

What Happens After the First Episode? A Review of Progressive Brain Changes in Chronically Ill Patients With Schizophrenia

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Numerous imaging studies have revealed structural brain changes in schizophrenia. Decreases in brain tissue are accompanied by increases in ventricle volumes and cerebrospinal fluid. Whether or not these brain changes are progressive beyond the first episode is subject to debate. To assess if progressive brain changes occur in chronically ill patients, 11 longitudinal magnetic resonance imaging and computed tomography studies were reviewed. Patients were ill for on average 10 years at their initial scan. Follow-up intervals varied between 1 and 10 years. Overall, the findings suggest continuous progressive brain tissue decreases and lateral ventricle volume increases in chronically ill patients, up to at least 20 years after their first symptoms. The extent of progressive brain tissue decrease in patients (−0.5% per year) is twice that of healthy controls (−0.2% per year). These findings are consistent with the extent of postmortem brain tissue loss in schizophrenia. Progressive volume loss seems most pronounced in the frontal and temporal (gray matter) areas. Progressive lateral ventricle volume increases are also found. More pronounced progressive brain changes in patients is associated with poor outcome, more negative symptoms, and a decline in neuropsychological performance in one or some of the studies, but not consistently so. Higher daily cumulative dose of antipsychotic medication intake is either not associated with brain volume changes or with less prominent brain volume changes. The progressive brain changes present in chronic schizophrenia may represent a continuous pathophysiological process taking place in the brains of these patients that warrants further study.

Key words: schizophrenia/brain/MRI/CT/structural/longitudinal/outcome/progressive

Introduction

Numerous brain imaging studies have revealed structural brain changes in schizophrenia. Decreases in whole brain volume of approximately 3% in patients with schizophrenia as compared with healthy comparison subjects have been found, with decreases somewhat more prominent for gray matter (−2%) than for white matter (−1%). These decrements are accompanied by increases in lateral (20%) and third ventricle volumes and in cerebrospinal fluid (CSF).¹

Currently, it is not known when these structural brain decreases occur and how they develop over time. It has been postulated that (some of) the brain changes are already present early in life, possibly even prenatally.² However, direct evidence for this hypothesis is sparse, and it is inconsistent with the finding that in adulthood the cranial volume of patients with schizophrenia is normal.^{3,4} Because the cranium develops under the influence of brain tissue growth and has reached 95% of its size by the age of 6 years,⁵ the overall brain changes in schizophrenia are therefore more likely to occur after that age. Thus, it is unlikely that abnormal brain development in childhood in subjects who later go on to develop schizophrenia is substantial, because if it were, cranial volumes would be smaller in subjects who developed the illness. During puberty, after a period of both gray and white matter growth, decreases in gray matter volume and increases in white matter volume take place, whereas total brain volume remains stable.⁵ In schizophrenia, results from several longitudinal studies suggest that gray matter decreases just prior to and during the first psychotic episode.^{6,7} Thus, considering that the first psychotic episode usually occurs in late puberty and young adulthood, there is evidence for aberrant brain development during puberty and young adulthood in patients with schizophrenia.

Cross-sectional magnetic resonance imaging (MRI) studies in first-episode and chronically ill patients with schizophrenia have been reviewed extensively.^{7–10} Longitudinal MRI studies in first-episode patients have been reviewed earlier.^{11,12} These studies and studies on childhood-onset schizophrenia are discussed in other articles in the current issue of *Schizophrenia Bulletin*. The issue that is addressed here involves what happens with regard to *progressive brain changes beyond* the first episode, ie, in

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more chronically ill schizophrenia patients. In other words, are the brain changes in schizophrenia progressive in the more chronic phase of the disease? This question is relevant because progressive brain changes beyond the first episode in schizophrenia provide suggestive evidence that the brain changes represent an ongoing pathophysiological process. Finding the causes for this pathophysiological process could enable us attenuate or even reverse the progressive brain changes.

That progressive brain changes take place in chronic schizophrenia would be consistent with (a subgroup of) patients deteriorating clinically beyond the first episode, although the deterioration is particularly prominent during the first 5 years after disease onset and becomes relatively more stable after that time.¹³ As a group, chronically ill patients have greater morbidity on most clinical and biological dimensions of the illness as compared with first-episode patients.¹³ If one hypothesizes that a brain that is undergoing dynamic changes is more vulnerable to disease impact, then progressive brain changes taking place in chronic schizophrenia would be consistent with continuous dynamic changes that occur in the healthy adult brain. Indeed, in contrast to what has long been thought, the healthy brain changes dynamically throughout life. In fact, decreases in gray matter and related increases in white matter continue into adulthood up to at least 35 years of age.¹⁴ Thus, aberrant adult brain development could possibly explain brain changes in the more chronic phase of the disease in schizophrenia.

In this review longitudinal MRI and computed tomography (CT) brain measurements are reviewed that include chronically ill patients and healthy control subjects. These studies provide suggestive evidence for progressive brain changes in schizophrenia far beyond the first episode.

Methods

A PubMed search was conducted including the following keywords: schizophrenia, MRI or CT, longitudinal, or progressive. In addition, earlier works as referenced in the articles that were retrieved using the PubMed procedure were added. To be included in the review, the study was required to include patients with adult-onset chronic schizophrenia, defined as illness duration of longer than 2 years at the time of the first scan. Also, the study had to include a healthy control group of patients. Finally, 10 studies used volumetric brain imaging methodologies, whereas one study applied an area measurement based on CT scans. Both studies reporting on brain tissue changes (eg, in whole brain volume, frontal and temporal lobes, hippocampus etc) as well as those reporting on CSF and lateral and third ventricle volume or density changes were included. Exclusion of articles on patients with an illness duration shorter than 2 years at the time of the first scan considerably reduced the number of articles

included in the review because the majority of studies have concentrated on progressive changes in the early stages of the disease. The number of articles initially found using CT scanning was considerably reduced when articles including patients only (ie, excluding a healthy comparison group) were excluded from the search.

