Original Investigation

Association of IQ Changes and Progressive Brain Changes in Patients With Schizophrenia

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IMPORTANCE Although schizophrenia is characterized by impairments in intelligence and the loss of brain volume, the relationship between changes in IQ and brain measures is not clear.

OBJECTIVE To investigate the association between IQ and brain measures in patients with schizophrenia across time.

DESIGN, SETTING, AND PARTICIPANTS Case-control longitudinal study at the Department of Psychiatry at the University Medical Center Utrecht, Utrecht, the Netherlands, comparing patients with schizophrenia and healthy control participants between September 22, 2004, and April 17, 2008. Magnetic resonance imaging of the brain and IQ scores were obtained at baseline and the 3-year follow-up. Participants included 84 patients with schizophrenia (mean illness duration, 4.35 years) and 116 age-matched healthy control participants.

MAIN OUTCOMES AND MEASURES Associations between changes in IQ and the total brain, cerebral gray matter, cerebral white matter, lateral ventricular, third ventricles, cortical, and subcortical volumes; cortical thickness; and cortical surface area.

RESULTS Cerebral gray matter volume (P = .006) and cortical volume (P = .03) and thickness (P = .02) decreased more in patients with schizophrenia across time compared with control participants. Patients showed additional loss in cortical volume and thickness of the right supramarginal, posterior superior temporal, left supramarginal, left postcentral, and occipital regions (P values were between <.001 and .03 after clusterwise correction). Although IQ increased similarly in patients with schizophrenia and control participants, changes in IQ were negatively correlated with changes in lateral ventricular volume (P = .05) and positively correlated with changes in cortical volume (P = .007) and thickness (P = .004) only in patients with schizophrenia. Positive correlations between changes in IQ and cortical volume and thickness were found globally and in widespread regions across frontal, temporal, and parietal cortices (P values were between <.001 and .03 after clusterwise correction). These findings were independent of symptom severity at follow-up, cannabis use, and the use of cumulative antipsychotic medications during the 3 years of follow-up.

CONCLUSIONS AND RELEVANCE Progressive brain tissue loss in schizophrenia is related to relative cognitive decline during the early course of illness.

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There is growing evidence for progressive brain alterations in schizophrenia. These changes are manifested as gray matter (GM) volume reduction, lateral ventricular (LV) enlargement, and cortical thinning[1-5] and emerge particularly in the early phase of illness.[6,7] These brain changes appear to be clinically relevant because they are linked to outcome,[4,5,8] although confounding effects of antipsychotic medications cannot be ruled out.[9-12]

Schizophrenia is characterized by global cognitive impairments[13] and deficits in specific domains, such as verbal, memory, and executive functioning.[14] Because multiple cognitive domains are affected in schizophrenia[15] and about half the variance across domains is explained by differences in general cognitive ability,[16] cognitive functioning in schizophrenia is likely to be reflected by changes in IQ. Patients with schizophrenia demonstrate premorbid IQ scores half a standard deviation below that of the general population[17] and there is consistent evidence that IQs in patients with schizophrenia show a declining course well before illness onset.[18] In contrast, it is less clear whether cognitive abilities continue to deteriorate after illness onset. A meta-analysis on IQ changes in patients with schizophrenia concluded that IQ improves less after repeated testing in patients with schizophrenia compared with healthy control participants; however, this conclusion was based on only 8 small case-control studies.[19]

A multitude of studies have found that in the general population, intelligence is positively correlated with intracranium (IC) and brain volume.[20-23] Studies relating IQ changes to brain changes are much more sparse. Several studies in children and adolescents reported that changes in IQ are positively correlated with cortical thickness or volume of the left motor cortex, anterior cerebellum, and frontal lobe, in particular.[24-26]

Johnstone et al[27] reported a significant correlation between cognitive impairments and increased ventricular size in patients with chronic schizophrenia as early as 1976. Since then, correlations between intelligence and the total brain (TB) and GM volumes have been found in patients with schizophrenia.[28-30] Progressive brain volume loss has also been reported in patients with first-episode psychosis with neurocognitive deficits.[31] However, to our knowledge, relationships between the changes in IQ and brain structures across time in schizophrenia have not been examined.

Based on consistent evidence of an association between IQ and brain volume in healthy individuals,[24,32] we investigated whether some of the reported brain volume changes across time in schizophrenia[2,6,7,33] could be explained by changes in IQ during the course of illness. We hypothesized that associations between decreases in IQ brain tissue loss would be more pronounced in patients with schizophrenia compared with healthy control participants.

Methods

Participants

This 3-year longitudinal magnetic resonance imaging (MRI) study is part of the Genetic Risk and Outcome of Psychosis consortium.[34] We analyzed participants recruited at the University Medical Center Utrecht from September 22, 2004, to April 17, 2008.[35] A total of 162 patients with schizophrenia and 167 control participants were assessed at baseline with MRI. We rescanned 94 patients with schizophrenia and 117 control participants. Several participants were excluded for various reasons (eAppendix 1 in the Supplement). Consequently, a total of 84 patients with schizophrenia and 116 control participants participated in the current study. The study was approved by the University Medical Center Utrecht Medical Ethics Committee for Research in Humans. Written informed consent was obtained from all participants.

