Accelerated Gray and White Matter Deterioration With Age in Schizophrenia

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Objective: Although brain changes in schizophrenia have been proposed to mirror those found with advancing age, the trajectory of gray matter and white matter changes during the disease course remains unclear. The authors sought to measure whether these changes in individuals with schizophrenia remain stable, are accelerated, or are diminished with age.

Method: Gray matter volume and fractional anisotropy were mapped in 326 individuals diagnosed with schizophrenia or schizoaffective disorder and in 197 healthy comparison subjects aged 20–65 years. Polynomial regression was used to model the influence of age on gray matter volume and fractional anisotropy at a whole-brain and voxel level. Between-group differences in gray matter volume and fractional anisotropy were regionally localized across the lifespan using permutation testing and cluster-based inference.

Results: Significant loss of gray matter volume was evident in schizophrenia, progressively worsening with age to a maximal loss of 8% in the seventh decade of life. The inferred rate of gray matter volume loss was significantly accelerated in schizophrenia up to middle age and plateaued thereafter. In contrast, significant reductions in fractional anisotropy emerged in schizophrenia only after age 35, and the rate of fractional anisotropy deterioration with age was constant and best modeled with a straight line. The slope of this line was 60% steeper in schizophrenia relative to comparison subjects, indicating a significantly faster rate of white matter deterioration with age. The rates of reduction of gray matter volume and fractional anisotropy were significantly faster in males than in females, but an interaction between sex and diagnosis was not evident.

Conclusions: The findings suggest that schizophrenia is characterized by an initial, rapid rate of gray matter loss that slows in middle life, followed by the emergence of a deficit in white matter that progressively worsens with age at a constant rate.

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Abnormalities in gray matter and white matter structure are consistently observed in schizophrenia and are known to progress over the course of the illness, particularly during the earliest stages of the disorder (1–3). In parallel, it is recognized that dynamic changes in brain structure occur with normal brain development, maturation, and aging (4–6). Despite consistent observations of reduced gray matter volume and white matter integrity in schizophrenia, it remains unclear whether these deficits become exaggerated with increases in age or duration of illness, or whether the rate of deterioration is constant across the lifespan compared with normal age-related trajectories.

Previous neuroimaging studies have provided some evidence for abnormal brain aging in schizophrenia, as demonstrated by cross-sectional studies examining individuals at different stages of adult life. Supporting propositions that schizophrenia is a syndrome of "accelerated aging" (7), a number of studies have found that individuals with schizophrenia exhibit an elevated age-related decline in gray matter volume (8–10), white matter volume (11), and fractional anisotropy (12–15), where the latter is a composite measure of axonal packing density, diameter, and myelination. However, discordance between these studies is evident, with reports indicating a diminished rate (11, 16, 17) or no difference (18) in the rate of age-related brain structural loss in the illness. More recently, machine learning has been used to predict the age of an individual based on gray matter density maps derived from structural MRI (19, 20). When applied to patients with schizophrenia, the predicted age, or the so-called brain age, was, on average, more than 3 years greater than a patient's chronological age, with this apparent age gap increasing at follow-up. Interestingly, the rate of brain aging was rapid at illness onset and plateaued 5 years after onset (20). Together, these studies suggest that an exaggerated age-related decline of gray matter and white matter manifests in schizophrenia, particularly at the earliest stages of the disorder.

Although such studies are informative, several questions concerning the nature, extent, and timing of brain structural

changes with aging in schizophrenia remain. First, it is unclear whether age-related gray matter and white matter pathology in schizophrenia follows the same or different trajectories across the lifespan. To date, no studies have simultaneously examined both gray matter and white matter with age in schizophrenia; thus, it is not clear if gray matter changes precede white matter changes or vice versa. Second, the majority of published studies have consisted of small to medium sample sizes (<70 individuals per group). This may explain some of the heterogeneity in findings, due to insufficient power to model the influence of age, particularly if the age of a cohort is distributed within a narrow range. Third, most studies have examined the influence of age on global (total or whole-brain averaged) brain measures or on a restricted number of regions, thus precluding the examination of age-related effects across brain regions or outside the specific regions sampled. Given that different brain regions, such as the prefrontal cortices, are more vulnerable to aging than others (4), it is possible that individuals with schizophrenia show exaggerated age-related trajectories only in specific brain areas. Few previous studies have modeled the effect of age in schizophrenia on a voxel-by-voxel basis, unrestricted by a priori selection of regions (9, 18). Finally, the majority of previous studies have employed linear modeling of age-related effects, despite evidence of nonlinear trajectories of brain structural change with age both in individuals with schizophrenia and in healthy individuals (5, 10).

Using structural and diffusion-weighted imaging of brain anatomy in an age-diverse cross-sectional design, the present study examined change in gray matter and white matter over the lifespan in a large sample of schizophrenia patients and healthy subjects. We aimed to determine whether the rate of change of structural neuropathology associated with schizophrenia was stable, accelerated, or diminished with age. We also aimed to determine whether any periods showing an altered rate of change coincided between gray matter and white matter or followed largely independent trajectories. We hypothesized that schizophrenia patients would show accelerated gray matter and white matter trajectories with age, particularly in early adulthood, corresponding to the early stages of illness.

