A Follow-up Magnetic Resonance Imaging Study of Schizophrenia

Relationship of Neuroanatomical Changes to Clinical and Neurobehavioral Measures

Raquel E. Gur, MD, PhD; Patricia Cowell, PhD; Bruce I. Turetsky, MD; Fiona Gallacher, MS; Tyrone Cannon, PhD; Warren Bilker, PhD; Ruben C. Gur, PhD

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±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.

Arch Gen Psychiatry. 1998;55:145-152

From the Mental Health Clinical Research Center, Neuropsychiatry Section, Department of Psychiatry, University of Pennsylvania School of Medicine, Philadelphia.

CROSS-SECTIONAL computed tomographic[1] and magnetic resonance imaging (MRI)[2-6] studies have reported decreased brain volume in schizophrenia, affecting frontal[2,3] and temporal[4-6] 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 neuroanatomy[7-11] 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 controls[14] found no ventricular changes. DeLisi et al[15] found no consistent change in ventricular 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-

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 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 algorithm[22] used proton densities and T_2-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]

---

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, 0.76, and 0.82) ($P<.001$). The diagnosis $\times$ session $\times$ 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 $\times$ session $\times$ 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 $\times$ session $\times$ 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 $\times$ session interaction ($T=0.08$,

Ratings included the Scales for Assessment of Negative Symptoms (SANS)[33] and Positive Symptoms (SAPS).[34]

NEUROBEHAVIORAL TESTING

The neuropsychological battery examined 8 domains. The tests are established and procedures for administration and scoring have been published.[35-38]

DATA ANALYSIS

None of the distributions differed significantly from normal and there were no outliers. The hypothesis testing requires several analyses, raising the issue of multiple comparison correction. As recommended,[39-41] we refrained from such corrections in planned analyses or when decomposing a significant higher order interaction. We applied a conservative Bonferroni correction for the exploratory analyses on medication effects.

The focus was MRI changes and their ability to predict clinical and neurobehavioral changes. We tested the hypothesis of higher rate of reduction of brain volume in patients compared with controls by examining changes between evaluations (intake and follow-up) in MRI volumes. We then examined whether changes differed for subgroups of patients (FE and PT). We have reported clinical scale changes[42] and follow-up neuropsychological measures.[43] Therefore, these analyses were considered corollary, aiming to ensure that this subsample shows the same effects.

The repeated volumes for WB, CSF (ventricular and sulcal), and frontal and temporal lobes were the dependent measures in repeated-measures multiple analyses of variance (MANOVAs), with diagnosis (controls vs patients) as a grouping factor and session (intake vs follow-up) as a within-group (repeated-measures) factor. Significance was tested using the Hotelling-Lawley Trace statistic.

The hypothesis of greater reduction in patients would be supported by a group × session interaction and subsequent demonstration with planned univariate contrasts that the reduction is greater in patients than controls. Subgroups (FE, PT, men, and women) were contrasted in subsequent analyses with the same design. For the clinical scales analyses were performed on the SANS and SAPS subscales, and for the neuropsychological evaluations scores were grouped into the 8 functions.[38]

The second hypothesis posits correlations between volume reduction and clinical and neurobehavioral changes. Change rates were calculated for MRI, clinical, and neurobehavioral measures as follow-up measures minus intake measures. To control for initial values (regression to the mean), these scores were corrected to the intake measure using linear regressions and divided by the intermeasure interval for an index of change per month. The neuroanatomical predictors of clinical and neurobehavioral change were determined by regression analyses, entering clinical and neuropsychological change scores as dependent measures to be predicted from change in WB compared with CSF volumes and temporal compared with frontal lobe volumes. For significant volume predictors, sequential regressions added duration of illness and age as regressors (in all cases the volume measures remained significant predictors). Repeated analysis without the interscan interval as divisor likewise did not diminish effects. Regarding directionality, the second hypothesis postulates that volume reduction is associated with worsening of (or less improvement in) negative symptoms and deterioration of neuropsychological performance related to affected regions (eg, executive functions and attention with frontal lobe reduction, and memory with temporal lobe reduction). Medication effects were examined by correlating the daily neuroleptic dose for the period between intake and follow-up with the change scores.

F[1,53]=4.19, P=.04), reflecting less volume reduction in patients (3.4% and 2.8% reduction for the left and right hemispheres, respectively) than controls (7.5% and 7.2%, respectively).

The MANOVAs comparing FE with PT patients on frontal lobe volumes showed a group × session interaction (T=0.17, F[2,52]=4.31, P=.02), and a group × session × hemisphere interaction (T=0.13, F[2,52]=3.34, P=.04). This reflected more pronounced left hemispheric reduction in FE than in PT patients (**Figure 1**). For temporal lobe volume, there was a group × session interaction (T=0.12, F[2,52]= 3.24, P=.05). First-episode patients showed greater bilateral tissue reduction (Figure 1).