The following information was extracted: the number of subjects (males/females) within the chronic schizophrenia group, possible other patient groups, and healthy comparisons; age at first measurement of each group; interval between the 2 imaging scans (mean, range in years); duration of illness (mean, SD, or range, in years); antipsychotic medication taken during the interval; brain imaging methodology that was applied (MRI or CT, Tesla [MRI] slice thickness in millimeters; scan direction; gap in millimeter if applicable); the brain areas in which progressive brain tissue volume changes were measured if any; the percentage change in brain tissue in patients with schizophrenia; the percentage change in brain tissue in healthy comparisons; the progressive CSF and lateral ventricle volume changes that were measured if any; the percentage change in CSF and ventricles in patients with schizophrenia; and the percentage change in CSF and ventricles in healthy comparisons.

Moreover, if available, associations between progressive brain changes in patients and outcome, severity of symptoms, cognitive functioning, and antipsychotic medication intake during the interval were examined. Finally, in case of a direct comparison within a study between progressive brain changes in chronically ill patients and first-episode patients and in case of 3 scans per person, this information was used. Seven studies reported on brain tissue changes over time, and 9 studies reported on ventricle (8) and/or CSF (2) changes over time. In 5 of these studies the measurements overlapped, ie, both brain tissue and ventricle and/or CSF changes over time were measured.

The percentage change in brain tissue and CSF and ventricle volume over time was calculated from the available material if not directly provided in the article, as follows: The average volume at follow-up was subtracted from the average volume at baseline, divided by the baseline volume, and multiplied by 100. Hence, in some instances the percentages change provided in this review have to be considered as an approximation of the actual changes.

The findings are summarized in table 1. Studies were numbered according to the order of appearance in table 1 and these identity numbers were included in the text.

Results

Studies That Were Retrieved

Eleven studies were retrieved that reported on changes in brain volumes over time in chronically ill patients with schizophrenia and healthy control subjects (table 1).

All studies but one included subjects with an average age over 30 years at the first scan (or at the second scan but including a third measurement). The mean (min–max) number of patients included in the studies was 28 (10–96). The mean (min–max) number of healthy comparison subjects was 24 (5–113). Average duration of illness at first measurement ranged from 5 to 21 years between studies. Nine studies were based on MRI scans and 2 on CT scans. The interval between scans ranged from 1 to 5 years between studies. Brain tissue changes were reported in 7 studies. Lateral ventricle volume changes were reported in 8 studies, third ventricle volume in 1, and CSF volume changes in 2 studies. Cerebellum volume changes were reported in one study.

Progressive Brain Changes in Chronic Schizophrenia

Significant progressive whole-brain volume decreases over time in patients with schizophrenia as compared with control subjects were reported in 2 studies [#1][#5].^{14,19} In 3 studies no significant progressive whole-brain (or whole hemisphere) changes were reported in patients as compared with controls [#3][#4][#9].^{17,18,23} Progressive decreases in volume and density of the frontal lobe were found in patients as compared with controls in all 3 cohorts that measured this brain region [#1][#6][#9],^{14,15,18,23} 2 of which measured frontal lobe gray matter [#1][#6].^{15,20} Progressive decreases in volume and density in the (left) (superior) temporal gray matter were found in patients as compared with controls in 2 studies [#1][#6].^{14,15,20} In one study temporal lobe changes were not significantly different between groups, and in one other study temporal lobe volume decreases were even more pronounced in controls than in patients [#9].²³ Other areas that revealed progressive decreases in tissue over time in patients as compared with controls included the thalamus and the caudate nucleus. Progressive decreases in tissue over time in patients as compared with controls were also found in the thalamus in 2 studies. In one study a progressive decrease in thalamus density was found in patients as compared with controls using voxel-based morphometry (VBM) [#1].¹⁵ In one study the volume of the thalamus was measured over time and a more pronounced decrease was found in thalamus volume in patients, although at baseline the thalamus volume was larger in patients than in controls [#2].¹⁶ Density of the caudate nucleus was measured in one study, applying VBM. A progressive decrease in caudate nucleus density over time was found in patients as compared with controls [#1].¹⁵ No progressive changes in patients as compared with controls in the 2 studies that measured hippocampus volume were found [#5][#3].^{17,19} One study measured cerebral (ie, whole brain except for cerebellum) gray matter volume and reported a progressive decrease in patients as compared with controls [#1].¹⁴ In that same study cerebral white matter volume showed a more pro-

nounced increase in patients as compared with controls. The one study measuring volume changes in the cerebellum over time revealed no significant changes in patients or in controls [#1].¹⁴

Progressive increases in (left) lateral ventricle volume in the brains of patients with schizophrenia as compared with control subjects were found in 7 of 8 studies [#1][#4][#6][#7][#8][10][#11],^{14,18,20–22,24,25} whereas it was not found in 1 study [#3].¹⁷ Five of these used MRI and 2 used CT to measure ventricle volume, whereas the negative study used MRI. (Right frontal) CSF volume increases in patients were reported in one study [#6],²⁰ whereas it was not found in one other study [#9].²³ Progressive increase in third ventricle volume in patients as compared with controls was found in the one study that reported on this cavity [#1].¹⁴

