Quantitative $D_2$ Dopamine Receptor PET and Structural MRI Changes in Late-Onset Schizophrenia


Abstract

Late-onset schizophrenia (LOS) is likely a syndrome of diverse etiology. In a series of related studies, we compared LOS patients with normal controls, elderly patients with early-onset schizophrenia (EOS), and Alzheimer’s disease patients, using magnetic resonance imaging (MRI) and neuroreceptor positron emission tomography measures, which had previously been reported to be abnormal in EOS. EOS and LOS patients showed similar MRI changes. LOS drug-naive patients had elevated $B_{\text{max}}$ (receptor density) values for dopamine $D_2$ receptors compared with age and gender norms, a phenomenon previously reported by our group in young schizophrenia patients.

The relatively uncommon schizophrenia-like illness occurring in later life (late-onset schizophrenia [LOS], or “late paraphrenia”) (Roth 1955; Jeste et al. 1988) shows both important phenomenological similarities to and important differences from the classic early-onset form of schizophrenia. LOS is generally characterized by prominent and vivid hallucinations and delusions but by significantly less thought disorder and fewer negative symptoms than occur in early-onset schizophrenia (EOS), and LOS patients are more likely to be female (Bleuler 1943; Roth 1955; Kay and Roth 1961; Pearlson and Rabins 1988; Pearlson et al. 1989b). These and other differences have raised unresolved questions about the likely heterogeneity of late-life psychoses (of which LOS is but one example), and about the relationship of those psychoses both to the EOS syndrome and to neuropathologic changes occurring more commonly in late life, such as microvascular disease (Miller and Lesser 1988; Rabins and Pearlson, in press).

“Biotyping,” or the identification of biologic changes associated with clinical syndromes, is one way to help classify psychiatric illnesses that are more usually approached through their clinical phenomenology (Andreasen 1983). Use of biotyping via neuroimaging techniques in LOS can potentially shed light on the above questions now that there are reports of brain abnormalities associated with EOS, beginning with controlled neuropathological studies of the syndrome (Bogerts et al. 1985; Falkai et al. 1988; Arnold et al. 1991). Recently, quantitative magnetic resonance imaging (MRI) has provided further information regarding regional pathological brain changes in schizophrenia patients (e.g., Barta et al. 1990; Suddath et al. 1990). Some positron emission tomography (PET) neuroreceptor studies comparing never-treated young schizophrenia patients with controls have indicated elevated dopamine (DA) $D_2$ receptor measures (e.g., Wong et al. 1986a, 1986c) although other such studies have not (e.g., Farde et al. 1987, 1990), and to date, no study has reported similar PET investigations in LOS patients. In addition to identifying putative disease markers, newer brain-imaging tech-

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niques can also demonstrate the presence of less specific age-related pathologic changes. Thus, brain-imaging studies applied to LOS can help address the nature and specificity of cerebral changes and their resemblance to those changes associated with EOS. Several neuroimaging studies have been carried out in LOS patients. These are reviewed in more detail both in this issue of the Bulletin (Lesser et al. 1993) and elsewhere ( Förstl et al. 1992; Pearson and Petty, in press). Rather than repeating this material, this article integrates those findings and adds new data.

The lateral ventricle-to-brain ratio (VBR), a nonspecific marker of cerebral atrophy, has been widely observed to be larger in young schizophrenia patients than in normal controls (Shelton and Weinberger 1986; Pearson et al. 1989a). In several studies using computed tomography (CT), investigators have also reported ventricular size to be larger in LOS patients than in elderly normal controls (Naguib and Levy 1987; Pearson et al. 1987; Rabins et al. 1987; Burns et al. 1989), but less large than in patients with Alzheimer’s disease (AD) (Rabins et al. 1987). Although cases of late-life organic delusional disorder, primarily due to stroke, are well documented (Cummings 1985; Flint et al. 1991), Roth (1955) and others have shown no special tendency for elderly schizophrenia patients in their series to develop dementing illnesses. Hallucinations and delusions can occur in AD (Wragg and Jeste 1989), but they are usually a later manifestation of the illness (Deutsch et al. 1991). A neurodegenerative etiology for at least some cases of LOS, however, is certainly feasible. Miller et al. (1991) and Breitner et al. (1990) have shown fairly high percentages of subtle brain lesions, especially of white matter in late-onset psychotic patients. Miller et al. (1991), Flint et al. (1991), and Holden (1987) suggest that cases less clinically typical of schizophrenia (e.g., those lacking hallucinations, having a greater degree of cognitive impairment, manifesting fewer first-rank symptoms, or experiencing prominent visual hallucinations) are more likely to show a neurodegenerative etiology. The nature of the brain changes in the more typical patients, the true proportion of such cases, and their relation to EOS remain unclear.

