Progressive Gray Matter Reduction of the Superior Temporal Gyrus During Transition to Psychosis

Tsutomu Takahashi, MD, PhD; Stephen J. Wood, PhD; Alison R. Yung, MD, MPM, FRANZCP; Bridget Soulsby, BSc; Patrick D. McGorry, MD, PhD, FRCP, FRANZCP; Michio Suzuki, MD, PhD; Yasuhiro Kawasaki, MD, PhD; Lisa J. Phillips, MPysch (Clin), PhD; Dennis Velakoulis, MBBS, FRANZCP; Christos Pantelis, MD, MRCPsych, FRANZCP

Context: Longitudinal magnetic resonance imaging studies have shown progressive gray matter reduction in the superior temporal gyrus during the earliest phases of schizophrenia. It is unknown whether these progressive processes predate the onset of psychosis.

Objective: To examine gray matter reduction of the superior temporal gyrus over time in individuals at risk for psychosis and in patients with first-episode psychosis.

Design: Cross-sectional and longitudinal comparisons.

Setting: Personal Assessment and Crisis Evaluation Clinic and Early Psychosis Preventions and Intervention Centre.

Participants: Thirty-five ultrahigh-risk individuals (of whom 12 later developed psychosis [UHRP] and 23 did not [UHRNP]), 23 patients with first-episode psychosis (FEP), and 22 control subjects recruited from the community.

Main Outcome Measures: Volumes of superior temporal subregions (planum polare, Heschl gyrus, planum temporale, and rostral and caudal regions) were measured at baseline and follow-up (mean, 1.8 years) and were compared across groups.

Results: In cross-sectional comparisons, only the FEP group had significantly smaller planum temporale and caudal superior temporal gyrus than other groups at baseline, whereas male UHRP subjects also had a smaller planum temporale than controls at follow-up. In longitudinal comparison, UHRP and FEP patients showed significant gray matter reduction (approximately 2%-6% per year) in the planum polare, planum temporale, and caudal region compared with controls and/or UHRNP subjects. The FEP patients also exhibited progressive gray matter loss in the left Heschl gyrus (3.0% per year) and rostral region (3.8% per year), which were correlated with the severity of delusions at follow-up.

Conclusions: A progressive process in the superior temporal gyrus precedes the first expression of florid psychosis. These findings have important implications for underlying neurobiologic features of emerging psychotic disorders and emphasize the importance of early intervention during or before the first episode of psychosis.

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Several lines of evidence support the notion that schizophrenia arises as a consequence of both an “early neurodevelopmental” disturbance and a pathological process in “late neurodevelopment” occurring during the initial stage of illness. Previous magnetic resonance (MR) imaging studies have demonstrated progressive brain changes in the years following illness onset, whereas more recent longitudinal studies of high-risk populations around the period of transition to psychosis have provided a clue to the underlying neurobiologic features of emerging psychotic disorders.

In our previous voxel-based morphometric (VBM) study in ultrahigh-risk (UHR) individuals, those who had developed psychosis within 12 months (30%-40% of UHR subjects) showed progressive gray matter reductions in temporal, orbitofrontal, and cingulate regions over the transition phase, although there was no significant group × follow-up interaction in that study, comparing those who developed psychosis with those who did not. In a VBM study from the Edinburgh High-Risk Study, genetically high-risk individuals with transient or isolated psychosis or who later developed schizophrenia showed progressive changes mainly in the left temporal lobe regions. Despite the lack of a comparison cohort of patients with first-episode psychosis (FEP) and potential methodologic problems of brain registration, these VBM findings provide evidence that brain abnormalities associated with psychotic disorders predate the on-
set of frank symptoms and are not due to medication. Our recent study based on cortical pattern matching, which allows more sensitive analysis of the lateral cortical surface than does VBM, demonstrated increased brain surface contraction in prefrontal regions during illness transition. This approach cannot examine the medial brain surface or detailed cortical regions in deep sulci such as the Heschl gyrus (HG).

