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.

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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 chronic[3] 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 al[8]). 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 (2.82)
Parental level of education, y	12.00 (3.43)	12.16 (3.14)
Follow-up duration, y	4.83 (0.55) [3.48-6.34]	4.84 (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.
[a] Unless otherwise indicated, data are expressed as mean (SD) or mean (SD) [range].
[b] Level of education was significantly lower in patients than in controls ($P=.02$).

vestigated 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 rescanning 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 al[11] 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 criteria[19] 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.

[a] During 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, $1 \times 1 \times 1.2$ mm^3) and T2-weighted (voxel size, $1 \times 1 \times 1.6$ 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 change[13] 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 × 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 controls vs 2.93 [0.13] mm for patients [$P=.25$]).

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 $F_{left}=7.56$; false discovery rate–corrected $F_{right}=7.23$) 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).