

Changes in Cortical Thickness During the Course of Illness in Schizophrenia

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Context: Whether cortical thickness changes in schizophrenia over time are more pronounced relative to the changes that can be attributed to normal aging has not been studied.

Objective: To compare patients with schizophrenia and healthy control participants on cortical thickness change.

Design: A 5-year longitudinal study comparing schizophrenic patients and healthy controls using 2 magnetic resonance images of the brain.

Setting: Patients were recruited from the Department of Psychiatry at the University Medical Centre Utrecht and from other psychiatric hospitals in the Netherlands. Healthy controls were recruited via advertisement in newspapers and notice boards.

Participants: Ninety-six schizophrenic patients and 113 healthy controls aged 16 to 56 years.

Main Outcome Measures: Cortical thickness and change in cortical thickness on a vertex-by-vertex basis across the cortical mantle, measures of functional and symptomatic outcome, and cumulative intake of antipsychotics during the scan interval.

Results: At baseline, the schizophrenic patients had thinner left orbitofrontal and right parahippocampal and superior temporal cortices and a thicker superior parietal lobule and occipital pole compared with the controls. Mean cortical thickness did not differ between the groups. Over time, excessive cortical thinning was found in widespread areas on the cortical mantle, most pronounced bilaterally in the temporal cortex and in the left frontal area. Poor outcome in patients was associated with more pronounced cortical thinning. Higher cumulative intake of typical antipsychotics during the scan interval was associated with more pronounced cortical thinning, whereas higher cumulative intake of atypical antipsychotic medication was associated with less pronounced cortical thinning.

Conclusions: In schizophrenia, the cortex shows excessive thinning over time in widespread areas of the brain, most pronounced in the frontal and temporal areas, and progresses across the entire course of the illness. The excessive thinning of the cortex appears related to outcome and medication intake.

Arch Gen Psychiatry. 2011;68(9):871-880

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EVIDENCE IS ACCUMULATING that schizophrenia is characterized by excessive loss of cerebral gray matter (GM) volume over time in the early^{1,2} and chronic³ stages of the disease. Because most GM tissue is found in the cortex, excessive cortical thinning may explain part of the excessive decreases in GM volume reported in this disease. Indeed, a number of cross-sectional studies have found that cortical thickness, particularly in frontal and temporal regions, is thinner in patients with childhood-onset,⁴ first-episode,⁵ and chronic^{6,7} schizophrenia compared with healthy control individuals (but see Wiegand et al⁸). However, unlike changes in global GM in schizophrenia over time, cortical thickness has not been studied longitudinally, to our knowledge, except in patients with childhood-onset

schizophrenia.⁹ That study found excessive thinning in the parietal cortices, progressing anteriorly into the temporal lobes, sensorimotor and dorsolateral prefrontal cortices, and frontal eye fields in the patients as they develop through adolescence. Thinning in the areas that consistently show decreased volume in schizophrenia in cross-sectional studies, such as the dorsolateral prefrontal cortex and superior temporal gyri,¹⁰ occurred last in these children.

This study examined change in cortical thickness over time by repeating magnetic resonance imaging (MRI) brain scans after a 5-year interval in patients with schizophrenia and matched healthy controls in adulthood. At the follow-up measurement, 19 patients had an illness duration of less than 2 years, whereas the others were chronically ill. In areas showing progressive decrease in cortical thickness, we in-

Table 1. Demographic Characteristics at Inclusion and Follow-up of Patients With Schizophrenia and Healthy Control Individuals^a

Characteristic	Patients With Schizophrenia (n=96)	Healthy Controls (n=113)
Sex, No. of participants		
Male	70	76
Female	26	37
Age at inclusion, y	32.22 (11.10) [16.88-56.25]	35.28 (12.25) [16.75-56.27]
Handedness, right/left/ambidextrous, No. of participants	83/10/3	96/15/2
Level of education, y ^b	11.10 (3.00)	12.04 (2.83)
Parental level of education, y	12.00 (3.43)	12.18 (3.14)
Follow-up duration, y	4.83 (0.55) [3.48-6.34]	4.94 (0.32) [4.15-5.71]
Age at first psychotic symptoms, y	21.27 (5.41)	...
Duration of illness, y	10.95 (10.23) [0.40-36.25]	...
PANSS score at inclusion		
Positive symptoms	16.88 (5.79)	...
Negative symptoms	17.79 (5.49)	...
General psychopathologic symptoms	35.72 (8.31)	...
PANSS score at follow-up		
Positive symptoms	13.75 (5.23)	...
Negative symptoms	13.22 (6.03)	...
General psychopathologic symptoms	26.75 (8.32)	...

Abbreviations: ellipses, not applicable; PANSS, Positive and Negative Syndrome Scale.

^aUnless otherwise indicated, data are expressed as mean (SD) or mean (SD) [range].

^bLevel of education was significantly lower in patients than in controls ($P=.02$).

investigated whether the cortical changes were modulated by clinical variables, such as the stage and outcome of the illness and antipsychotic treatment during the scan interval.

METHODS

SUBJECTS

We performed a 5-year follow-up MRI study that included schizophrenic patients and healthy controls. At inclusion, 154 patients and 156 healthy controls underwent scanning.¹¹ A total of 96 patients (70 male and 26 female) and 113 controls (76 male and 37 female) completed the longitudinal study and underwent re-scanning after an interval of 5 years. The study was approved by the Human Ethics Committee of the University Medical Center Utrecht. Written informed consent was obtained for all participants. Change in global brain volumes and in GM and white matter (WM) density in this sample has been described previously.^{12,13} Demographic information is given in **Table 1**.