Morphologic abnormalities of the superior temporal gyrus (STG) and its functionally relevant subregions such as the primary auditory cortex (HG) and planum temporale (PT), have been repeatedly described in schizophrenia. Volume reduction of these regions, especially in the left hemisphere, have been found to correlate with auditory hallucinations or thought disorder. In contrast, the auditory association cortex located anterior to the HG (planum polare [PP]) or the lateral portion of the STG, which is related to auditory speech perception or mentalizing tasks, have rarely been studied as specific regions of interest (ROIs) in psychotic disorders. Longitudinal MR imaging studies in first-episode schizophrenia have reported marked progressive reductions in left posterior portions of the STG gray matter during the initial years after the first hospitalization. These changes were highly correlated with progressive impairments of the normal neurophysiologic response of the region, specifically mismatch negativity. However, progressive gray matter changes of other STG subregions are not well documented. Borgwardt et al demonstrated that clinical high-risk subjects, recruited via criteria similar to ours, had a smaller left STG than did control subjects in a cross-sectional VBM study, whereas one volumetric MR imaging study in genetically high-risk individuals reported bilateral STG reduction. An inverse correlation between the volume of the left STG, especially the PT, and the duration of the initial untreated period of psychosis in schizophrenia suggests a regional progressive pathological process in the STG during the earliest stages of psychosis. To our knowledge, no ROI-based MR imaging studies have undertaken a detailed longitudinal examination of the STG subregions in a high-risk cohort.

The present study aimed to clarify the timing and course of the gray matter changes of the STG as well as its subregions in psychotic disorders by detailed ROI analyses of longitudinal MR imaging data in healthy controls, individuals at UHR of developing psychosis, and patients with FEP. On the basis of our own and other work, we predicted that UHR subjects who later developed psychosis (UHRP) would show progressive gray matter loss in the STG during the transition into psychosis to a degree similar to that observed in FEP, and that UHR subjects who did not develop psychosis (UHRNP) would not show marked STG volume changes over time.

| METHODS |

**PARTICIPANTS**

Thirty-five UHR subjects were recruited from admissions to the Personal Assessment and Crisis Evaluation Clinic. The UHR identification criteria (Table 1) and the rationale for these criteria have been previously described. The UHR subjects were assessed with the Brief Psychiatric Rating Scale, the Scale for the Assessment of Negative Symptoms, and the Comprehensive Assessment of At Risk Mental States. All UHR subjects were approximately age 14 to 30 years, had not experienced a previous psychotic episode, had never received antipsychotic medication, and were not intellectually disabled (IQ > 70). After baseline MR imaging, UHR subjects were monitored regularly on the basis of operationalized criteria for psychosis onset and were then divided into subgroups according to 12-month outcome; 12 UHR subjects (34%) developed psychosis (UHRP) and 23 (66%) did not (UHRNP). The disorders in the 12 UHRP subjects were schizophrenia (n = 4), schizoaffective disorder (n = 1), brief psychotic episode (n = 1), psychosis not...
otherwise specified (n = 1), bipolar disorder with psychotic features (n = 2), and major depression with mood incongruent psychotic disorder (n = 3). After baseline imaging, 9 subjects (7 without and 2 with psychosis) received risperidone (mean dosage, 1.3 mg/d) and cognitive behavior therapy, and 5 (3 without and 2 with psychosis) received supportive therapy as part of a double-blind randomized study examining a 6-month therapeutic intervention study.13 Most UHRP subjects were receiving atypical antipsychotics after onset, but complete information on medications was not available. Three subjects (2 without and 1 with psychosis) were receiving antidepressants at baseline for depressive symptoms.

Twenty-three FEP inpatients were recruited from the Early Psychosis Prevention and Intervention Centre.49 Inclusion criteria for FEP patients were (1) age at onset between 16 and 30 years and (2) current psychosis as reflected by the presence of at least 1 symptom (delusions, hallucinations, disorder of thinking and/or speech other than simple acceleration or retardation, and disorganized, bizarre, or markedly inappropriate behavior).50 The DSM-IV diagnoses were based on medical record review, Structured Clinical Interview for DSM-IV,44 and the Royal Park Multidiagnostic Instrument for Psychosis50 administered during the initial treatment episode (median illness duration, 29.0 days). All patients were neuroleptic-naive before admission, but 17 had received neuroleptics for a short period before the first imaging; 8 were treated with atypical antipsychotics and 9 were receiving typical antipsychotics (mean [SD] dosage, 161.8 [102.2] mg/d, chlorpromazine equivalent). Accurate values for the duration of medication use were not available, but the mean duration of such a period in our center is about 30 days.51 Patients were also receiving benzodiazepines (n = 10), antidepressants (n = 2), and/or lithium carbonate (n = 3). The medication status was unknown for 4 patients at the first imaging. The final diagnoses of these patients during the follow-up were as follows: schizophrenia (n = 16; 3 paranoid, 3 disorganized, 3 undifferentiated, and 7 residual subtypes), schizoaffective disorder (n = 3), schizophreniaform disorder (n = 1), delusional disorder (n = 1), psychotic disorder not otherwise specified (n = 1), and a psychosis with affective features (diagnosis by Structured Clinical Interview for DSM-IV unavailable, n = 1). Clinical symptoms were assessed at follow-up imaging by means of the Positive and Negative Syndrome Scale (PANSS)50 (Table 2). At the second imaging, 15 of 23 patients were taking antipsychotic medication; 8 were using atypical antipsychotics and 7 were using typical antipsychotics (mean [SD] dosage, 193.5 [198.9] mg/d, chlorpromazine equivalent). They were also receiving benzodiazepines (n = 4), antidepressants (n = 2), lithium carbonate (n = 2), or combination lithium carbonate and valproate sodium (n = 1). Twenty-two healthy volunteers were recruited from sociodemographic areas similar to those of the patients by approaching ancillary hospital staff and through advertisements.52