METHOD

Participants

Participant data were obtained from the Australian Schizophrenia Research Bank, which is a storage facility of medical research data collected across five Australian states and territories. Full details related to recruitment procedures have been published elsewhere (21). Participants were English speaking, predominantly of European ancestry, and aged between 18 and 65 years. Inclusion and exclusion criteria and details about the clinical assessment can be found in the data supplement accompanying the online edition of this article. For this study, participants with both a structural MRI scan and a diffusion-weighted imaging scan were selected. The study comprised 523 participants: 326 individuals (225 males) diagnosed with either schizophrenia (N=273) or schizoaffective disorder (N=53), and 197 healthy comparison subjects (99 males). Each participant underwent a single imaging acquisition, which was not repeated. All participants provided informed consent for the analysis of their stored data. Study procedures were approved by the Melbourne Health Human Research Ethics Committee.

Group differences in demographic information were tested using independent t tests for continuous variables and chi-square tests for categorical variables.

Image Acquisition and Processing

Relative gray matter volume maps were calculated for each participant by using the optimized voxel-based morphometry toolbox for SPM8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/). Skeletonized fractional anisotropy maps were calculated for each participant using tract-based spatial statistics (22) and the FMRIB diffusion toolkit (23). Further details on MRI acquisition parameters and image processing can be found in the online data supplement.

Statistical Modeling

Statistical inference was performed at the scale of the whole brain and individual voxels. For whole-brain analyses, total gray matter volume was averaged over all gray matter voxels, and fractional anisotropy was averaged over all voxels making up the white matter skeleton. The influence of age on gray matter volume was modeled as:

$$\begin{aligned}\text{Gray matter volume}\ (i) &= \beta_1 + \beta_2 \times \text{diagnosis}(i) + \beta_3 \times (\text{age}(i) - A) \\ &+ \beta_4 \times (\text{age}(i) - A) \times \text{diagnosis}(i) \\ &+ \beta_5 \times (\text{age}(i) - A)^2 \\ &+ \beta_6 \times (\text{age}(i) - A)^2 \times \text{diagnosis}(i) \\ &+ C(i) + \varepsilon(i)\end{aligned}$$

where $\beta_1, \beta_2, \ldots \beta_6$ are unknown parameters fitted with least squares estimation, diagnosis(i) is a binary indicator of the diagnostic status of the ith participant (patient: 1, comparison subject: 0), age(i) is the age of the ith participant, $C(i)$ represents nuisance confounds, and $\varepsilon(i)$ is a normally distributed error term. The nuisance confounds were scanner location, sex, and the interaction between sex and diagnostic status.

The explanatory variables can be understood as follows: β_1 is the intercept term, and β_2 models the between-group difference in gray matter volume at age A; β_3 models the inferred rate of gray matter volume loss at age A, while β_4 models the between-group difference in this rate; and finally, β_5 models the change in rate (i.e., acceleration) of gray matter volume loss, while β_6 models the between-group difference in the change in rate of gray matter volume loss.

The regression model defined by the equation above was independently fitted with age centered between 20 and 65 years in yearly increments; that is, A=20, 21, … 65.

TABLE 1. Demographic and Clinical Characteristics in a Study of Accelerated Gray and White Matter Deterioration With Age in Schizophrenia

Variable	Schizophrenia Patients (N=326)		Healthy Comparison Subjects (N=197)		t or χ^2	p
	Mean	SD	Mean	SD		
Age (years)	38.9	10.5	40.5	14.0	1.4	0.17
Wechsler Abbreviated Scale of Intelligence score	103.0	15.67	116.5	11.1	11.5	<0.001
Duration of illness (years)	15.9	9.9				
Age of onset (years)	23.0	6.3				
Scale for the Assessment of Negative Symptoms total score[a]	26.9	18.2				
Diagnostic Interview for Psychosis lifetime positive symptom score[b]	8.0	3.5				
	N	%	N	%		
Gender (male)	225	69.0	99	50.3	18.3	<0.001
Current medication status[c]						
Antipsychotics	259	86.0	0	0.0		
Atypical antipsychotics	246	81.7	0	0.0		
Typical antipsychotics	31	10.3	0	0.0		
Antidepressants	89	29.6	8	4.2		
No antipsychotic or antidepressant medication	38	12.6				

[a] Data unavailable for 14 case subjects.
[b] Data unavailable for 34 case subjects.
[c] Data unavailable for 25 case and 13 comparison subjects.

Statistical modeling was performed from age 20 onward (and not age 18) because of the limited number of participants younger than age 20. When the regression was estimated with age centered at A, the amount of gray matter volume loss (β_1 and β_2) and the rate of gray matter volume loss (β_3 and β_4) specifically pertained to an age of A years. Therefore, fitting the model independently at each year yielded cross-sectional snapshots of gray matter volume across the adult lifespan in schizophrenia and comparison subjects (24).

At the scale of the whole brain, between-group differences in gray matter volume and the rate of gray matter volume loss were quantified and plotted as a function of age. The between-group difference in gray matter volume was quantified as $\beta_2/\beta_1 \times 100\%$, while the between-group difference in the inferred rate of gray matter volume loss (herein referred to as rate) was quantified as $\beta_4/\beta_3 \times 100\%$.

At the voxel scale, the regression model defined by the equation above was fitted independently for all voxels classified as gray matter volume. Permutation testing and cluster-based statistics were used to localize between-group differences in the amount and rate of gray matter volume loss to specific brain regions across the lifespan, controlling for multiple comparisons across the set of all voxels (25). These steps were performed using Randomise (26), available as part of the FMRIB Software Library (23), with threshold-free cluster enhancement (27) and 5,000 permutations for each age centering. For reasons of computational tractability, age was centered at every fifth year between 25 and 55 years; that is, A=25, 30, 35, … 55 years.