Procedures for clinical assessment have been described in detail by Hulshoff Pol et al¹¹ and van Haren et al.¹³ In short, individuals with a major medical or neurological illness, including past head trauma, hypertension, cardiac disease, diabetes mellitus, cerebrovascular disease, epilepsy, migraine, endocrine disorders, and alcohol or other drug dependence, or with an IQ of less than 80 were excluded at baseline measurement. At inclusion and follow-up, the presence or absence of psychopathologic symptoms was established by using the Comprehensive Assessment of Symptoms and History (CASH)¹⁴ and was assessed by 2 independent raters (among others, N.E.M.vH. and W.C.). Diagnostic consensus was achieved in the presence of a psychiatrist (W.C.). At follow-up, all patients met criteria for schizophrenia except for 4 who received a diagnosis of schizoaffective disorder. Three patients received the additional DSM-IV diagnosis of drug abuse or dependence at follow-up as measured with the alcohol and other drug section of the World Mental Health Composite International Diagnostic Interview. Severity of illness was measured with the Positive and Negative Syndrome Scale.¹⁵ Outcome was assessed using

the Global Assessment of Functioning (GAF)¹⁶ and the Camberwell Assessment of Need.¹⁷ Age at the onset of illness was defined as the first time the patients experienced psychotic symptoms, as obtained from the CASH interview.¹⁴ Duration of illness was defined as the time from age at the onset of illness to age at the first MRI scan. Information on the number of hospitalizations and the total duration of hospitalization during the scan interval was obtained from the CASH interview. Of the patients who participated at follow-up, 19 had recent-onset illness, with a duration of less than 2 years, and 77 had chronic illness at inclusion in the study based on the CASH interview and clinical records. Patients gave permission to have their treating physician or nurse contacted for further information, and medical records were used when necessary. To calculate the cumulative dosage of typical antipsychotics during the scan interval, a table from the Dutch National Health Service was used to derive the haloperidol equivalents.¹⁸ For atypical antipsychotics, the respective pharmaceutical companies suggested conversion rates for determining haloperidol equivalents (clozapine, 40:1; olanzapine, 2.5:1; risperidone, 1:1; sulpiride, 170:1; quetiapine fumarate, 50:1; and sertindole, 2:1). No reliable information on medication intake during the scan interval was available for 6 patients. Clozapine and olanzapine were the types of atypical antipsychotics most often prescribed. Of the 96 patients included in the follow-up study, 36 (38%) were prescribed only atypical antipsychotics during the interval, whereas only 10 (10%) were taking typical medication exclusively. The remainder of patients had received both types of medication in the period between the scans (**Table 2**).

All healthy controls met research diagnostic criteria¹⁹ for never being mentally ill and had no first-degree family members with a psychotic illness. The controls were matched for age, sex, handedness, socioeconomic status of their parents (expressed as the highest level of education completed by one of the parents), and follow-up duration.

BRAIN IMAGING

Magnetic resonance images were acquired on a scanner operating at 1.5T in all participants (Philips NT; Philips Health-

Table 2. Cumulative Medication Intake During the Scan Interval for 96 Patients With Schizophrenia

Type of Antipsychotic (No. of Patients) ^a	Cumulative Dose			
	Typical Antipsychotic, HEQ/y	Atypical Antipsychotic, HEQ/y	Clozapine, mg/y	Olanzapine, mg/y
Only typical (n=10)	1827 (1238)			
Only atypical (n=13)		1718 (1039)		4895 (2622) (n=10)
Only clozapine (n=14)			126 615 (42 247)	
Atypical + clozapine (n=9)		946 (879)	72 080 (30 138)	2121 (1998) (n=7)
Typical + atypical (n=8)	716 (557)	976 (491)		2183 (1728) (n=4)
Typical + clozapine (n=15)	290 (483)		109 887 (50 057)	
Typical + atypical + clozapine (n=20)	283 (314)	698 (742)	63 198 (46 185)	1447 (1321) (n=16)

Abbreviation: HEQ, haloperidol equivalents.

^aDuring the scan interval, 52 patients switched between at least 2 typical antipsychotics, atypical antipsychotics, and clozapine. For example, 43 of these patients used typical antipsychotics at some point during the scan interval, but also took atypical antipsychotics and/or clozapine. One patient took no antipsychotics, and information was missing for 6.

care, Best, the Netherlands). The protocol for acquisition of the T1-weighted (voxel size, $1 \times 1 \times 1.2 \text{ mm}^3$) and T2-weighted (voxel size, $1 \times 1 \times 1.6 \text{ mm}^3$) images and the preprocessing of the scans has been described in detail.¹¹ In short, T1-weighted images were put in Talairach orientation (no scaling) and corrected for intensity nonuniformity artifacts.^{13,20} Intensity histogram analysis on the T1-weighted image yielded thresholds for separating brain tissue from cerebrospinal fluid and, within the brain, GM from WM. Segments of GM and WM were created by applying these thresholds to the images.²¹

For the cortical thickness analysis at inclusion, MRI data were available for 154 patients and 156 controls. For 96 patients and 113 controls, follow-up MRI data were suitable for analysis.

