thus, the hypothesis that psychosis is neurotoxic and that medication is neuroprotective remains speculative.

The present data suggest that neurodegenerative processes operate during the course of schizophrenia and that brain volume deficits are not simply static manifestations of anomalous neurodevelopment.^{69,70} A principal argument against a neurodegenerative pathophysiology in schizophrenia is the absence of gliosis in most⁷¹⁻⁷³ but not all⁷⁴⁻⁷⁶ neuropathological studies; however, observations of gliosis depend on techniques used, brain regions examined, and presence or absence of associated dementia.⁷⁷ Furthermore, lack of gliosis by itself does not prove that degenerative processes are absent in schizophrenia, because gliosis does not always accompany neuronal injury⁷⁶ and does not occur in apoptosis,^{78,79} a pro-

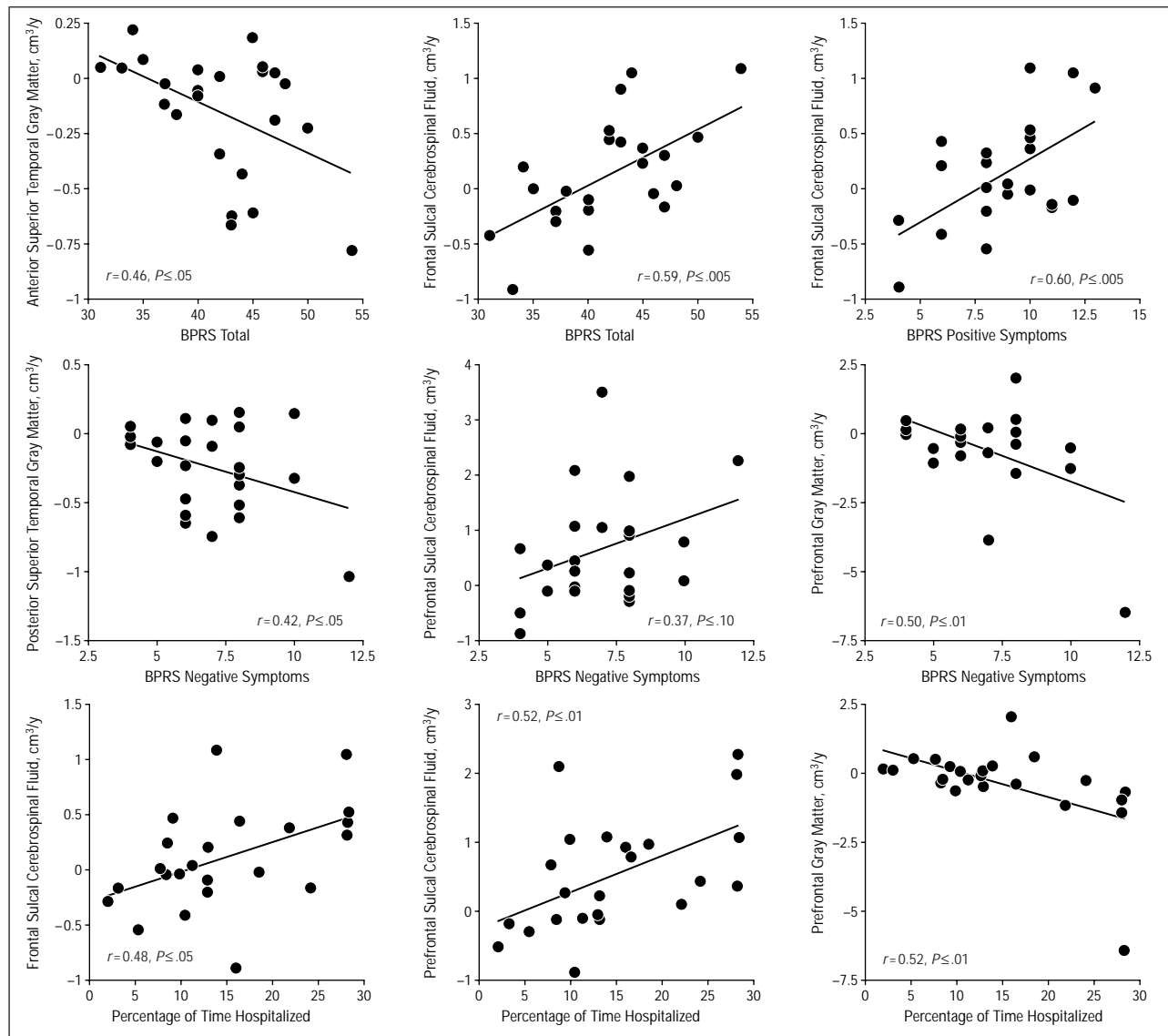


Figure 3. Scatterplots depicting significant correlations between magnetic resonance imaging slopes (cubic centimeters per year) and mean Brief Psychiatric Rating Scale (BPRS) scores (mean of baseline and follow-up ratings) and percentage of time hospitalized in schizophrenic patients. In general, patients who exhibited more severe clinical symptoms at baseline and follow-up and who spent a greater proportion of the interscan interval hospitalized showed faster rates of regional cortical gray matter volume decline and sulcal cerebrospinal fluid expansion.

cess which could produce progressive neural tissue loss. In addition, neuropil abnormalities observed in schizophrenia^{76,80} involving axonal, dendritic, and synaptic organization and alterations in neuronal size can occur throughout life. Excitatory amino acid neurotransmitters, abnormalities of which have been implicated in schizophrenia,⁸¹⁻⁸³ can produce excitotoxic cellular damage leading to dendritic neuropil reduction and neuronal loss⁸⁴ without gliosis.⁸¹ Thus, brain volume deficits in schizophrenia may result from multiple pathophysiological processes, including anomalous neurodevelopment and progressive neuronal injury, that do not produce neuropathological changes typical of established neurodegenerative disorders.

This study has limitations. Our results can be generalized only to men. Interscan interval variability may have contributed measurement error to volume change estimates, which was not entirely remedied by employ-