The same regression model and age-centering approach was used to model the influence of age on fractional anisotropy. However, the explanatory variables involving the square of age (β_5 and β_6) were not significant predictors of fractional anisotropy (see the Results section). Therefore, these variables were omitted from the model to avoid overfitting, and a linear model was estimated. Analysis at the voxel scale with fractional anisotropy was confined to the voxels making up the white matter skeleton.

RESULTS

Demographic Information

Sample characteristics are shown in Table 1. Age did not differ significantly between patients and comparison subjects and did not differ in distribution in the 25–50 age range (Kolmogorov-Smirnov test, see Figure S1 in the online data supplement). The mean and variance in age between sites did not significantly differ. Compared with the comparison subjects, the schizophrenia group had lower IQ (t=11.5, df=507.9, p<0.001) and a greater proportion of males (χ^2=18.3, df=1, p<0.001). A breakdown of the medication status of the sample is provided in Table S1 of the data supplement.

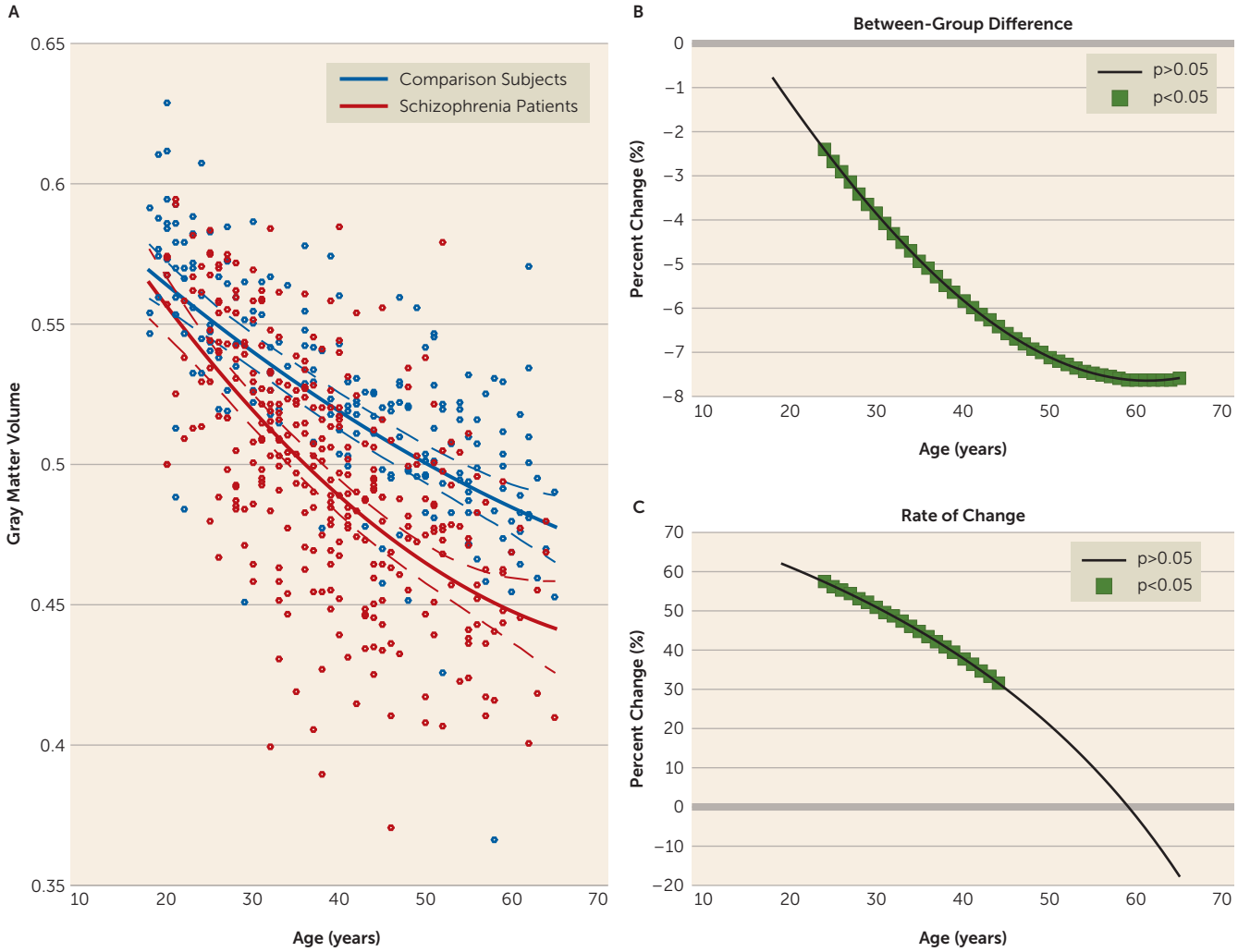
Gray Matter Volume

Total gray matter volume. The square of age was the highest order term found to be significant ($\beta_5=3.3\times10^{-5}$, t=2.4, p=0.018), and thus the quadratic regression model was considered to provide the most parsimonious explanation of the relation between total gray matter volume and age (Figure 1A).

As shown in Figure 1, individuals with schizophrenia rapidly lost gray matter volume throughout early adulthood and middle age, but this loss plateaued thereafter, at which point gray matter volume loss slowed to rates comparable to those in healthy individuals. More specifically, total gray matter volume was significantly reduced in schizophrenia from age 23 and onward, peaking at a loss of 8% relative to comparison subjects in the seventh decade of life (Figure 1B). The rate of gray matter volume loss was significantly accelerated in schizophrenia up to middle age (30%−60% faster rate of loss between 20 and 45 years of age, p<0.05; Figure 1C). However, from age 50 and onward, the rate of loss slowed in schizophrenia to a degree that was not significantly different from comparison subjects.