Demographic information is given in the eTable in the Supplement. Significant differences in sex ratio (patients with schizophrenia included more men compared with control participants), participants' education levels (higher in control participants compared with patients with schizophrenia), and cannabis use during the interval (higher in patients with schizophrenia compared with control participants) were found. The possibility of an attrition bias was investigated by comparing those who did and did not participate on baseline measures (eAppendix 2 and eAppendix 3 in the Supplement).

Diagnosis was established with the Comprehensive Assessment in Neuropsychiatry[36] at baseline and Schedules for Clinical Assessment in Neuropsychiatry[37] at follow-up. The interviews were performed by a trained and independent rater. Patients were only included who fulfilled *DSM-IV* criteria for schizophrenia or schizoaffective disorder at follow-up. In addition, except for 2 patients (1 with pervasive developmental disorder and 1 with major depressive disorder), there were no patients with comorbid disorders at inclusion.

For healthy control participants, inclusion criteria both at baseline and at follow-up were absent of a previous or current psychotic disorder and absent of family history (first- or second-degree family member) of a psychotic disorder as established with the Family Interview for Genetic Studies.[38] None of the participants had a major medical or neurological illness.

Clinical and Neuropsychological Assessments

The IQ scores were based on 4 subtests of the Dutch version of the Wechsler Adult Intelligence Scale III (digit-symbol coding, information, arithmetics, and block design). High correlations were reported between the short version and full-scale IQ for both patients with schizophrenia (R^2 = 0.90) and healthy control participants (R^2 = 0.86).[39] The severity of symptoms was measured using the Positive and Negative Syndrome Scale.[40] Outcome was assessed using the Global Assessment of Functioning.[41] Cannabis use at baseline and follow-up were established using the Composite International Diagnostic Interview.[42] The cumulative use of antipsychotic medication intake during the interval (haloperidol equivalent[43] per year) was estimated (eAppendix 4 in the Supplement).

MRI Acquisition

Structural T1-weighted MRI scans of the whole brain were obtained on a 1.5-T Achieva scanner (Philips; for details see eAppendix 5 in the Supplement). All images were coded to ensure investigator blindness to participant identification and diagnosis.

Table 1. Comparisons of Brain Measures Between Patients With Schizophrenia and Control Participants at Baseline[a]

Brain Measure	Patients With Schizophrenia (n = 84)		Control Participants (n = 116)		Statistics			
	No. (%)	Mean (SD)	No. (%)	Mean (SD)	zβ	*t*	*P* Value	*r* Coefficient
Volume, mL								
Intracranium	82 (98)	1559.04 (137.13)	116 (100)	1539.08 (151.18)	−38.50	−2.05	.04[b]	0.56
Total brain	82 (98)	1304.42 (124.04)	116 (100)	1310.32 (145.81)	−29.2	−4.97	<.001[b]	0.96
Cerebral gray matter	82 (98)	627.58 (61.95)	116 (100)	622.96 (67.72)	−2.2	−0.58	.56	0.93
Cerebral white matter	82 (98)	511.64 (60.36)	116 (100)	522.85 (76.61)	−24.0	−4.245	<.001[b]	0.86
Lateral ventricular	82 (98)	17.25 (8.34)	116 (100)	14.59 (7.28)	2.8	2.38	.02[b]	0.34
Third ventricles	82 (98)	0.96 (0.35)	116 (100)	0.84 (0.42)	0.09	1.53	.13	0.35
Thalamus	81 (96)	16.55 (1.61)	115 (99)	16.70 (1.85)	−0.53	−2.82	.005[b]	0.74
Caudate	82 (98)	7.76 (1.11)	115 (99)	7.82 (1.09)	−0.21	−1.60	.11	0.65
Putamen	81 (96)	11.69 (1.28)	115 (99)	11.36 (1.44)	0.01	0.08	.93	0.68
Pallidum	82 (98)	3.78 (0.40)	115 (99)	3.59 (0.47)	0.05	0.99	.32	0.67
Hippocampus	80 (95)	9.35 (0.99)	109 (94)	9.52 (0.98)	−0.42	−3.53	.001[b]	0.67
Amygdala	82 (98)	3.19 (0.38)	115 (99)	3.21 (0.38)	−0.12	−2.68	.008[b]	0.69
Accumbens	82 (98)	1.11 (0.15)	115 (99)	1.14 (0.18)	−0.06	−2.68	.008[b]	0.62
Cortical	82 (98)	487.93 (53.56)	115 (99)	497.03 (58.53)	−17.21	−3.90	<.001[b]	0.87
Cortical thickness, mm	82 (98)	2.53 (0.12)	115 (99)	2.57 (0.11)	−0.034	−2.045	.04[b]	0.44
Cortical surface area, mm^2	82 (98)	174 388 (16 706)	115 (99)	175 477 (18 657)	−4974	−3.67	<.001[b]	0.88

[a] Age, sex, and intracranium volume (except when the intracranium volume or cortical thickness were dependent variables) were added as covariates. Apparent larger mean intracranium volume in patients with schizophrenia was owing to male preponderance in the group of patients with schizophrenia (men had significantly larger intracranium volumes in both groups).