Clinical information including handedness, illness onset, premorbid IQ (where available) as assessed by the National Adult Reading Test data were available for 65 subjects (18 controls, 18 UHR nonpsychotic subjects, 11 UHR psychotic subjects, and 18 with FEP). Data were available for 21 patients with FEP.

### Table 2. Demographic and Clinical Data of Healthy Control Subjects, UHR Individuals, and Patients With FEPa

<table>
<thead>
<tr>
<th></th>
<th>Control Subjects (n=22)</th>
<th>Nonpsychotic Subjects (n=23)</th>
<th>Psychotic Subjects (n=12)</th>
<th>Patients With FEP (n=23)</th>
<th>Group Comparisons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, No. M/F</td>
<td>12/10</td>
<td>12/11</td>
<td>7/5</td>
<td>16/7</td>
<td>( \chi^2 = 1.88, P = .64 )</td>
</tr>
<tr>
<td>Handedness, No. right/mixedfeelb</td>
<td>22/0/0</td>
<td>18/1/4</td>
<td>10/0/2</td>
<td>18/0/5</td>
<td>( \chi^2 = 7.70, P = .02 )</td>
</tr>
<tr>
<td>Height, cm²</td>
<td>175.3 (12.0)</td>
<td>169.0 (10.1)</td>
<td>173.2 (9.2)</td>
<td>171.3 (7.8)</td>
<td>( F_{3,75} = 1.43, P = .24 )</td>
</tr>
<tr>
<td>Premorbid IQ</td>
<td>102.7 (8.6)</td>
<td>93.3 (15.7)</td>
<td>94.3 (13.6)</td>
<td>92.8 (15.0)</td>
<td>( F_{3,75} = 4.30, P = .08 )</td>
</tr>
<tr>
<td>Age at baseline imaging, y</td>
<td>22.0 (4.7) [16.2 to 32.8]</td>
<td>20.2 (4.0) [14.3 to 27.5]</td>
<td>19.5 (5.1) [13.9 to 29.1]</td>
<td>21.5 (3.5) [16.8 to 28.3]</td>
<td>( F_{3,75} = 1.28, P = .29 )</td>
</tr>
<tr>
<td>Age at second imaging, y</td>
<td>24.1 (4.9) [18.1 to 35.7]</td>
<td>21.6 (4.0) [15.4 to 28.5]</td>
<td>20.7 (5.2) [15.4 to 30.9]</td>
<td>23.6 (4.0) [17.7 to 32.3]</td>
<td>( F_{3,75} = 2.29, P = .08 )</td>
</tr>
<tr>
<td>Days between imaging</td>
<td>780 (312) [313 to 1428]</td>
<td>511 (289) [329 to 1361]</td>
<td>443 (186) [237 to 826]</td>
<td>739 (279) [294 to 1527]</td>
<td>( F_{3,75} = 6.39, P &lt; .001 )</td>
</tr>
<tr>
<td>Age at onset, y</td>
<td>NA</td>
<td>NA</td>
<td>20.1 (5.0) [15.3 to 29.5]</td>
<td>21.4 (3.6) [15.6 to 28.3]</td>
<td>( F_{3,75} = 0.78, P = .38 )</td>
</tr>
<tr>
<td>Days between baseline image and onset</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Days between onset and baseline imaging</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Days between onset and second image</td>
<td>NA</td>
<td>NA</td>
<td>232 (144) [15 to 534]</td>
<td>803 (266) [345 to 1676]</td>
<td>( F_{3,75} = 47.46, P &lt; .001 )</td>
</tr>
<tr>
<td>BPRS score at intake</td>
<td>NA</td>
<td>18.0 (7.7)</td>
<td>20.1 (8.7)</td>
<td>NA</td>
<td>( F_{3,75} = 0.53, P = .47 )</td>
</tr>
<tr>
<td>SANS score at intake</td>
<td>NA</td>
<td>18.7 (10.7)</td>
<td>29.3 (16.1)</td>
<td>NA</td>
<td>( F_{3,75} = 5.43, P = .03 )</td>
</tr>
<tr>
<td>PANSS positive at follow-up</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>PANSS negative at follow-up</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>PANSS general at follow-up</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Intracranial volume, cm³</td>
<td>1401.7 (149.9)</td>
<td>1415.3 (154.3)</td>
<td>1485.6 (135.8)</td>
<td>1402.0 (137.4)</td>
<td>( F_{3,75} = 1.12, P = .35 )</td>
</tr>
</tbody>
</table>