The extent of progressive volume decrease of whole-brain volume in patients with schizophrenia was approximately twice that reported in healthy control subjects. Whole-brain volume tissue loss in patients per year was -0.5% as compared with -0.2% in controls, as based on [#1][#4][#9].^{14,18,23} This measure was calculated by summing the percentage volume change per year in each relevant study (ie, [average volume at follow-up – average volume at baseline]/average volume at baseline \times 100/years at follow-up \times number of subjects) divided this number by the total number of subjects in the included studies. Cortical (frontal and temporal) gray matter showed a somewhat more pronounced tissue loss than other areas in patients (-0.9% per year) as compared with controls ($+0.3\%$ per year), as based on [#1][#6].^{14,20} For the calculation of the overall decrease in gray matter in [#6]²⁰ the percentages change of subregions were averaged. The extent of progressive volume increase of total lateral ventricle volume in patients with schizophrenia varied from 1.5 to 4 times of that in healthy control subjects. Studies that reported a 4-fold increase in lateral ventricle volume in patients included a study with a 10-year interval [#7]²¹ and one including a subgroup of severely symptomatic patients (ie, the Kraepelinian group) [#8].²² The extent of progressive volume increase of third ventricle volume in patients with schizophrenia was approximately twice that reported in healthy control subjects, and for CSF this number was less than 1.5 times of that found in controls [#1].¹⁴

Associations With Clinical Variables

Outcome In a CT study, patients with very poor outcome schizophrenia, termed Kraepelinian patients, were compared with better prognosis (ie, non-Kraepelinian) patients [#8].²² The poor-outcome (ie, Kraepelinian) patients were characterized by continuous hospitalization or complete dependence on others for food, clothing, and shelter; no useful employment or work; and no evidence of remission of symptoms. Compared with normal control

Table 1. Longitudinal structural brain imaging studies in patients with schizophrenia beyond the first episode

Study (identity number)	No. of subjects per group (m/f)	Age at first scan (mean, SD, and range in y)	Interval (mean, SD, and range in y)	Duration of illness (mean, SD, or range)	Antipsychotics medicines during interval	Brain imaging	Progressive brain tissue volume (or density) changes	% change in SZ ^a	% change in NC	Progressive CSF and lateral ventricle volume changes	% change in SZ	% change in NC
[# 1] Van Haren et al. (2007a,b) ^{14,15}	96 SZ (70/26) 113 NC (76/37) (nb: 19 of those patients were FE)	32.2 (11.1) (17–56) 35.3 (12.3) (17–56)	4.8 (0.56) (3.5–6.3) 4.9 (0.3) (4.2–5.7)	11.0 (10.2) (0.4–36.3) y	10 typical 13 atypical 14 clozapine 52 switched	1.5 T MRI 1.2 mm coronal volumes VBM (change in SZ relative to NC)	Whole brain	–1.5	–0.8	Lateral ventricles Third ventricle	+9.6	+6.9
							Cerebral gray	–4.5	–2.5		+7.9	+3.2
							Cerebral white	+2.6	+1.6			
							Cerebellum	+0.7	+0.7			
							Frontal gray	NA	NA			
							Temporal gray	NA	NA			
							Parietal gray	NA	NA			
							Occipital gray	NA	NA			
							Left superior frontal gray	–03 ^b				
							Left superior temporal gray	–02				
Right caudate	–04											
Right thalamus	–03											
[# 2] Khorram et al. (2006) ¹⁶	10 chronic SZ (7/3) 20 NC	35.3 (8.8) (7.7)	1.1 (.3) 1.2 (.2)	NA	All treated with olanzapine	1.5-T MRI 4-mm coronal, 1-mm gap	Relative decrease in thalamus volume over interval	NA	NA			
[# 3] Whitworth et al. (2005) ¹⁷	17 multiple-episode SZ (21 FE SZ) 20 NC (all males)	28.4 (4.0) (nb: age at follow-up) 31.5 (4.9)	3.29 (1.2) 3.70 (1.6)	7.8 (1.5)	NA	1.5-T MRI 0.9–1.4 mm sagittal	Whole-brain hippocampus	NS NS		Lateral ventricles	NS	
[# 4] DeLisi et al. (2004) ¹⁸	26 SZ (17/9) 10 NC (6/4)	Age at follow-up: 37.0 (7.3) 35.5 (5.4)	5 y (second interval)		7 typical 23 atypical 6 none	1.5-T MRI 5-mm coronal, 2-mm gap	Left hemisphere	–0.03, NS	–0.11 –0.36	Left lateral ventricle Right lateral ventricle	+3.3	+0.8
							Right hemisphere	–0.05, NS			+2.2, NS	–0.04
[# 5] Wood et al. (2001) ¹⁹	12 chronic SZ (11/1) (30 FE SZ) 26 NC (14/12)	33.6 (8) 23.8 (7.9)	2.3 (1.0–4.1) 2.2 (0.9–4.2)	10.8 (1.8–25.4)	5 typical 5 atypical 2 none or Not complicated	1.5-T MRI 1.5-mm coronal	Whole brain loss	NA				
							Temporal lobe hippocampus (IC corrected)	NS NS				

