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## Lack of Clinically Significant Gross Structural Abnormalities in MRIs of Older Patients With Schizophrenia and Related Psychoses

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*The authors examined the reports of MRI brain studies of 69 patients with DSM-III-R–diagnosed psychotic disorders (30 early-onset and 24 late-onset schizophrenia patients and 15 with other psychoses) and 41 normal comparison subjects. Participants' ages ranged from 45 to 87 years. A qualitative rating scheme determined type and severity of clinically detectable abnormalities, including volume loss, infarcts, lacunae, and white matter hyperintensities. In this clinically well-characterized sample, the vast majority of the MRIs were within normal limits. There were no significant differences between psychosis patients and normal comparison subjects or between early-onset and late-onset schizophrenia patients in frequency, type, or severity of gross structural abnormalities. The results indicate that late-onset schizophrenia and related disorders can exist without clinically significant gross structural abnormalities in the brain.*

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The appearance of schizophrenia and other psychoses for the first time late in life is a puzzling phenomenon, and there is considerable controversy about the nature and cause of these clinical entities. Some groups have suggested that late-onset schizophrenia is secondary to various brain lesions. Several authors have noted an association between late-onset schizophrenia and white matter disease or vascular lesions.<sup>1–3</sup> Similar suggestions have been made regarding the etiology of late-onset depression.<sup>4–8</sup> If structural brain abnormalities such as those apparent on magnetic resonance imaging are a contributory factor or are, in fact, the cause of at least a proportion of late-onset schizophrenia cases, then late-onset schizophrenia may, in fact, be different from the early-onset form of the disease, both in clinical presentation and etiology.

The current leading hypothesis regarding the etiology of schizophrenia is that it is a neurodevelopmental disorder.<sup>9,10</sup> It is possible that schizophrenia with a late onset is less related to neurodevelopmental factors than it is to specific brain abnormalities or insults that are

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acquired later in life. This notion would be supported if certain brain abnormalities associated with age (such as white matter hyperintensities on T<sub>2</sub>-weighted MR images) were more frequent in individuals with late-onset schizophrenia.

A few years ago, however, we published a preliminary report that argued against the theory that late-onset schizophrenia was caused by brain abnormalities acquired later in life.<sup>11</sup> In that report, the MRI films of 9 schizophrenia patients were compared with the films of 9 normal comparison subjects on qualitative measures of ventricular enlargement and white matter abnormalities. The two groups did not differ on either measure. A recent report by Howard et al.<sup>12</sup> extended those findings to a sample of 38 "late paraphrenic" patients and 31 healthy volunteers. In that study, the two groups were compared on measures of periventricular and deep white matter hyperintensities and subcortical gray matter changes; there were no significant differences between the groups on any of the measures. Late paraphrenia is an ill-defined diagnostic category that usually includes not only late-onset schizophrenia, but also late-onset paranoia (or delusional disorder) as well as other unspecified psychotic disorders.<sup>13</sup>

In light of the current controversy in the literature, we asked the question: Is late-onset psychosis (including schizophrenia) associated with an unusually high prevalence of gross structural brain abnormalities that are detectable on clinical magnetic resonance imaging scans? To answer this question we studied an expanded subject database that included groups of both early-onset and late-onset schizophrenia patients as well as other early-onset and late-onset psychosis patients and normal comparison subjects. We sought to restrict the study to a group of patients who were carefully diagnosed and clinically well characterized. We hypothesized that if late-onset psychosis were secondary to gross structural brain abnormalities, then, in this larger sample, late-onset psychosis patients would show a greater number of clinically significant structural brain abnormalities compared with early-onset schizophrenia patients and normal comparison subjects.

## METHODS

Sixty-nine middle-aged and elderly consenting patients with schizophrenia or related psychoses were recruited from the San Diego Veterans Affairs Medical Center, University of California San Diego Psychiatry Outpatient Services, San Diego County mental health services, and private physicians. Exclusion criteria were presence of dementia (by DSM-III-R<sup>14</sup> criteria), seizure disorder,

head injury with loss of consciousness for more than 30 minutes, substance abuse or dependence that could be causally related to the psychosis, clinical evidence (based on history and physical examination) of stroke or brain tumor, and a severe major medical illness (including hypertension) that required recent hospitalization.