Regional gray matter volume. The quadratic regression model was fitted to each gray matter voxel, and cluster-based inference was used to localize age-related gray matter volume

FIGURE 1. Quadratic Modeling of Differential Aging of Whole-Brain Averaged Gray Matter Volume in Schizophrenia Patients and in Healthy Comparison Subjects[a]



[a] Panel A presents curves modeling age-related loss of gray matter volume in comparison subjects (blue curve) and in schizophrenia patients (red curve). Dashed lines indicate 95% confidence intervals estimated with bootstrapping (1,000 bootstrapped samples; R^2=0.52). Panel B presents the between-group difference in the amount of gray matter volume loss as a function of age, quantified by $\beta_2/\beta_1 \times 100\%$. Negative percentages indicate greater gray matter volume loss in patients. Panel C presents the between-group difference in the rate of gray matter volume loss as a function of age, as quantified by $\beta_4/\beta_3 \times 100\%$. Positive percentages indicate a faster rate of loss in patients. For example, if patients atrophy at a rate of 1.5 mm per year, whereas comparison subjects atrophy at a rate of 1 mm per year, then the rate of change is 50% greater in patients relative to comparison subjects, as calculated by $(1.5-1) / 1 \times 100\%$. The amount and rate of gray matter volume loss was quantified yearly using age centering between 20 and 65 years. Age epochs at which the amount (Panel B) or rate (Panel C) of gray matter volume loss significantly differed between schizophrenia and comparison subjects are denoted with a green square ($p<0.05$), as determined by the significance of the β_2 and β_4 regression coefficients, respectively.

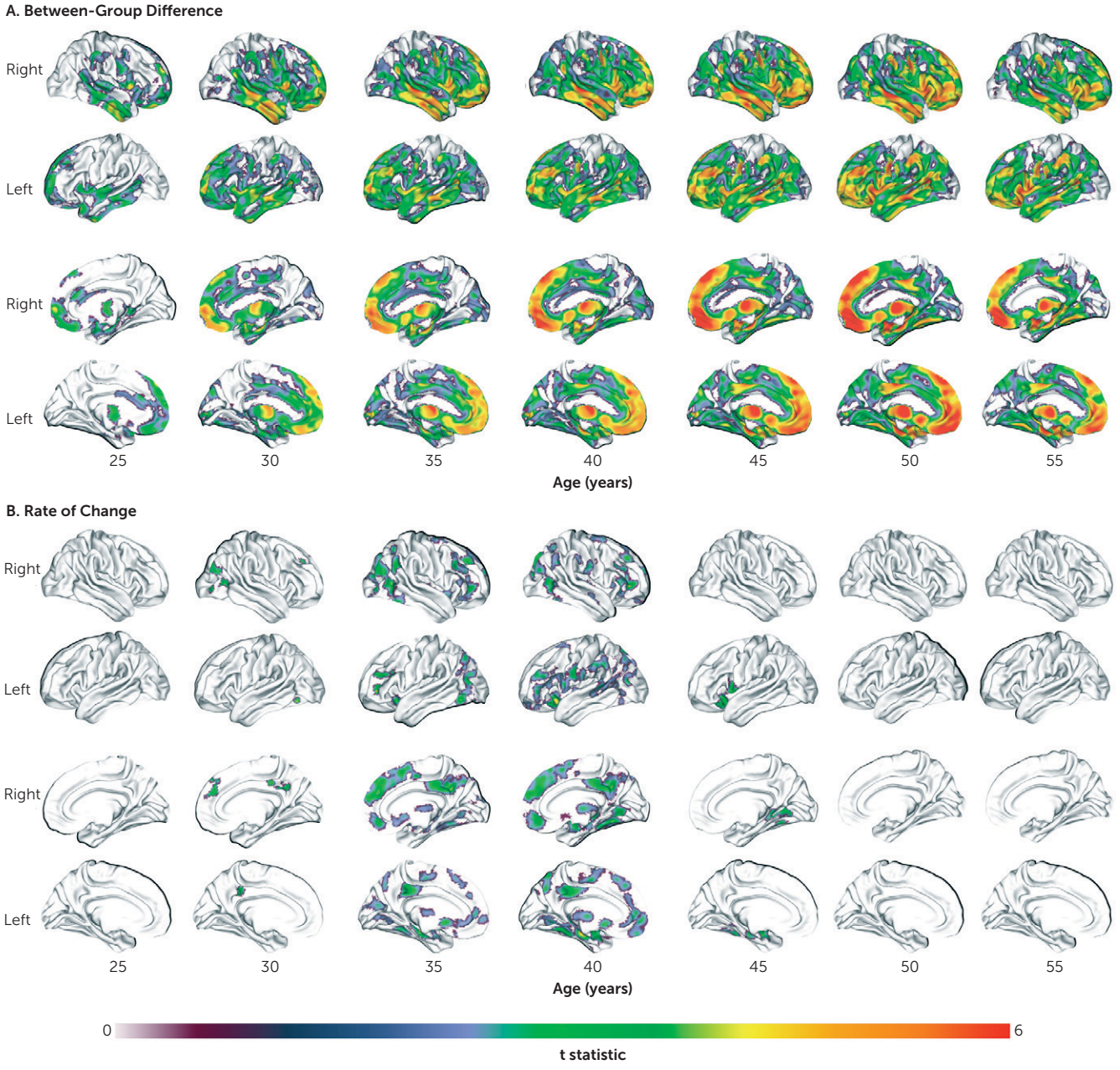
loss to specific brain regions. Figure 2A presents regions of significantly reduced gray matter volume in schizophrenia relative to comparison subjects ($p<0.05$, family-wise error corrected). Brain regions with significant gray matter volume loss were evident in schizophrenia relative to comparison subjects at all ages. This loss was primarily circumscribed to frontal and temporal brain regions in early adulthood, gradually progressing to most cortical and subcortical areas with advancing age (Figure 2A). Areas most severely affected were the medial prefrontal cortex, hippocampus, and thalamus (see Movie 1 in the online edition of this article).