Table 1. Continued

Study (identity number)	No. of subjects per group (m/f)	Age at first scan (mean, SD, and range in y)	Interval (mean, SD, and range in y)	Duration of illness (mean, SD, or range)	Antipsychotics medicines during interval	Brain imaging	Progressive brain tissue volume (or density) changes	% change in SZ ^a	% change in NC	Progressive CSF and lateral ventricle volume changes	% change in SZ	% change in NC
[# 6] Mathalon et al. (2001) ²⁰	24 SZ 25 NC (all males)	39.4 (6.4) (24–51) 40.7 (8.5) (22–54)	3.6 (2.2) (0.6–7.5) 4.2 (1.9) (0.6–6.7)	15.3 (6.4) (2.2–26.5)	NA	1.5-T MRI 5-mm, 2.5-mm gap, axial	Right frontal gyrus Left superior temporal gyrus Right superior temporal gyrus	–1.7 –2.7 –3.4	+2.3 +1.6 +0.2	Left lateral ventricle Right frontal CSF	+13.0 +2.7	+4.8 +2.2
[# 7] Saijo et al. (2001) ²¹	15 SZ (9/6) 12 NC	37.5 (8.9) 37.1 (4.2)	4, 10	15.1 (5.8)	Average daily dose haloperidol eq 41.5 (21.6)	0.2-T MRI T1w, 9-mm, 1-mm gap, coronal				Lateral ventricles after 4 y after 10 y	+4.8 +22.9	+4.2 +5.2
[# 8] Davis et al. (1998) ²²	22 Kraepelinian 31 non-Kraepelinian 13 NC (all males)	42 (8.6) 38 (12.2) 60 (17.8)	4.9 (1.1) 5.2 (1.1) 5.3 (0.9)	21.1 13.9	NA	CT, 8-mm, axial, multiple slices				Lateral ventricles Kraepelinian Non-Kraepelinian	+4.30 0	NS NS
[# 9] Gur et al. (1998) ²³	20 (12/8) previously treated SZ (20 FE SZ) 17 NC (13/4)	30.6 (7.7) 27.8 (8.2) 31.9 (0.9)	2.5 (1.0) (all patients) 2.7 (1.2)	8.5 (4.7) (2.8 [3.8])	Average daily dose in chlorpromazine equal units) 515 (224) 260 (166)	1.5-T MRI T2w 5-mm, axial	Whole brain Left frontal Right frontal Left temporal Right temporal (nb FE plus PT patients)	NS –4.2% –2.8% –3.4% –2.8%	NS 0% 0% –7.5% –7.2%	CSF	NS	NS
[# 10] Nair et al. (1997) ²⁴	18 SZ (8/2) 5 NC (2/3)	31 (9) 41 (11)	2.6 (0.7) 2.6 (0.7)	8.6	On neuroleptics 78% of time	1.5-T MRI 1.95 mm, coronal				Lateral ventricle	+24	+9
[# 11] Kemali et al. (1989) ²⁵	18 SZ (7/11) 8 (4/4)	31 (6) (19–42) 32(7) (21–39) At follow-up	3 (3.0–3.2)	12.1 (4–18)		CT, area (1 slice)				Ventricle-to-brain ratio	+6	0

CSF, cerebrospinal fluid; CT, computed tomography; FE, first episode; IC, intracranial volume; MRI, magnetic resonance imaging; NA, not available; NC, healthy comparisons; NS, not significant; PT, previously treated; SZ, patients with schizophrenia; VBM, voxel-based morphometry.

^a% change refers to the percentage brain volume (or density) change over the interval. Thus, for an estimate of the yearly change, this % has to be divided by the interval: eg, in #1 a –1.5% change in patients with schizophrenia was measured over a 5-year interval. Hence, the yearly change was $-1.5/5 = -0.3\%$ yearly.

^bDensity change as compared with normal as based on voxel-based morphometry.

subjects, lateral ventricle volume increase was present in the poor-outcome patients and not in the better prognosis patients after a 5-year follow-up period. Both poor-outcome and better prognosis patients with larger ventricles had spent more months in the hospital [#8].²² In another study, ventricular enlargement over a 5-year period was correlated with the amount of time spent in hospital but not with any of the (other) outcome measurements [#4].¹⁸ In a third study using a 5-year interval, poor-outcome patients (based on the Global Assessment of Functioning scale) showed larger decreases in total brain volume and a larger increase in lateral ventricle volume as compared with good outcome patients [#1].¹⁴ Moreover, excessive gray matter density decrease in the superior frontal gray matter as measured using VBM was related to increased number of hospitalizations as an approximation of outcome, in that same cohort [#1].¹⁵

Symptoms In a study comparing chronically ill patients (defined as previously treated patients with an average duration of illness of over 8 years) and first-episode patients with healthy comparison subjects, frontal and temporal lobe volume loss was found over a 2.5-year interval. More pronounced frontal and temporal lobe volume loss in the chronically ill patients correlated with greater improvement across most symptoms as measured by using the Scale for the Assessment of Negative Symptoms subscales (SANS) and the Scale for the Assessment of Positive Symptoms subscales (SAPS). More specifically, in chronically ill patients, more pronounced temporal lobe volume loss predicted improved affective flattening and avolition over the interval [#9].¹² In another study, more pronounced anterior superior temporal lobe gray matter volume loss and frontal sulcal expansion (as measured by local CSF volume) in a chronically ill patients after a 4-year interval was associated with more severe clinical symptoms as measured by a higher Brief Psychiatric Rating Scale (BPRS) total score. The total BPRS score was averaged over time. Higher BPRS-positive symptom scores were associated with more pronounced frontal sulcal expansion. Higher BPRS-negative symptoms scores were associated with more pronounced prefrontal and posterior superior temporal gray matter volume loss as well as with more pronounced right frontal sulcal expansion. Finally, a higher percentage of the time that patients were hospitalized during the interscan interval was associated with more prefrontal gray matter volume loss and with more pronounced frontal sulcal expansion over the interval period [#6].²⁰ In a study with a scan interval of 10 years, lateral ventricle volume increase was not significantly associated with the BPRS scores in patients, although there was a nonsignificant positive association with the BPRS-negative symptoms. Worsening of negative symptom subscale was associated with more pronounced ventricle volume increase over the 10-year interval [#7].²¹ No

significant correlations with total BPRS, SAPS, or SANS scores and lateral ventricle volume were found in another study over a 5-year interval [#4].¹⁸ No significant correlations with SAPS or SANS scores at baseline and any of the progressive brain volume changes were found in another study over a 5-year interval [#1].¹⁴

Cognition In one study that associated progressive brain volume changes with cognitive measures in chronically ill patients with schizophrenia, a progressive decrease in whole brain volume and an increase in CSF volume were associated with worsening of neuropsychological performance [#9].²³ More prominent frontal and temporal lobe volume decreases were associated with more pronounced neuropsychological decline, with one exception, ie, in chronically ill patients less temporal lobe volume decrease was associated with worsening of verbal functioning [#9].²³