To estimate the cortical thickness, we used the CLASP (Constrained Laplacian Anatomic Segmentation Using Proximity) algorithm designed at the McConnell Brain Imaging Centre of the Montréal Neurological Institute.²²⁻²⁴ A 3-dimensional surface consisting of 81 920 polygons was fitted to the WM-GM interface. This defined the inner surface of the cortex, which was then expanded to fit the GM-cerebrospinal fluid interface, thereby creating the outer cortical surface.^{23,24} Cortical thickness was estimated by taking the distance between the 2 surfaces; thus, each polygon vertex on the outer surface had a counterpart vertex on the inner surface. Each participant's thickness measurements were smoothed across the surface using a 20-mm full-width-half-maximum surface-based blurring kernel as performed previously.^{25,26} This method of blurring improves the chances of detecting population differences but also follows the curvature of the surface to preserve any anatomical boundaries within the cortex.²⁷ The surfaces of both measurements for each participant were registered to an average surface created from 152 individuals,²⁸ allowing comparison of cortical thickness locally between participants at baseline and the follow-up measurement. For each person, the change in cortical thickness was calculated for each of the 81 924 vertices.

All MRIs were obtained on the same scanner running the identical scan protocol at both visits. During the study, several software and hardware upgrades took place, which we could not control. All images were processed using the same processing pipeline, using methods that have been thoroughly validated. Patients and controls underwent scanning randomly over time, so a potential scanner drift will be expected to be similar in both groups. Moreover, 5 healthy controls underwent scanning twice within 3 months on the same scanner used in the present study.^{29,30} We found that almost 70% of all vertices reached an intraclass correlation of 0.70 (left, 68%; right, 72%),

whereas more than 80% of vertices had an intraclass correlation of at least 0.50 (left, 84%; right, 86%). Areas of low intraclass correlation (ie, <0.50) were usually small and scattered over the cortex.

STATISTICAL ANALYSIS

First, an analysis was performed to evaluate the cross-sectional differences in cortical thickness at inclusion between the 154 patients and 156 controls. In addition, a within-subject analysis was performed to evaluate cortical thickness change at each point between 96 patients and 113 controls. Finally, the clinical relevance of the areas showing excessive cortical thickness change was investigated.

GROUP DIFFERENCES IN CORTICAL THICKNESS (CHANGE)

Group difference in average cortical thickness (change) across the cerebrum (ie, across all vertices) was calculated by using general linear model univariate analyses, with age and sex as covariates. In addition, group differences in cortical thickness change per vertex were calculated by using regression analyses, with age and sex as covariates. This produced *F* statistics at each vertex for the effect of group (patient or control). Results have been corrected for multiple comparisons using a false discovery rate correction with a false discovery rate of 0.05.³¹ Correlations between cortical GM volume and change¹³ and the mean cortical thickness and change were calculated. The difference in correlation between patients and controls was estimated using a Fisher *r*-to-*z* transformation.

CLINICAL RELEVANCE OF EXCESSIVE CHANGE

For those cortical areas that showed significant differences in cortical thickness change between patients and controls, the vertex with the highest *F* value in a particular area (peak vertex) was identified using visualization software (BrainView; Montréal Neurological Institute, Montréal, Quebec, Canada). This procedure identified a relevant region of interest. In addition, it limited the number of comparisons because, for these vertices, we examined whether the excessive cortical thickness change in patients was clinically relevant.

Several approaches were undertaken. First, based on the median GAF score at follow-up, the patients were divided into a

poor outcome group (n=47) and a good outcome group (n=47) (the GAF score was missing for 2 patients). Cortical thickness change was compared between these groups, with age and sex as covariates.

Second, we compared patients with recent-onset and chronic illness while controlling for age by not excluding the controls from the analysis. For this purpose, the control group was divided into a younger group (<28 years; 37 participants) and an older group (≥ 28 years; 76 participants). Instead of the continuous age variable, a variable age (0, recent onset/young; 1, chronic/older) and the age \times group interaction were added to the regression analyses for each vertex. A significant interaction would indicate that the difference between patients with recent-onset and chronic illness is larger than the difference between younger and older controls. This can then be explained by an effect of illness (which is specific for patients with recent-onset or chronic illness only) in addition to an effect of age (which is present in patients and controls).

Third, as was expected, scores on the Camberwell Assessment of Need, GAF, and Positive and Negative Syndrome Scale at follow-up measurement are highly correlated. Therefore, we performed a factor analysis to estimate from these variables 1 or more factors by using a principal component analysis (no rotations). A new variable was created for each factor in the final solution. Correlation analyses were performed to investigate the associations between the clinical variables (ie, variables from the factor analysis), medication variables, and cortical thickness loss (in peak vertices). In case of a significant correlation between cortical thickness change and a class of antipsychotics, the analysis was repeated, adding individually the dose of the other classes into a partial correlation. The dose was set to 0 when patients never received the class of drug for which the analysis was controlled.

Finally, because patients needing clozapine are also more likely to have a more severe form of schizophrenia, we compared those who received clozapine during the interval with those who did not on clinical measures, baseline cortical thickness, and cortical thickness change using analysis of variance or regression analyses. Within the group of patients who had received clozapine during the interval, the correlation between clozapine dose and outcome was investigated.

DIFFERENTIAL LOSS TO FOLLOW-UP

To investigate a possible differential loss to follow-up in the sample, several clinical and demographic baseline variables were compared between those who did and did not participate in the follow-up using analysis of variance. Also, baseline cortical thickness was compared between those who did and did not undergo follow-up imaging.

We used commercially available statistical software (SPSS, version 17.0, package for Windows; SPSS, Inc, Chicago, Illinois) for these post hoc analyses. Correlations and group comparisons reaching a 2-tailed α level of .01 (uncorrected) are reported.

RESULTS

GROUP DIFFERENCES IN CORTICAL THICKNESS (CHANGE)

No significant differences were found at inclusion in overall mean (SD) cortical thickness between patients and healthy individuals (left side, 2.95 [0.12] mm for patients vs 2.95 [0.12] mm for controls [$P = .18$]; right side, 2.93 [0.13] mm for patients vs 2.93 [0.13] mm for controls [$P = .25$]).