Although Blessed et al. (1968) found no more plaques and tangles in LOS patients than in normal controls, the above-mentioned occurrence of hallucinations and delusions in some cases of AD makes AD subjects and normal controls appropriate comparison groups for studies of LOS to use in addressing the specificity of brain changes. In vivo studies of brain morphology in AD using CT have revealed both regional and global cerebral atrophy (Albert et al. 1984; Pearlson et al. 1989c). These reports have found significant overlap between AD patients and normals, which is due in part to the variability of brain atrophy associated with normal aging (Schwartz et al. 1985; Takeda and Matsuzawa 1985).

Single photon emission computed tomography studies by Miller et al. (1992) have revealed evidence of blood flow changes suggestive of cerebrovascular disease in some late-onset psychotic patients. Eighty-three percent of their late-life psychotic subjects and 27 percent of their normals had one or more small temporal or frontal areas of hypoperfusion. Similar changes have been seen in elderly psychotic depressives (e.g., Lesser et al. 1991).

Several other aspects of LOS patients need to be considered in designing brain-imaging studies. Because some of these cases may represent the late-onset form of a usually early-onset process, a comparison group of currently elderly EOS patients is useful to help control for aging-related factors in the context of the illness. This group should be used in addition to appropriately matched normal controls. Followup of index patients is desirable to demonstrate that progressive cognitive impairment is not occurring as a result of a dementing illness. As already noted, LOS patients are more likely to be female. Because women generally have smaller heads and different age-related rates of loss of dopamine D₂ receptors than men (Wong et al. 1984), controlling for head size and sex should be considered. Finally, careful descriptions of populations are important. Age at onset of symptoms; family history of schizophrenia; presence, type, and degree of cognitive impairment; symptomatic patterns; Hachinski scores; workup for organic factors; and neurological characterization are all likely to be relevant since both phenomenology and etiology may be associated with these variables (e.g., Holden 1987; Flint et al. 1991).

Because LOS is not a common syndrome, we chose to carry out a series of preliminary, small-scale structural and functional brain-imaging studies. Our major questions were the following: (1) Were LOS patients similar or dissimilar to AD patients and to normal controls on volumetric MRI measures? (2) Were LOS patients different from comparably aged EOS pa-
tients on MRI analog measures? and (3) When age and sex were accounted for, did never-treated LOS patients have higher-than-expected values on PET measures of DA D₂ receptor density ($B_{max}$).

Study 1: MRI Volumetric Measures

LOS and normal subject groups overlapped considerably for the three studies reported in this article. The most detailed description is therefore provided for the first study.

Subjects. The MRI index group consisted initially of 16 patients of the Johns Hopkins Department of Psychiatry who met DSM-III-R (American Psychiatric Association 1987) criteria for schizophrenia and were diagnosed at interview using the Structured Clinical Interview for DSM-III-R (SCID; Spitzer et al. 1987). Five patients were excluded as described below. Of the remaining 11, 3 were outpatients of the Schizophrenia Research and Treatment Clinic specifically admitted to the inpatient Clinical Research Center for testing; the remainder were general psychiatric inpatients. All 11 had onset of positive symptoms of illness (judged by first psychiatric contact and history) after age 55 (mean age at onset ± standard deviation [SD] = 70 ± 9, range = 56–80 years), as assessed by record review and by careful interview of relatives or other reliable informants. Some demographic data are summarized in table 1. The group was poorly educated (mean years of education = 8.2 ± 3.1). The mean Mini-Mental State Exam (MMSE; Folstein et al. 1975) score before neuroleptic treatment was 26 ± 3.

