

A Follow-up Magnetic Resonance Imaging Study of Schizophrenia

Relationship of Neuroanatomical Changes to Clinical and Neurobehavioral Measures

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Background: Cross-sectional neuroanatomical studies have reported abnormalities in schizophrenia that relate to disease variables. Longitudinal neuroimaging investigations that integrate anatomical, clinical, and neurobehavioral measures may help clarify the pathogenesis of schizophrenia.

Methods: Magnetic resonance brain imaging and neurobehavioral studies were conducted at baseline and after 30.63 ± 12.92 months (mean \pm SD) in 40 patients with schizophrenia (23 men and 17 women) and 17 healthy controls (13 men and 4 women). The schizophrenia group included 20 first-episode and 20 previously treated subjects. Volumes of whole-brain, cerebrospinal fluid, and frontal and temporal lobes were measured. The severity of negative and positive symptoms was assessed, medications were monitored, and neurobehavioral functioning in 8 domains was evaluated.

Results: Both first-episode and previously treated patients had smaller brains and frontal and temporal lobes than controls at intake. Longitudinally, reduction in frontal lobe volume was found only in patients, whereas temporal lobe reduction was also seen in controls. The association between volume reduction and symptom changes differed between patient groups, but volume reduction was associated with decline in some neurobehavioral functions in both groups. Exploratory analysis suggested that neuroleptic dose is correlated with changes in all 3 domains.

Conclusions: The existence of neuroanatomical and neurobehavioral abnormalities in patients with first-episode schizophrenia indicates that the brain dysfunction occurred before clinical presentation. However, there is also evidence of progression, in which anatomical changes may affect some clinical and neurobehavioral features of the illness in some patients.

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CROSS-SECTIONAL computed tomographic¹ and magnetic resonance imaging (MRI)²⁻⁶ studies have reported decreased brain volume in schizophrenia, affecting frontal^{2,3} and temporal⁴⁻⁶ regions. Abnormalities in patients with first-episode (FE) schizophrenia support a neurodevelopmental hypothesis because brain dysfunction precedes clinical presentation. However, a longitudinal design is necessary to examine the progressive deterioration suggested by the neurodegenerative hypothesis.

Computed tomographic follow-up studies reported no changes in neuroanatomy⁷⁻¹¹ or increased cerebrospinal fluid (CSF) in some patients.^{12,13} These studies had small samples of patients with chronic illness and limited scanning and measurement procedures. An MRI follow-up scan (at 1-2 years) of 13 FE patients and 8 controls¹⁴ found no ventricular changes. DeLisi et al¹⁵ found no consistent change in ven-

tricular size in 16 FE patients and 5 controls 2 years after intake. Decreased right temporal lobe volume was found in FE patients, but did not persist in a larger sample.¹⁶ A report on 20 of these patients and 5 controls who underwent rescanning during the next 4 years noted decreases in whole-brain (WB) volume and enlargement in left ventricular volume in FE patients.¹⁷ The limited number of longitudinal MRI studies leaves unresolved the question of progression and precludes the distinction of disease-related changes from those associated with normal aging.¹⁸⁻²¹

We have applied a reliable and validated MRI method for measuring brain volume,²² yielding parameters related to sex differences and aging^{18,19} and to clinical features in schizophrenia.²³⁻²⁷ We reported an age-related reduction in frontal and temporal lobe volumes in healthy men, and lower frontal and temporal lobe volumes in patients with schizophrenia. Temporal lobe volume correlated with impairment in memory and se-

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SUBJECTS AND METHODS

SUBJECTS

Forty patients (20 FE and 20 previously treated [PT]; 24 inpatients, 16 outpatients) and 17 healthy controls (**Table 1**), whose intake data has been previously reported, participated in the longitudinal MRI study.^{18,19,23-27} Two women were excluded because of movement during the MRI procedure. Subjects had the same clinical, neurobehavioral, and neuroanatomical measures at intake and follow-up.

Patients had a *DSM-IV* diagnosis of schizophrenia that had been established by measures detailed earlier.^{28,29} Healthy controls underwent standard evaluations.^{30,31} Subjects had no disorder that might affect brain function. Informed consent was obtained prior to participation.