Focal cortical thickness at inclusion revealed a significantly thinner cortex in the left orbitofrontal and right superior temporal cortex and parahippocampal gyrus in patients compared with controls (**Figure**). In addition, areas in the superior parietal lobule and occipital pole were thicker in patients relative to controls. Significance levels after false discovery rate correction were $F = 14.78$ for the left hemisphere and $F = 10.56$ for the right hemisphere.

The correlation between cortical GM volume and overall mean cortical thickness at inclusion was 0.55 ($P < .001$). The correlation did not differ between patients and controls (at inclusion, $r = 0.56$ for patients [$P < .001$] and $r = 0.55$ for controls [$P < .001$]; $P = .90$ between groups).

In healthy individuals, mean cortical thickness change (ie, the average cortical thickness change across all vertices) during the 5-year interval was minimal (mean [SD] = -0.01 [0.07] mm after 5 years). In 49 (57%) of the healthy controls, mean cortical thickness across the brain decreased during the 5-year interval, whereas the remaining 49 (43%) showed an increase in mean cortical thickness. In patients, the decrease in mean cortical thickness across the brain was significantly more pronounced (mean [SD], -0.05 [0.08] mm after 5 years; $P < .001$), showing decreases in 72 (75%) of the patients. The correlation between cortical GM volume change and mean cortical thickness change was 0.55 ($P < .001$). The correlations did not differ between patients and controls ($r = 0.55$ for patients [$P < .001$]; $r = 0.48$ for controls [$P < .001$]; $P = .41$ between groups).

Excessive focal decreases in cortical thickness during the 5-year interval ranging from 0.05 to 0.19 mm (false discovery rate–corrected $F_{\text{left}} = 7.56$; false discovery rate–corrected $F_{\text{right}} = 7.23$) were found in patients relative to controls (**Table 3**). The **Figure** and **Table 3** demonstrate extensive areas in the frontal and temporal cortices with excessive decrease in cortical thickness in patients on the left side of the brain. Right-sided excessive decreases were pronounced in the frontal lobe, the posterior inferior temporal cortex, and the cuneus. No significant increases in cortical thickness during the 5-year interval were found in patients relative to controls, as is visible from the **Figure**.

CLINICAL RELEVANCE OF EXCESSIVE CHANGE

The mean GAF scores of the patients with good and poor outcomes were 38.2 (SD, 10.2) and 66.7 (SD, 9.0), respectively. The median GAF score was 55. The outcome groups did not differ in age, sex, scan interval, socioeconomic status, illness duration, or antipsychotic medication intake. Significantly more pronounced decreases in cortical thickness were found in patients with poor outcomes in the left-sided middle temporal cortex ($P = .04$), superior temporal cortex ($P = .01$), Heschl gyrus ($P = .05$), anterior cingulate ($P = .02$), and right-sided cuneus ($P = .04$) compared with patients with good outcomes.

Characteristics of the patients with recent-onset and chronic illness and the younger and older controls are summarized in the supplementary material (eTable 1, available at <http://www.archgenpsychiatry.com>).