CLINICAL RATINGS

The intake severity ratings on the SANS and SAPS, respectively, were 2.7±1.1 and 2.4±0.7 for FE patients and 2.8±1.0 and 2.2±0.8 for PT patients. The corresponding follow-up ratings were 1.9±1.2 and 1.0±0.9 for FE patients and 1.9±1.1 and 1.6±1.0 for PT patients. The session × clinical subscale ANOVA showed main effects of session for both SANS (F[1,37]=15.37, P<.001) and SAPS (F[1,37]= 27.31, P<.001), indicating improvement of negative and positive symptoms. With the FE vs PT grouping there were no

differences for SANS. For SAPS there was a group × session interaction (F[1,36]=4.46, P=.04), FE patients showing more improvement (**Table 2**).

NEUROBEHAVIORAL TESTING

The diagnosis × session × function ANOVA showed main effects of diagnosis (F[1,52]=22.33, P<.001; patients performing overall worse), function (F[7,364]=3.62, P=.001), and a function × diagnosis interaction (F[7,364]=6.65, P<.001), reflecting selective deficits in abstraction, attention, and verbal memory. Analyses contrasting FE with PT patients showed no effects. Thus, the neuropsychological measures were relatively stable over time and severity and pattern of deficit was similar in patient subgroups.

ASSOCIATIONS AMONG CHANGE INDEXES

MRI and Clinical Changes

For FE patients, reduced frontal and temporal volumes was correlated with less improvement in negative and some positive symptoms, and better improvement in delusions and thought disorder. For PT patients, volume reductions were correlated with greater improvement across most symp-

toms (**Figure 2**).Regression analyses entering change in frontal and temporal volumes as predictors of clinical change showed rate of temporal lobe reduction as the main unique predictor of clinical improvement. For FE patients, a lack of correlation between volume and clinical change was a unique predictor of improvement in negative symptoms. For positive symptoms, rate of temporal volume reduc-tion predicted improvement rate in thought disorder (β=.10, P=.007 [because the β weights are in "natural units," for every milliliter of temporal lobe tissue lost per month we expect a clinical improvement of .1 per month in thought disorder rating]). For the PT group, temporal lobe reduction predicted improved affective flattening (β=.19, P=.001) and avolition (β=.16, P=.02). These predictors remained significant when age or duration of illness were added to the model.

MRI and Neurobehavioral Changes

For controls there were modest correlations between reduced WB volume and decline in performance, significant for attention and verbal memory (r=0.49 and 0.53, respectively; df = 14, P<.05). The correlations for WB and CSF changes in FE and PT patients showed reciprocity between reduced WB volume and increased CSF volume associated with decline in performance. This was evident for verbal memory, where rate of reduction in WB volume was associated with worsening of performance in both FE (r=0.35, P<.05) and PT groups (r=0.62, P<.01); the opposite correlations were observed for CSF (r=−0.21, P=.38 and r=−0.55, P<.01, for FE and PT patients, respectively). The frontal and temporal volume changes showed positive correlations, less volume reduction being associated with less neuropsychological decline. The exception was a negative correlation between temporal lobe reduction and verbal functioning in the PT group (**Figure 3**).

Regression analyses showed that rate of temporal lobe reduction predicted worsening performance on language tests in controls (β=−.05, P=.02). In FE patients, the rate of frontal lobe reduction predicted decline in abstraction-flexibility and language (β=.19, P=.02, and β=.09, P=.03, respectively). Neither frontal nor temporal lobe changes uniquely predicted neuropsychological changes for the PT group.

Table 1. Demographic and Clinical Characteristics*

Characteristic	Controls (13 Men, 4 Women)	First-Episode Schizophrenia (11 Men, 9 Women)	Previously Treated Schizophrenia (12 Men, 8 Women)
Age, y	31.9 (8.9)	27.8 (8.2)	30.6 (7.7)
Education, No. of y	15.2 (2.1)	12.7 (2.2)	12.6 (1.8)
Paternal	13.4 (3.0)	11.8 (3.6)	13.5 (2.8)
Maternal	13.3 (2.5)	11.7 (3.0)	12.9 (2.2)
Duration, y	. . .	2.8 (3.8)	8.5 (4.7)†
Age at onset, y	. . .	24.8 (8.0)	21.5 (5.5)
Neuroleptic drugs‡			
Duration	. . .	. . .	2.7 (2.8)
Intake dose	. . .	. . .	601.7 (361.5)
Follow-up dose	. . .	259.9 (165.6)	515.3 (224.0)§
Months medicated	. . .	17.4 (8.1)	19.7 (14.1)