Phenomenologically, all LOS patients displayed high scores on the Schedule for Assessment of Positive Symptoms (SAPS; Andreasen 1984), items for both global hallucinations and auditory hallucinations. Mean scores on these items were 3.8 ± 1.6 (range = 0–5) and 3.2 ± 1.8 (range = 0–5), respectively. SAPS total delusion ratings were 3.8 ± 1.8 (range = 0–5) and thought disorder ratings were 0.5 ± 1.0 (range = 0–3). These ratings are in accord with previous observations of vivid hallucinations and delusions but diminished thought disorder in late-onset cases (Kay and Roth 1961; Pearlson et al. 1989b).

Comparison patients were 12 subjects with possible or probable AD, according to the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association (McKhann et al. 1984). AD subjects were chosen from a larger series of 26 consecutive consenting referrals to the outpatient Dementia Research Clinic of the Johns Hopkins Department of Psychiatry, whose data are reported elsewhere (Pearlson et al. 1992). The subgroup was selected from those 26 referrals to match the index patients for age and sex. No AD patient had displayed hallucinations or delusions or met DSM-III-R criteria for major depressive episode either before or following

### Table 1. Descriptive data for patients and comparison groups in the three studies

<table>
<thead>
<tr>
<th>Study and group</th>
<th>n</th>
<th>Mean age</th>
<th>% Female</th>
<th>Age at Onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. MRI volumetric measures</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LOS</td>
<td>11</td>
<td>72 ± 10</td>
<td>82</td>
<td>70 ± 9</td>
</tr>
<tr>
<td>NL</td>
<td>18</td>
<td>67 ± 6</td>
<td>72</td>
<td>NA</td>
</tr>
<tr>
<td>AD</td>
<td>12</td>
<td>74 ± 7</td>
<td>67</td>
<td>NA</td>
</tr>
<tr>
<td>2. CERAD MRI measures</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LOS</td>
<td>11</td>
<td>70 ± 6</td>
<td>64</td>
<td>68 ± 5</td>
</tr>
<tr>
<td>EOS</td>
<td>11</td>
<td>65 ± 9</td>
<td>64</td>
<td>41 ± 11</td>
</tr>
<tr>
<td>3. PET receptor measures</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LOS</td>
<td>13</td>
<td>74 ± 13</td>
<td>77</td>
<td>72 ± 13</td>
</tr>
<tr>
<td>NL</td>
<td>17</td>
<td>39 ± 25</td>
<td>29</td>
<td>NA</td>
</tr>
</tbody>
</table>

Note.—Study 3 used age and sex corrections. NL = normal controls; AD = Alzheimer’s disease; LOS = late-onset schizophrenia patients; EOS = early-onset schizophrenia patients; MRI = magnetic resonance imaging; CERAD = Consortium to Establish a Registry for Alzheimer’s Disease; PET = photon emission tomography; NA = not applicable.
dementia onset. Before testing, all patients in this and in the subsequently reported studies were examined by an attending physician, and all underwent physical and neurological examinations and relevant blood testing for reversible causes of dementia; a detailed history was taken from one or more relatives. Patients with other causes of dementia, CT scans with focal findings, or Hachinski scores (Hachinski et al. 1974) higher than 4 were excluded from the study. Each patient's MMSE score was recorded at the time of initial assessment. The mean age of AD subjects was 74 ± 7 years and their mean MMSE score was 19.1 ± 4.9; 67 percent were female.

Normal controls (n = 18) were selected from employees of Johns Hopkins Hospital and members of the surrounding community, group-matched to the index and comparison subjects by age and sex. Control subjects had a mean age of 67 ± 6 years and a mean MMSE score of 28.8 ± 1.7; 72 percent were female.

Patients and controls were not different in age (analysis of variance [ANOVA], F = 2.65, df = 2,39, not significant [NS]) or gender (x² = 0.69, df = 2, NS). All subjects were examined and their medical records were reviewed. Exclusion criteria for all subjects were identical to those used in a recent study from our group (Barta et al. 1990)—that is, any history of central nervous system illness (other than AD, for AD patients), head injury causing unconsciousness for more than 1 hour, headaches sufficiently severe to have led to medical consultation, heavy alcohol or street drug use in the preceding 12 months, oral steroid use in the preceding 3 months, or loss of 25 percent or more of original body weight in the preceding 12 months. None of the controls or AD patients had histories of major psychiatric illness or hospitalization as assessed with the SCID. These screening procedures resulted in the exclusion of five schizophrenia patients: one had positive syphilis serology in both plasma and cerebrospinal fluid (CSF), one had MRI evidence of an old frontoparietal infarct, two had cognitive deterioration on followup with rediagnosis as probable AD, and one was discovered to have had psychiatric contact in her thirties for unknown reasons. This left 11 index patients with a diagnosis of LOS. All 11 remained cognitively stable over at least a 12-month period, as judged by MMSE scores.