Figure 2B presents regions with a significantly faster rate of gray matter volume loss in schizophrenia relative to comparison subjects ($p<0.05$, family-wise error corrected). The rate of gray matter volume loss was significantly faster in schizophrenia at ages 30–45 within the frontal, cingulate, temporal, occipital, and cerebellar cortices, as well as in the caudate nucleus and thalamus. Consistent with total gray matter volume, the rate of regional gray matter volume loss slowed beyond age 45 (Figure 1C) to levels that were not significantly different from those associated with healthy aging.

Fractional Anisotropy

Total fractional anisotropy. The explanatory variables involving the square of age were not significant predictors of age-related changes in total fractional anisotropy

FIGURE 2. Areas of Age-Related Gray Matter Volume Loss and Faster Rates of Loss in Schizophrenia Patients Relative to Healthy Comparison Subjects[a]



[a] Panel A presents cortical renderings of clusters of significantly reduced gray matter volume in schizophrenia patients relative to comparison subjects ($p<0.05$, family-wise error corrected). Cortical renderings for seven different ages are shown, ranging from 25 to 55 years in increments of 5 years. Reduced gray matter volume was found in schizophrenia at all ages. Gray matter volume loss was primarily circumscribed to frontal and temporal regions in early adulthood, including the bilateral frontal pole, the superior and inferior frontal gyrus, the anterior cingulate gyrus, the left superior and inferior temporal gyrus, and the right middle temporal gyrus. The area of significant gray matter volume reduction expanded to the medial prefrontal cortex, all cortical regions of the temporal lobe, subcortical structures, and the inferior parietal cortex by middle age (30–40 years). In older age (40–60 years), gray matter volume loss progressed to encompass the cerebellum, and the magnitude of loss was increased across the cortex. At no age was there significantly increased gray matter volume in schizophrenia patients relative to comparison subjects. Panel B presents areas where the rate of gray matter volume loss was significantly faster in schizophrenia relative to comparison subjects ($p<0.05$, family-wise error corrected). The rate of gray matter volume loss was significantly faster in schizophrenia at ages 30–45 years. At age 30, this faster loss was focally localized to the right medial superior frontal gyrus, posterior cingulate gyrus, and lateral occipital cortex; it extended to include dorsal aspects of the right superior frontal gyrus and the right precuneus; and there was a bilateral extension to the head of the caudate, thalamus, gyrus rectus, inferior frontal gyrus, medial occipital, temporal, and cerebellar cortices by ages 35 and 40. Regions with significantly slower rates of gray matter volume loss in schizophrenia were not found. To show regional variation in effect sizes, the color scale used to represent significant clusters is proportional to the voxel-specific t statistic for the between-group difference in gray matter volume (β_2) and the between-group difference in the rate of gray matter volume loss (β_4).

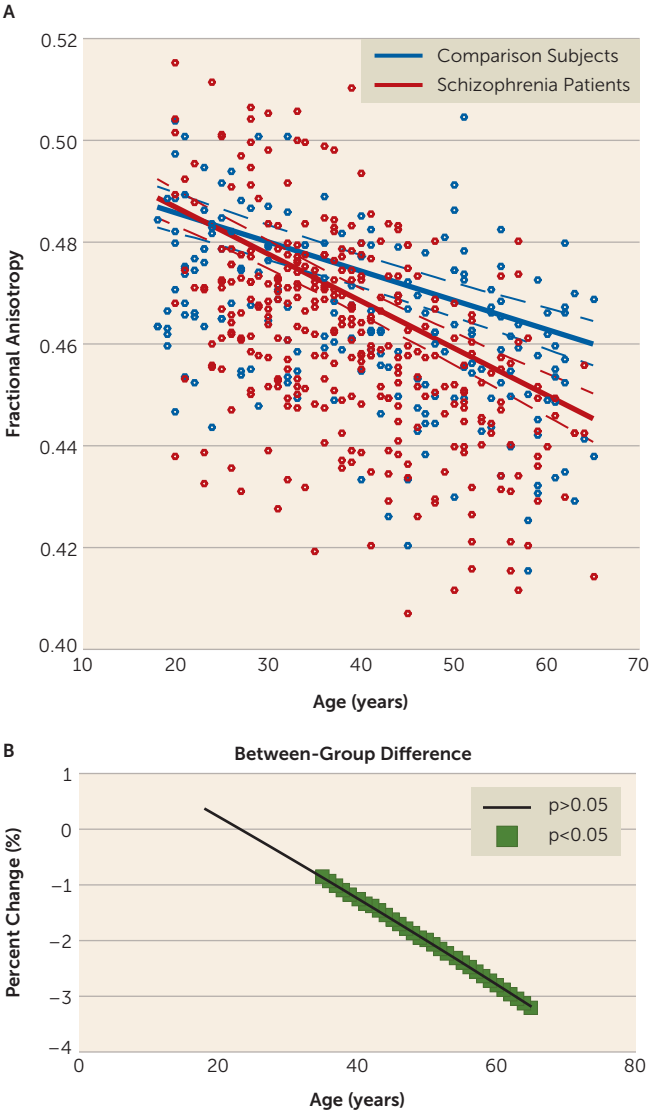
(β_5=6.0×10^{-6}, t=0.9; β_6=6.0×10^{-6}, t=0.6). Therefore, these two explanatory variables were omitted from the regression, and the influence of age on fractional anisotropy was modeled linearly (Figure 3A). We found a significant age-by-diagnosis interaction (β_4=3.5×10^{-4}, t=3.0, p=0.002). The slope of the straight line association between age and fractional anisotropy was 60% steeper in schizophrenia compared with comparison subjects, indicating a significantly faster rate of white matter deterioration with age. The reduction of fractional anisotropy in schizophrenia was 9.2×10^{-4} units per year in schizophrenia and was 5.7×10^{-4} units per year in comparison subjects. Significant reductions in fractional anisotropy emerged in schizophrenia from age 35, progressively increasing to 3% relative to comparison subjects at the oldest age considered (Figure 3B).