*Data are reported as mean (SD). Ellipses indicate not applicable.
†For previously treated vs first-episode schizophrenia, t=4.11, df=38, P<.001.
‡Neuroleptics are calculated as average daily dose in chlorpromazine-equivalent units (milligram per kilogram). Duration indicates number of years of cumulative neuroleptic use; intake dose, the average daily dose during the year prior to intake; and follow-up dose, the average daily dose between intake and follow-up measurements. The following neuroleptics were used: chlorpromazine (n=11), haloperidol (n=13), fluphenazine (n=13), loxapine succinate (n=4), mesoridazine besylate (n=7), molindone hydrochloride (n=6), perphenazine (n=9), pimozide (n=7), thioridazine hydrochloride (n=7), thiothixene (n=5), trifluoperazine (n=7), clozapine (n=5), and risperidone (n=6). Some patients were treated with more than 1 medication during the follow-up period.
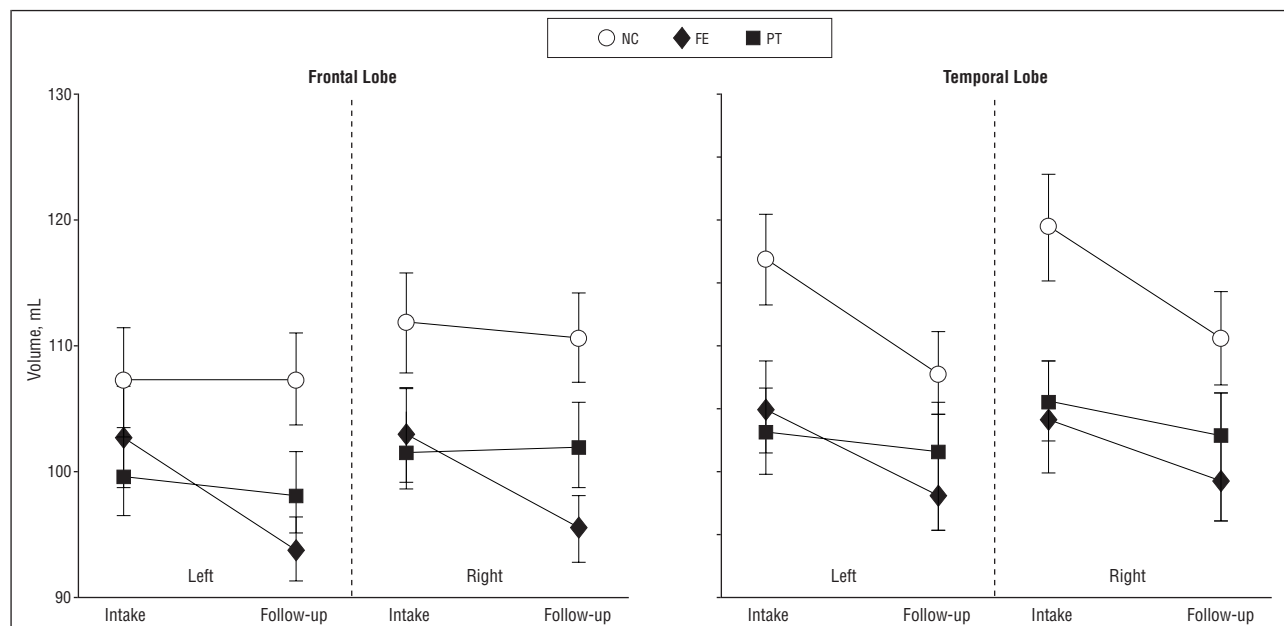§t=3.85, df=38, P<.001.

Figure 1. *Frontal and temporal hemispheric volumes at the 2 testing times. NC indicates normal controls; FE, first-episode patients; and PT, previously treated patients.*

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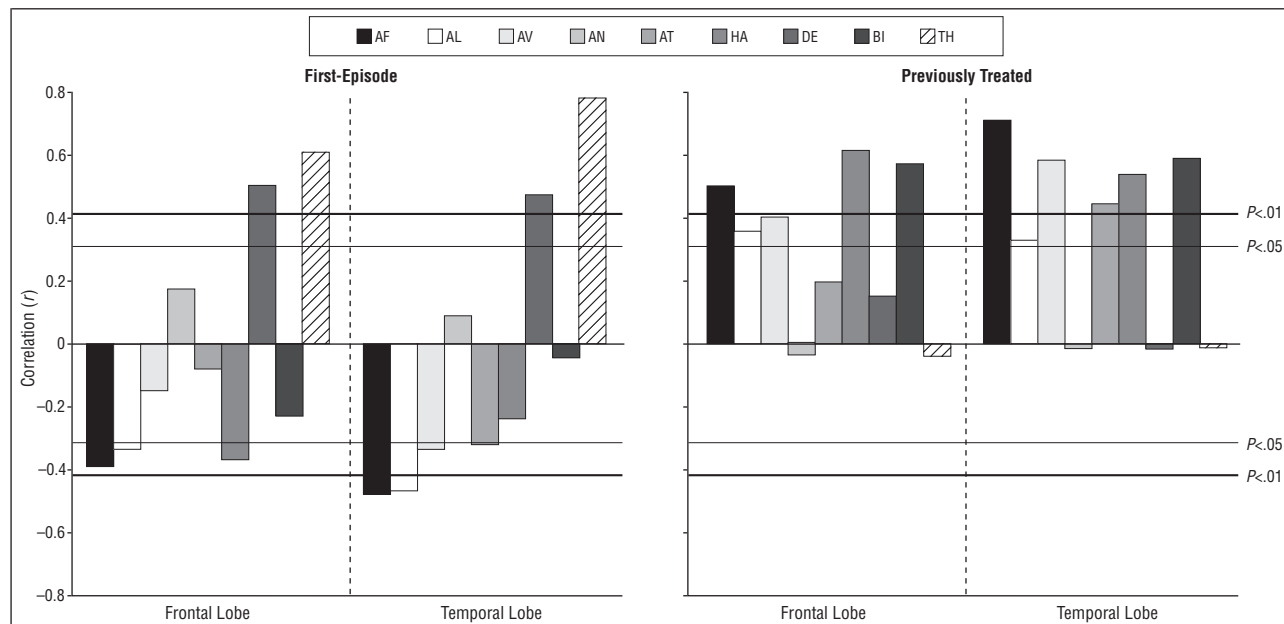
Table 2. Mean (SD) Symptom Ratings for First-Episode (FE) and Previously Treated (PT) Patients at Intake and Follow-up*