PROCEDURES

Studies were conducted at intake and a mean±SD of 29.8±12.2 (range, 12-63) and 32.6±14.7 (range, 15-68) months later for patients and controls, respectively. The range of follow-up, while similar in both groups, varied across subjects. The MRI follow-up was planned for about 2 years after intake. However, logistics produced variability in scheduling unrelated to clinical status. Outpatient follow-up, with ratings at 6-month intervals, permitted assessment of the course of illness and ensured the absence of any new pathological process that might affect brain function. Patients with schizophreniform disorder met criteria for schizophrenia at follow-up.

At intake, FE patients were neuroleptic-naive, and PT patients had not received neuroleptics for at least 2 weeks.²⁵ Therapeutic interventions were clinically based, starting with typical neuroleptics and introducing atypical ones as indicated (**Table 1**). The medication record was updated

verity of negative symptoms. These were observed in FE patients, but the cross-sectional design is inadequate for establishing progression. The purpose of this prospective study was to assess changes in MRI parameters and relate them to clinical and neurobehavioral measures. Two hypotheses were tested. Patients with schizophrenia show a decline in frontal and temporal lobe volume that exceeds the age-related decline observed in controls. The degree of decline is correlated with worsening of negative symptoms, improvement of positive symptoms, and deteriorating neuropsychological performance. We also examined the association of medication dose with neuroanatomical changes.

RESULTS

MAGNETIC RESONANCE IMAGING

WB and CSF Volumes

Mean±SD volume estimates (in milliliters) for WB at intake were 1201.2±131.0, 1100.8±121.9, and 1079.4±121.3 for controls, FE patients, and PT patients, respectively. Volumes from the 2 sessions were highly intercorrelated for controls (0.98, 0.91, 0.85, 0.93 for WB, CSF, frontal lobe, and temporal lobe, respectively) and patients (0.94, 0.87,

between intake and follow-up using information from patients, caregivers, and medical records. Compliance was assessed by monitoring ingestion, supply, and visits, but not blood levels. Average daily dose was quantified as chlorpromazine-equivalent milligrams per kilogram of body weight units.³²

MRI MEASUREMENTS

Acquisition

Scans were acquired on the same, daily calibrated Signa 1.5-tesla scanner (General Electric, Milwaukee, Wis) with uniform protocol and software. Scanning was over the same epoch, with no relationship between scan date and volume estimates. Transaxial images were obtained in planes parallel to the orbitomeatal line. A multiecho acquisition sequence (TR=3000, TE=30, 80 milliseconds) was used, and slices were 5 mm thick without gaps.

Volumetric Measures

A segmentation algorithm²² used proton densities and T₂-weighted values of pixels within operator-defined regions of interest, and volumetric calculations in milliliters were performed for WB, CSF, and the frontal and temporal lobes. Brains were realigned in 3 dimensions and resliced along the anterior commissure/posterior commissure axis to correct for head tilt.¹⁹ The borders of the frontal and temporal lobes were drawn by 2 investigators using standardized reliable (intraclass correlation >0.85) procedures.^{19,26} The scans were blinded and mixed.

CLINICAL RATINGS

Assessments were conducted by trained investigators with established (intraclass correlation >0.85) procedures.^{25,29}

0.76, and 0.82) ($P<.001$). The diagnosis × session × hemisphere MANOVA for WB showed a significant main effect for diagnosis ($F[1,53] = 9.64, P=.003$), patients having lower volumes than controls. No other main effect or interaction was significant. No effects or interactions were significant for CSF. The MANOVAs comparing FE patients with PT patients showed no main effects or interactions.

Frontal and Temporal Lobe Volumes

The diagnosis × session × hemisphere MANOVA for frontal lobe volumes showed main effects for diagnosis ($F[1,53] = 5.67, P=.02$), patients having lower volumes than controls, and hemisphere ($T=0.31, F[1,53] = 16.51, P<.001$), higher volumes on the right. There was a diagnosis × session × hemisphere interaction ($T=0.13, F[1,53] = 6.71, P=.01$). Decomposition of this interaction indicated that the reduction in patients was more pronounced in the left (4.2% reduction) than the right hemisphere (2.8% reduction).

