

## Aging Effects on Regional Brain Structural Changes in Schizophrenia

Igor Nenadić\*, Heinrich Sauer, Stefan Smesny, and Christian Gaser

Department of Psychiatry and Psychotherapy, Friedrich-Schiller-University of Jena, Philosophenweg 3, D-07743 Jena, Germany

\*To whom correspondence should be addressed; tel: 49-3641-935-682, fax: 49-3641-935-410, e-mail: igor.nenadic@uni-jena.de

**Background:** Although mostly conceptualized as a neurodevelopmental disorder, there is an increasing interest in progressive changes of cognitive deficits and brain structure and function in schizophrenia across the life span. **Methods:** In this study, we investigated age-related changes in regional gray matter using voxel-based morphometry in a sample of 99 patients (age range 18–65 years) with Diagnostic and Statistical Manual of Mental Disorders-IV schizophrenia and 113 healthy controls (age range 19–59 years) using a cross-sectional design. **Results:** We found steeper age-related decline in gray matter in patients in a cluster comprising the left superior temporal cortex and adjacent inferior parietal lobule. We then divided the schizophrenia sample in 3 subgroups based on a 3-factor model of psychopathology ratings. Age-related changes were markedly different in each of the 3 subgroups (compared with healthy controls). While patients with predominantly paranoid symptoms showed stronger age-related progression in the left superior temporal cortex and right inferior frontal gyrus, those of the disorganized subgroup had stronger gray matter loss in the left lateral cerebellum, while the predominantly negative subgroup showed minor effects in the left superior temporal gyrus. **Conclusions:** Our findings show that differences in brain structural changes associated with aging diverge between schizophrenia patients and healthy subjects and that different subgroups within a patient sample might be at higher risk of age-related regional gray matter loss.

**Key words:** aging/cerebellum/magnetic resonance imaging (MRI)/psychosis/prefrontal cortex/schizophrenia/superior temporal gyrus

### Introduction

Although schizophrenia has increasingly been conceptualized as a neurodevelopmental disorder,<sup>1</sup> there is amounting evidence on progression not only of cognitive but also of brain structural and functional pathology.<sup>2,3</sup>

Even though this progressive component might not be related to classical neuropathological markers of neurodegeneration such as astrogliosis, it has significant relevance for our understanding of disease course, especially with respect to cognitive deterioration and general clinical outcomes.<sup>4,5</sup>

Brain structural alterations have been observed in schizophrenia at different stages of the disorder, including prodromal, first-episode, and chronic patients, and recent meta-analyses comparing the cross-sectional pattern of difference with healthy subjects suggest that there might be an increase in structural pathology over the course of the disease.<sup>6</sup> In addition, there are both structural and functional imaging studies suggesting changes at later disease stage (ie, during presenile aging) to be reminiscent of accelerated aging compared with healthy individuals.<sup>2</sup> In the case of structural magnetic resonance imaging (MRI), there are studies implicating a disease by age interaction in amygdala volume,<sup>7</sup> but there are also studies suggesting a similarity in the localization of superior prefrontal and orbitofrontal cortical volume loss in healthy older subjects and (younger) schizophrenia patients.<sup>8</sup> In a more recent study, brain structural changes associated with aging, ie, changes across the life span, were studied with voxel-based morphometry (VBM), indicating that schizophrenia patients show stronger total and regional gray matter loss than healthy controls.<sup>9</sup> Volume loss seen in longitudinal MRI studies has been associated with poor outcome,<sup>10,11</sup> but altogether, there are only few studies investigating the variability of progressive changes in relation to clinical variables. Thus, both the present cross-sectional imaging studies in schizophrenia as well as the longitudinal MRI studies with follow-up periods of up to 10 years are suggestive of progressive changes exceeding those seen in healthy subjects (for overviews, see ref.<sup>12,13</sup>). This seems to occur at different stages of the disease, including the transition to psychosis, the early course of schizophrenia, and senescence.