	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 Symptoms[33]; 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.*
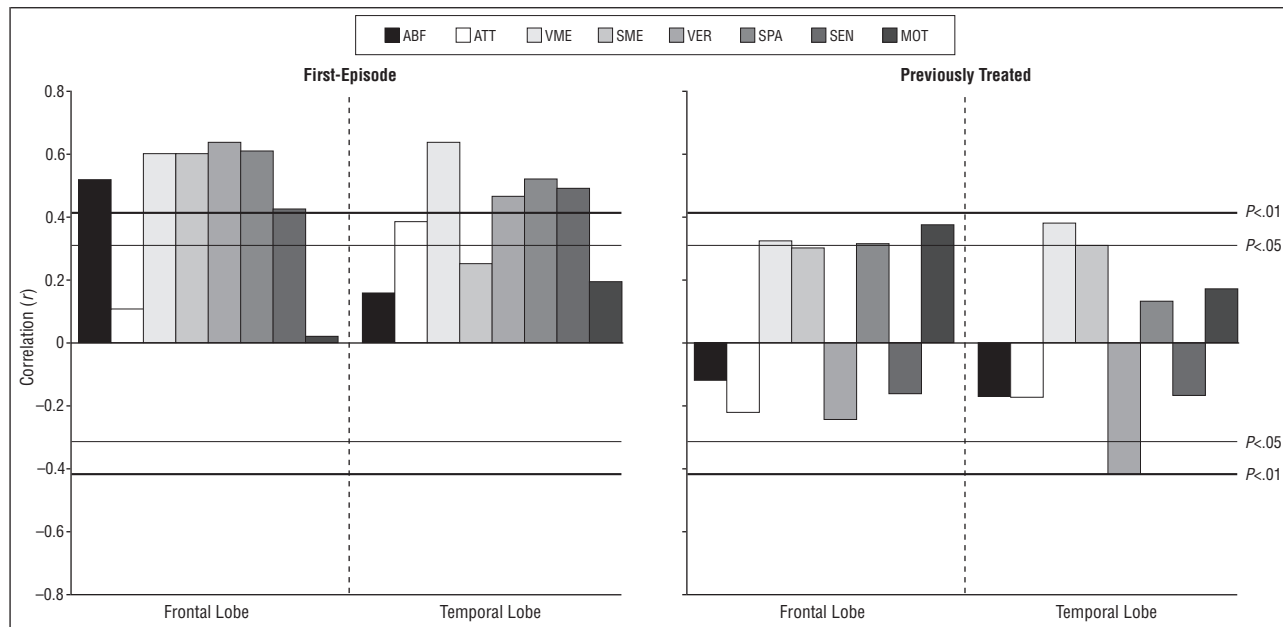
Figure 3. *Correlations between brain volume and neurobehavioral change. Frontal and temporal lobe brain tissue volumes are presented for first-episode and previously treated patients. The neurobehavioral domains include abstraction and flexibility (ABF), attention (ATT), verbal memory (VME), spatial memory (SME), verbal abilities (VER), spatial abilities (SPA), sensory (SEN), and motor (MOT). Positive correlations indicate less tissue loss associated with less neurobehavioral deterioration and negative correlations indicate less tissue loss associated with more deterioration (or, conversely, more tissue loss associated with less neurobehavioral deterioration).*

An ANOVA on clinical change scores showed better improvement in women across positive and negative symptoms ($F[1,37]=5.39, P=.02$). The ANOVA on the volume measures showed only a main effect of sex ($F[1,37]= 5.93, P=.02$), men having higher brain volumes than women. Similarly for both frontal and temporal lobes, only main effects of sex were observed ($F[1,37]=4.79, P=.04$ and $F[1,37]=6.03, P=.02$, respectively). On the neurobehavioral measures there were no sex differences in performance or change scores.

COMMENT

As in cross-sectional neuroanatomical studies,[25,26] our intake measures show that patients had lower WB and frontal and temporal lobe volumes. Also consistent with earlier reports, the volumes were similar in FE and PT patients. Clinically, the patients' presentation was comparable to that observed in larger samples.[42,43] The neuropsychological profile was also similar to that reported in schizophrenia, showing differential deficits in abstraction, attention, and verbal memory[35-38] and no differences between FE and PT patients.[36] These consistencies suggest that this subsample resembles both the larger sample and samples from other centers regarding the main dependent measures.