The same analysis for temporal lobe yielded significant main effects for diagnosis ($F[1,53] = 6.94, P=.01$, patients had lower volumes), session ($T=0.52, F[1,53] = 27.61, P<.001$, lower volume for follow-up), and hemisphere ($T=0.08, F[1,53] = 4.14, P=.05$, higher values in the right). There was also a diagnosis × session interaction ($T=0.08,$

CORRELATIONS OF CHANGE INDEXES WITH MEDICATION DOSE

For FE patients, higher medication dose was associated with greater reduction in frontal and temporal volume ($r = -0.75$ and -0.66 , respectively; $P < .001$). The corresponding correlations for PT patients were nil (0.03 and 0.16). For FE patients, higher dose was also associated with less improvement in affect ($r = 0.38$), alogia ($r = 0.38$), and avolition ($r = 0.40$) (all $P < .05$) and in the positive symptom of bizarre behavior ($r = 0.66$, $P < .01$), but with better improvement in delu-

sions ($r = -0.35$) and thought disorder ($r = -0.46$) (both $P < .05$). These correlations were negligible in PT patients except for hallucinations ($r = 0.50$, $P < .05$), higher dose being associated with less improvement. The correlations between neuroleptic dose and change in neuropsychological measures were generally negative for FE patients, higher dose being associated with relative worsening of neuropsychological functioning. These reached significance for abstraction-flexibility ($r = -0.45$), spatial memory ($r = -0.53$), and verbal ($r = -0.53$) and spatial ($r = -0.41$) abilities. The corresponding correlations for PT patients were not significant.

We also examined whether correlations between volume change and clinical change were mediated by dose. The partial correlations between volume and symptom change (neuroleptic dose partialled out) did not change significance. For example, the correlation between volume reduction in temporal lobe and improvement in thought disorder in the FE group was $r = 0.77$, and partialling out the dose resulted in a partial correlation $r_{vol \times symptom, dose} = 0.71$, both $P < .01$. Another potential source of variability is compliance with the medication regimen. This was quantified as the number of months in which medication was taken during the follow-up period (Table 1). No correlation was found between this measure and the average daily dosage of medication ($r = 0.14$, $P = .41$) nor was the correlation significant when the measure of months receiving medication was divided by the length of follow-up ($r = -0.01$, $P = .95$). Thus, it does not appear that less compliant patients were given higher doses. We performed regression analyses predicting regional brain volume change based on neuroleptic dose after controlling for compliance. The dose effects remained significant for both frontal ($P < .001$) and temporal ($P = .005$) volumes in FE patients, with no compliance or dose effects for the PT group.

Table 2: Mean (SD) Symptom Ratings for First-Episode (FE) and Previously Treated (PT) Patients at Intake and Follow-up*

	FE Patients		PT Patients	
	Intake (SD)	Follow-up (SD)	Intake (SD)	Follow-up (SD)
SANS				
AF	2.7 (1.4)	2.3 (1.1)	2.7 (1.1)	2.0 (0.9)
AL	2.5 (1.4)	2.1 (1.3)	2.7 (0.9)	2.3 (1.1)
AV	2.7 (1.2)	2.4 (1.3)	2.7 (1.1)	2.4 (1.1)
AN	3.4 (1.0)	2.9 (1.1)	3.4 (1.2)	3.0 (1.0)
AT	2.2 (0.8)	1.5 (0.6)	2.1 (1.3)	1.6 (0.8)
SAPS				
HA	3.3 (1.3)	1.7 (1.0)	2.3 (1.2)	1.9 (1.1)
DE	3.4 (1.0)	2.2 (1.3)	2.9 (0.9)	2.5 (1.1)
BI	1.7 (0.7)	1.4 (0.8)	1.9 (1.1)	1.7 (0.9)
TH	2.1 (1.0)	1.4 (0.7)	2.6 (1.2)	2.0 (1.1)

*SANS indicates Scale for Assessment of Negative Symptoms³⁹; SAPS, Scale for Assessment of Positive Symptoms.³⁴ See Figure 2 legend for an explanation of the subscale abbreviations.