Medication In 4 studies, medication intake during the scan interval was associated with brain volume changes in patients. A higher cumulative dose of olanzapine during the scan interval was associated with a less prominent decrease in cerebral (gray matter) volume in patients [#1].¹⁴ A higher cumulative dose of clozapine and olanzapine during the scan interval was associated with a smaller decrease in right superior frontal gray matter density as measured using VBM [#1].¹⁵ A higher cumulative dose of typical antipsychotics during the scan interval was associated with caudate nucleus density increase [#1].¹⁵ In another study, a higher daily medication dose was not associated with greater reduction in frontal and temporal lobe volumes in chronically ill patients [#9].²³ This finding was in contrast to a second group of patients in that study, who had been neuroleptic-naive at the time the first MRI scan was made. In the neuroleptic-naive patients at the time of the first scan, a higher daily medication dose as measured over the time interval was positively associated with greater reduction in frontal and temporal lobe volumes [#9].²³ In a study in chronically ill patients with a 10-year scan interval, there was no significant correlation between ventricular enlargement and daily antipsychotic medication intake dose [#7].²¹ Finally, in another study, patients were treated with typical antipsychotic medications until the first MRI scan after which they were switched to olanzapine and rescanned 1 year later. Compared with controls, in the patients there was a relative decrease in thalamus volume over the interval compared with controls. At baseline, the thalamus was larger in patients as compared with controls [#7].¹⁹

First Episode Directly Compared With Chronically Ill Patients

In 2 studies MRI brain scans from chronically ill schizophrenia patients included in longitudinal studies were

directly compared with patients who were experiencing their first psychotic episode of the illness. In one study with a 2-year follow-up period, the rate of whole brain volume loss was not different in first-episode patients as compared with chronically ill patients [#5].¹⁹ In the second study, left frontal and bilateral temporal lobe reductions over a 2-year interval were more pronounced in neuroleptic-naive patients as compared with chronically ill patients who had not received antipsychotic medication at least 2 weeks before the first scan [#9].²³ Apart from these studies, there is a third study in which both first-episode patients as well as chronically ill patients were examined over a 5-year interval period. First-episode patients had received antipsychotic medication at the time of the first scan. No direct comparison between the 2 patient groups was made. However, a post hoc analysis done for the purpose of this review revealed no significant differences in the extent of brain volume loss over the 5-year interval in the first-episode patients as compared with the chronically ill patients (N. E. van Haren, H. E. Hulshoff Pol, H. G. Schnack, unpublished data based on [#1]).¹⁴

Studies With 3 Measurements

In 2 studies 2 follow-up measurements were included. In both studies, MRI scans were made in patients and controls after a 4- to 5-year interval and again after a 10-year interval. In one study the patients were in their first episode at the time of the baseline measurement [#4],¹⁸ whereas in the other study patients were already in a chronic phase of their disease at the time of the baseline measurement [#7].²¹ In both studies it was found that the most pronounced changes in lateral ventricle volumes seemed to be present during the second interval. In the study that also measured changes in brain tissue (ie, left and right hemisphere volumes) at 2 consecutive intervals, these were found to be more pronounced during the first interval as compared with the second interval [#4].¹⁸

Discussion

This article reviewed 11 longitudinal MRI (9) and CT (2) imaging studies including an average (min-max) number of 28 (10–96) patients with chronic schizophrenia and 24 (5–113) healthy comparison subjects. On the basis of this review, we conclude that brain volume changes are progressive over the course of the illness in chronically ill adult-onset schizophrenia patients. Thus, the progressive brain volume changes in schizophrenia are not limited to the early (first episode) phase of the disease. In fact, ongoing decreases in brain tissue and increases in lateral ventricle volumes are found in patients who have been ill for more than 20 years. More pronounced brain tissue decreases and/or lateral ventricle/CSF volume increases in the patients were associated with poor outcome, more severe negative symptoms, and worsening of cogni-

tive function. Higher cumulative dose of antipsychotic medication intake during the interval was either not associated with brain volume changes or with less prominent brain volume changes. Finally, the 2 studies that included 3 measurements revealed no clear indication that progressive brain changes leveled off with increased illness duration. Thus, in chronically ill patients with schizophrenia, continuous progressive brain tissue loss is occurring many years after the onset of the illness.

How Extensive Is the Progressive Brain Volume Loss in Schizophrenia?

Progressive brain tissue loss is in the order of a few tenths of percent yearly in patients with schizophrenia beyond the first episode, with an average value of approximately -0.5% tissue decrease per year and up to twice that found in healthy comparison subjects (-0.2% per year). However, effects varied considerably across studies, and direct estimations of the extent of progressive brain tissue decrease in patients across studies are complicated by variation in acquisition and processing methodology. Therefore, to estimate the milliliter brain tissue loss we based our calculations on our own study only. In that study on average a -0.3% (a -1.5% change divided by the 5-year interval) per year tissue loss was found in 96 patients per year, which was approximately twice that of healthy comparison subjects (-0.15%) [#1].¹⁴ These percentages were in between those found for the combined effect, and therefore seem representative. Considering an average young adult brain volume of approximately 1150 ml (based on 113 healthy subjects from [#1]),¹⁴ this percentage amounts to brain tissue loss of 69 ml after 20 years of illness as compared with 34.5 ml brain volume loss in controls after 20 years. Thus, the loss in brain tissue that occurs in patients in excess of that which is due to normal aging is estimated at $69 - 34.5 = 34.5$ ml. This calculation is based on the assumption that tissue loss remains constant over an interval of 20 years. Moreover, this calculation does not take into consideration a small overestimation which occurs when extrapolating the extent of brain tissue loss over a longer period than the actual scan interval. Also, the calculation does not take into account decreases already present in brain tissue at the time of the first measurement, resulting in a small underestimation of the total tissue loss after 20 years. Despite these limitations, it seems reasonable to state that after 20 years of illness, patients show a cumulative loss of brain tissue in the order of 34.5 ml in excess of what is expected with normal aging, using 1150 ml as a reference brain size. This cumulative loss of brain tissue results in a 3% overall brain volume loss after 20 years of illness. Interestingly, 3% volume loss was also found in a meta-analysis of cross-sectional structural brain imaging studies in schizophrenia as compared with control subjects.¹