Our longitudinal clinical and neurobehavioral results are also consistent with earlier studies. Both groups of patients showed the expected clinical improvement associated with treatment, as in our larger sample[42] and other samples.[44-46] Also corresponding with follow-up studies, improvement was more pronounced for positive symptoms, particularly hallucinations and delusions, than for negative symptoms. This was more evident in FE than in PT patients. Regarding neurobehavioral measures, the neuropsychological profile remained relatively stable in pa-

tients and controls.[47-49] This stability is noticeable against a background of improvement in symptoms for patients, suggesting that neurobehavioral deficits are present at the onset of illness and do not change systematically over time. These consistencies with earlier reports justify some confidence in this sample's representativeness and the validity of our clinical and neuropsychological parameters.

The longitudinal neuroanatomical findings are harder to place in the context of earlier reports because of the paucity of such research and the lack of consistent findings in the literature. Direct comparison of longitudinal with cross-sectional studies is problematic because intersubject variability in the latter is likely to cause an underestimate of individual change rates. Our study found reductions in the volumes of both frontal and temporal lobes in patients, but there was also a temporal lobe volume reduction in controls. Reduction in controls could be consistent with cross-sectional studies indicating age-related decline.[18-21] The rate of decrease is difficult to estimate from cross-sectional studies, may vary across the lifespan,[50] and is more pronounced for men,[19] who made up the majority of our controls. Our ability to detect subtle changes (4%-9%) may reflect the power of the within-subjects design and the reliability of the measures.[19,26] However, without sufficient longitudinal data available, this finding should be interpreted with caution and replicated. The more pronounced reduction in frontal and temporal lobes in FE than in PT patients may suggest that neuroanatomical changes are more evident early in psychosis. The lack of difference between patient groups at intake may reflect sample variability, since this contrast is cross-sectional. Thus, the expectation of greater volume decline in patients than controls was not supported for the temporal lobe, but for the frontal lobe the FE group shows volume reduction not observed in controls or in PT patients.

Correlations between volume change and clinical and neurobehavioral changes have not been examined before. Our findings generally support an association between brain and behavioral changes. Some results, however, were not predicted and may appear counterintuitive. We attempted to control statistically for initial values, age, illness duration, and medication dose. A higher rate of reduction in frontal and temporal lobe volumes was associated with less improvement in negative symptoms and hallucinations in FE patients, but in both groups it was associated with greater improvement in other positive symptoms. The association between lower brain volumes and a greater severity of symptoms has been reported in cross-sectional studies.[5,6,26] The association between volume reduction and improvement in some positive symptoms is new, and hence tentative and requiring replication. An association in schizophrenia between improvement in positive symptoms and reduced volume in regions with presumed neuropathological characteristics has not been established. Such effects are reported in irritative lesions, where symptomatic improvement is associated with suppression or removal of diseased tissue. Volume reductions have been interpreted as atrophy, reflecting neurodegeneration or neural injury, yet postmortem studies in schizophrenia do not show astrocytosis[51,52] but possibly reduced cell size.[53] Neuroleptics may contribute to further reduction in neuronal density, as suggested in animal studies,[54] but there is also evidence that neuroleptics may increase neuronal size in specific regions.[55]

Neurobehaviorally, in both healthy subjects and patients we found positive correlations between volume change and neuropsychological change, volume reduction being associated with decreased performance. While there are no earlier longitudinal studies for comparison, these results are consistent with studies showing a correlation between brain volume and neurocognitive measures.[38] Note that no significant overall change in cognitive performance occurred for patients, but those with temporal volume reduction also had greater reduction in neurocognitive performance.

Medication effects, in this naturalistic treatment setting, are tentative and in need of verification with controlled therapeutic interventions. In exploratory evaluation, we found that for FE patients a greater rate of reduction in frontal and temporal lobe volumes was associated with improvement of delusions and thought disorder and higher neuroleptic dose. These changes were concomitant with less improvement in affective flattening and alogia. However, neuroleptic dose alone does not account for the correlations between reduced temporal lobe volume and clinical improvement. The anatomical changes remained significant predictors of clinical improvement when medication dose was partialled out and when age or duration of illness were included in the regression analysis. The change values were corrected for initial severity, making less plausible the alternative explanation that the initially sicker patients received higher doses and also had an accelerated process of neuroanatomical and neurobehavioral deterioration. Medication regimens were individualized and related to treatment response. However, the effects were also maintained when controlling for compliance, and this militates against the possibility that the less compli-

ant patients were given higher doses and represent a subgroup with neurodegenerative features. Still, we can not establish causality without systematic manipulation of medication and dose.