In this study, we focus on brain structural changes over the life span and compare age-related gray matter

changes in patients with schizophrenia with those in healthy controls using a cross-sectional design. In particular, we were interested to see whether prefrontal and temporal gray matter changes show steeper age-related decline in patients than in controls. In addition, we test the hypothesis that effects of stronger brain structural progression would be related to subgroups of schizophrenia patients, ie, that these changes would show heterogeneity across subgroups of patients based on their psychopathology profiles.

## Methods

### *Subjects*

We analyzed imaging data from 212 subjects: 99 patients (42 female and 57 male) with Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) schizophrenia and 113 healthy control subjects (43 female and 70 male). The age range in patients was 18.5–65 years (mean age 36.2 y, SD 11.2) and in controls 19–59.5 years (mean age 32.4 y, SD 10.3). All patients and controls were right-handed.<sup>14</sup> We only included right-handed subjects to minimize effects related to lateralization. None of the study subjects had a history or comorbidity of learning disability. Further general exclusion criteria were neurological conditions, including history of head trauma, and major medical conditions. We have previously described this sample in a study on disease effects on brain structure, which addressed the question of resolving heterogeneity of brain structural patterns in subgroups of schizophrenia and the use of a classification algorithm.<sup>15</sup> All subjects gave written informed consent to a study protocol approved by the Ethics Committee of the Friedrich-Schiller-University of Jena, Germany.

Patients were recruited from wards and outpatient clinics of the Department of Psychiatry in Jena. Patients had normally received a diagnoses based on ICD-10 criteria (International Statistical Classification of Diseases and Health Related Problems, 10th Revision) from their treating clinician before being referred to the study. Diagnostic assessment by an experienced research psychiatrist included a semistructured interview, which (together with a chart review, where necessary) confirmed DSM-IV criteria for schizophrenia. None of the patients had a second psychiatric axis I diagnosis, concurrent alcohol or substance dependence, or neurological condition. All patients were chronic schizophrenia patients as defined by the criterion for chronic course of DSM-III-R, had shown clinically stable psychopathology for at least 2 weeks, and were on stable antipsychotic medication during the time of this study. Assessment of psychopathology included the Scale for Assessment of Negative Symptoms (SANS<sup>16</sup>) and the Scale of Assessment of Positive Symptoms (SAPS<sup>17</sup>), which were administered by an experienced psychiatrist.

Healthy controls were recruited by newspaper ads and word-of-mouth. A research psychiatrist used a short semistructured interview for screening controls in order to exclude a history of or a current psychiatric axis I disorder, including any current or previous alcohol/substance abuse or dependence. None of the healthy controls took psychotropic medication.

For formation of subgroups within the schizophrenia sample, we considered a 3-factor model using the psychopathology ratings. This model was chosen because it is among the most stable and best replicated solutions using cluster analyses/factor analyses of schizophrenia psychopathology,<sup>18</sup> and we have previously demonstrated validity also in old age samples.<sup>19</sup> We used SANS and SAPS single items and factor analysis with Promax rotation. As described in more detail in a previous article,<sup>15</sup> this resulted in 3 approximately equally large subgroups of schizophrenia patients, which were similar in age and gender distributions:

1. The first group (negative subgroup) showed mostly negative symptoms (affective flattening, avolition, and anhedonia) and included 35 patients (17 female and 18 male; age range 18.5–58.4 y; mean age 35.1 y, SD 9.3).
2. The second group (disorganized) scored high on formal thought disorder, disorganized, and bizarre behavior items, but also affective flattening, and included 29 patients (14 female and 15 male; age range 19.8–59.2 y; mean age 36.0 y, SD 12.0).
3. The third group (paranoid) scored mostly on SAPS items of delusions and hallucinations and included 35 subjects (11 female and 24 male; age range 19.2–65 y; mean age 37.6 y, SD 12.3).