Comparing Brain Imaging With Postmortem Studies in Schizophrenia

The loss in brain tissue that patients have in excess of that due to normal aging (ie, 34.5 ml) is comparable with that which has been reported on average in postmortem studies of brain weight in patients with schizophrenia as compared with comparison groups. Based on 6 studies reviewed in Brown et al.²⁶ and summarized in Johnstone and Owens²⁷ the difference in weight between patients with a functional psychosis (diagnoses included functional psychotics, dementia praecox, and schizophrenia with defect state) as compared with the control group (based on norms of Marchand; norms of Vierodt; combined norms of Taguchi, Hasa, and Kurikawa; and norms for Roessle and Roulet) was on average -38 g.^{28–34} For the calculation of this average weight difference between patients and controls, a correction for the number of patients was done to prevent that relatively small studies would have a disproportionate influence as follows: The provided average difference in brain weight of each of the 6 studies was multiplied by the number of patients included in each study. The brain weight differences multiplied by the number of patients in each study were then summed and divided by the total number of patients included in all the studies: $[50 \text{ g} \times 185 + 19 \text{ g} \times 55 + 34 \text{ g} \times 101 + 63 \text{ g} \times 106 + 87 \text{ g} \times 95 + 1 \text{ g} \times 219] / 761 = -37.96$ g. Because 1.06 g of brain weight stands approximately for 1 ml (or 1 mm³) brain volume, (based on)³⁰ the brain tissue loss over 20 years that patients show in excess of normal aging equals $-34.5 \times 1.06 = -36.6$ g. Thus, the extent of brain tissue loss as found based on longitudinal MRI studies in chronic schizophrenia is remarkably similar to the -38 g found in postmortem studies in schizophrenia. Indeed, the suggestion that estimations of tissue loss in schizophrenia based on longitudinal imaging studies are overrated and inconsistent with the postmortem findings³⁵ is therefore not supported by the findings of this review. Estimates implying a dramatic brain tissue loss in schizophrenia are probably based on the extent of volume loss in the first few months around the first episode in patients. Brain volume decreases of 1.2% have been reported over a 1-year interval.⁶ Indeed, an extrapolation of this rate of loss over a 20-year period would have resulted in considerably more volume loss than is actually found in chronically ill patients. That studies including 3 measurements did not find consistent evidence for differences between the first and second interval in brain tissue loss could be due to the larger (4–5 year) intervals. Apparently, brain volume loss in the first few months at and after onset of the first symptoms of schizophrenia is considerably larger than in subsequent stages of the illness. Although progressive brain tissue loss continues in the chronic phase of the disease, it does so at a slower rate.

Regional Differences in the Rate of Progressive Brain Changes in Schizophrenia

In some brain areas, a more pronounced progressive brain tissue loss was found than in other areas. In fact, the progressive brain volume [#1][#6][#9]^{14,20,23} and brain density [#1]¹⁵ changes may be most evident in the frontal and temporal brain regions. In addition, progressive decrease in density of the right caudate and right thalamus was found in patients [#1].¹⁵ Hippocampus volume did not change over time in patients as compared with controls in the 2 studies that measured this structure [#3][#5]^{17,19} and also did not show progressive density changes in a VBM study [#1].¹⁵ Thus, it seems that (cortical gray matter) brain areas which show the most pronounced changes in schizophrenia^{10,36} are those which also show the most prominent progressive changes, with the possible exception of the hippocampus.

More pronounced progressive *increases* in brain volumes have been reported in overall (but not focal) white matter volume [#1].^{14,15} The increase in white matter volume did not compensate for the decrease in gray matter volume. Moreover, the progressive increases in white matter volume do not imply that overall there is no white matter decrease in patients with schizophrenia. A small decrease in overall white matter volume was reported in a meta-analysis of imaging studies.¹ Also, in the baseline measurement of the sample, decreases in frontal white matter volume were found in patients with schizophrenia as compared with the controls,⁴ as well as decreased density in the anterior corpus callosum based on VBM.³⁷ The progressive increase in white matter volume probably warrants further study especially in light of current findings in schizophrenia using diffusion tensor imaging^{38,39} and gene expression studies in schizophrenia postmortem samples.⁴⁰

Increased lateral ventricle volume is the brain change most often reported in schizophrenia. Ventricular volume change is considered to reflect changes in brain tissue surrounding it. Indeed, associations between ventricular size and brain structure have been found.³⁷ The increase is approximately 20% when comparing volumes in patients with those in healthy comparison subjects.^{1,4} For an extensive review, see Johnstone and Owens.²⁷ Here we briefly touch upon some studies for the discussion on longitudinal changes. After the cross-sectional landmark article revealing increased ventricular volume in chronically institutionalized patients with schizophrenia using CT,⁴¹ several other CT studies in schizophrenia were completed. The results of these studies confirmed increased lateral ventricle volumes in patients with schizophrenia. However, from the CT studies it was also concluded that the lateral ventricle volume increase in chronically ill patients was not progressive.⁴² The conclusion was largely based on cross-sectional studies in which no significant associations with duration of illness were