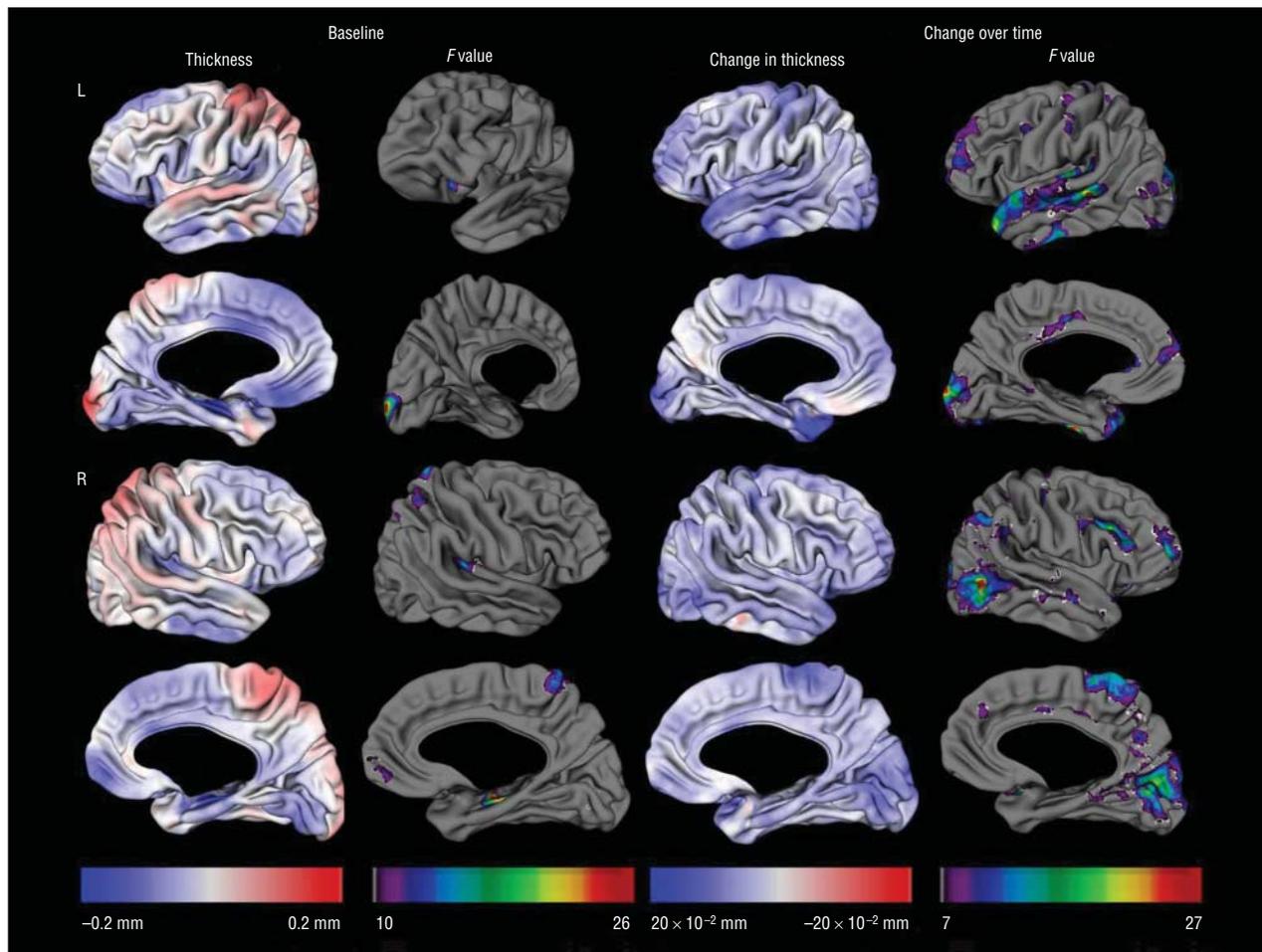


Figure. Maps of change in cortical thickness in millimeters and *F* values, comparing patients with schizophrenia and healthy control individuals. Patients with schizophrenia show cortical thinning/excessive thinning (in blue) or thickening/excessive thickening (in red) compared with healthy controls. Maps with *F* values show where patients ($n=154$) have significantly thinner or thicker cortex relative to controls ($n=156$) at inclusion or where change in cortical thickness during the 5-year interval is significantly more pronounced in patients ($n=96$) relative to controls ($n=113$).

No significant interaction between age (recent-onset illness/young controls vs chronic illness/older controls) and group (patient vs control) was found, indicating that the cortical thickness loss in patients with recent-onset illness relative to their age-matched controls was similar to that in patients with chronic illness relative to controls of comparable age.

The factor analysis revealed that scores on the GAF, Camberwell Assessment of Need, and Positive and Negative Syndrome Scale loaded on 1 component with an eigenvalue of 3.03, explaining 60.5% of the variance. This factor represents functional and symptomatic outcome, and it was used to investigate the clinical relevance of excessive loss in cortical thickness in patients. A higher score on the factor indicates poorer outcome. A significant correlation was found between a peak vertex in the superior temporal cortex and functional and symptomatic outcome, reflecting more thinning in the superior temporal cortex in patients with poorer outcome (**Table 4**). No significant correlations were found between the factor representing functional and symptomatic outcome and any of the variables on medication intake.

Significant correlations between medication variables and cortical thickness change showed that, for typi-

cal antipsychotics, correlations were negative (higher intake was associated with more pronounced decreases in cortical thickness), whereas correlations with atypical antipsychotics were positive (ie, higher intake was related to less decreases in cortical thickness) (Table 4). Specifically, correlations were found between less thinning in several frontal areas and the right cingulate and a higher dose of clozapine per year ($n=58$ patients). These findings did not change after correcting for the dose of typical or atypical medication per year.

Patients who received clozapine during the scan interval had poorer outcomes (indicated by the factor representing functional and symptomatic outcome) than those who did not receive clozapine ($P=.03$). There was no correlation within the group of patients who received clozapine during the interval between the dose and the functional and symptomatic outcome factor. No significant differences were found between the groups on baseline cortical thickness. The patients who received clozapine at some point during the interval showed more pronounced cortical thinning in the left superior temporal cortex compared with those who did not use clozapine ($P=.003$), that is, the same area that showed a significant correlation with functional and symptomatic

Table 3. Areas Showing Excessive Loss of Cortical Thickness in Patients Relative to Healthy Control Individuals