[b] Statistically significant.

Data Processing

In-house Volumetric Processing

Our automatic processing pipeline was used for segmentation of the IC, TB, cerebral GM, cerebral white matter (WM), LV, and third ventricles (V3)[44] (eAppendix 6 in the Supplement).

Image Processing With FreeSurfer

FreeSurfer software, version 5.1.0 (http://surfer.nmr.mgh.harvard.edu) was used for surface-based cortical processing[45,46] and volumetric subcortical segmentation[47] (eAppendix 7 in the Supplement).

After quality checks of each image, cortical thickness, surface area, and volume and bilateral volumes of the thalamus, caudate, putamen, pallidum, hippocampus, amygdala, and accumbens were extracted (eAppendix 8 in the Supplement).

The regional values at each vertex for each participant were mapped to the surface of a brain template (https://surfer.nmr.mgh.harvard.edu/fswiki/FsAverage). To perform longitudinal vertexwise analyses, a change map was created by computing annual percentage changes for each vertex. The cortical map of each participant was smoothed with a gaussian kernel of 15-mm full width at half maximum for vertexwise analyses.

Statistical Analysis

We examined data for outliers and normality of the distribution, using the Kolmogorov-Smirnov test for significance. Independent-sample *t* tests and χ^2 tests were used to examine group differences in continuous demographic variables and categorical variables, respectively. We used SPSS, version 20 (SPSS Inc), with a statistical significance threshold of $P < .05$.

IQ Differences Between Groups

Independent-sample *t* tests were applied to investigate group differences in baseline and annual IQ changes during the interval.