Details of the clinical assessment have been described previously.<sup>15</sup> Briefly, each subject was administered the Structured Clinical Interview for DSM-III-R<sup>16</sup> (SCID) by one of the board-certified or board-eligible geriatric psychiatry fellows. Interrater reliability for diagnostic category on the SCID was assessed for a random sample of 20 subjects. The kappa value was 0.944 (SE = 0.073, Z = 12.87, P < 0.001). At least two board-certified psychiatrists had to agree on the DSM-III-R<sup>14</sup> diagnosis at a diagnostic conference; if there were questions about the diagnosis, that particular subject was not included in the study. Because a diagnosis of late-onset psychosis may be problematic, we excluded patients from this group for whom there was any evidence of psychosis before the age of 45, as indicated by any of the following: appearance of prodromal symptoms or documentation of functional decline; any psychiatric hospitalization; or treatment with neuroleptics, antidepressants, or lithium for more than a month. None of the patients in this study had been chronically institutionalized; patients who lived in board-and-care facilities were, however, included.

Normal comparison subjects were 41 individuals over the age of 45 who had no evidence of a major psychiatric disturbance or neurological disorder and who met the same exclusion criteria as the patients. They were drawn from among volunteers recruited at the Veterans Affairs Medical Center and through local advertisements. The study sample included 9 patients and 9 comparison subjects whose MRI data (analyzed differently) had been reported previously.<sup>11</sup>

## Clinical Evaluation

A structured neurological and other medical history was obtained, and a physical examination was administered to all patients and normal comparison subjects. Any patient in whom a neurologic or other major medical disorder was suspected also received appropriate laboratory evaluations (such as thyroid function tests or a serological test for syphilis).

Several clinical rating instruments were used to assess psychiatric and cognitive status. These instruments included the Brief Psychiatric Rating Scale<sup>17</sup> (BPRS), Scales for the Assessment of Positive and Negative Symptoms<sup>18,19</sup> (SAPS and SANS, respectively), Mini-Mental State Examination<sup>20</sup> (MMSE), and Dementia Rating

Scale<sup>21</sup> (DRS). Interrater reliability, as assessed with intraclass correlation coefficients, was 0.77 or higher on all clinical rating scales. All raters were blind to other clinical information.

#### MRI and Clinical Reports

MRIs were obtained on all those subjects 1) who entered the Geriatric Psychiatry Clinical Research Center between September 1992 and December 1994; 2) who consented to the procedure; and 3) for whom an MRI was not contraindicated (as by the presence of a pacemaker or a metal implant). There were no significant differences between those patients or normal comparison subjects who received MRIs ( $n = 110$ ) and those who did not ( $n = 57$ ) in terms of age, education, psychiatric diagnosis, duration of psychiatric illness, current neuroleptic dose, or on any of the clinical rating scales. When the entire subject pool was considered together, however, there was a slight but significant difference in mean age between those who received MRIs and those who did not (MRI: 62.6 years; no MRI: 59.7 years; Mann-Whitney  $U$ -test,  $P = 0.02$ ).

All scans were obtained with a GE 1.5-tesla superconducting magnet. Forty scans, obtained before March 1994, were dual-echo series with TR = 2,000, TE = 25, 70; sections 5 mm thick were collected in the axial plane throughout the entire brain; there were 2.5-mm gaps between adjacent sections. The remaining 70 scans were acquired by using a fast spin-echo protocol (TR = 3,000, 3,800; TE = 17, 102), which was adopted in March 1994 and involved acquiring consecutive 4-mm-thick sections in the coronal plane with no gap. Signal hyperintensities were equally visible in the two methods. The relative proportions of normal comparison subjects and psychosis patients were similar for the two protocols.<sup>22</sup> Acquired images were read by experienced board-certified neuroradiologists. The neuroradiologists were not given any special instructions, and they dictated the reports as they would for any clinical patient.