MNI Coordinates, x, y, z	Area	Patients, Mean (SD)		Healthy Controls, Mean (SD)		Change	
		Baseline Value, mm (n=154)	Change, ×10 ⁻² mm/5 Years (n=96)	Baseline Value, mm (n=156)	Change, ×10 ⁻² mm/5 Years, (n=113)	F Value	P Value
Left Side							
-49, -18, -35	Inferior temporal	2.75 (0.36)	-10.31 (26.51)	2.72 (0.36)	7.53 (26.99)	25.31	<.001
-54, -41, 2	Middle temporal	3.01 (0.20)	-5.82 (12.01)	2.98 (0.21)	2.20 (10.80)	24.94	<.001
-38, 20, -38	Superior temporal	3.59 (0.27)	-5.60 (21.64)	3.59 (0.29)	8.20 (21.55)	22.11	<.001
-11, 55, -1	Medial frontal	3.07 (0.21)	-2.23 (14.67)	3.08 (0.18)	4.73 (14.33)	12.64	<.001
-11, 69, 6	Superior frontal	3.09 (0.25)	-2.45 (20.17)	3.07 (0.27)	6.92 (18.33)	13.30	<.001
-29, 53, 2	Middle frontal	3.08 (0.20)	-3.46 (18.98)	3.07 (0.22)	6.01 (16.19)	14.14	<.001
-39, 6, 31	Inferior frontal	3.03 (0.19)	-5.16 (13.28)	3.04 (0.19)	1.25 (11.07)	13.97	<.001
-26, -25, 68	Precentral	2.44 (0.29)	-15.09 (24.27)	2.36 (0.25)	-4.53 (22.37)	11.62	<.001
-38, -23, 52	Postcentral	2.59 (0.27)	-15.29 (21.89)	2.55 (0.28)	-3.71 (26.30)	10.78	.001
-45, -22, 12	Transverse temporal	2.96 (0.27)	-10.41 (14.12)	3.00 (0.26)	-2.06 (13.60)	19.52	<.001
-8, -7, 43	Cingulate	3.33 (0.20)	-3.70 (13.65)	3.34 (0.20)	2.68 (12.26)	12.62	<.001
-7, -101, 8	Cuneus	2.14 (0.25)	-12.48 (21.75)	2.02 (0.23)	1.13 (18.58)	27.32	<.001
-15, 102, 12	Middle occipital	2.12 (0.28)	-10.46 (23.11)	2.02 (0.24)	3.37 (10.14)	23.67	<.001
Right Side							
52, -64, 2	Inferior temporal	2.96 (0.18)	-5.22 (12.61)	2.94 (0.22)	4.75 (15.21)	26.47	<.001
52, -5, -20	Middle temporal	3.34 (0.20)	-5.72 (12.51)	3.33 (0.19)	0.93 (12.30)	13.51	<.001
41, 5, -21	Superior temporal	3.86 (0.36)	-7.36 (50.99)	3.83 (0.35)	0.37 (39.55)	14.03	<.001
6, -10, 65	Medial frontal	2.90 (0.32)	-18.35 (25.25)	2.85 (0.36)	-4.58 (22.23)	17.42	<.001
45, 30, 17	Middle frontal	2.87 (0.19)	-9.95 (14.53)	2.88 (0.22)	-1.40 (12.43)	19.49	<.001
24, 57, -3	Superior frontal	3.04 (0.22)	-1.21 (17.24)	3.03 (0.20)	7.78 (15.92)	17.25	<.001
58, -39, 30	Supramarginal	3.04 (0.19)	-3.96 (12.16)	3.04 (0.17)	2.45 (12.65)	12.69	<.001
53, -48, 42	Inferior parietal lobule	2.99 (0.19)	-6.57 (16.24)	2.95 (0.18)	1.06 (14.08)	13.99	<.001
26, -96, 19	Middle occipital	2.42 (0.25)	-12.30 (19.98)	2.37 (0.26)	-0.77 (18.76)	21.99	<.001
8, 14, 35	Cingulate	3.37 (0.23)	-4.83 (13.24)	3.38 (0.22)	1.77 (13.66)	13.10	<.001
14, -56, 10	Posterior cingulate	3.23 (0.22)	-8.33 (12.65)	3.23 (0.23)	-1.18 (12.57)	17.36	<.001
10, -54, 42	Precuneus	2.91 (0.18)	-6.01 (12.28)	2.90 (0.19)	-0.42 (10.87)	13.24	<.001
3, -73, 15	Cuneus	2.37 (0.24)	-11.03 (14.54)	2.38 (0.25)	-1.61 (16.02)	20.54	<.001
3, -29, 75	Paracentral lobule	2.11 (0.27)	-15.21 (19.16)	2.01 (0.23)	-4.40 (18.02)	15.97	<.001

Abbreviation: Montréal Neurological Institute.

outcome. After correction for outcome, this finding was still trend-level significant ($P = .02$).

DIFFERENTIAL LOSS TO FOLLOW-UP

Baseline characteristics of those who did or did not participate at follow-up are given in the supplementary material (eTable 2). Older participants were more likely to be lost to follow-up; consequently, patients with longer illness duration were less likely to participate at follow-up. No significant differences in baseline cortical thickness were found between patients or controls who were included at follow-up and those who were not.

COMMENT

To our knowledge, this is the first longitudinal brain imaging study measuring cortical thickness change over time in adults with schizophrenia. The main finding of the study was a progressive cortical thinning in patients. Although mean cortical thinning across the cerebrum was minimal in healthy individuals (-0.01 mm after 5 years), that in patients was significantly more pronounced (-0.05 mm after 5 years). The most extensive loss was found in the frontal and temporal areas, but posterior brain areas were also implicated. Thus, to our

knowledge, we show for the first time that the progressive brain tissue loss in schizophrenia^{2,3} is at least in part due to cortical thinning. We found the pattern of progressive tissue loss to be similar in patients with recent-onset illness and those who have been ill for many years. However, we acknowledge that the present study does not have the proper longitudinal design to reliably answer this question because we do not have information on cortical thickness change during the first year of illness.

In addition, we found that, at inclusion, the frontal and temporal cortices were thinner in patients relative to controls, whereas the parietal and occipital cortices were thicker. Because the excessive loss of cortical thickness in patients also affects parietal and occipital areas, it is not surprising that, at the follow-up measurement, a significantly thicker cortex in patients was no longer present (data not shown).

Cross-sectional and longitudinal studies have shown that GM volume change is abnormal in patients with schizophrenia.^{2,3,32} Because most GM tissue is found in the cortex, cortical thinning may in part explain the excessive decreases in cerebral GM volume reported in this disease. Indeed, highly significant correlations were found between the change in cortical GM volume and the mean change in cortical thickness in both patients and healthy

Table 4. Correlations With Clinical Variables and Cumulative Antipsychotic Intake

	Peak Vertex	Pearson Product Moment Correlation	Spearman Rank Correlation	P Value
Clinical factor				
Functional and symptomatic outcome	Left superior temporal	-0.30		.004
Cumulative antipsychotic intake				
Typical (n=53)	Left precentral		-0.36	.008
Atypical (n=50)	Right medial frontal		0.37	.008
Clozapine (n=58)	Left middle frontal		0.40	.002
	Right medial frontal		0.36	.005
	Right cingulate		0.41	.001
	Right superior frontal		0.41	.002

controls. However, these correlations did not explain more than 25% of the common variance, suggesting that cortical thickness and cortical volume are only partially overlapping variables.