There are several limitations to this study. While the sample has adequate power for testing hypotheses on global measures of anatomical, clinical, and neurobehavioral changes, larger samples are needed to probe with confidence more detailed and specific low-magnitude correlations. Another limitation is the choice of a follow-up interval determined by time rather than symptom severity. This design was chosen to permit some variability in the outcome measures while maintaining a standard interval. However, as presented in Table 2, patients were moderately symptomatic at intake and had mild symptoms or remission of symptoms at follow-up. The findings regarding medications are also tentative because data on medication prior to admission for PT patients is retrospective, and the choice of medication and dose during follow-up were clinically determined. Targeted sampling may permit comparison of informative groups of patients treated with specific medications. There is no evidence that neuroleptic treatment is associated with neuropathological changes in postmortem studies of schizophrenia.[56]

Our results do not contradict the neurodevelopmental hypothesis, which stipulates an early insult and presence of abnormalities at clinical presentation. However, we found evidence for continued structural changes in some patients. They showed reduction in frontal lobe volume within the limited age and interscan time interval, but for the temporal lobe, healthy subjects also showed volume reduction. This underscores the need to examine effects of normal aging to put in perspective findings in schizophrenia, where aging operates on compromised neural substrates undergoing concomitant disease- and treatment-related changes. In FE patients, we are perhaps documenting the psychotic process at a virulent phase and possibly for this reason we obtain associations between rate of reduction in brain volume and clinical improvement in positive symptoms. In PT patients, these associations are more general. The time course of these changes can be established by more frequent measurements in early phases of illness. The role of neuroleptics can be elucidated through controlled medication regimens. Such studies may help explain why negative symptoms, the manifestations of core pathological processes[57] emanating perhaps from neurodevelopmental aberrations,[58,59] are resistant to treatment with typical neuroleptics, whereas positive symptoms, which reflect lack of inhibition,[60] improve. The psychotic process may itself induce neurotoxic effects with consequent structural changes.[60]