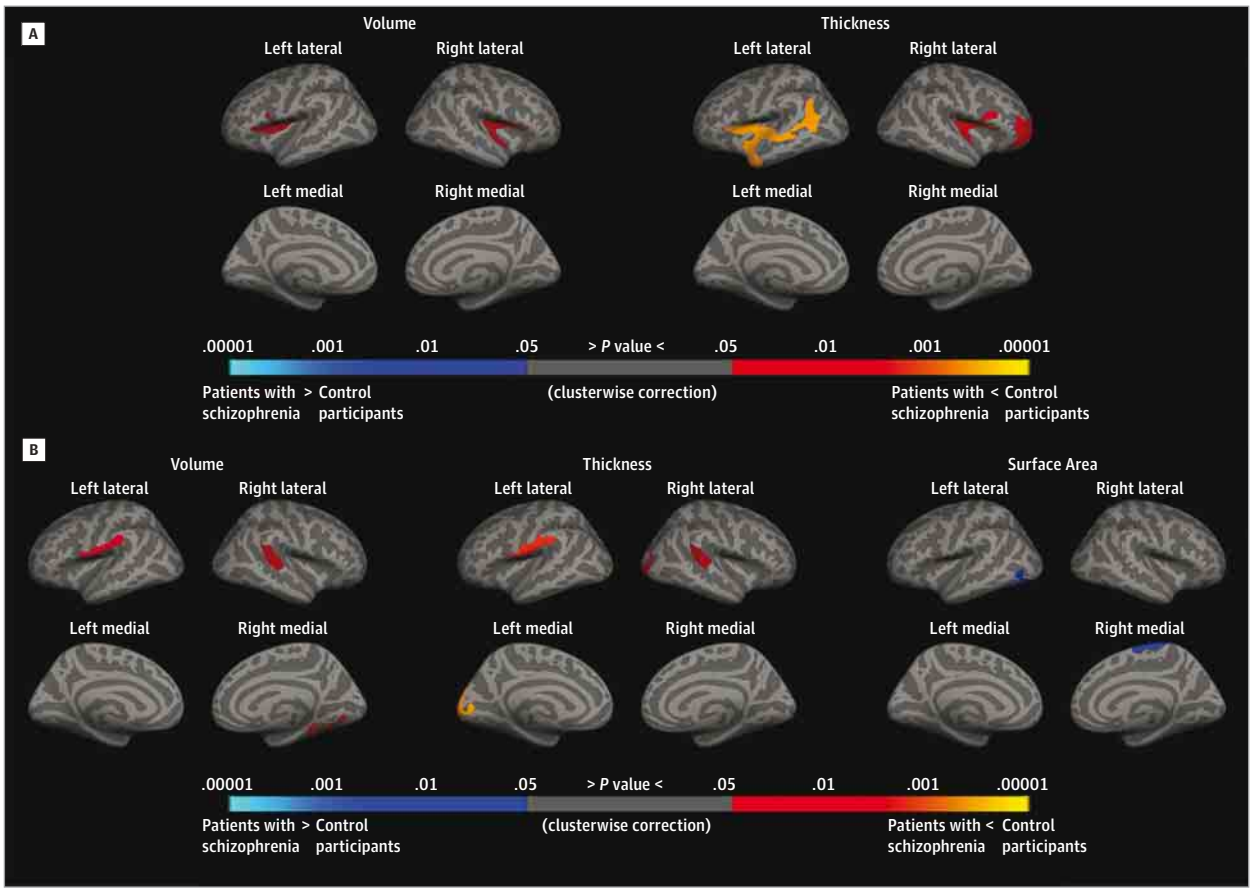
Brain Differences Between Groups

Multiple linear regression analyses (for local cortical measures, this was done in a vertexwise general linear model implemented in FreeSurfer) were applied to investigate group differences in baseline or annual changes in brain volumes (ie, IC [baseline only], TB, GM, WM, LV, V3, and subcortical structures) and global and local cortical measures (volume, thickness, and surface area). Age, sex, and IC volume (for baseline brain measures only except when IC volume or cortical thickness were dependent variables) were added as covariates. In vertexwise analyses, the cluster-forming and clusterwise significance thresholds were set at $P < .05$ by Monte Carlo simulation.

Effects of IQ on Brain Measures

To evaluate the interaction between IQ and each group on global and focal brain measures (baseline and annual change), multiple linear regression analyses were conducted. For baseline measures, brain measure was the dependent variable, while IQ (deviations from IQ = 100), group (patients, 0.5; control participants, −0.5), and their interaction were added as independent variables. Age, sex, and IC volume (for baseline brain measures only except when IC volume or cortical thickness were dependent variables) were added as covariates. The analyses for annual change measures were similar, except annual IQ change and group (patients, 1; control participants, 0) were added as independent variables. Bonferroni correction for multiple comparisons was applied for

Figure 1. Statistical Maps of Baseline Cortical Measures (A) and Annual Cortical Change (B) Comparing Patients With Schizophrenia With Control Participants



Each hemisphere in the lateral and medial views is shown for patients with schizophrenia (n =82) and control participants (n = 115) ($P < .05$, clusterwise correction controlled for age, sex, and intracranial volume [for analysis on baseline cortical volume only]). A, Red and orange areas indicate a smaller volume or thinner cortex in patients with schizophrenia. B, Red and orange areas indicate excessive loss in volume or thickness in patients with schizophrenia and blue areas indicate smaller loss in cortical surface area in patients with schizophrenia.

the analyses on subcortical volumes, leading to an α level of $P < .007$ (0.05/7 subcortical structures).

Next, the influences of confounding factors on annual change in brain measures were investigated in patients. Analyses were restricted to brain measures that showed a significant association with IQ. The Positive and Negative Syndrome Scale total score at follow-up, Global Assessment of Functioning score at follow-up, cannabis use during the scan interval (yes or no), cumulative antipsychotic medication intake during the interval (haloperidol equivalent per year), duration of illness, and level of education were added as covariates.

Results

Demographic Data and IQ Differences

Clinical data are shown in the eTable in the Supplement. Baseline IQ was significantly lower in patients with schizophrenia (IQ = 93.3) than in control participants (IQ = 113.2). Patients with schizophrenia and control participants did not differ on annual IQ change (+0.79 IQ point per year and +0.87 point per year, respectively; eTable in the Supplement).

Differences in Brain Measures

Baseline

Volumes of the IC, TB, WM, thalamus, hippocampus, amygdala, and accumbens and global cortical volume, thickness, and surface area were significantly smaller at baseline. The LV volume was significantly larger in patients with schizophrenia compared with control participants (**Table 1**).

Locally, patients with schizophrenia showed significantly smaller volumes in the bilateral inferior frontal cortex and insula and a significantly thinner cortex in the right rostral middle frontal, bilateral inferior frontal, bilateral insula, left superior temporal, left middle temporal, and left inferior parietal regions (**Figure 1**). No significant group difference was found in the local cortical surface area.

Change Across Time

Patients with schizophrenia showed significantly more pronounced reductions in GM and global cortical volume as well as excessive cortical thinning and a more pronounced V3 volume increase compared with control participants (**Table 2**).

Locally, patients showed significantly more pronounced decreases in cortical volume and thickness of the right supra-

Table 2. Comparisons of Brain Measures Between Patients With Schizophrenia and Control Participants Across Time[a]