Indeed, because cortical GM volume is the product of cortical thickness and cortical surface area, the reduced volume might also be the result of a smaller surface area. The size of the surface area can be estimated using the gyrification index. *Gyrification* refers to the development of the folding surface patterns on the brain that result in a dramatic increase in the cortical surface area and, thus, in the volume of cortical GM. Evidence suggests that the gyrification index, which represents the degree of cortical folding, is reduced in schizophrenia,^{33,34} particularly in bilateral superior temporal sulci, the left middle frontal sulcus, and the Broca area³⁵ (but compare findings by Vogeley et al³⁶). A recent study in high-risk individuals showed a reduction in surface area along with the preservation of or a slight increase in cortical thickness compared with healthy individuals.³⁷ Consistent with the original gyrification study in healthy individuals by Zilles et al,³⁸ increasing age (or, in patients, progression of the illness) appears not to be associated with reductions in the gyrification index (at least in young men), suggesting that measures of gyrification—and, thus, the cortical surface area—are most likely determined by processes in early neurodevelopment.

Based on our finding of no overall thinning of the cortex in the presence of decreased GM volume before follow-up, one may speculate that the decrements of GM volume found at illness onset is more a consequence of a diminished surface area than a result of cortical thinning. In addition, our data suggest that the loss of GM volume over time may be mostly attributable to thinning of the cortex. In other words, the loss of GM volume in schizophrenia may be the result of the following 2 distinct processes: one neurodevelopmental in nature, expressed as a decreased surface area, and one of a more progressive nature, expressed as cortical thinning over time. If that is so, our findings may have important implications in understanding the causes of schizophrenia, suggesting that the brain changes in this illness are the consequence of at least 2 different biological processes. However, our study cannot confirm this hypothesis because our sample consists of patients with recent-onset and those with chronic illness. To test this, a large sample of patients with first-episode illness would need to be followed up for several years.

We found a relationship between excessive thinning over time in the left superior temporal cortex and poor outcome. This is in line with several cross-sectional studies showing smaller GM volume in the superior temporal cortex and thought disorder,^{39,40} hallucinations,⁴⁰ and negative symptoms.⁴¹ Also, earlier longitudinal studies provide evidence of a relationship between excessive brain changes and outcome in patients with chronic illness⁴² and those with first episodes.⁴³ However, other studies report poor outcome to be related to increases in brain volume.^{44,45} This discrepancy might be explained by the fact that brain abnormalities in schizophrenia and outcome are found to be associated with antipsychotic intake.⁴⁶⁻⁴⁸ The interdependence among these 3 domains is rarely investigated. Herein, we showed that functional and symptomatic outcomes were not related to cumulative typical or atypical antipsychotic intake, but we found evidence of the assumption that patients who need clozapine (as a group) are more likely to have a more severe form of schizophrenia. Although this was not reflected in lower baseline cortical thickness, patients receiving clozapine showed more pronounced thinning in the left superior temporal cortex relative to those who were not receiving clozapine during the scan interval. This might be related to the difference in outcome.

That outcome is associated with excessive brain tissue loss independent of cumulative medication intake, suggesting that medication intake cannot explain the relationship between poor outcome and loss of brain tissue, at least in this sample.

Use of antipsychotics, independent of outcome, explained change in cortical thickness in schizophrenic patients. Earlier cross-sectional studies examining cortical thickness in schizophrenia found no evidence of dose or type of antipsychotic causing variation in cortical thickness.⁶⁻⁸ However, Narr et al⁴⁹ found some small circumscribed regions where patients not receiving medication showed a thinner cortex compared with patients who had received medication for 1 week. In our study, we estimated the cumulative intake of antipsychotic medication during the scan interval. However, that treatment assignment during the study was uncontrolled.

Cortical thinning was more pronounced in patients receiving more typical antipsychotics, whereas patients who had used more atypical antipsychotics showed less thinning of the cortex. Protective effects on the brain of

atypical medication intake have been suggested earlier in patients with first-episode disease.⁵⁰ Important in this respect is a recent study showing differential trajectories of cortical development for patients using atypical vs typical antipsychotics. In haloperidol-treated patients, a rapidly advancing parietal-to-frontal deficit trajectory was found that mirrored normal cortical maturation but that was greatly intensified. Areas with the fastest tissue loss shifted anteriorly in the first year of psychosis. This trajectory was not seen in patients treated with olanzapine.⁵¹ On average, patients with recent-onset illness had a lower cumulative dose of typical antipsychotics during the scan interval than patients with chronic illness. If typical antipsychotic medication is indeed associated with more cortical thinning, we might have underestimated the loss of thickness in recent-onset illness relative to chronic illness.

In contrast to our findings, recent human and animal studies provide evidence of volume loss being associated with higher doses of atypical (and typical) antipsychotics. The administration of haloperidol and olanzapine to macaque monkeys during a 2-year period resulted in a significant overall brain tissue loss in both GM and WM across several brain regions.^{52,53} In rats, 8-week exposure to these same compounds resulted in a significant decrease in whole-brain volume (6% to 8%) compared with rats that were not treated with antipsychotics. This volume loss was driven mainly by a decrease in frontal parts of the brain.⁵⁴ Recently, a large longitudinal study showed similar findings in patients with schizophrenia. A higher dose of antipsychotic medication was related to greater loss of GM volume, even after correcting for illness severity.⁵⁵

The strengths of this study are the longitudinal nature and the comparatively large group of participants. In addition, all individuals underwent careful clinical characterization at both measurements. Potential effects of alcohol and other drug abuse or dependence were ruled out because this was an exclusion criterion at baseline. A previous study using this sample⁵⁶ found no evidence that cigarette smoking can explain the excessive GM volume loss in patients, despite the fact that there was a significantly higher percentage of smokers among the patients than the controls.