These clinical reports were subsequently read, blind to diagnosis or any other subject characteristics. Each report was rated for the presence of the following three structural brain characteristics: 1) volume loss (central volume loss, peripheral volume loss, ventricular enlargement), 2) infarcts, and 3) white matter hyperintensities on T<sub>2</sub>-weighted images. We used a scale similar to that employed by Coffey *et al.*,<sup>23</sup> with the exception that in our use of the scale for volume loss we collapsed the scores of 0 ("none") and 1 ("slight") into one score of 0, yielding a 4-point rather than a 5-point scale.

Severity ratings for volume loss, ventricular enlargement, and white matter hyperintensities were obtained using the exact words contained in the narrative re-

ports. Volume loss described in the reports was thus rated on a 4-point scale (0 = "no" volume loss or "slight" volume loss and no ventricular enlargement other than that judged to be within normal limits for age; 1 = "mild" volume loss and/or "mild" ventricular enlargement; 2 = "moderate" volume loss and/or "moderate" ventricular enlargement; 3 = "severe" or "extreme" volume loss or "severe" ventricular enlargement). Infarcts were rated as either absent (0 = none) or present (1 = any infarct regardless of location or number). White matter hyperintensities noted in the reports were rated on a 4-point scale (0 = no abnormalities; 1 = "mild," "focal," or "punctate" abnormalities; 2 = "moderate," "diffuse," or "patchy" abnormalities; 3 = "severe," "confluent," or "extensive" abnormalities). Subject characteristics were then attached to the overall abnormality rating, and appropriate statistical analyses were performed.

#### Statistical Analysis

Psychosis patients were compared with normal subjects on continuous variables by using the Mann-Whitney  $U$ -test for independent samples, and on categorical variables by using either the Pearson chi-square test or, if there were fewer than 5 subjects expected per cell, Fisher's exact probability test. Early-onset schizophrenia patients and late-onset schizophrenia patients were similarly compared on the same variables.

In order to determine if study participants (patients and control subjects) who had abnormal scans differed from their counterparts with normal scans, we collapsed the groups of subjects across abnormality ratings: subjects with abnormality ratings of 0 or 1 on measures of volume loss and white matter hyperintensities as well as a 0 on the measure of infarcts were rated as "normal," and those with abnormality ratings of 2 or 3 on either volume loss or white matter hyperintensity or 1 on the measure of infarcts were rated as "abnormal." The two patient groups (normal vs. abnormal scans) were then compared with each other on the demographic and clinical variables by using Mann-Whitney  $U$ , Pearson chi-square, or Fisher's exact probability tests as appropriate. The two corresponding normal subject groups were likewise compared with each other.

Finally, because the ages of the patient and the normal comparison groups differed significantly, a subset of patients was matched by age to the normal comparison group, and the two groups were compared on demographic, clinical, and MRI abnormality variables by using the matched-paired  $t$ -test for continuous variables or McNemar's test for categorical variables. All statistical tests were two-tailed.

RESULTS

Clinical and Demographic Characteristics

Table 1 summarizes the demographic and clinical characteristics of the study subjects by diagnosis (early-onset schizophrenia, *n* = 30; late-onset schizophrenia, *n* = 24; all patients [the early-onset schizophrenia patients, the late-onset schizophrenia patients, and 15 other psychosis patients], *n* = 69; and normal comparison subjects, *n* = 41). The 15 nonschizophrenic patients carried the following DSM-III-R diagnoses: mood disorder with psychotic features (*n* = 6; 2 early-onset, 4 late-onset), schizoaffective disorder (*n* = 4; 3 early-onset, 1 late-onset), delusional disorder (*n* = 3; 1 early-onset, 2 late-onset), and psychosis not otherwise specified (*n* = 2; both late-onset). Among the 54 schizophrenia patients, 35 were characterized as having the paranoid subtype, 9 as undifferentiated, 9 as residual, and 1 as disorganized. The sample was 81.8% Caucasian. There was a small but statistically significant age difference between patients and normal comparison subjects. Years of education did not differ significantly between these groups. The normal comparison group had significantly more female subjects than the patient group. As expected, normal comparison subjects differed significantly from the pa-

tients on various measures of psychopathology and cognitive functioning.