reported. In addition, it was based on longitudinal CT studies in which no evidence for progressive changes in lateral ventricle volume in patients was found in 4 of 5 studies.^{43–46} The discrepancy between the lack of progressive findings in those longitudinal CT studies and the consistent finding of progressive lateral ventricle volume changes in the CT and MRI studies reviewed here probably is attributable to methodological issues. One such methodological issue concerns failing to include a healthy control group.^{43–46} This makes longitudinal findings in patients impossible to interpret in light of the continuous changes that take place in the brain with increasing age. Because inclusion of a healthy control group was a criterion for a study to be included in the current review, these longitudinal CT studies were not included. Also, differences in the methodology between CT and MRI may have resulted in a lack of finding progressive brain changes in the earlier schizophrenia (CT scan) studies: slice thickness of around 5–10 mm as was used in CT studies made the measurements cruder than those of the later MRI studies using a slice thickness of 1.2–1.5 mm. To measure the subtle changes in brain morphology that occur in patients and find these to be significantly different from normal (eg, 1.67 ml (9.6%) ventricle volume increase in patients compared with 1.02-ml (6.9%) increase in controls after a 5-year period [#1],¹⁴ high-resolution images are needed. Finally, the processing of the older CT images as compared with the newer CT and MRI studies probably resulted in discrepancies between those studies and the current ones. The older studies were based on area measurements of the ventricular system at its largest. Slice orientation could influence the area measure considerably. Instead, the newer studies used more realistic volume measurements.

Clinical Severity and Progressive Brain Changes

In only a few studies were clinical parameters examined in relation to possible changes in brain volume over time. Those that did found that patients with a poor disease outcome display more pronounced brain tissue loss as compared with patients with a relatively good outcome. There was one notable exception of a study in which improvement of symptoms (particularly of affective flattening and avolition) over time was associated with more pronounced brain volume loss (#9).²³ In one other study, more severe negative symptoms were associated with more pronounced brain volume decreases [#7].²¹ Moreover, in 2 studies, no such associations were found [#1][#4].^{14,18} Overall, some results are thus in line with a review on cross-sectional MRI studies that related poor outcome of the disease to larger brain tissue decreases and lateral ventricle volume increases in patients as compared with controls,⁴⁷ but results are not conclusive. The counterintuitive finding of an association of improvement of symptoms with more pro-

nounced brain tissue loss is not easily explained by a chance finding because several indicators of symptoms showed a comparable pattern. Although speculative, the brain tissue loss could involve some sort of adaptation, resulting in alleviation of symptoms.

Only one study examined the association between several cognitive measures and progressive brain volume changes in schizophrenia. It was found that a more pronounced cognitive decline over a 2-year interval was associated with more prominent frontal and temporal lobe volume decreases over that same time interval [#9].²³ In that study one exception was reported, ie, a worsening of verbal functioning associated with less temporal lobe volume decrease after the 2-year interval [#9].²³ This counterintuitive finding may be a chance finding among several other neurobehavioral correlations with brain structure changes. Alternatively, it may be explained by the relative improvement in clinical symptoms that also occurred in association with more pronounced brain tissue loss over the time interval. However, overall, studies seem to show that patients with a worse clinical outcome display more pronounced progressive brain tissue volume loss.

Antipsychotic Medication Intake and Progressive Brain Changes

Antipsychotic medication intake has been considered to constitute an important potential confounder of the progressive brain volume changes in schizophrenia. Because virtually all schizophrenia patients receive antipsychotic medication at some point during their illness, it is very problematic to establish the extent of the influence of medication of brain volume in schizophrenia. Assessing the association of cumulative (daily) dosage of antipsychotic medication intake of patients during the interval with the brain volume changes during that same period allowed us to make a reasonable estimate of its influence. Interestingly, in the studies in chronically ill patients reviewed here, 3 of 4 studies showed no association with cumulative medication intake or a positive association (ie, more cumulative antipsychotic medication intake was associated with less volume decrease or with volume increase), whereas in 1 study a negative association was found (ie, more cumulative antipsychotic medication intake was associated with more pronounced thalamus volume decrease, but at baseline the thalamus was increased in patients). Thus, overall, the progressive brain volume changes in these chronically ill patients cannot be explained by antipsychotic medication intake. Possibly, (atypical) antipsychotic medication may even counteract brain volume loss.

Indications that antipsychotic medication influences brain structure in schizophrenia have been reported. An increase in caudate nucleus volume was found to be associated with typical antipsychotic medication in

first-episode patients.⁴⁸ This influence of typical antipsychotic medication could be reversed following exposure to atypical antipsychotic medication.^{49,50} Indeed, differential effects on basal ganglia volume of atypical (decrease) as compared with typical (increase) antipsychotic medication on progressive brain changes in the caudate nucleus have been shown in chronically ill patients within the schizophrenia spectrum.⁵¹ The only study to date that was designed to measure the influence of antipsychotic medication on overall gray matter volume change involved a double-blind randomized multicenter trial in first-episode patients. First-episode patients randomized to haloperidol showed progressive brain volume changes while patients randomized to olanzapine did not as compared with healthy comparisons.⁵² These studies were not included in the review because they did not include a control group, and could therefore not report on the normal changes expected during the scan interval, or involved first-episode patients only. In chronically ill patients, there is almost always a long history of medication intake prior to the first MRI scan which often is impossible to track retrospectively in a reliably manner. Thus, the influence of prior antipsychotic medication intake upon the progressive changes that take place in a later stage of the disease is very difficult to establish. Nevertheless, the findings in first-episode patients do corroborate the results from a longitudinal study largely consisting of chronically ill patients. More olanzapine intake during a 5-year interval was associated with less decrease in cerebral (gray matter) volume and with less gray matter density decrease in the left superior frontal cortex, and typical antipsychotic medication use was associated with an increase in basal ganglia density in patients [#1].^{14,15}

In conclusion, we do not find evidence for typical or atypical antipsychotic medication intake as the explanatory factor in the progressive brain changes in schizophrenia. However, we have to take into consideration that this conclusion is based on a lack of association or protective association between cumulative (atypical antipsychotic) medication intake during the scan interval. Indeed, possible influences of reversibility, dose correlation, and the specific characteristics of brain volume changes induced by different antipsychotics have not been adequately studied. Moreover, dose equivalency between different antipsychotics is not clearly established.