All MRIs were obtained on the same scanner using the identical protocol at both visits. All images were processed using the same processing pipeline and by methods that have been thoroughly validated.

However, some limitations need to be addressed. First, patients differed in the amount of medication that they had used before inclusion in the study, although reliable information was unavailable on their lifetime cumulative intake. Also, most patients changed medication during the scan interval, making it difficult to reliably investigate the individual effects of different types of antipsychotics. Controlling for the intake of other types of antipsychotics in the analyses would lead to loss of power because the number of study participants would become substantially smaller. Also, no information was available on medication adherence. Second, we found some evidence of a differential loss at follow-up. Patients and controls who completed the follow-up scan did not sig-

nificantly differ in cortical thickness at baseline compared with those who did not. In addition, many correlations were performed to investigate the relationships among cortical thickness change, outcome, and medication intake. We chose a rather liberal significance threshold. Even if we applied a Bonferroni correction for multiple testing (which is a stringent correction), many of the correlations would still be at trend-level significance. However, our conclusions have to be treated with caution.

Finally, a cross-sectional study⁵⁷ of individuals aged 7 to 87 years has shown that the trajectory of normal aging (or maturational) effects varied considerably across the cortex. This finding implies that age might not be associated with change in cortical thickness in a linear fashion. Indeed, from our volumetric findings, we know that, at least in controls, change in whole brain volume does not show a linear fit with age. However, to be able to compare the groups, we chose to correct for age in a linear fashion.

CONCLUSIONS

At the time of inclusion in the study, the overall cortex was not much thinner in patients compared with controls (except for thinning in the frontal and temporal lobes) despite decreased cortical GM volume. In contrast, we found compelling evidence of excessive and progressive thinning of the cortex over time in patients with schizophrenia in widespread areas of the cortical mantle, with the largest loss of cortical thickness in frontal and temporal areas of the brain. Our findings suggest that excessive cortical thinning in these areas still takes place in patients who have been ill for many years and is not limited to the first years after onset of the psychotic symptoms. Thinning of the cortex was mediated by outcome of the illness, as well as independently by the intake of antipsychotic medication. These findings suggest that excessive thinning of the cortex over time in schizophrenia is related to disease-related factors.

Submitted for Publication: November 25, 2010; final revision received April 26, 2011; accepted May 3, 2011.

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Author Contributions: Dr van Haren had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Financial Disclosure: Dr van Haren has received honoraria for educational programs for AstraZeneca, Eli Lilly, and Janssen-Cilag. Dr Hulshoff Pol has received honoraria for educational programs for Ferris and Lundbeck. Dr Kahn has received grants or honoraria for educational programs or has served as a consultant for Astellas, AstraZeneca, BMS, Eli Lilly, Janssen-Cilag, Pfizer, Roche, and sanofi-aventis. Dr Cahn is a member of the advisory boards of Eli Lilly and Janssen-Cilag BV and has received honoraria for educational programs for Eli Lilly,

Janssen-Cilag BV, Bristol-Myers Squibb, Astra Zeneca BV, Organon, and Lundbeck BV. Dr Evans is a paid consultant for Biospective Inc, which is an imaging contract research organization; he is founder and director of the company and receives stock options and licensing fees.

Online-Only Materials: The eTables are available at <http://www.archgenpsychiatry.com>.

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Correction

Incorrect Data. In the Original Article titled “Association of Genetic Variants on 15q12 With Cortical Thickness and Cognition in Schizophrenia” by Bakken et al, published in the August issue of the *Archives* (2011;68[8]:781-790), incorrect *P* values appear in the text, Table 1, and Figures 1 and 4 and the accompanying figure legends. In addition, the text in the “Results” section of the abstract on page 781 should read as follows: “Two closely linked genetic variants (rs4906844 and rs11633924) within the Prader-Willi and Angelman syndrome region on chromosome 15q12 showed a genome-wide significant association ($P=1.08 \times 10^{-8}$) with average cortical thickness and modest association with cognitive performance (permutated $P=.03$) specifically among patients diagnosed as having schizophrenia.” On page 782, in the right-hand column, under the “Genotype” subheading, the third sentence should have read as follows: “A total of 597 198 SNPs passed quality control filters (call rate >95%, minor allele frequency >5%, Hardy-Weinberg disequilibrium $P < 1 \times 10^{-6}$) and were merged with HapMap 3 reference populations.” Also, on page 785, in the right-hand column in the first full paragraph, the third sentence should read as follows: “Furthermore, in a combined sample of patients with schizophrenia and controls, the SNP \times diagnosis interaction *P* value is significant ($P=1.56 \times 10^{-7}$) but less significant than the initial finding among patients with schizophrenia.” Also, on page 787, in the left-hand column in the first full paragraph, the second sentence should read as follows: “Twenty-one SNPs were significantly associated ($P < 1 \times 10^{-7}$) with average cortical thickness and are closely linked ($r^2 > 0.7$) to rs4906844.” The fourth sentence in the same paragraph should read as follows: “Five imputed SNPs show more significant association with cortical thickness than rs4906844 and are within 3.5 kb downstream of this SNP.” On the same page, in the first paragraph beneath the “Comment” heading, the first sentence should read as follows: “In this study, we identified a common genetic variant that is associated with cortical thickness with genome-wide significance ($P=1.1 \times 10^{-8}$), specifically in schizophrenia.” This article was corrected online.