Regional fractional anisotropy. The linear regression model was independently fitted to each voxel making up the white matter skeleton to localize age-related reductions in fractional anisotropy to specific white matter pathways. Figure 4 presents clusters of significantly reduced fractional anisotropy in schizophrenia relative to comparison subjects ($p<0.05$, family-wise error corrected) at seven different ages, ranging from 25 to 55 years, in increments of 5 years. Consistent with total fractional anisotropy, significant fractional anisotropy reductions in schizophrenia did not emerge until age 35. These reductions were primarily localized to the genu and body of the corpus callosum as well as to temporal aspects of the superior longitudinal fasciculus at age 35, and then the reductions became more widespread, extending to white matter tracts of all cortical lobes and the cerebellum, as age increased (see Movie 2 in the online edition of this article).

Sex Differences

To investigate the influence of sex on age-related trajectories, the regression model was refitted with two additional explanatory variables: the interaction between age and sex, and the three-way interaction between age, sex, and diagnostic status (see the online data supplement). Stratification by sex revealed that gray matter volume was significantly increased in females compared with males at most ages (see Figure S2d in the data supplement). Furthermore, the rate of gray matter volume loss was significantly slower in females compared with males (see Figure S2e in the data supplement), leading to a widening gap with age in gray matter volume between the sexes. By the seventh decade of life, gray matter volume was approximately 6% greater in females compared with males (irrespective of diagnosis). In contrast, fractional anisotropy was significantly increased in males compared with females in early adulthood but deteriorated significantly faster in males, leading to no significant sex differences in fractional anisotropy beyond middle age (see Figure S3 in the data supplement). The interaction between diagnosis and sex and the three-way interaction between age, sex, and diagnostic status were not significant predictors of gray matter volume or fractional anisotropy.

FIGURE 3. Linear Modeling of Differential Aging of Whole-Brain Averaged Fractional Anisotropy in Schizophrenia Patients and in Healthy Comparison Subjects[a]

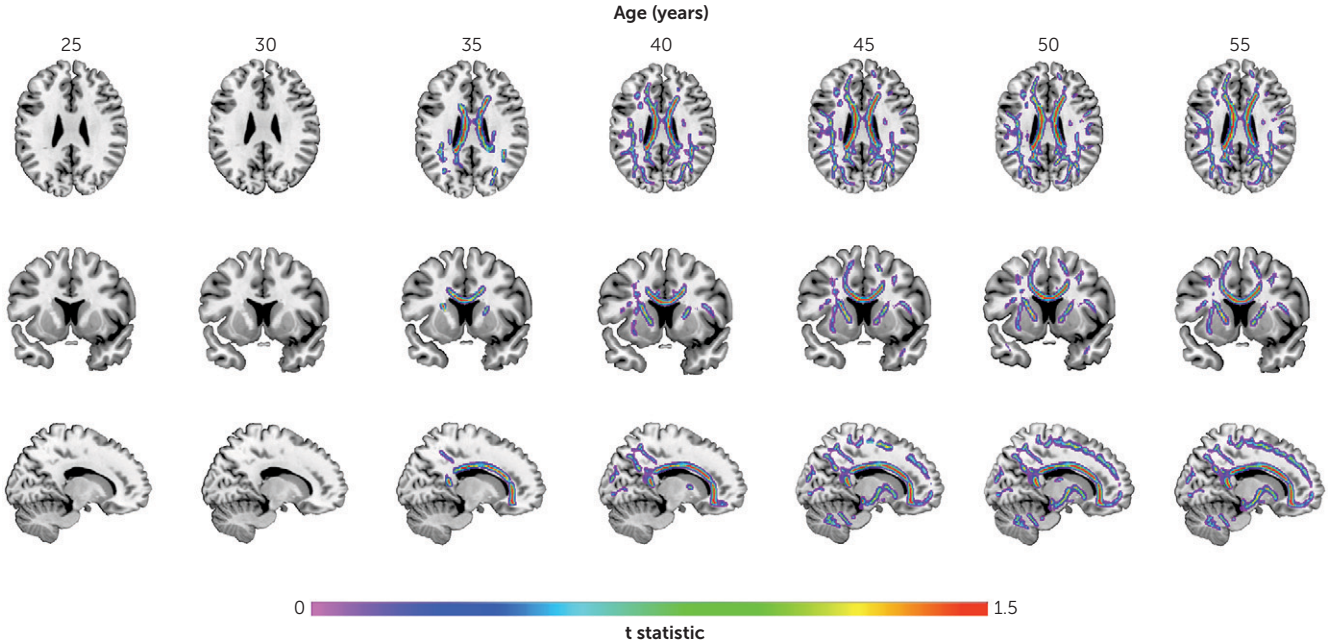


[a] Panel A presents fitted linear curves modeling age-related loss of fractional anisotropy in comparison subjects (blue curve) and in schizophrenia patients (red curve). Dashed lines indicate 95% confidence intervals estimated with bootstrapping (1,000 bootstrapped samples; R^2=0.32). Panel B presents the between-group difference in the amount of fractional anisotropy deterioration as a function of age. Negative percentages indicate lower fractional anisotropy in patients. The amount of fractional anisotropy deterioration was quantified yearly using age centering between 20 and 65 years and expressed as a percentage. Age epochs at which the amount of fractional anisotropy loss significantly differed between schizophrenia and comparison subjects are denoted with a green square ($p<0.05$), as determined by the significance of the β_2 regression coefficients.