All 3 groups had comparable duration of illness (negative group: mean 7.8 y, SD 7.5; disorganized group: mean 8.7 y, SD 8.5; and paranoid group: mean 10.3 y, SD 8.7) and age of onset (negative group: mean 27.4 y, SD 7.9; disorganized group: 26.3 y, SD 8.8; and paranoid group: mean 27.7 y, SD 8.6).

### *Imaging Protocol and Pre-Processing*

MRI images were obtained on a 1.5 T Philips scanner (Gyrosan ASCII; Philips, Best, The Netherlands) for each subject using a whole-brain T<sub>1</sub>-weighted high-resolution sequence with 256 sagittal slices and isotropic voxel size of 1 × 1 × 1 mm (repetition time 13 ms; echo time 5 ms; flip angle 25°; field-of-view 256 mm). Images were visually inspected for potential movement artifacts, and none of the subjects of this cohort had to be excluded for that purpose.

For processing of MRI scans, we applied VBM using an optimized VBM framework.<sup>20,21</sup> We used VBM2, which is a toolbox implemented in SPM2 software (Statistical Parametric Mapping, Institute of Neurology,

London, UK) and which makes use of hidden Markov random fields models for increasing signal-to-noise ratio.<sup>22</sup> Details of the preprocessing protocol are available on <http://dbm.neuro.uni-jena.de/vbm/> and in previous publications.<sup>15</sup> The processing algorithm starts with the creation of a custom template image (study-specific template) constructed in a 2-step segmentation approach, whereby each individual subject image is segmented to extract a gray matter image and then all individual segmented gray matter images are normalized to a standard template (Montreal Neurological Institute template) and average to obtain the custom template. We then normalized each subject's gray matter image to this custom template. These normalized gray matter images were then used for statistical comparison in the general linear model framework implemented in Statistical Parametric Mapping (SPM). The VBM2 protocol also includes an automated quality control for images, which is based on image homogeneity, where the standard deviation is calculated as the squared distance of each images from the sample mean image. All subject images passed this quality check successfully.

### Statistical Analysis

We performed 2 sets of analyses, all within the general linear model of SPM, in which we defined the variables group and age as variables of interest, while removing effects of gender. This approach detects differences in age-related regression between 2 given groups, which are calculated in each voxel of the gray matter maps, ie, a voxel-wise group  $\times$  age interaction.

First, we assessed aging effects in schizophrenia patients vs controls, using the complete samples to test for group-related differences in age regression across the gray matter of the entire brain. We applied a statistical threshold of  $P < .001$  (uncorrected) on the basis of the anatomical hypotheses lined out above and data from related previous studies.<sup>7-9</sup>

Second, we tested differential aging effects in the 3 schizophrenia subgroups, performing a voxel-wise comparison of age-related regressions of each of the 3 subgroups to the healthy control sample (ie, negative vs controls, disorganized vs controls, and paranoid vs controls). In order to deal with the problem of multiple comparisons, especially for false positives, we used small volume correction.<sup>23</sup> This approach reduces the number of voxel-wise comparisons with those voxels that were found to be significant in the previous analysis. For the subgroup analyses, we thus report only clusters that survive small volume correction and are significant at  $P < .05$ , family wise error (FWE) corrected at voxel level.

### Results

Comparing schizophrenia patients and controls, we found different age-related regression of gray matter in schizo-

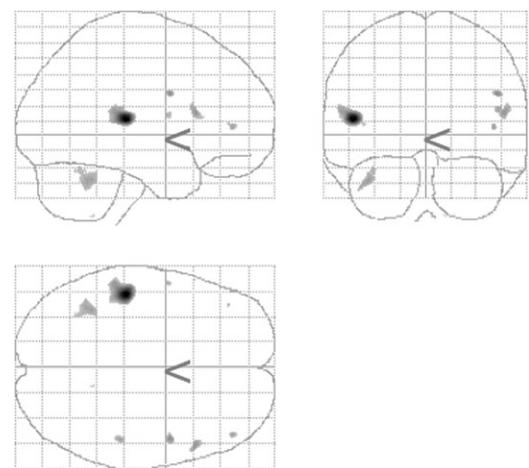
phrenia patients vs healthy controls, including large clusters in the left superior temporal cortex (coordinates of maximum voxel:  $-48, -27, 10; T = 4.28$ ), left inferior cerebellum ( $-38, -49, -30; T = 3.42$ ), and right inferior frontal gyrus ( $52, 20, 15$ ). An overview of all clusters is given in table 1 and figure 1.