REFERENCES

1. Coffman JA. Computed tomography in psychiatry. In: Andreasen NC, ed. *Brain Imaging: Applications in Psychiatry*. Washington, DC: American Psychiatric Press; 1989:1-65.
2. Andreasen NC, Ehrhardt JC, Swayze V II, Alliger RJ, Yuh WTC, Cohen G, Ziebell S. Magnetic resonance imaging of the brain in schizophrenia: the pathophysiologic significance of structural abnormalities. *Arch Gen Psychiatry*. 1990;47:35-44.
3. Breier A, Buchanan RW, Elkashef A, Munson RC, Kirkpatrick B, Gellad F. Brain morphology and schizophrenia: a magnetic resonance imaging study of limbic, prefrontal cortex, and caudate structures. *Arch Gen Psychiatry*. 1992;49:921-926.
4. Suddath RL, Casanova MF, Goldberg TE, Daniel DG, Kelsoe JR, Weinberger DR. Temporal lobe pathology in schizophrenia. *Am J Psychiatry*. 1989;146:464-472.
5. Barta PE, Pearlson GD, Powers RE, Richards SS, Tune LE. Auditory hallucinations and smaller superior temporal gyral volume in schizophrenia. *Am J Psychiatry*. 1990;147:1457-1462.
6. Shenton ME, Kikinis R, Jolesz FA, Pollak SD, LeMay M, Wible CG, Hokama H, Martin J, Metcalf D, Coleman M, McCarley RW. Abnormalities of the left temporal lobe and thought disorder in schizophrenia: a quantitative magnetic resonance imaging study. *N Engl J Med*. 1992;327:604-612.
7. Nasrallah HA, Olson SC, McCalley-Whitters M, Chapman S, Jacoby CG. Cerebral ventricular enlargement in schizophrenia. *Arch Gen Psychiatry*. 1986;43:157-159.
8. Pillowsky B, Juliano DM, Bigelow LB, Weinberger DR. Stability of CT scan findings in schizophrenia: results of an 8 year follow-up study. *J Neurol Neurosurg Psychiatr*. 1988;51:209-213.
9. Vita A, Sacchetti E, Valvassori G, Cazzullo CL. Brain morphology in schizophrenia: a 2 to 5 year CT scan follow-up study. *Acta Psychiatr Scand*. 1988;78:618-621.
10. Hoffman WF, Ballard L, Turner EH, Casey DE. Three-year follow-up of older schizophrenics: extrapyramidal syndromes, psychiatric symptoms, and ventricular brain ratio. *Biol Psychiatry*. 1991;30:913-926.
11. Sponheim SR, Iacono WG, Beiser M. Stability of ventricular size after the onset of psychosis in schizophrenia. *Psychiatry Res Neuroimaging*. 1991;40:21-29.
12. Kemali D, Maj M, Galderisi S, Milici N, Dalvati A. Ventricle-to-brain ratio in schizophrenia: a controlled follow-up study. *Biol Psychiatry*. 1989;26:753-756.
13. Woods BT, Yurgelum-Todd D, Benes FM, Frankenburg FR, Pope HG Jr, McSparren J. Progressive ventricular enlargement in schizophrenia: comparison to bipolar affective disorder and correlation with clinical course. *Biol Psychiatry*. 1990; 27:341-352.
14. Degreef G, Ashtari M, Bogerts B, Bilder RM, Jody DN, Alvir JM, Lieberman JA. Volumes of ventricular system subdivisions measured from magnetic resonance images in first-episode schizophrenic patients. *Arch Gen Psychiatry*. 1992; 49:531-537.
15. DeLisi LE, Hoff AL, Schwartz JE, Shields GW, Halthore SN, Gupta SM, Henn FA, Anand AK. Brain morphology in first-episode schizophrenic-like psychotic patients: a quantitative magnetic resonance imaging study. *Biol Psychiatry*. 1991; 29:159-175.
16. DeLisi LE, Stritzke P, Riordan H, Holan V, Boccio A, Kushner M, McClelland J, Van Eyl O, Anand A. The timing of brain morphological changes in schizophrenia and their relationship to clinical outcome. *Biol Psychiatry*. 1992;31:241-254.
17. DeLisi LE, Tew W, Xie S, Hoff AL, Sakuma M, Kushner M, Lee G, Shedlack K, Smith AM, Grimson R. A prospective follow-up study of brain morphology and cognition in first-episode schizophrenic patients: preliminary findings. *Biol Psychiatry*. 1995;38:349-360.
18. Gur RC, Mozley PD, Resnick SM, Gottlieb GE, Kohn M, Zimmerman R, Herman G, Atlas S, Grossman R, Berretta D, Erwin R, Gur RE. Gender differences in age effect on brain atrophy measured by magnetic resonance imaging. *Proc Natl Acad Sci U S A*. 1991;88:2845-2849.
19. Cowell PE, Turetsky BT, Gur RC, Grossman RI, Shtasel DL, Gur RE. Sex differences in aging of the human frontal and temporal lobe. *J Neurosci*. 1994;14: 4748-4755.
20. Coffey C, Wilkinson W, Parashos I, Soady S, Sullivan R, Patterson L, Figiel G, Webb M, Spritzer C, Djang W. Quantitative cerebral anatomy of the aging human brain: a cross-sectional study using magnetic resonance imaging. *Neurology*. 1992;42:527-536.
21. Condon B, Grant R, Hadley D, Lawrence A. Brain and intracranial cavity volumes: in vivo determination by MRI. *Acta Neurol Scand*. 1988;78:387-393.
22. Kohn MI, Tanna NK, Herman GT, Resnick SM, Mozley PD, Gur RE, Alavi A, Zimmerman RA, Gur RC. Analysis of brain and CSF volumes from magnetic resonance imaging: methodology, reliability and validation. *Radiology*. 1991;178:115-122.
23. Gur RE, Mozley PD, Resnick SM, Shtasel D, Kohn M, Zimmerman R, Herman G, Atlas S, Grossman R, Erwin R, Gur RC. Magnetic resonance imaging in schizophrenia, I: volumetric analysis of brain and cerebrospinal fluid. *Arch Gen Psychiatry*. 1991;48:407-412.
24. Mozley PD, Gur RE, Shtasel DL, Resnick SM, Richards J, Kohn M, Grossman R, Herman G, Gur RC. Magnetic resonance imaging in schizophrenia, II: relationship to clinical measures. *Schizophr Res*. 1994;12:195-203.
25. Gur RE, Mozley PD, Shtasel DL, Cannon TD, Gallacher F, Turetsky B, Grossman R, Gur RC. Clinical subtypes of schizophrenia differ in brain and cerebrospinal fluid volume. *Am J Psychiatry*. 1994;151:343-350.
26. Turetsky BT, Cowell PE, Gur RC, Grossman RI, Shtasel DL, Gur RE. Frontal and temporal lobe brain volumes in schizophrenia: relationship to symptomatology and clinical subtype. *Arch Gen Psychiatry*. 1995;52:1061-1070.