MRI. All subjects were examined with the same 1.5 Tesla General Electric Signa MRI Scanner. An initial high-quality sagittal series was used to identify the anterior commissure-posterior commissure (AC-PC) line for slice orientation. T1-weighted coronal slices were then acquired, at 90 degrees to the AC-PC line, beginning at the genu of the corpus callosum and extending posteriorly through the temporal lobe to the splenium using imaging parameters TR 800 and TE 20, with 3-mm-thick interleaved slices and field of view of 20–24 cm. Finally, proton- and T2-weighted axial cuts were obtained through the entire brain, parallel to the AC-PC line, using imaging parameters of TR 2500 and TE 30/80, with 5-mm-thick slices and a field of view of 20–24 cm. All images were acquired using 256 × 256 spatial resolution, archived on nine-track magnetic tape, and transferred to read/write optical disks. MRI images were rated on a DEC-Station 3100 graphics workstation. Direct display from magnetic tape was chosen to avoid differences introduced by film processing and to take maximum advantage of image data. Custom graphics software was developed locally in ULTRIX (UNIX) using X-Windows. Slices containing structures of interest were identified on MRI films. Corresponding images were then displayed on the graphics workstation and interactively outlined. Areas so defined were summed across contiguous images and multiplied by slice thickness to yield volumes.

From coronal images, we assessed the volume of the third ventricle. The midline ventricle was defined in two consecutive coronal levels between the anterior commissure and the mammillary bodies, bounded laterally and inferiorly by the hypothalamus and superiorly by the fornix. Within-rater reliability by intraclass correlation (ICC) was 0.96, and between-rater reliability was > 0.93.

The VBR, defined as the lateral ventricular area divided by the area of the whole brain in the same slice, was calculated from the T2 axial cut in which the lateral ventricles had their maximal area. Within-rater reliability by ICC was 0.95; between-rater reliability was > 0.93. MRI ratings were made blind to diagnosis by a neuropathologist. Additionally, whole brain and CSF volumes were assessed from the entire 5-mm axial series with our semi-automated technique (Harris et al. 1991). For each slice, the brain edge was defined by means of a semi-automated edge-follower algorithm and the area within this border was obtained. Areas for all slices were summed and multi-
plied by slice thickness to yield brain volume (tissue plus CSF). Using thresholding techniques on T2 minus T1 images to highlight CSF, ventricular plus sulcal CSF volumes were estimated and compared with total brain volume (minus CSF) as a percentage (Harris et al. 1991). Interrater and intrarater reliability was high \( r > 0.93 \) for all regions. Validity of volumetric measures was estimated using a realistic anatomic phantom, scanned on the same MRI scanner, and using identical scan acquisition parameters to our subjects. Correlation of actual and estimated volumes was excellent (intraclass \( r > 0.95 \)); no volumes varied by more than 5 percent.

**Study 2: MRI Visual Analog Measures**

**Subjects.** Index subjects were 11 LOS patients, 6 of whom had participated in study 1. Demographic data are shown in table 1. Comparison subjects were an equal number of age- and sex-matched patients with onset of DSM-III-R schizophrenia before age 55. No index subject had onset of any psychotic symptoms before age 55. There was an approximate 25-year difference in the age of clinical onset in the two schizophrenia groups.

**Methods.** As described in study 1, 5-mm-thick axial proton and T2-weighted MRI scans were acquired on all subjects. Using a adaptation of the MRI rating scale developed by the Consortium to Establish a Registry for Alzheimer’s Disease (CERAD; Davis et al. 1989), we rated degree of atrophy in 11 regions on the MRI hard-copy scans. Methods for a similar study of young schizophrenia patients versus young normals are described in detail elsewhere (Schwartz et al. 1992), together with the reliability of the method.