aAbbreviations: BPRS, Brief Psychiatric Rating Scale; FEP, first-episode psychosis; NA, not applicable; PANSS, Positive and Negative Syndrome Scale; SANS, Scale for the Assessment of Negative Symptoms; UHR, ultrahigh-risk.
bData are presented as mean (SD) [range].
cData were not available for 7 subjects.
dBy analysis of variance.
eNational Adult Reading Test data were available for 65 subjects (18 controls, 18 UHR nonpsychotic subjects, 11 UHR psychotic subjects, and 18 with FEP).
fData were available for 21 patients with FEP.

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size55,56; the 4 groups did not differ significantly in their ICVs vertebral as major landmarks to correct for differences in head undersurface of the frontal lobe, dorsum sellae, clivus, and C1 mat of the original 3-dimensional data set using the dura mater, intracranial volume (ICV) was measured on a sagittal refor-
ditionally colored: planum polare, green; Heschl gyrus, blue; planum temporale, red; and lateral STG, yellow.

Figure 1. Three-dimensional reconstructed images presenting lateral (A) and top-down (B) views and a sample coronal image (C) of superior temporal subregions of the left hemisphere. The frontal and parietal lobes in B are partially cut away to disclose the regions examined. The lateral superior temporal gyrus (STG) was further subdivided into rostral STG and caudal STG by a plane containing the anterior end of the Heschl gyrus (dotted line in A). Each of the STG subregions is differentially colored: planum polare, green; Heschl gyrus, blue; planum temporale, red; and lateral STG, yellow.

35 UHR subjects, 16 of 23 FEP patients, and 14 of 22 controls were included in our recent studies using cortical pattern matching.10,14 Eighteen FEP patients and 20 controls were the same as those in our study of the hippocampus.11

MR IMAGE ACQUISITION AND PROCESSING

Subjects underwent imaging twice on a 1.5-T imager (GE Signa; General Electric Medical Systems, Milwaukee, Wisconsin). A 3-dimensional volumetric spoiled gradient-recall echo in the steady state sequence generated 124 contiguous 1.5-mm coronal sections. Imaging parameters were as follows: echo time, 3.3 milliseconds; repetition time, 14.3 milliseconds; flip angle, 30°; matrix size, 256 × 256; field of view, 24 × 24-cm matrix; and voxel dimensions, 0.9375 × 0.9375 × 1.5 mm. Head movement was minimized by using foam padding and Velcro straps across the forehead and chin. The imager was calibrated fortnightly with the same proprietary phantom to ensure the stability and accuracy of measurements.

On a Unix workstation (Silicon Graphics Inc, Mountain View, California), the image data were coded randomly and analyzed with the software package Dr View (AJS, Tokyo, Japan). Brain images were realigned in 3 dimensions to standardize for differences in head tilt and reconstructed into entire contiguous coronal images, with a 0.9375-mm thickness, perpendicular to the intercommissural line. The whole cerebrum was manually separated from the brainstem and cerebellum. According to the Alpert algorithm,53 the signal-intensity histogram distributions from the T1-weighted images across the whole cerebrum were then used to semiautomatically segment the voxels into gray matter, white matter, and cerebrospinal fluid.34 The intracranial volume (ICV) was measured on a sagittal reformat of the original 3-dimensional data set using the dura mater, undersurface of the frontal lobe, dorum sellae, clivus, and C1 vertebra as major landmarks to correct for differences in head size55,56; the 4 groups did not differ significantly in their ICVs (Table 2).