Early-onset versus late-onset schizophrenia patients did not differ significantly on age, education, race, gender, or diagnostic subtype. As expected, late-onset schizophrenia patients had significantly shorter duration of illness than early-onset patients. A significantly greater proportion of early-onset schizophrenia patients were on neuroleptic medication, and among those schizophrenia patients who were on neuroleptic medication, early-onset patients received significantly higher daily doses. There were no significant differences between the early-onset and the late-onset schizophrenia groups in terms of scores on psychopathology rating scales (BPRS, SAPS, SANS), or cognitive rating scales (MMSE, DRS).

Structural Brain Abnormalities

Table 2 shows the distributions of the types of abnormalities found in the four different groups. There were no significant differences between the early-onset and late-onset schizophrenia groups or between the patient and normal comparison subject groups in clinical ratings of volume loss, white matter hyperintensities, or presence of infarcts.

TABLE 1. Group comparisons: demographic and clinical variables

Variable	EOS ( <i>n</i> = 30)	LOS ( <i>n</i> = 24)	Pts ( <i>n</i> = 69)	NCs ( <i>n</i> = 41)	Analysis <sup>a</sup>
Age, years	58.6 ± 9.8	60.9 ± 8.2	60.8 ± 10.0	65.5 ± 8.7	Pts < NCs, <i>U</i> = 985.0, <i>P</i> = 0.008; EOS & LOS, <i>U</i> = 328.5, <i>P</i> = 0.583
Education, years	13.1 ± 2.8	12.7 ± 3.5	13.0 ± 3.1	13.9 ± 2.4	Pts & NCs, <i>U</i> = 1,186.5, <i>P</i> = 0.150; EOS & LOS, <i>U</i> = 320.5, <i>P</i> = 0.484
Gender, <i>n</i> (%)					Pts < NCs, $\chi^2 = 5.9$ , <i>df</i> = 1, <i>P</i> = 0.014; LOS & EOS, $\chi^2 = 1.4$ , <i>df</i> = 1, <i>P</i> = 0.231
Female	9 (30)	11 (46)	24 (35)	24 (58)	
Male	21 (70)	13 (54)	45 (65)	17 (42)	
Age at onset of psychosis, years	26.1 ± 7.5	55.8 ± 8.9	41.6 ± 17.9	—	LOS < EOS, <i>U</i> = 0, <i>P</i> = 0.001
Duration of illness, years	32.0 ± 10.9	4.1 ± 4.5	17.8 ± 16.7	—	LOS < EOS, <i>U</i> = 2.5, <i>P</i> = 0.001
On neuroleptic medication, <i>n</i> (%)	25 (83)	12 (50)	48 (70)	—	EOS > LOS, $\chi^2 = 6.9$ , <i>df</i> = 1, <i>P</i> = 0.009
Current neuroleptic dose, mg/day (chlorpromazine equivalents)	574.4 ± 770.4	85.0 ± 129.1	364.9 ± 818.1	—	EOS > LOS; <i>U</i> = 177.0, <i>P</i> = 0.001
BPRS total score	32.7 ± 10.5	36.3 ± 9.6	33.9 ± 10.0	19.9 ± 2.4	NCs < Pts, <i>U</i> = 135.0, <i>P</i> < 0.001; EOS & LOS, <i>U</i> = 214.0, <i>P</i> = 0.259
SAPS total global score	5.7 ± 4.4	6.8 ± 4.8	5.5 ± 4.5	0.2 ± 0.5	NCs < Pts, <i>U</i> = 245.0, <i>P</i> = 0.001; EOS & LOS, <i>U</i> = 229.0, <i>P</i> = 0.420
SANS total global score	6.8 ± 3.5	4.6 ± 4.7	5.8 ± 4.0	0.5 ± 1.1	NCs < Pts, <i>U</i> = 198.0, <i>P</i> = 0.001; LOS < EOS, <i>U</i> = 160.0, <i>P</i> = 0.07
MMSE total score	28.2 ± 2.1	26.3 ± 4.6	27.5 ± 3.1	29.0 ± 1.1	Pts < NCs, <i>U</i> = 598.0, <i>P</i> = 0.006; LOS < EOS, <i>U</i> = 205.0, <i>P</i> = 0.09
DRS total score	134.2 ± 8.1	130.4 ± 13.1	133.9 ± 9.5	140.5 ± 2.9	Pts < NCs, <i>U</i> = 281.0, <i>P</i> = 0.001; EOS & LOS, <i>U</i> = 151.1, <i>P</i> = 0.625