Brain Measure	84 Patients With Schizophrenia		116 Control Participants		Statistics		P Value	r Coefficient
	No. (%)	Mean (SD)	No. (%)	Mean (SD)	β	t		
Annual change, %								
Volume								
Total brain	81 (96)	−0.25 (0.52)	115 (99)	−0.15 (0.43)	−0.08	−1.08	.28	0.12
Cerebral gray matter	81 (96)	−0.61 (0.69)	115 (99)	−0.26 (0.79)	−0.32	−2.79	.006[b]	0.22
Cerebral white matter	81 (96)	0.18 (0.94)	115 (99)	0.05 (1.07)	0.13	0.84	.40	0.07
Lateral ventricular	81 (96)	1.90 (3.85)	115 (99)	0.94 (2.78)	0.73	1.44	.15	0.19
Third ventricles	81 (96)	7.34 (6.31)	115 (99)	4.24 (7.12)	2.91	2.80	.006[b]	0.25
Thalamus	81 (96)	−0.25 (0.88)	115 (99)	−0.18 (0.60)	0.01	0.11	.92	0.17
Caudate	82 (98)	−0.63 (1.28)	115 (99)	−0.48 (0.75)	−0.15	−0.9	.34	0.10
Putamen	80 (95)	−0.17 (0.75)	114 (98)	−0.24 (0.50)	0.03	0.33	.74	0.11
Pallidum	81 (96)	0.10 (0.71)	114 (98)	0.16 (0.74)	−0.07	−0.63	.53	0.08
Hippocampus	78 (93)	−0.20 (0.71)	107 (92)	0.02 (0.55)	−0.13	−1.31	.19	0.26
Amygdala	82 (98)	−0.20 (0.93)	115 (99)	−0.02 (0.83)	−0.06	−0.46	.65	0.23
Accumbens	82 (98)	−0.28 (1.61)	115 (99)	−0.43 (1.90)	0.07	0.26	.80	0.08
Cortical	82 (98)	−0.81 (0.99)	115 (99)	−0.49 (0.83)	−0.31	−2.22	.03[b]	0.21
Cortical thickness	82 (98)	−0.55 (0.82)	115 (99)	−0.25 (0.69)	−0.28	−2.41	.02[b]	0.21
Cortical surface area	82 (98)	−0.25 (0.44)	115 (99)	−0.25 (0.41)	0.02	0.27	.79	0.16

[a] Age and sex were added as covariates.

[b] Statistically significant.

Table 3. Effects of IQ in Control Participants and Interaction Effects Between IQ and Group on Brain Measures at Baseline[a]

Brain Measure	No. (%)	df	Effect of Group Statistics		P Value	Effect of IQ Statistics		P Value	Interaction Effect Statistics		P Value	r Coefficient
			β	t		β	t		β	t		
Volume, mL												
Intracranium	195 (98)	189	17.18	0.80	.43	2.47	4.18	<.001[b]	−0.24	−0.20	.84	0.62
Total brain	195 (98)	188	−24.75	−3.51	.001[b]	0.21	1.04	.30	−0.14	−0.37	.72	0.96
Cerebral gray matter	195 (98)	188	−2.93	−0.66	.51	−0.04	−0.34	.73	0.05	0.19	.85	0.93
Cerebral white matter	195 (98)	188	−19.34	−2.86	.005[b]	0.20	1.05	.29	−0.23	−0.62	.54	0.86
Lateral ventricular	195 (98)	188	2.03	1.45	.15	−0.03	−0.74	.46	0.06	0.73	.47	0.35
Third ventricles	195 (98)	188	0.02	0.35	.73	−0.003	−1.39	.17	0.002	0.54	.59	0.37
Thalamus[c]	193 (97)	186	−0.40	−1.76	.08	0.006	0.94	.35	0.0005	0.04	.97	0.74
Caudate[c]	194 (97)	187	−0.14	−0.86	.39	0.004	0.79	.43	−0.002	−0.21	.84	0.65
Putamen[c]	193 (97)	186	0.22	1.13	.26	0.009	1.66	.10	−0.003	−0.29	.77	0.69
Pallidum[c]	194 (97)	187	0.14	2.22	.03	0.004	2.36	.02	−0.0002	−0.04	.97	0.69
Hippocampus[c]	186 (93)	179	−0.43	−3.05	.003[b]	0.0009	0.23	.82	0.009	1.21	.23	0.68
Amygdala[c]	194 (97)	187	−0.09	−1.82	.07	0.002	1.35	.18	0.003	1.12	.26	0.71
Accumbens[c]	194 (97)	187	−0.06	−2.33	.02	−0.0001	−0.19	.85	0.0002	0.13	.90	0.62
Cortical	194 (97)	187	−11.69	−2.22	.03[b]	0.26	1.72	.09	−0.09	−0.30	.77	0.87
Cortical thickness, mm	194 (97)	188	−0.02	−1.06	.29	0.001	1.01	.31	0.0003	0.28	.78	0.44
Cortical surface area, mm^2	194 (97)	187	−3298.95	−2.04	.04[b]	86.97	1.90	.06	−19.80	−0.23	.82	0.88

[a] Age, sex, and intracranium volume (except when the intracranium volume or cortical thickness were dependent variables) were added as covariates.

[b] Statistically significant.

[c] Bonferroni correction for multiple comparisons was applied for the analyses on the subcortical volumes leading to an α level of $P < .007$ (0.05/7 subcortical structures).

marginal, posterior superior temporal, left supramarginal, left postcentral, and occipital regions and significantly less reduction in the right paracentral and left lateral occipital surface areas (Figure 1).