VOLUMES OF STG SUBREGIONS

The gray matter of the STG subregions (PP, HG, PT, rostral STG, and caudal STG) was manually traced on 0.9375-mm consecutive coronal sections (Figure 1).

The parcellation strategy and terminology have been previously described.26 Briefly, on the basis of the established trac-
ing guidelines,37 the first coronal section showing the temporofrontal junction and the coronal plane containing the posterior end of the posterior horizontal limb of the sylvian fissure were chosen as anterior and posterior boundaries of the whole STG, respectively. On each coronal section, the whole STG was bounded superiorly by the sylvian fissure and inferiorly by the superior temporal sulcus. The whole STG was then segmented into the supratemporal plane and inferior portion (lateral STG)36,37 by the lateral limb of the supratemporal plane. The HG was traced posterior to anterior, beginning with the first section containing the Heschl sulcus and ending anteri-
orly with the section containing the most anterior point of the Heschl sulcus or the sulcus intermedius if it existed. On each coronal section, the HG was bounded medially by the sylvian fissure, inferior circular insular sulcus, or first transverse sulcus and laterally by the Heschl sulcus. When 2 convolutions were oriented separately from the retroinsular regions, the most anterior gyrus was regarded as the HG. When they were ori-

tented medially from the common stem, however, both were defined as the HG. After tracing of the HG, which takes a diag-

onal course on the supratemporal plane, the regions lying anteromedial and posterolateral to the HG within the remain-
ing gray matter of the supratemporal plane were regarded as the PP and PT, respectively. The inferior portion of the STG (lateral STG) was divided into rostral and caudal STG por-
tions by the plane including the anterior tip of the HG.

All volumetric data reported herein were measured by 1 rater (T.T.), who was blinded to the subjects’ identities and time of imaging. Intrarater (for T.T.)/interrater (between T.T. and Y.K.) intraclass correlation coefficients in 8 randomly selected brains in this sample were as follows: 0.96/0.88 (PP), 0.97/0.98 (HG), 0.96/0.95 (PT), 0.99/0.96 (rostral STG), and 0.98/0.93 (caudal STG).

STATISTICAL ANALYSIS

Clinical and demographic differences between groups were examined with 1-way analysis of variance or the χ² test.

For cross-sectional comparison at baseline and second imaging, the absolute STG volume was assessed by means of a repeated-measures analysis of variance with ICV as a covariate (analysis of covariance [ANCOVA]), with group (controls, UHRNP, UHRP, and FEP) and sex as between-subject factors, and subregion (PP, HG, PT, rostral STG, and caudal STG) and side (left and right) as within-subject variables. We then investigated each subre-
For the longitudinal comparison, the STG changes over time (absolute volume at second imaging−absolute volume at baseline) were analyzed by means of a repeated-measures ANCOVA with ICV and interimage interval (year) as covariates, with group and sex as between-subject factors, and with subregion and side as within-subject variables. On the basis of interactions with subregion and side but no effects involving sex in this analysis (Table 3), 5 subregions for each hemisphere were then separately analyzed covarying for baseline volume of each subregion and interimage interval with only group as a between-subject factor. The post hoc Tukey honestly significant difference test was used.

For the FEP patients whose PANSS scores at follow-up were available (n=21), Spearman ρ was calculated to explore correlations between the percentage of volume change per year of the left and right STG subregions and 4 selected positive syndrome subscores of PANSS (delusions, conceptual disorganization, hallucinatory behavior, and suspiciousness/persecution). To minimize type I error due to multiple comparisons, we limited the analyses to the severity of these positive symptoms based on previous observations.26,31-33,39 Correlations between daily dosage of antipsychotics and relative volumes (100 \( \text{absolute volume/ICV} \)) and annual gray matter loss (percentage of change) for each subregion as well as the PANSS subscores were also evaluated. Statistical significance was defined as \( P < .05 \) (2-tailed).