Note: Values are means ± SD unless otherwise indicated. EOS = patients with early-onset schizophrenia; LOS = patients with late-onset schizophrenia; Pts = all psychosis patients; NCs = normal comparison subjects; BPRS = Brief Psychiatric Rating Scale; SAPS = Scale for the Assessment of Positive Symptoms; SANS = Scale for the Assessment of Negative Symptoms; MMSE = Mini-Mental State Examination; DRS = Mattis Dementia Rating Scale.

<sup>a</sup>Mann-Whitney *U* or Pearson chi-square.

**TABLE 2. Group comparisons: clinical ratings of MRI**

Variable	Clinical Rating	EOS (n = 30)	LOS (n = 24)	Pts (n = 69)	NCs (n = 41)	Analysis <sup>a</sup>
Volume loss	0	17	7	34	24	Pts & NCs, comparisons of ratings 0,1,2&3: $\chi^2 = 1.84$ , df = 3, $P = 0.607$ ; comparisons of ratings 2&3: FET = 0.168, df = 1, $P = 1.00$ EOS & LOS, comparisons of ratings 0,1,2&3: $\chi^2 = 10.776$ , df=3, $P = 0.013$ (EOS > LOS for no volume loss; LOS > EOS for mild volume loss) <sup>b</sup>
	1	6	15	25	10	
	2	5	2	8	5	
	3	2	0	2	2	
Infarct	0	29	22	66	38	Pts & NCs: $\chi^2 = 0.440$ , df = 1, $P = 0.669$ EOS & LOS: FET = 0.635, df = 1, $P = 0.579$
	1	1	2	3	3	
White matter hyperintensity	0	15	8	30	15	Comparisons of ratings of 0,1,2&3, Pts & NCs: $\chi^2 = 3.103$ , df = 3, $P = 0.376$ ; EOS & LOS: $\chi^2 = 2.870$ , df = 3, $P = 0.412^c$
	1	14	13	34	20	
	2	1	2	4	6	
Collapsed abnormality rating	“Normal”	22	18	53	28	Pts & NCs: $\chi^2 = 0.961$ , df = 1, $P = 0.327$ EOS & LOS: $\chi^2 = 0.19$ , df = 1, $P = 0.890$
	“Abnormal”	8	6	16	13	

Note: EOS = patients with early-onset schizophrenia; LOS = patients with late-onset schizophrenia; Pts = all psychosis patients; NC = Normal comparison subjects.

<sup>a</sup>Pearson chi-square or Fisher’s exact test (FET).

<sup>b</sup>Insufficient power in this sample to statistically analyze a difference between volume loss ratings of 2 and 3 for EOS vs. LOS.

<sup>c</sup>Insufficient power in this sample to statistically analyze a difference between white matter hyperintensity ratings of 2 and 3 for Pts vs. NCs or for EOS vs. LOS.

**TABLE 3. Comparison of demographically matched groups**

Variable	Patients (n = 41)	Normal Comparison (n = 41)	Analysis <sup>a</sup>
Education, years	13.2 ± 3.1	13.9 ± 2.4	$t = 1.23$ , $P = 0.224$
BPRS total score	32.9 ± 9.8	19.9 ± 2.4	$t = -6.20$ , $P = 0.0$
SAPS total global score	5.06 ± 4.74	0.2 ± 0.5	$t = -5.43$ , $P = 0.0$
SANS total global score	5.36 ± 3.73	0.5 ± 1.1	$t = -6.29$ , $P = 0.0$
MMSE total score	26.78 ± 3.76	29.0 ± 1.1	$t = 2.65$ , $P = 0.014$
DRS total score	133.93 ± 10.02	140.5 ± 2.9	$t = 3.38$ , $P = 0.004$
Gender, n (%)			
Female	18 (43.9)	24 (58.5)	$\chi^2 = 2.33$ , $P = 0.127$
Male	23 (56.1)	17 (41.5)	

Note: Values are means ± SD unless otherwise indicated. BPRS = Brief Psychiatric Rating Scale; SAPS = Scale for the Assessment of Positive Symptoms; SANS = Scale for the Assessment of Negative Symptoms; MMSE = Mini-Mental State Examination; DRS = Mattis Dementia Rating Scale.