For the second set of analyses, we found different areas of age-related decline in each of the 3 subgroups. Applying small volume correction, the main significant clusters surviving the correction procedure were (1) for the negative subgroup in the left superior temporal cortex and a very small cluster in the right inferior frontal gyrus, (2) for the disorganized subgroup in the left cerebellum, and (3) for the paranoid subgroup in the left superior temporal cortex and right inferior frontal gyrus. As shown in table 1, the superior temporal cortical cluster was more extensive in the paranoid subgroup than the negative subgroup. Coordinates and  $z$  scores for all significant clusters ( $P < .05$ , FWE corrected, cluster level) are given in table 1. All the reported clusters in the subgroup analyses also reach significance at  $P < .05$  using false discovery rate correction. In addition, figure 2 shows a graphical depiction of the spatial overlap of clusters for the subgroups analyses with a threshold of  $P < .001$  uncorrected.

We did not find any area of age-related gray matter reduction being stronger/steeper in healthy subjects compared with either (1) all schizophrenia patients or (2) any of the subgroups of schizophrenia patients.

### Discussion

This study used cross-sectional MRI data to investigate age-related progression of regional gray matter in schizophrenia patients vs healthy controls, across an age range from 18 to 65 years. Our findings support the notion of a different age-related decline of regional gray matter in



**Fig. 1.** Maximum Intensity Projection (MIP) Showing Stronger the Spatial Distribution of Age-Related Decline in Gray Matter Comparing Schizophrenia Patients ( $n = 99$ ) With Healthy Subjects ( $n = 113$ ) at  $P < .001$  (Uncorrected).

**Table 1.** Overview of Areas Showing Significantly Stronger Age-Related Decline in Local Gray Matter in (a) All Schizophrenia Patients vs Controls ( $P < .001$ , Uncorrected) and (b) Each of the 3 Schizophrenia (Sz) Subgroups (Negative, Disorganized, and Paranoid) Compared With Healthy Controls.

|                             | Coordinates          | <i>z</i> Score | Voxels | Anatomical Labels                                     |
|-----------------------------|----------------------|----------------|--------|---|
| All Sz patients vs controls | -48, -27, 10         | 4.18           | 1660   | Left superior temporal cortex                         |
|                             | <i>-56, -34, 16</i>  | 3.37           |        | <i>Transverse temporal gyrus (BA 41/42)</i>           |
|                             | 47, 2, 27            | 3.48           | 69     | Right precentral/inferior operculum                   |
|                             | 52, 20, 15           | 3.41           | 199    | Right inferior frontal gyrus                          |
|                             | -38, -49, -30        | 3.37           | 444    | Left lateral cerebellum                               |
|                             | <i>-36, -55, -24</i> |                |        |   |
|                             | <i>-45, -53, -37</i> |                |        |   |
|                             | 48, -30, 17          | 3.33           | 90     | Right superior temporal cortex/rolandic operculum     |
|                             | 45, 45, 6            | 3.32           | 44     | Right middle frontal gyrus                            |
|                             | -56, 1, 13           | 3.22           | 26     | Left rolandic operculum/postcentral gyrus             |
|                             | -42, 41, 7           | 3.16           | 9      | Left frontal inferior gyrus                           |
|                             | 13, -48, -54         | 3.13           | 4      | Right cerebellum                                      |
|                             | -36, -60, -25        | 3.13           | 1      | Left cerebellum                                       |
| Negative Sz vs controls     | -50, -26, 12         | 3.35           | 141    | Left superior temporal cortex                         |
|                             | 53, 20, 11           | 3.26           | 12     | Right inferior frontal gyrus                          |
| Disorganized Sz vs controls | -33, -56, -24        | 3.93           | 440    | Left lateral cerebellum                               |
|                             | <i>-45, -53, -37</i> | 3.90           |        |   |
|                             | <i>-35, -55, -25</i> | 3.81           |        |   |
|                             | <i>-36, -50, -26</i> | 3.58           |        |   |
|                             | <i>-38, -56, -29</i> | 3.55           |        |   |
| Paranoid Sz vs controls     | -36, -60, -25        | 3.75           | 1      | Left lateral cerebellum                               |
|                             | -58, -33, 20         | 3.72           | 1068   | Left superior temporal gyrus/inferior parietal lobule |
|                             | <i>-49, -27, 12</i>  | 3.65           |        |   |
|                             | <i>-55, -28, 15</i>  | 3.50           |        |   |
|                             | 54, 16, 20           | 3.68           | 121    | Right inferior frontal cortex/operculum               |
|                             | 48, -28, 16          | 3.47           | 53     | Right superior temporal gyrus                         |
|                             | -57, 1, 13           | 3.26           | 5      | Left postcentral gyrus                                |