Relationship Between IQ and Brain Measures

Baseline

The group effect (**Table 3**) presented the difference between the groups for those with an IQ of 100. The IQ effect (Table 3)

Table 4. Effects of IQ in Control Participants and Interaction Effects Between IQ and Group on Brain Measures in Change Across Time[a]

Brain Measure	No. (%)	*df*	Effect of IQ in Control Participants			Interaction Effect Between IQ and Group			*r* Coefficient
			β	*t*	*P* Value	β	*t*	*P* Value	
Annual change, %									
Volume									
Total brain	190 (95)	184	0.005	0.29	.78	0.06	1.95	.05	0.21
Cerebral gray matter	190 (95)	184	0.01	0.35	.72	0.05	0.98	.33	0.24
Cerebral white matter	190 (95)	184	−0.004	−0.11	.91	0.10	1.51	.13	0.17
Lateral ventricular	190 (95)	184	−0.07	−0.55	.58	−0.42	−1.99	.05[b]	0.27
Third ventricles	190 (95)	184	−0.39	−1.56	.12	−0.16	−0.36	.72	0.29
Thalamus[c]	190 (95)	184	−0.003	−0.12	.90	0.11	2.30	.02	0.26
Caudate[c]	191 (96)	185	0.02	0.51	.61	0.11	1.64	.10	0.20
Putamen[c]	188 (94)	182	0.006	0.24	.81	0.03	0.73	.47	0.14
Pallidum[c]	189 (95)	183	0.03	0.81	.42	0.04	0.81	.42	0.15
Hippocampus[c]	180 (90)	174	0.003	0.12	.90	0.06	1.38	.17	0.27
Amygdala[c]	191 (96)	185	0.05	1.53	.13	0.009	0.17	.87	0.27
Accumbens[c]	191 (96)	185	0.01	0.17	.87	0.09	0.73	.47	0.11
Cortical	191 (96)	185	0.02	0.54	.59	0.15	2.74	.007[b]	0.33
Cortical thickness	191 (96)	185	0.01	0.49	.63	0.14	2.94	.004[b]	0.34
Cortical surface area	191 (96)	185	−0.007	−0.45	.65	0.05	1.84	.07	0.20

[a] Age and sex were added as covariates.

[b] Statistically significant.

[c] Bonferroni correction for multiple comparisons was applied for the analyses on the subcortical volumes leading to an α level of $P < .007$ (0.05/7 subcortical structures).

was the mean effect in the 2 groups and the interaction (Table 3) presented the difference in the interaction between the groups. Only TB, WM, and hippocampus and cortical volume and surface area remained significantly smaller in patients with schizophrenia compared with control participants. A significant positive association of IQ with the IC was found across both groups. No significant interactions were found between IQ and the groups on any brain measures, indicating that the association between IQ and brain measures was not significantly different between patients with schizophrenia and healthy control participants.

Separate vertexwise analyses per group did not show significant correlations between IQ and cortical measures in either group, nor did the groups show significantly different relationships between IQ and cortical measures.

Change Across Time

No significant associations were found between IQ and brain changes in control participants (**Table 4**). However, significant interactions between the groups and changes in IQ were found for changes in the LV and cortical volume and thickness as well as trend-level significance for TB volume and cortical surface area (Table 4 and **Figure 2**) because a decrease in IQ was associated with a decrease in cortical volume and increased LV volume in patients with schizophrenia and not control participants. In addition, a decrease in IQ was associated with less cortical thickening in patients with schizophrenia and not in healthy control participants.

Locally, patients with schizophrenia and control participants showed significantly different relationships between IQ changes and changes in cortical volume and thickness in widespread regions across the frontal, temporal, parietal, and cingulate cortices as well as in the cortical surface areas of the frontal pole, right temporal, left postcentral, left precuneus, and left occipital regions. Correlation analyses per group showed that in these areas, patients with schizophrenia showed significant positive correlations between IQ change and changes in local cortical volume, thickness, and surface area, while no significant correlations were present in control participants (Figure 2).