<sup>a</sup>Matched paired *t*-test or McNemar chi-square test.

Next, we compared subjects with “normal” MRI scores and those with “abnormal” scores (as defined earlier) within the normal comparison group, within the patient group as a whole, and within the group of schizophrenia patients. The results were the same for all three groups. Subjects with normal MRI scores did not differ significantly from those with abnormal scores in gender, education, or scores on BPRS, SAPS, SANS, MMSE, or DRS. In addition, those with normal and those with abnormal MRI scores within the patient group did not differ significantly on psychiatric diagnosis, duration of disease, or daily neuroleptic dose. Those

with normal and those with abnormal scores within the schizophrenia patient group did not differ significantly on schizophrenia subtype. In each of the three groups, however, those with normal scores and those with abnormal scores did differ significantly in age; those with abnormal scores were older ( $P = 0.004$  for each of the three groups). There was also a trend in the two patient groups for normal MRI scores to be associated with higher BPRS scores, a result at least partially due to the fact that younger patients tended to have somewhat higher BPRS scores.

The significant age difference between the normal scan subgroups and the abnormal scan subgroups raised the possibility that the lack of a difference between patients and normal comparison subjects in clinical abnormality ratings could be due to the older age of the normal comparison subjects, which might have biased that group toward individuals who were more likely to have abnormal scans. To test for this possibility, a subset of patients was created to closely match the normal comparison subjects in age. All 41 normal comparison subjects were included and were matched as closely as possible to psychosis patients of similar age; 31 of the patients in this demographically matched subgroup carried the diagnosis of schizophrenia. Table 3 shows the results of comparing the matched patient and control groups. There were no significant differences in education or gender. As expected, psychopathology ratings and scores on cognitive tests continued to be significantly different between the two groups. Yet the frequencies of clinical abnormality ratings on MRI for

the patients and normal comparison subjects were very similar, and in the case of infarcts they were identical.

## DISCUSSION

The major finding of this study is that qualitative ratings of gross volume loss, infarcts, or white matter disease taken from clinical reports of MRI studies did not differ between late-onset and early-onset schizophrenia patients; nor did the ratings differ between a mixed psychosis-patient group and normal comparison subjects.

Potential limitations of this study are that the ratings of abnormality were qualitative in nature and they were based on the neuroradiologists' reports. In this study we were careful to include a severity rating in our qualitative categories, but it is possible that the written reports did not themselves uniformly carry the kind of detail necessary to make accurate severity ratings. On the other hand, a strength of the current study is that these results relate more directly to the utility of clinical MRI reports, which are often relied on by psychiatrists and other physicians managing patients with late-life psychosis. There are also several other strengths of the current study. A relatively large number of well-characterized patients and normal subjects were included; all clinical reports were generated blind to the purpose of this study; and all ratings were done blind to any subject characteristics.

Several published studies on neuroimaging and late-life psychosis suggest that structural brain abnormalities on CT or MRI, especially white matter disease, are contributory and might even be causal factors in these illnesses. In a study of eight late-onset psychosis patients who had no apparent focal neurological signs, Breitner et al.<sup>1</sup> reported that all 8 patients had significant abnormalities in white matter; such abnormalities appeared in none of the 8 controls. Miller, Lesser, and their colleagues<sup>2,3,24-26</sup> have found a greater frequency of white matter lesions and other structural abnormalities in late-onset psychosis patients than in normal comparison subjects. In contrast, Howard et al.<sup>12</sup> failed to detect such a difference between a group of 38 patients with "late paraphrenia" and 31 healthy volunteers.