27. Cowell PE, Kostianovsky DJ, Gur RC, Turetsky BI, Gur RE. Sex differences in neuroanatomical and clinical correlations in schizophrenia. *Am J Psychiatry*. 1996; 153:799-805.
28. Spitzer RL, Williams JBW, Gibbon M. *Structured Clinical Interview for DSM-III-R, Patient Version (SCID-P)*. New York, NY: New York State Psychiatric Institute; 1986.
29. Gur RE, Mozley D, Resnick SM, Levick S, Erwin R, Saykin AJ, Gur RC. Relations among clinical scales in schizophrenia: overlap and subtypes. *Am J Psychiatry*. 1991;148:472-478.
30. Spitzer RL, Williams JBW, Gibbon M. *Structured Clinical Interview for DSM-III-R: Non-Patient Version (SCID-NP)*. New York, NY: New York State Psychiatric Institute; 1989.
31. Shtasel DL, Gur RE, Mozley PD, Richards J, Taleff MM, Heimberg C, Gallacher F, Gur RC. Volunteers for biomedical research: recruitment and screening of normal controls. *Arch Gen Psychiatry*. 1991;48;1022-1025.
32. Kaplan HI, Sadock BI. *Synopsis of Psychiatry*. 6th ed. Baltimore, Md: Williams & Wilkins; 1992:639.
33. Andreasen NC. *The Scale for the Assessment of Negative Symptoms (SANS)*. Iowa City, Iowa: The University of Iowa; 1984.
34. Andreasen NC. *The Scale for the Assessment of Positive Symptoms (SAPS)*. Iowa City, Iowa: The University of Iowa; 1984.
35. Saykin AJ, Gur RC, Gur RE, Mozley D, Mozley LH, Resnick SM, Kester DB, Stafiniak P. Neuropsychological function in schizophrenia: selective impairment in memory and learning. *Arch Gen Psychiatry*. 1991;48:618-624.
36. Saykin AJ, Shtasel DL, Gur RE, Kester DB, Mozley LH, Stafiniak P, Gur RC. Neuropsychological deficits in neuroleptic-naive, first-episode schizophrenic patients. *Arch Gen Psychiatry*. 1994;51:124-131.
37. Saykin AJ, Gur RC, Gur RE, Shtasel DL, Flannery KA, Mozley LH, Malamut BL, Watson B, Mozley PD. Normative neuropsychological test performance: effects of age, education, gender and ethnicity. *Appl Neuropsychol*. 1995;2:79-88.
38. Kareken DA, Gur RC, Mozley PD, Mozley LH, Saykin AJ, Shtasel DL, Gur RE. Cognitive functioning and neuroanatomic volume measures in schizophrenia. *Neuropsychology*. 1995;9:211-219.
39. Rothman KJ. No adjustments are needed for multiple comparisons. *Epidemiology*. 1990;1:43-46.
40. Miettinen OS. *Theoretical Epidemiology*. New York, NY: John Wiley & Sons; 1985: 114-116.
41. Walker AM. Reporting the results of epidemiologic studies. *Am J Public Health*. 1986;75:577-558.
42. Szymanski S, Cannon TD, Gallacher F, Erwin R, Gur RE. The course of treatment response in first-episode and chronic schizophrenia. *Am J Psychiatry*. 1996; 153:519-525.
43. Shtasel DL, Gur RE, Gallacher F, Heimberg C, Cannon TD, Gur RC. Phenomenology and functioning in first episode schizophrenia. *Schizophr Bull*. 1992;18:449-462.
44. Ram R, Bromet EG, Eaton WW, Pato C, Schwartz JE. The natural course of schizophrenia: a review of first admission studies. *Schizophr Bull*. 1992;18:182-207.
45. Eatpm WW, Thara R, Federman B, Melton B, Liang K. Structure and course of positive and negative symptoms in schizophrenia. *Arch Gen Psychiatry*. 1995; 52:127-134.
46. Lieberman JA, Alvir JA, Woerner M, Degreef G, Bilder R, Ashtari M, Bogarts B, Mayerhoff D, Geisler S, Loebel A, Levy DL, Hinrichsen G, Szymanski S, Chakos M, Koreen A, Borenstein M, Kane J. Prospective study of psychobiology in first-episode schizophrenia at Hillside Hospital. *Schizophr Bull*. 1992;18:351-371.
47. Nopoulos P, Flashman L, Flaum M, Arndt S, Andreasen N. Stability of cognitive functioning early in the course of schizophrenia. *Schizophr Res*. 1994;14:29-37.
48. Goldberg TE, Hyde TM, Kleinman JE, Weinberger DR. Course of schizophrenia: neuropsychological evidence for a static encephalopathy. *Schizophr Bull*. 1993; 19:797-804.
49. Bilder RM, Lipschutz-Broch L, Reiter G, Geisler SH, Mayerhoff DI, Lieberman JA. Intellectual deficits in first-episode schizophrenia: evidence for progressive deterioration. *Schizophr Bull*. 1992;18:437-448.
50. Jernigan TL, Trauner DA, Hesselink JR, Tallal PA. Maturation of human cerebrum observed in vivo during adolescence. *Brain*. 1991;114:2037-2049.
51. Shapiro RM. Regional neuropathology in schizophrenia: where are we? where are we going? *Schizophr Res*. 1993;10:187-239.
52. Arnold SE, Franz BR, Trojanowski JQ, Moberg PJ, Gur RE. Glial fibrillary acidic protein–immunoreactive astrocytosis in elderly patients with schizophrenia and dementia. *Acta Neuropathol*. 1996;91:269-277.
53. Arnold SE, Franz BR, Gur RC, Gur RE, Shapiro RM, Moberg PJ, Trojanowski JQ. Smaller neuron size in schizophrenia in hippocampal subfields that mediate cortical-hippocampal interactions. *Am J Psychiatry*. 1995;152:738-748.
54. Jeste DV, Lohr JB, Manley M. Study of neuropathological changes in the striatum following 4, 8 and 12 months of treatment with fluphenazine in rats. *Psychopharmacology*. 1992;106:154-160.
55. Benes FM, Paskevich PA, Domesick V. Haloperidol-induced plasticity of axon terminals in rat substantia nigra. *Science*. 1983;221:969-971.
56. Baldessarini RJ, Hegarty JD, Bird ED, Benes FM. Meta-analysis of postmortem studies of Alzheimer's disease–like neuropathology in schizophrenia. *Am J Psychiatry*. 1997;154:861-863.
57. Carpenter WT, Heinrichs DW, Wagman AMI. Deficit and nondeficit forms of schizophrenia: the concept. *Am J Psychiatry*. 1988;145:578-583.
58. Weinberger DR. Implications of normal brain development for the pathogenesis of schizophrenia. *Arch Gen Psychiatry*. 1987;44:660-669.
59. Wyatt RJ. Neurodevelopmental abnormalities and schizophrenia: a family affair. *Arch Gen Psychiatry*. 1996;53:11-15.
60. Olney JW, Farber NB. Glutamate receptor dysfunction and schizophrenia. *Arch Gen Psychiatry*. 1995;52:998-1007.