Delay of Untreated Psychosis, Medical Diseases, Drug Abuse, Age, and Gender

A longer delay of untreated psychosis (DUP) has been associated with more pronounced (superior) temporal lobe gray matter decreases in patients with a first-episode psychosis (included were patients with schizophrenia, affective, and other psychosis)⁵³ and in schizophrenia patients with less than 5 years of illness duration.⁵⁴ How-

ever, no associations with progressive changes in chronically ill patients were reported that measured longitudinal changes in brain structure over time in the studies reported in the current review. Thus, influences on progressive brain volume changes in chronically ill patients of a progressive pathological process that is active prior to treatment, a more insidious onset of illness, or a later presentation to services⁵³ that may be related to a longer DUP are inconclusive. Medical diseases and drug abuse were exclusion criteria in the majority of studies (at least 8) and were not found to influence the results in one other study, implying that medical disease and drug abuse could not explain the findings.

Healthy comparison subjects were matched to the patients' groups for age in 8 studies, controlled for statistically in 2 where patients were on average older, whereas in 1 study the patients were younger than the control subjects, making findings, if anything, more conservative in the direction of the patients. Therefore, it is unlikely that differences between groups in age explained the findings. Gender was matched between patients and controls in 5 studies, in 4 studies males were relatively more represented than females among patients as compared with controls, whereas in 1 study females were relatively more represented than males. Thus, gender was not well accounted for in half the studies. However, considering that longitudinal brain volume changes did not seem to differ between males and females (#1),¹⁴ gender is unlikely to have confounded results in the studies.

What Underlies the Progressive Brain Volume Changes in Schizophrenia?

The finding that progressive brain changes are continuing in chronically ill patients provides suggestive evidence for one or more active pathophysiological processes taking place in the brains of these patients. Finding pathophysiological processes underlying the progressive brain changes in schizophrenia is of importance because this knowledge may ultimately enable us to halt or even reverse the disease process. As to the nature of the pathophysiological process underlying the progressive brain changes in schizophrenia we can only speculate at this point. Postmortem studies have revealed possible myelin-related dysfunction,⁴⁰ and this could be responsible for the ongoing decreases in brain tissue. Changes in dynamic properties of neural networks in adulthood could also be responsible for the progressive brain changes in schizophrenia. It is known from electron microscopy studies in rodent brains that neural circuits are sculpted by spontaneous activity and sensory experience.⁵⁵ Also, evidence is accumulating that functional rewiring takes place in the adolescent and adult rodent brain, which may involve structural alternations with synapse formation and elimination.^{56,57} In addition to synaptic remodeling, evidence suggests that action potential firing can

influence myelination.⁵⁸ Thus, possibly, in schizophrenia the progressive volumetric changes represent aberrant dynamics of functional neural networks. These can now be studied using, eg, resting-state functional MRI.^{59,60} In light of the dopamine hypothesis of schizophrenia with its suggested dopaminergic hypofunction in the frontal lobe,⁶¹ poorer functional processing as found in schizophrenia has not been directly related to progressive brain changes in schizophrenia. However, in recent-onset schizophrenia patients, it was recently shown that auditory mismatch negativity (MMN) reduction at longitudinal testing was highly correlated with longitudinal left hemisphere Heschl gyrus reduction.⁶² Auditory MMN is a bioelectric brain index of functional echoic memory processes arising mainly from the temporal lobe auditory cortex in and around the Heschl gyrus.⁶² Thus, the presence of interrelated structural and functional progressive abnormalities in the temporal cortex in schizophrenia suggests that progressive structural brain changes in schizophrenia may underlie functional brain changes in these areas, or vice versa. Involvement of genetic or familial factors upon the progressive brain changes in schizophrenia was recently suggested in a study in childhood-onset schizophrenia and their healthy siblings. Decreases in the prefrontal and temporal gray matter cortical thickness appeared to be a familial trait marker. However, the loss of cortical thickness in the siblings disappeared by the age of 20.⁶³ Considering the apparent influence of gene (or familial) factors upon brain structure in schizophrenia⁶⁴ and in healthy subjects,⁶⁵ further studies to assess the influence of genetic or familial influences upon progressive brain changes in schizophrenia seem warranted.

Also of relevance are further studies into longitudinal brain changes in healthy subjects because knowledge of these processes may aid us in finding aberrant processes in schizophrenia. Importantly, high-field and ultrahigh field (3 T and 7 T) MRI may enhance our possibilities to search for some clues about pathophysiological processes responsible for the progressive brain changes in schizophrenia. At 7 T the resolution is approximately 0.5 mm for structural brain measurements. This resolution can be enhanced in measurements focusing on particular brain areas. These new methods may allow us to zoom in on areas of progressive brain changes, particularly the frontal and temporal lobes, as well as on white matter fibers connecting these areas, such as the uncinate fasciculus. New imaging acquisition procedures that may aid in getting closer to the pathophysiological processes taking place in the brains of patients with schizophrenia are diffusion tensor imaging fiber tracking and resting-state functional MRI. At high and ultrahigh field MRI these methods may allow us to study local neural networks in the brain. With these new methods we can be carefully optimistic about the future progress in finding pathophysiological processes in schizophrenia.

There are limitations in this review which have to be considered when interpreting its findings. First and foremost, conclusions of ongoing progressive brain tissue loss in schizophrenia were based on studies in adult-onset and chronically ill patients as compared with controls only. A relatively limited number of such studies were conducted. We chose to include studies applying different acquisition methods (ie, MRI and CT) and different processing methods (areas, volumes, and densities measured using VBM). Direct comparison of findings from these different methodologies has limitations. However, within-subject measurements of multiple scans in longitudinal studies makes the direction of the effects (increase or decrease) rather straightforward. Finally, because all but 2 studies included 2 measurements only, we could make inferences as to what other dynamic changes may or may not have taken place during the follow-up period.

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