Briefly, scans were rated blind to diagnosis under the supervision of a member of the CERAD neuroimaging task force, according to the 1989 draft of the CERAD MRI rating. This method provides photographs of representative MRI scans illustrating atrophic changes of CSF spaces. Using these photographs as a guide, raters judged the amount of atrophy for specific areas (0 = no atrophy, 1 = mild atrophy, 2 = moderate atrophy, and 3 = severe atrophy). Because many scans fall between the designated ratings, we selected representative scans for intermediate ratings (0.5, 1.5, and 2.5) by consensus, thus expanding the number of possible ratings from the original four to a total of seven. Schwartz et al. (1992) demonstrated that, using this method on 16 scans, the kappa coefficient for blind intrarater reliability was \( \geq 0.60 \) for all measurements.

**Results.** As shown in table 3, no significant differences were detected between the early- and late-
Table 3. MRI Atrophy ratings in late-onset (> 60 years) versus early-onset schizophrenia patients, using CERAD analog rating scale

<table>
<thead>
<tr>
<th>CERAD measures (ranks)</th>
<th>Late onset (n = 11)</th>
<th>Early onset (n = 11)</th>
<th>Statistic(^1) (all NS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>L Sylvian fissure</td>
<td>12.4</td>
<td>10.6</td>
<td>Z = 0.68</td>
</tr>
<tr>
<td>R Sylvian fissure</td>
<td>11.9</td>
<td>11.1</td>
<td>Z = 0.30</td>
</tr>
<tr>
<td>L Temporal sulci</td>
<td>11.8</td>
<td>11.2</td>
<td>Z = 0.24</td>
</tr>
<tr>
<td>R Temporal sulci</td>
<td>11.6</td>
<td>11.5</td>
<td>Z = 0.03</td>
</tr>
<tr>
<td>L Temporal horn</td>
<td>10.0</td>
<td>11.9</td>
<td>Z = 0.71</td>
</tr>
<tr>
<td>R Temporal horn</td>
<td>10.2</td>
<td>11.7</td>
<td>Z = 0.55</td>
</tr>
<tr>
<td>L Lateral ventricle</td>
<td>12.0</td>
<td>11.0</td>
<td>Z = 0.37</td>
</tr>
<tr>
<td>R Lateral ventricle</td>
<td>11.9</td>
<td>11.1</td>
<td>Z = 0.27</td>
</tr>
<tr>
<td>Third ventricle</td>
<td>12.1</td>
<td>10.9</td>
<td>Z = 0.47</td>
</tr>
<tr>
<td>L Cerebral sulci</td>
<td>13.3</td>
<td>9.7</td>
<td>Z = 1.38</td>
</tr>
<tr>
<td>R Cerebral sulci</td>
<td>13.4</td>
<td>9.6</td>
<td>Z = 1.45</td>
</tr>
</tbody>
</table>

Note.—CERAD = Consortium to Establish a Registry for Alzheimer's Disease, NS = not significant; L = left; R = right.

\(^1\)Comparisons used Mann-Whitney U and Wilcoxon matched-pairs signed rank W statistics; all Z scores are tie corrected.

onset groups for any region examined.

Study 3: DA D\(_2\) Receptor PET Measures

Subjects. Index patients were 13 late-onset neuroleptic-naive schizophrenia patients meeting DSM-III-R criteria for chronic schizophrenia, all with clinical onset at 55 years of age or later, 7 of whom had participated in study 1. Mean age was 74 ± 13 years (range = 55-94); demographic data are shown in table 1. To assess presence and degree of prior neuroleptic exposure, all patients were interviewed before the initial scan and once again before discharge. All patients received serum neuroleptic drug-level screening by radioreceptor assay (Tune et al. 1980) before scan. In most cases, drug history was also obtained from a family member who corroborated the history of neuroleptic nonexposure.

Seventeen control subjects aged 18-83 years were recruited through advertisements in local newspapers and from among hospital staff. The sample included 12 men and 5 women. Mean age was 39 ± 25 years. Before subjects inclusion in the protocol, a general medical neurologic and psychiatric examination was administered. Reasons for exclusion included any past history of significant drug or alcohol abuse, any history of prior neuroleptic or antidepressant exposure, any history of DSM-III-R psychiatric diagnosis, and pregnancy, as well as the exclusionary criteria listed for study 1 and any focal CT scan abnormality.

Methods. Two PET scans were obtained for each subject to estimate caudate D\(_2\) DA receptor density (B\(_{\text{max}}\)) (Wong et al. 1986a, 1986b, 1986c) with prior CT scan localization. The first scan was performed before any neuroleptic exposure. Four hours prior to the second scan, a single dose of 7.5-mg unlabeled oral haloperidol was administered to reveal binding under conditions in which the DA D\(_2\) receptor was virtually completely blocked.