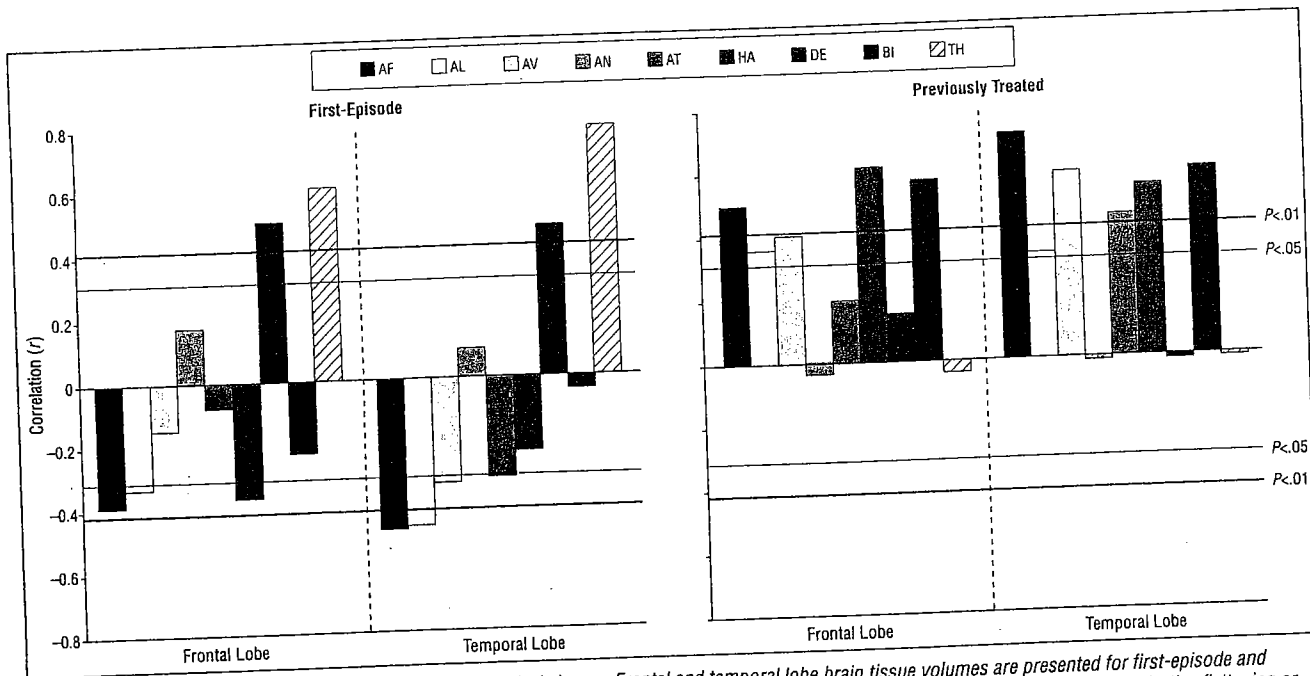


Figure 2. Correlations between brain volume change and clinical change. Frontal and temporal lobe brain tissue volumes are presented for first-episode and previously treated patients. Clinical change was measured by the Scale for the Assessment of Negative Symptoms subscales (AF indicates affective flattening or blunting; AL, alogia; AV, avolition-apathy; AN, anhedonia-asociality; and AT, attention) and by the Scale for the Assessment of Positive Symptoms subscales (HA indicates hallucinations; DE, delusions; BI, bizarre behavior; and TH, positive formal thought disorder). Since clinical improvement is reflected in lower severity ratings at follow-up, lower (and more negative) change scores (follow-up minus intake) reflect more improvement. For volumetric change measures, lower values reflect more tissue loss. Therefore, positive correlations indicate that higher rates of tissue loss are associated with higher rates of clinical improvement, whereas negative correlations indicate that tissue loss is associated with clinical worsening for that symptom.