Medication and Site Effects

Supplementary analyses were performed to examine the influence of medication and site on age-related trajectories (see the Methods section in the online data supplement). Atypical antipsychotics (t=−1.9), typical antipsychotics (t=−1.88), and antidepressants (t=1.16) were not significant predictors of gray matter volume, although atypical and

FIGURE 4. Areas of Age-Related Fractional Anisotropy Loss in Schizophrenia Patients Relative to Healthy Comparison Subjects[a]



[a] Clusters of significantly reduced fractional anisotropy in schizophrenia relative to comparison subjects ($p<0.05$, family-wise error corrected) are shown at seven different ages, ranging from 25 to 55 years in increments of 5 years. To show regional variation in effect sizes, the color scale used to represent significant voxels making up the white matter skeleton is proportional to the voxel-specific t statistic for the between-group difference in fractional anisotropy (β_2). The white matter skeleton has been thickened to aid visualization using the fill routine available as part of tract-based spatial statistics. The low t-statistic values seen at the periphery of the white matter skeletons result from the interpolation performed by this fill routine. At no age was there significantly increased fractional anisotropy in schizophrenia patients relative to comparison subjects.

typical antipsychotics showed a trend for lower gray matter volume (see Figure S4a in the data supplement). Fractional anisotropy was significantly increased in patients medicated with antidepressants (t=2.32, p=0.02; see Figure S4b in the data supplement), but atypical (t=−0.81) and typical (t=−0.81) antipsychotics were not significant predictors of fractional anisotropy. No significant interactions were observed between medication category and age. Site showed a significant main effect on fractional anisotropy (F=5.05, p=0.0005) but not on gray matter volume (F=0.81). The interaction between site and diagnosis was not a significant predictor of gray matter volume (F=0.99) or fractional anisotropy (F=0.77). Site-stratified trajectories of brain aging are shown in Figure S5 in the data supplement. Site and the interaction between site and diagnosis were not significant predictors of age.

DISCUSSION

This cross-sectional imaging study examined age-related changes in gray matter volume and fractional anisotropy in a large cohort of patients with established schizophrenia and healthy comparison subjects. We aimed to determine the pattern of gray matter and white matter trajectories to assess whether the structural neuropathology associated with schizophrenia was stable, accelerated, or diminished with age.

We found larger age-related abnormalities of both gray matter volume and fractional anisotropy in schizophrenia compared with comparison subjects. Interestingly, we also found that the time course of these structural pathologies differed. Specifically, we found that the loss of gray matter volume in schizophrenia was evident from young adulthood, with the rate of loss being significantly faster in schizophrenia until middle age, slowing thereafter to a stable rate. In contrast, the rate of age-related white matter decline was constant across the lifespan and best modeled as a linear function. The rate of white matter decline was 60% steeper in schizophrenia compared with comparison subjects, with significant between-group differences emerging in midlife and progressively widening between the two groups with age. These findings suggest that schizophrenia is characterized by early loss of gray matter followed by white matter deficits that widen with age at a constant rate. Importantly, while males showed more severe deficits with age, this pattern of differences by sex did not differ between patients and comparison subjects (see the online data supplement), a finding consistent with other studies (28).

Our findings are consistent with previous studies demonstrating elevated age-related decline in gray (8–10) and white (11–14) matter in schizophrenia. However, we extend these findings by characterizing the regional pattern, nature, and timing of these age-related trajectories. Although gray matter volume was reduced in schizophrenia at all ages, this reduction was initially confined to frontotemporal regions in young adulthood before becoming more widespread by middle age. Frontotemporal volume loss is consistently

reported in schizophrenia across a range of illness and maturational stages (29–31). Because, in our sample, this circumscribed loss coincides with the end of the maturational posterior-to-anterior gradient of gray matter loss (32), this reduction may reflect accelerated neuromaturational processes. Interestingly, the regional pattern of gray matter volume loss in schizophrenia followed a largely anterior-to-posterior direction with increasing age, targeting frontal and temporal regions first before extending to parietal and then occipital and cerebellar areas, while sensorimotor areas remained relatively preserved. This pattern supports the "last-in, first-out" hypothesis of brain aging, whereby late-developing regions are thought to degenerate first (33), and it suggests that this process might be exaggerated in schizophrenia.