A four-compartment model was used to describe the tracer kinetics in brain and plasma; full details of the B\(_{\text{max}}\) calculation have been published elsewhere (Wong et al. 1986a, 1986b, 1986c; submitted for publication). The rate constant of \([\text{\textsuperscript{11}}\text{C}]\text{-Methylspiperone binding to DA receptors both from the plasma pool and from the free and nonspecifically bound radioligand in the brain is k},_3. For the caudate nucleus, k\(_3\) was calculated from the radioactivity both in plasma (due to unmetabolized tracer) and in the caudate nucleus and cerebellum. The B\(_{\text{max}}\) calculation in all cases was determined from the forward rate binding constant to the D\(_2\) receptor k\(_3\) in the unblocked and in the blocked (following administration of haloperidol) cases, using the quantitative model and an assumed
blood/brain partition coefficient for haloperidol and the \( k_{\text{off}} \) for haloperidol. All \( B_{\text{max}} \) calculations were carried out by one of the authors (D.F.W.), who was blind to the clinical diagnosis, and were consistent with our earlier report (Wong et al. 1986c).

To account for the variation in \( B_{\text{max}} \) values with age (Wong et al. 1986b, 1986c) and sex, \( B_{\text{max}} \) values for all normal subjects were treated as outcomes in a two-variable regression equation with age and sex of subject as the predictor variables. This regression equation had an \( R^2 \) value of 0.43 and reflected dependence of \( B_{\text{max}} \) on age and sex. A predicted \( B_{\text{max}} \) value was computed for each schizophrenia subject, based on the normal regression equation. The residual value for each patient was then determined by subtracting predicted from observed \( B_{\text{max}} \) values. Under the hypothesis that \( B_{\text{max}} \) values are not elevated in schizophrenia patients, the raw residual values would have an approximately normal distribution with a mean of 0. Standardized residuals were computed by using a data-generated estimate of residual variance and rescaling the observed residuals to a mean value of 0 and an SD of 1. The observed mean value of these residuals, under the usual statistical assumptions, should have a standard normal distribution.

Results. A one-sample \( t \) test of the standardized residual \( B_{\text{max}} \) values for schizophrenia subjects showed a significant elevation from mean value. The residual \( B_{\text{max}} \) values for the entire group differed significantly from 0 (\( t = 2.66, df = 12, p < 0.05 \), one-tailed). Individual normal and schizophrenic residual values are shown in figure 1. This analysis suggests that \( B_{\text{max}} \) values are elevated in this group of schizophrenia subjects, even when age and sex are taken into account.

Correlations between clinical rating instrument scores and \( D_2 \) receptor measures (raw \( B_{\text{max}} \) scores and age-adjusted standardized residuals) revealed no significant relationship between \( B_{\text{max}} \) and measures of clinical severity.

Conclusions (All Studies)

Overall, the populations of LOS patients that we examined were not identical across the three studies, but they contained many of the same subjects and were similar to those populations previously described by us and others. That is to say, the subjects were mainly female and had many delusions and hallucinations, whereas thought disorders or negative symptoms were uncommon.

We believe study 1 to be the first study of LOS using quantitative volumetric measures on MRI. Previous studies (e.g., Breitner et al. 1990) used qualitative estimates of white-matter abnormalities. In contrast to earlier CT studies (e.g., Naguib and Levy 1987; Rabins et al. 1987), VBR was not significantly increased in our LOS patients compared with normal controls. Several explanations for this difference in findings are possible, including VBR differences on

![Figure 1. Scatterplot of standardized residual dopamine (DA) D_2 B_{\text{max}} values for normal control (left) and schizophrenia (right) subjects](image-url)

Horizontal bars show means; vertical bars show standard deviations. Male subjects are shown as solid circles, female subjects are shown as open circles. One male schizophrenia subject (solid circle on horizontal mean bar on right) was later found to have received haloperidol, 2mg orally administered by a physician on the day of his positron emission tomographic study. Findings are not different if this data point is removed.
MRI versus CT and the smaller number of patients and controls in the current study than in Rabins et al. (1987). Third ventricular size was significantly increased in our LOS subjects, consistent with a study by Boronow et al. (1985) involving young schizophrenia patients. Third ventricular enlargement likely represents nonspecific evidence of atrophy or hypoplasia associated with schizophrenia with onset at all ages.