What could account for this discrepancy in the literature? The younger ages of comparison subjects in some studies could account for some of it, since there is ample evidence that white matter pathology is common in normal, healthy, older individuals.<sup>27,28</sup> Some studies, however, had age-comparable subject groups. One important consideration could be the diagnosis of late-onset psychosis. Flint et al.<sup>29</sup> reported in their sample that there was a significantly higher incidence of clinically

unsuspected cerebral infarction in CT scans of patients with late-onset "paranoia" compared with the remaining "paraphrenia" patients. Similarly, in a prospective study of 27 patients, Miller et al.<sup>25</sup> described 5 patients with large, confluent deep white matter lesions; 3 of these patients had delusional disorder, 1 had mania, and 1 had schizophrenia. At least 4 of the 8 patients in the Breitner et al.<sup>1</sup> study carried a diagnosis of dementia or delusional disorder, while the remaining 4 had a diagnosis of schizophrenia. A diagnosis of delusional disorder, however, is unlikely to account for the reportedly high prevalence of structural abnormalities in late-onset psychosis patients. A few studies have specifically reported structural abnormalities in the late-onset schizophrenia samples.<sup>2,3,25</sup> Furthermore, Evans et al.<sup>30</sup> have found less cognitive impairment in late-onset delusional disorder compared with late-onset schizophrenia.

One important difference between the studies that reported higher frequency of structural abnormalities and those that reported no difference is likely to be in the exclusionary criteria applied to patients. Many of the abnormalities reported in other studies were in fact exclusionary criteria for this study, as well as for the report by Howard et al.<sup>12</sup> For example, Miller and Lesser<sup>31</sup> reported that approximately half of their 27 patients in a prospective study had major structural abnormalities, including tumors, vascular accidents, and traumatic brain injury on CT and MRI scans. Clinical evidence of such insults to the brain would have excluded patients from the current study. Even the appearance of infarcts in our subjects was rare, and when these occurred they were small and not detectable on clinical neurological examination. All subjects in our study were administered a thorough neurological examination at baseline to preclude the inclusion of subjects for whom there was clinical evidence (based on history and physical examination) of brain disease such as stroke.

Our findings do not necessarily rule out the possibility that clinically significant brain abnormalities themselves cause psychosis. In fact, we would argue that it is important that a neuroimaging study be performed in the diagnostic workup of late-onset psychosis patients. Before a diagnosis of late-onset schizophrenia can be made, "organic" factors such as tumors or other structural lesions must be ruled out. There is evidence that white matter lesions and other structural abnormalities can be associated with, and could possibly first manifest as, psychotic symptoms.<sup>25,31</sup> In addition, there are reports of the first appearance of schizophrenia-like symptoms in younger patients after cerebral trauma or specific stroke-induced lesions.<sup>32-34</sup>

Our findings do suggest, however, that if, as was true for the subjects in our study, thorough psychiatric, neurologic, and other medical histories and examinations are done (including mental status examination; reviews of past medical records; histories obtained from caregivers, patients, and physicians both past and present; and essential laboratory tests), then a neuroimaging examination will be very unlikely to reveal gross structural abnormalities. Finally, our findings indicate that late-onset psychosis, including late-onset schizophrenia, can exist without clinically detectable structural abnormalities in the brain. In this respect, late-onset and early-onset forms of schizophrenia can be similar.

Late-onset schizophrenia may be different in this regard from late-onset depression. There is a somewhat more consistent finding in the literature on severe depression in the elderly that white matter hyperintensities and other structural abnormalities are present at an unusually high rate among elderly depressed patients.<sup>5-8,35-39</sup> The etiological and pathological significance of this finding is, however, currently under debate.<sup>40,41</sup>

The results of the present study did not support the hypothesis that gross abnormalities were more prevalent in late-onset schizophrenia patients than in either early-onset schizophrenia patients or normal comparison subjects. Instead, the results demonstrated that late-life psychosis, including late-onset schizophrenia, was not necessarily accompanied by obvious structural brain abnormalities on MRI. In fact, in our sample, psychosis patients were no more likely than normal comparison subjects to have abnormalities noted on the neuroradiology report. It is possible, however, that more subtle abnormalities, such as those detected by computerized quantitative MRI, may be more common in patients with late-onset schizophrenia than in those with early-onset schizophrenia.<sup>42</sup>

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