In addition to gray matter volume being reduced in schizophrenia at all studied ages, we found that it declined significantly faster in patients within a discrete age window, specifically between early adulthood and middle age, with the steepest rate found between 20 and 30 years of age. Because our patients in this age band had a diagnosis of schizophrenia for an average of 6.5 years, these findings are consistent with longitudinal studies showing that the most pronounced cortical volume loss occurs in the early stages of the illness (2, 20). However, unlike these studies, ours found that a faster rate of decline of gray matter volume continued into middle life, which corresponded to around 15 years of illness in our sample. Consistent with other studies (34), this finding suggests that individuals with schizophrenia continue to lose gray matter volume beyond the first years of illness—up to 15 years postillness—albeit at a relatively slower rate. Regionally, this faster age-related loss was more widespread than previously reported (9, 10) and affected a number of cortical and subcortical regions within both hemispheres. By age 50, the rate of gray matter volume loss in schizophrenia had stabilized to rates seen in healthy comparison subjects and was actually more than 10% slower in schizophrenia after age 60, although this slowing was not significant. It remains to be investigated whether a decelerated rate of gray matter volume loss in schizophrenia continues into senescence. Our gray matter volume results suggest that there is a period of accelerated gray matter volume decline occurring against a background of extensive anterior-to-posterior gray matter volume loss with age in individuals with established schizophrenia, with the pattern of gray matter volume change possibly reflecting a disruption of both late maturational (e.g., synaptic pruning [35]) and early aging processes.

In contrast to gray matter volume, fractional anisotropy was unimpaired in individuals with schizophrenia at earlier ages. Although most studies of young people with schizophrenia have demonstrated reduced fractional anisotropy relative to comparison subjects, heterogeneity still exists with reports of increases and of no changes in fractional anisotropy (36, 37), possibly owing to variability in maturational and illness stages, clinical profile, duration of symptoms, and level of acuity, as well as sample size and regions selected (37). While deficits in fractional anisotropy have been observed in first-episode patients, our young patients had established schizophrenia of variable duration and were relatively stabilized; thus, illness-specific deficits relevant to first presentation of illness may not have been identified. Despite fractional anisotropy being unchanged in patients in early adulthood, significant reductions were present from midlife, and these reductions followed a linear decline, becoming widespread and more marked with increasing age. This finding replicates studies demonstrating a linear decline of fractional anisotropy with age in healthy subjects (6) and an elevated age-related decline in schizophrenia (12–14). However, like those found for gray matter volume, the fractional anisotropy deficits were more spatially extensive, possibly because our large sample size allowed us to detect subtle effects. Inconsistent findings have been reported, however, with some studies indicating that fractional anisotropy deficits in schizophrenia recover with age (16, 17).

A novel finding of this study is that neurostructural age-related abnormalities in schizophrenia follow a different temporal sequence in gray matter and white matter. Specifically, increased white matter pathology lagged that seen for gray matter, suggesting that gray matter changes precede white matter change in adults with schizophrenia. One possibility for this temporal pattern is that white matter deficits are an epiphenomenon of gray matter deficits such that they are secondary to, or a consequence of, progressive gray matter loss. Another possibility is that both deficits are a consequence of neurodevelopmental and aging processes that manifest differently throughout the disease (38). Interestingly, we found that fractional anisotropy deficits in schizophrenia lagged those seen in gray matter volume by about a decade, a result that parallels the timing of peak maturation in gray matter and white matter, whereby cerebral white matter matures about a decade after gray matter (39). Although the precise mechanisms underlying the accelerated age-related changes in gray matter and white matter are unclear, a number of shared or independent factors could contribute, including genetic background (40), inflammation (41), and lifestyle factors such as low socioeconomic status, poor nutrition, physical illness, inactivity, and substance use (42, 43), all of which are reported to be high in this population (44).

The main strengths of this study were the large sample (>500 subjects), the neurostructural mapping of both gray matter and white matter, and the age-specific localization of the neurostructural effects. In addition to these strengths, several limitations should be noted. First, our study was limited by the use of a cross-sectional design to infer age-related changes in brain structure. Therefore, cohort effects (generational and illness-related) may have confounded our findings. Although trajectories of brain aging would be best examined with a longitudinal design, performing such studies over the lifespan is largely infeasible. Therefore, the disadvantages of a cross-sectional design must be considered against the advantages of our very large sample size spanning the adult lifespan for both gray matter and white matter.

Second, our age range of 20–65 years precluded examination of brain trajectories related to early development and old age degeneration, which may be altered in schizophrenia differently in gray matter and white matter. Third, as in most studies of schizophrenia, we were unable to comprehensively examine the influence of medication given the unavailability of dosage and history information. Nevertheless, we found no evidence of a difference in trajectories of gray and white matter aging between patients not currently treated with antipsychotics compared with those treated with typical or atypical antipsychotics. Interestingly, antidepressant treatment was associated with higher fractional anisotropy, suggesting a possible neuroprotective action of the drug (45). Alternatively, patients medicated with antidepressants might represent a specific clinical subgroup characterized by improved white matter integrity. Although antidepressant use was significantly associated with a diagnosis of schizoaffective disorder, we found no group differences in fractional anisotropy between schizophrenia and schizoaffective disorder. Furthermore, patients treated and not treated with antidepressants did not differ on negative and positive symptoms, suggesting that patients treated with antidepressants do not represent a better clinical prognosis, at least symptomatically. Further studies are needed to clarify the association between antidepressant use and white matter integrity in schizophrenia. Finally, as age and duration of illness were positively correlated, and as the duration of illness was correlated with gray matter volume and fractional anisotropy, our findings in schizophrenia can also be interpreted in terms of illness duration because age and illness duration are inextricably linked.

In conclusion, we identified significant differences in gray matter volume and white matter integrity as a function of age in individuals with schizophrenia relative to healthy comparison subjects. We demonstrated faster age-related gray matter and white matter decline in schizophrenia at distinct age windows, with accelerated gray matter loss evident in early to mid-adulthood, while white matter deficits lagged gray matter loss, widening with age at a constant rate.

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