Study 2 from the current series showed no differences between aged EOS and LOS patients on an analog rating scale. This finding argues for similarities in pathobiology between the two patient groups. It is possible that this type of analog measure is insufficiently sensitive to detect more subtle between-group anatomic differences, if they exist, especially in a smallish series. We have previously shown differences between young EOS patients and young normals, using the same adaptation of the CERAD scale (Schwartz et al. 1992) used in study 2. That study demonstrated that young schizophrenia patients had bilateral Sylvian fissure enlargement.

Previously (Pearlson et al. 1991) we compared elderly unipolar and bipolar patients and normals with LOS patients, using the CERAD scale. In that study, the LOS patients had larger third ventricles and right temporal horns than did normal controls; affective patients did not show these changes. Those findings, overall, help to elucidate those of studies 1 and 2, perhaps localizing the changes in LOS patients more particularly to the temporal lobe and indicating some specificity—that is, changes different from those we have reported in elderly affective disorder subjects (Rabins et al. 1991a).

Findings from study 3 must be regarded as more speculative because of the lack of a direct comparison population of age- and sex-matched normal controls. Overall, however, these data support an elevation of \( \text{DA} D_2 \text{B}_{\text{max}} \) measurements in neuroleptic-naive LOS patients. This finding is similar to that reported by our group for early-onset drug-naive schizophrenia patients, using the same method (Wong et al. 1986c; Tune et al., in press), but not to the findings of others who used a different method (Farde et al. 1987, 1990). We are currently trying to collect a population of individually age-, sex-, and race-matched normal controls to compare directly with our LOS patients by means of these PET methods.

We have previously argued (Rabins and Pearlson, in press) that patients presenting a hallucinatory/delusional syndrome for the first time in late life probably represent subjects with diverse conditions. While the same could be said for EOS patients, diversity is perhaps more likely in these late-onset patients (e.g., Lesser et al. 1993, this issue; Pearlson and Petty, in press). Investigators may be tempted to be dogmatic and look for single etiologies among LOS patients. However, such a search is unlikely to be fruitful. The likely effect of the above-mentioned diversity means that one must be specific in describing and constituting patient, control, and comparison populations. There are obvious analogies between LOS and depressive illness with onset in the senium, where there is also less genetic risk than in early-onset cases of the disorder and more evidence of nonspecific brain changes in subpopulations of those patients (e.g., Pearlson and Rabins 1988; Lesser et al. 1991).

This has led some investigators to believe that late-onset depression is a heterogeneous mixture of delayed “true” cases and “organic phenocopies.”

The etiology and timing of the structural changes in LOS are unknown. These changes could be primarily initiated in late life, or, alternatively, they could be caused by age-related brain changes that unmask a preexisting vulnerability. If a developmental origin, similar to that proposed for early-onset cases (Weinberger 1987), pertains also to LOS (Pearlson and Rabins 1988), a key but unanswered question in late-onset cases is why symptomatic onset is delayed to later life. Precipitating factors could include neuronal loss due to normal aging, or vascular or other age-related neuropathology, as argued by Miller and Lesser (1988) and Miller et al. (1992). Aging could also remove putative protective factors, such as estrogen in women, or change the relative balance of neuroreceptor populations.

Conversely, one might regard the LOS patients in this study as aged EOS individuals who were untreated (until late in life). We feel that this is unlikely, however, because we conducted interviews with relatives or other reliable informants in all cases. These informants reported lifelong traits of suspiciousness or oddness in many cases (consistent with our previous report [Pearlson et al. 1989b]) but an absence of hallucinations or delusions until late in life. This supports the hypothesis that many patients have existing predispositions that are clinically revealed by a second precipitant in late life (a “two hit” model).