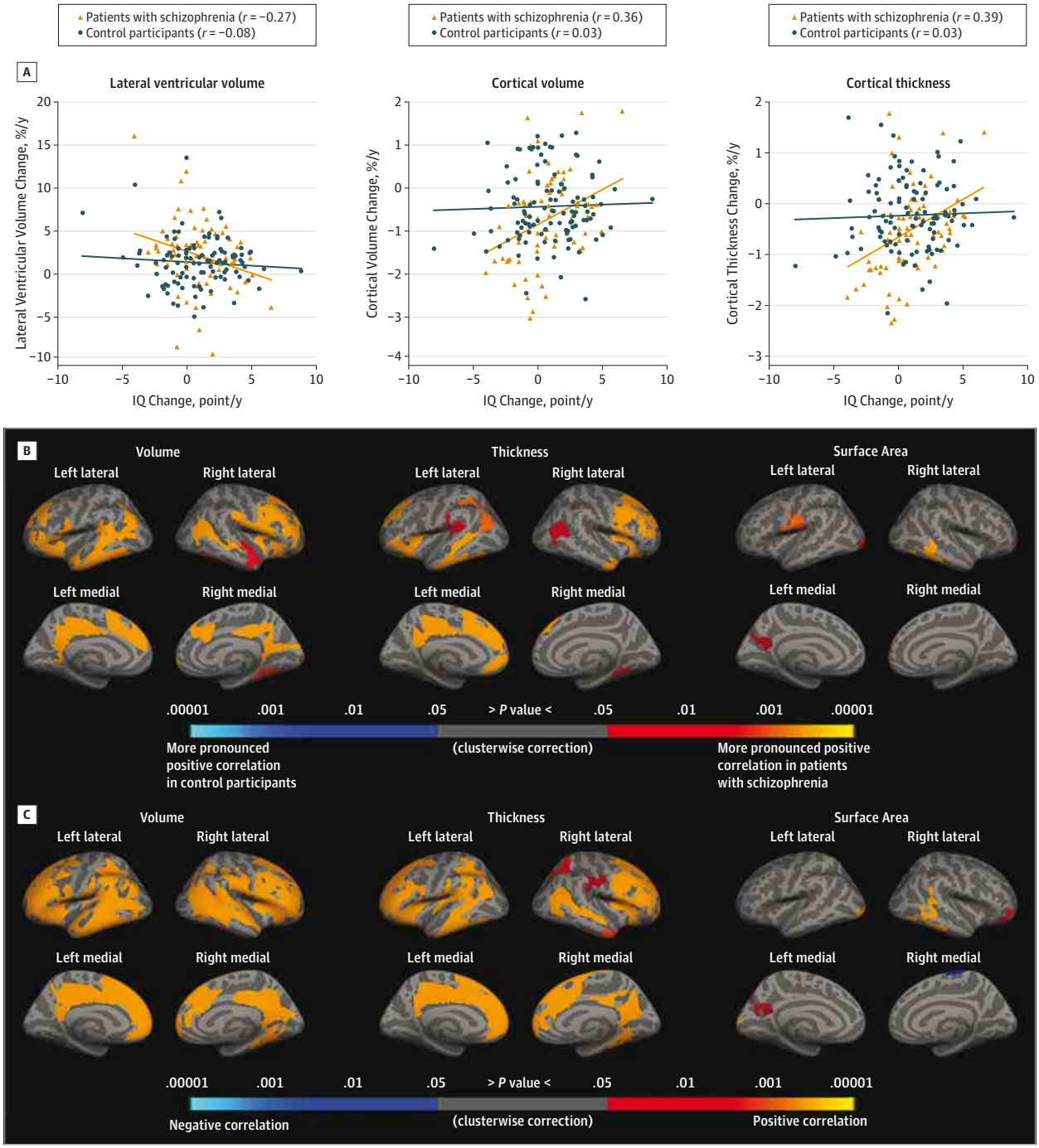
For effects of potential clinical confounders, see eAppendix 9 in the Supplement. For findings per the subscale of the Wechsler Adult Intelligence Scale III, see eAppendix 10 and the eFigure in the Supplement. For subgroup analyses, see eAppendix 11 in the Supplement. Repeating the analyses in men and women separately did not materially change the findings.

Discussion

To our knowledge, this is the first study to investigate associations between changes in IQ and brain measures during schizophrenia. The main finding was that changes in brain volume, especially in global and local cortical volume and thickness, showed robust positive correlations with changes in IQ during schizophrenia. More specifically, IQ changes in patients with schizophrenia was associated with changes in volume and thickness in widespread regions, including the frontal, temporal, and parietal cortices, suggesting that these areas are involved in cognitive functioning in schizophrenia.

Although IQ increased to a similar but subtle extent in patients with schizophrenia and control participants, the loss in cortical volume and thickness across time was associ-

Figure 2. Associations Between IQ and Cortical Measure Changes in Patients With Schizophrenia and Control Participants



A, Scatter plots and regression slopes of IQ changes compared with uncorrected lateral ventricular volume changes and cortical volume and cortical thickness changes. Pearson *r* correlation coefficients are included. Results are shown separately for patients with schizophrenia (n = 77 for lateral ventricular and n = 78 for cortical volume and thickness) and control participants (n = 113). B, Statistical maps showing regions in which an association between changes in IQ and cortical measures is significantly different between patients with schizophrenia (n = 78) and control participants (n = 113). For each hemisphere, the lateral and medial views are shown. Red and orange areas indicate regions where a significantly more pronounced positive correlation was shown between IQ and cortical changes in patients with schizophrenia ($P < .05$, clusterwise correction controlled for age and sex). C, Statistical maps showing regions of cortical change significantly correlated with IQ changes in patients with schizophrenia (n = 78). For each hemisphere, the lateral and medial views are shown. Red and orange areas indicate a positive correlation and blue areas indicate a negative correlation ($P < .05$, clusterwise correction controlled for age and sex).

ated with a relative decline (ie, less increase) in IQ only in patients with schizophrenia. These associations were not explained by the duration of illness, symptom severity, outcome, cannabis use, cumulative use of antipsychotic medications during the interval, or level of education. In patients with schizophrenia, about 15% of cortical thickness change could be explained by the *r* coefficient variance in IQ change ($\sqrt{0.15} = 0.39$). Thus, the progressive cortical thinning reported in this study and previous studies[3,48] appears relevant to the cognitive changes observed in at least some patients with schizophrenia.