ing slopes. The MRI protocol used is coarse by current standards: acquisition of noncontiguous slices precludes full voluming of brain regions, 7 axial slices covered only half the brain, and ROIs were geometrically defined. However, the protocol was retained for longitudinal study, provided a robust signal for tissue segmentation, and proved sensitive to brain changes. Although measurement precision was insufficient to express absolute volume change, relative differences between patients and controls could be interpreted with confidence because measurement error was similarly distributed across groups. Although we calculated slopes to account for interscan interval variability, we make no assumption that change is uniformly linear throughout the illness course. Accordingly, extrapolation to periods beyond the interscan intervals represented is unwarranted. Clinical assessments were limited because complexities of symptoms and illness during the interscan interval cannot be

fully characterized by BPRS ratings at only 2 time points. In addition, the results must be regarded as preliminary because the sample sizes were relatively small for the number of statistical tests performed. The validity of the present results will ultimately depend on their replication in a larger sample.

The ascendance of the neurodevelopmental hypothesis notwithstanding, several pieces of evidence suggest decline in cognitive, social, and occupational function in people with schizophrenia, consistent with progressive pathophysiology.⁸⁵⁻⁹³ Kraepelin described a deteriorating course for many schizophrenic patients and posited neurodegenerative processes.⁹⁴ The neurodegenerative hypothesis in schizophrenia has been overshadowed in recent years by the neurodevelopmental hypothesis, and although they are sometimes presented as mutually exclusive, a neurodevelopmental insult need not preclude a neurodegenerative process.^{3,63,95} Indeed, the present study suggests that dismissal of neurodegenerative processes in schizophrenia may be premature.

Accepted for publication September 25, 2000.

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This research was supported by grants MH58007, MH30854, AA05965, and AA10723 from the National Institutes of Health, Bethesda, Md; and by the Department of Veterans Affairs, Washington, DC.

Earlier reports of these data were presented at the International Congress on Schizophrenia Research, Colorado Springs, Colo, April 12-16, 1997; the Annual Meeting of the American College of Neuropsychopharmacology, Wai Koloa, Hawaii, December 8-12, 1997, and Acapulco, Mexico, December 12-16, 1999; and the Annual Meeting of the Society of Biological Psychiatry, Toronto, Ontario, May 27-31, 1998, and Chicago, Ill, May 11-13, 2000.

We would like to thank the staff of the Laboratory of Physiological and Structural Brain Imaging and Mental Health Clinical Research Center for their patient care and invaluable assistance in conducting this research project. In particular, we thank Brian Matsumoto, MA, for image analysis; Kenneth Chow, MA, for data processing; and Margaret Rosenbloom for editorial assistance.

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