Using the same methods previously employed on an earlier set
of patients to demonstrate elevated $B_{\text{max}}$ of DA $D_2$ receptors in young schizophrenia subjects versus controls (Wong et al. 1986b), we now have shown similar elevations in LOS patients. Many authors, including ourselves (Pearlson and Rabins 1988), have pointed out the preponderance of females among LOS patients. This is particularly relevant to the DA hypothesis of schizophrenia. Based on neuropathologic and PET scan studies, we have noted (Pearlson and Rabins 1988) that men start adult life with a larger number of DA receptors but lose them with increasing age at a greater rate than women do. (Wong et al. 1984). This leaves elderly women with a relative excess of DA $D_2$ receptors. Conceivably, high-DA receptor men may have a poorer survival rate into old age. There are also possible protective effects of estrogenic hormones at $D_2$ receptors, and women would lose these effects after menopause (Seeman 1981). Taken together, these factors may be responsible for the documented overrepresentation of male early-onset and female late-onset cases of schizophrenia. We have also shown the responsiveness of LOS patients to treatment with neuroleptic medication (Rabins et al. 1984; Pearlson et al. 1989b). This is also consistent with a hypothesis of dopaminergic overactivity.

It should be noted, however, that our findings were based on a relatively small group of LOS patients who were studied over several years. In a recent study of 25 neuroleptic-free (18 never-treated) schizophrenia patients by Tune et al. (in press), we found that clinical factors such as duration of illness may have a relationship to $B_{\text{max}}$ values. Our current finding of apparent $B_{\text{max}}$ elevations in LOS is one example of the importance of applying this biologic measure to clinical subtypes of schizophrenia.

Miller et al. (1991, 1992) have argued for the role of brain injury in the etiology of late-onset cases of psychosis. Clearly, such risk factors are present to a greater extent than earlier investigators originally realized and are only now visible through modern brain-imaging techniques. Our current screening methods are likely to have eliminated a proportion of such subjects, yielding a population containing fewer organic cases. Four (25%) of our initial index group were so excluded. Differences in screening criteria used in published reports probably account for differing proportions of clearly organic cases. Interactions between various risk factors for such pathologies as stroke, and the factors that distinguish those risks that are necessary from those that are sufficient to elicit clinical psychotic symptoms, are still undefined, however. An encompassing theory is still lacking. In particular, the interrelationship is unclear between known risk factors for LOS (including sensory impairment, social isolation, family histories of schizophrenia, premorbid personality traits of suspiciousness, and female sex) and the role of late-life brain changes (both “normal,” age-related neurodegeneration and brain damage due to stroke, etc.). Castle and Murray (1991) argue that most LOS patients may actually be cases of affective disorder. One point not supporting this hypothesis is our demonstrated difference between LOS cases and elderly affective patients on the CERAD rating scale for MRI (Pearlson et al. 1991).

Strengths of the current study include clinically characterized groups, including LOS patients without known organic hallucinosis/delusional disorder, and the use of reliable MRI region-of-interest rating methods used in previous studies. None of the LOS or AD patients had evidence (either clinically or on MRI) of stroke, which other investigators (Miller and Lesser 1988; Rabins et al. 1991b) have previously noted as a risk factor for late-onset psychoses. We doubt that our LOS patients were suffering from early AD because they remained cognitively normal on followup, apart from two (12.5%) who were excluded from the study owing to longitudinal cognitive decline.

Weaknesses of the study include the relatively small numbers of both index patients and comparison subjects. For study 3, LOS patients and normal controls were not comparable on age or sex, resulting in our use of standardized residual scores. Because of the small size of our normal sample, we cannot assume that we accurately accounted for age- and sex-related rates of change in $B_{\text{max}}$ of $D_2$ receptors. The small size of our LOS group is perhaps inevitable in studying well-demarcated subjects with an uncommon condition. Because of this demarcation, our findings should be seen as more specifically representative of patients with LOS and not as more broadly applicable to the probably more heterogeneous category of late-onset psychosis.

The current study included no comparison patients with AD who had delusions and hallucinations, but future studies could examine such patients to see if they more closely resemble LOS patients. Recommendations for future studies
include the following:

1. Continued longitudinal cognitive followup with eventual neuropathological examination of the schizophrenic patients in the current series to document that they show no pathological changes of Alzheimer’s or multi-infarct disease.

2. Larger scale brain-imaging studies comparing LOS with aged EOS and elderly affective disorder patients to illuminate issues of specificity.

3. Further studies comparing LOS patients with patients who show conditions of better demarcated neuropathology (e.g., multi-infarct dementia or AD).

4. Continued application of putative biologic markers derived from studies of EOS to the examination of late-onset psychoses.

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