Note: Clusters Reported for the Analysis of Subgroups vs Healthy Controls Are Corrected Using Small Volume Correction, ie, Only Those Clusters Are Shown, Which Are Significant in the Overall Group Comparison and Also Reach  $P < .05$ , FWE Corrected on the Voxel Level. Coordinates Indicate the Local Maximum Intensity Voxel of Each Cluster of Significant Voxels (Coordinates Given in Italics Refer to Local Maxima Within a Cluster). Anatomical Labels Are Based on Visual Inspection of Data and Use of the AAL System<sup>24</sup>

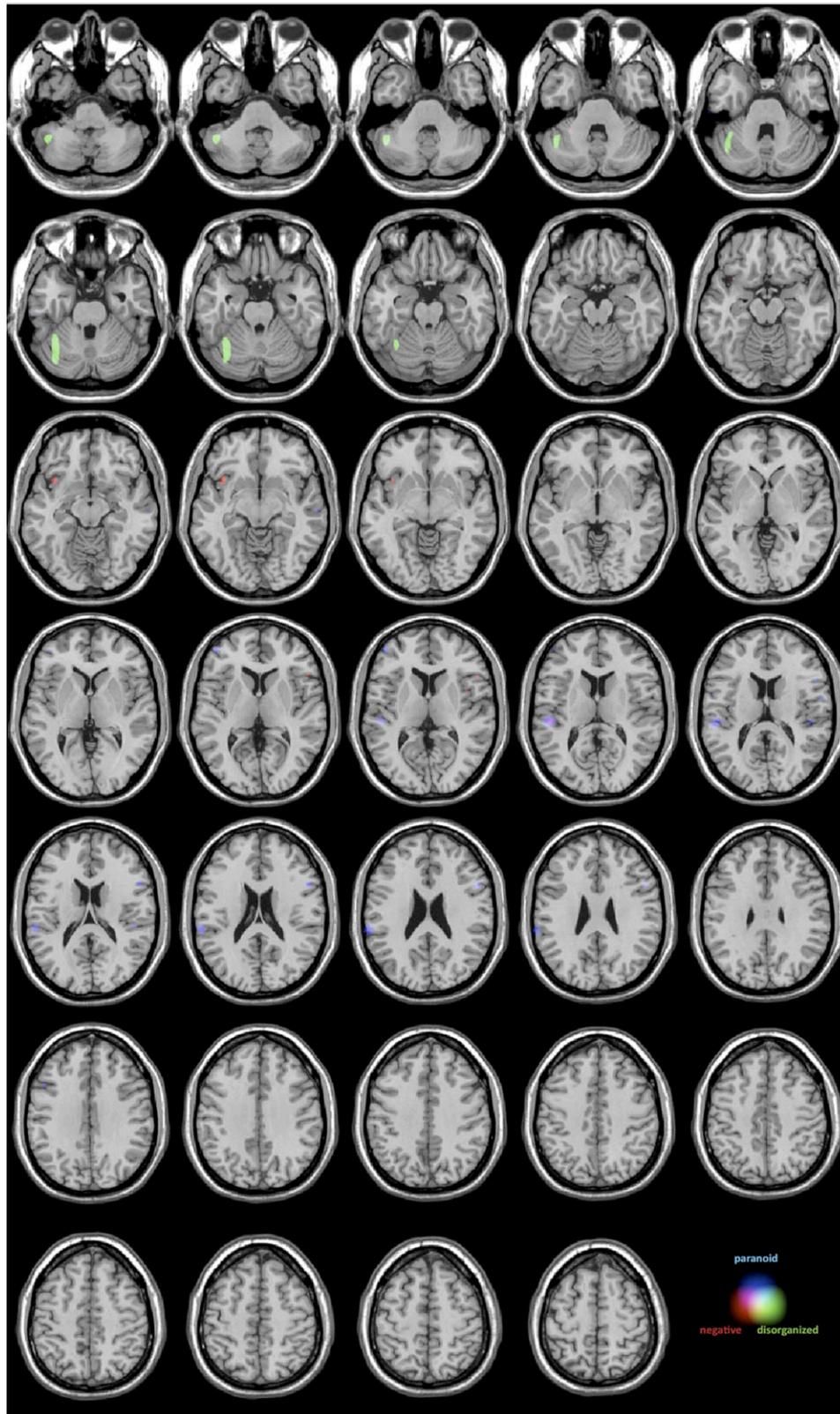
schizophrenia in an age range covering most of the adult life span. While across the group of schizophrenia patients the effects seem to converge in the superior temporal gyrus (STG) (and possibly the right inferior frontal gyrus), there is a considerable heterogeneity, which appears to be related to phenotypic differences and thus possibly underlying subtypes of the disorder.