Since the 19th century, many studies have demonstrated correlations of intelligence with IC and brain volume in healthy individuals.[20-23] Previous studies have also shown that volumes of the cranium,[49] whole brain,[29,30] GM,[30] and cortical surface area[50] are related to cognitive functioning in patients with schizophrenia. This is consistent with our baseline findings. In addition, our findings of progressive loss in cortical and cerebral GM volume, cortical thinning, and increases in V3 volume are consistent with previous findings.[1,3-6] Unlike previous studies,[3-5] we did not find significant volume or thickness loss in frontal regions. Possible reasons for the discrepancy include a longer duration of the illness or more severe symptoms in the patient samples included in those studies.

Although this is the first study, to our knowledge, to relate IQ changes with brain changes in schizophrenia, our findings were consistent with 2 previous studies that combined a longitudinal magnetic resonance imaging assessment with a single cognitive measure. One study included 27 patients with first-episode psychosis and 25 control participants and reported that reduction in cortical thickness at follow-up was predicted by baseline IQ in patients with schizophrenia.[48] Another study found brain volume change associated with cognitive performance at follow-up in 202 patients with first-episode schizophrenia.[6] Results of our post hoc analyses on the change in IQ subscales indicated that the associations between changes in IQ and brain measures in patients reflect a global cognitive effect rather than a specific cognitive domain.

What underlying mechanism could explain cortical thinning and relative IQ decrease across time in schizophrenia? While pruning was previously assumed to be completed in adolescence, evidence shows that this process of synaptic elimination continues into the third decade of life.[51] It has also been suggested that a level of synaptic pruning is critical for the healthy development of adult cognitive function.[52] In a previous study, cortical plasticity in adolescence and adulthood was found to be inversely associated with intelligence,[53] corroborating postmortem findings. Therefore, pathologically extended pruning[54] could explain both cortical thinning and cognitive impairment during the course of illness in schizophrenia, although other factors cannot be excluded. We did not find a significant correlation between changes in IQ and global cortical surface area, although locally significant correlations with cortical surface area change were present.

In our study, IQ changes did not differ between patients with schizophrenia and control participants. This could be explained by the presence of a subgroup of patients with schizophrenia showing a decrease in IQ across time with concomitant excessive cortical thinning and a different group of patients with IQ increases across time with concomitant cortical thickening or less thinning. Our post hoc analyses indicated that the first group of patients had a lower educational level and poorer symptomatic and functional outcomes at follow-up compared with the latter group. Thus, IQ decrease accompanied with brain loss was related to poorer outcomes and lower premorbid functioning, expressed by a lower level of education. In contrast, the latter group of patients who showed an increase in IQ might have benefitted from a similar practice effect as control participants.

We did not include a measure of premorbid IQ in this study. It is not unlikely that some individuals may have experienced excessive IQ decline prior to illness onset and the brain and IQ changes may have progressed at a different rate during follow-up in these individuals.

Several limitations of the study need to be taken into account. First, IQ was estimated from the performances on 4 subtests of the Wechsler Adult Intelligence Scale III; this procedure is shown to have good validity.[39] Second, groups were not matched on sex. Therefore, we included sex as a covariate in all analyses. Third, although we controlled for antipsychotic medication intake by haloperidol equivalent, the effect of medication cannot be excluded. Fourth, there was a difference in attrition rate between patients with schizophrenia and control participants. However, we found no significant differences between those who did and did not participate at follow-up in terms of demographic, clinical, and global brain variables, except for control participants, where those who participated at follow-up had higher levels of education and larger LV volumes at inclusion compared with those who did not participate. In addition, age or illness duration could have had a nonlinear influence on the association between changes in IQ and brain volume. In our study, more than half of the individuals in the sample were between 20 and 30 years of age (patients, 67.9%; control participants, 51.7%). We know that the brain is relatively stable during this period;[55] therefore, we did not proceed in analyzing different age groups separately or in running nonlinear statistics. Our study design did not allow any causal relationships to be inferred.

Conclusions

We reported that loss of cortical volume and thinning were significantly related to a relative IQ decrease across a 3-year interval in relatively young patients with schizophrenia. The effect might be explained by a subgroup characterized by both cognitive deterioration and brain tissue loss, which could well be clinically and genetically distinct with implications for diagnosis, treatment, and drug development. Conversely, patients who showed cognitive improvement may reflect a group of patients with preserved brain plasticity.

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