Progression of brain structural changes has mostly been assessed with longitudinal studies, most of which use follow-up periods of 2–5 years<sup>25–28</sup> and only few reaching up to 10 years.<sup>29</sup> While these designs offer high sensitivity due to within-subject comparison, they are often limited to a particular age range (even if computation of trajectories is used) and only few studies have included a wider age range.<sup>28</sup> Our cross-sectional design therefore took advantage of allowing coverage of changes occurring over most of the adult life span.

Three regional findings of our study merit particular attention: the age-related decline in the superior temporal cortex, which was evident both across the entire patient group and in particular in the paranoid subgroup but also negative

subgroup; the prefrontal decline, which was apparent in the overall analysis and particularly the paranoid subgroup; and the cerebellar decline, which was restricted to the disorganized subgroup.

Superior temporal cortical changes are of interest because they appear to be particularly prone to the effects of disease progression. Changes in the left STG have been identified both in the transition toward psychosis,<sup>30–33</sup> as well as some follow-up studies in chronic patients,<sup>28</sup> although not all.<sup>34</sup> A most recent follow-up study appears to confirm this progression: While no particular subregion of the STG was affected, the study also suggested that antipsychotic exposure is not positively correlated with gray matter loss.<sup>35</sup> This would be consistent with STG changes representing an inherent feature of the disorder rather than an artifact of medication. This is supported by postmortem studies identifying alterations of microcolumn spacing in schizophrenia in the STG region, which was found to be related to an alteration of features of physiological features of aging.<sup>36</sup> Our results in the paranoid subgroup suggest that prominent positive symptoms might be a stronger predictor



**Fig. 2.** Overlay (On Single Subject T1 Scan) of Areas Showing Stronger Age-Related Gray Matter Decline in the 3 Schizophrenia Subgroups (Each Compared With Healthy Subjects;  $P < .001$ , Uncorrected): Negative Subgroup (Red), Disorganized Subgroup (Green), and Paranoid Subgroup (blue). Note that those clusters surviving small volume correction ( $P < .05$  FWE corrected) are given in table 1.

of such changes because age-related STG change was not significant in the disorganized group and only in a smaller cluster in the negative subgroup.

Less consistent with our initial hypothesis, we found steeper prefrontal age-related decline to be restricted to a relatively small area in the right prefrontal lateral cortex. The cluster located in the right inferior frontal gyrus, part of the dorsolateral/ventrolateral prefrontal cortex, seen in the overall group comparison and in the paranoid subgroup (to a lesser extent also in the negative subgroup) was somewhat more inferior to the previous studies of the frontal lobe we had referred to earlier.<sup>8</sup> This would argue against a prominent widespread (as opposed to focal) effect of accelerated prefrontal substance loss, at least during presenile aging. It is interesting to note that this interaction was more prominent in the paranoid rather than the negative subgroup, even though prefrontal deficits are thought to be most prevalent in the latter subgroup of patients.<sup>5,15,37</sup> It appears that this finding does not contradict the general association of negative symptoms with prefrontal structural changes (or progression) because we need to consider the fact that negative symptoms—although most prominent in that 1 subgroup—were prevalent in all the 3 schizophrenia subgroups to varying degrees.

Finally, we found evidence for stronger age-related progression in the left cerebellum. While disease-related progression in the cerebellum has been detected in a recent smaller longitudinal study,<sup>31</sup> although in the right cerebellum, it is interesting to note that in our subgroup analyses, this effect was only significant in the disorganized subgroup but not the 2 other subgroups.

While our study adds several novel aspects to the problem of progressive change in brain structure in schizophrenia, we need to consider several limitations. First, our cohort focused on an age range from 18 to 65 years, ie, presenile aging. We therefore cannot infer on accelerated brain aging that occurs after age 60 years and which might be relevant for our understanding of cognitive and clinical outcomes in later life. Second, age and duration of illness are highly correlated, hence the observed changes could reflect not only an inherently progressive component of the disease but partially also effects of medication, clinical outcome, and other factors, which would render our findings more prone to type II errors and less sensitive than longitudinal designs. These factors, however, would still have limited effect on the testing of our second hypothesis, ie, the heterogeneity of age-related progression because the 3 subgroups were very similar in age of onset and disease duration. Several factors that can poorly be controlled for are more likely to affect our design (eg, duration of untreated psychosis, change of medication etc.). Finally, we need to consider the limitation of not being able to fully account for potential differences between the subgroups related to overall life time dose and type of antipsychotics used. Different previous use of first- vs

second-generation antipsychotics, overall life time exposure, and also difference in patients' adherence to medication schemes might influence not only the pattern of brain structural alteration at cross-sectional analysis but potentially also the effects of progressive brain structural change. Further studies would be needed to address this aspect in more detail.

Progression of brain structural deficits might be an important aspect in our understanding of the clinical impact of schizophrenia. As shown in a series of longitudinal studies in Kraepelinian vs non-Kraepelinian (ie, poor outcome vs good outcome) studies, brain structure is among the few biological markers that might bear relevance for this aspect as well.<sup>10,38</sup> This alternative approach has the advantage of using clinical longitudinal data and is therefore not directly comparable with our cross-sectional approach using a 3-factor solution in stratification of patient populations. It should, however, be noted that several studies support the validity of the 3-factor or subgroup model. This includes follow-up studies on temporal stability of the most important psychopathological features in these subgroups<sup>39,40</sup> and the identification of these subgroups even in old age schizophrenia patients, decades after disease onset.<sup>19</sup> Also, 2 studies in large patient samples have identified patterns of brain structural changes in these 3 subgroups.<sup>15,37</sup>

In conclusion, our study provides not only support for age-related excess changes of STG and right inferior prefrontal structure in schizophrenia but also suggests that these effects show considerable variability across the heterogeneous phenotype of schizophrenia.

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