**RESULTS**

**DEMOGRAPHIC VARIABLES**

Groups were matched for age, sex, handedness, height, or premorbid IQ, but there was a difference in time be-

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**Table 3. Absolute Gray Matter Volume of the Whole Brain and Superior Temporal Gyrus Subregions at Baseline and Second Image and Annual Percentage of Change**

<table>
<thead>
<tr>
<th>Brain Region</th>
<th>Control Subjects</th>
<th>Nonpsychotic</th>
<th>Psychotic</th>
<th>Patients With FEP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Whole brain</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>724 263 (84 307)</td>
<td>710 743 (95 937)</td>
<td>759 148 (78 830)</td>
<td>710 584 (63 151)</td>
</tr>
<tr>
<td>% Change</td>
<td>−1.7 (2.4)</td>
<td>−0.5 (4.2)</td>
<td>−2.1 (5.0)</td>
<td>−1.5 (2.3)</td>
</tr>
<tr>
<td><strong>Whole STG</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Left</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>13 461 (2587)</td>
<td>13 564 (3008)</td>
<td>13 475 (1902)</td>
<td>12 645 (2134)</td>
</tr>
<tr>
<td>% Change</td>
<td>0.4 (1.8)</td>
<td>0.1 (4.8)</td>
<td>−5.0 ( b,c ) (4.4)</td>
<td>−3.6 ( b,c ) (2.9)</td>
</tr>
<tr>
<td>Right</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>11 801 (2390)</td>
<td>11 538 (2022)</td>
<td>12 221 (1736)</td>
<td>10 807 (1627)</td>
</tr>
<tr>
<td>% Change</td>
<td>0.4 (2.1)</td>
<td>−0.5 (4.9)</td>
<td>−3.9 ( b ) (5.7)</td>
<td>−1.5 (4.1)</td>
</tr>
<tr>
<td><strong>Planum polare</strong></td>
<td></td>
<td></td>
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<tr>
<td>Left</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>1725 (580)</td>
<td>1874 (616)</td>
<td>2089 (302)</td>
<td>2130 (637)</td>
</tr>
<tr>
<td>% Change</td>
<td>1.0 (4.3)</td>
<td>0.1 (7.9)</td>
<td>−5.6 ( b ) (6.1)</td>
<td>−2.6 (4.5)</td>
</tr>
<tr>
<td>Right</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>1666 (509)</td>
<td>1664 (705)</td>
<td>1686 (389)</td>
<td>1817 (508)</td>
</tr>
<tr>
<td>% Change</td>
<td>0.6 (4.1)</td>
<td>0.2 (5.9)</td>
<td>−6.3 ( c ) (7.4)</td>
<td>−1.5 (4.6)</td>
</tr>
<tr>
<td><strong>Heschl gyrus</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Left</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>2226 (585)</td>
<td>2135 (666)</td>
<td>2252 (908)</td>
<td>1804 (869)</td>
</tr>
<tr>
<td>% Change</td>
<td>−0.1 (3.6)</td>
<td>−1.2 (5.4)</td>
<td>−4.3 (6.0)</td>
<td>−3.0 (3.6)</td>
</tr>
<tr>
<td>Right</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>1619 (483)</td>
<td>1655 (478)</td>
<td>1796 (587)</td>
<td>1470 (433)</td>
</tr>
<tr>
<td>% Change</td>
<td>0.5 (3.9)</td>
<td>−1.3 (7.5)</td>
<td>−3.5 (8.3)</td>
<td>−0.7 (9.3)</td>
</tr>
<tr>
<td><strong>Planum temporale</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>3519 (865)</td>
<td>3439 (989)</td>
<td>3096 (711)</td>
<td>3059 ( a,b,d ) (627)</td>
</tr>
<tr>
<td>% Change</td>
<td>0.9 (4.3)</td>
<td>0.9 (5.0)</td>
<td>−5.2 ( b,c ) (5.2)</td>
<td>−3.3 ( b,c ) (2.5)</td>
</tr>
<tr>
<td>Right</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>2846 (921)</td>
<td>2820 (750)</td>
<td>2874 (630)</td>
<td>2435 ( a,b,d ) (614)</td>
</tr>
<tr>
<td>% Change</td>
<td>2.1 (4.2)</td>
<td>0.3 (5.9)</td>
<td>−3.9 ( b ) (4.9)</td>
<td>−2.2 (4.4)</td>
</tr>
</tbody>
</table>

(continued)
The results of the STG measures are summarized in Table 3. At baseline, ANCOVA of the caudal STG showed a significant group difference ($F_{3,71} = 4.12, \ P = .009$); the FEP patients had a smaller caudal STG than did the other groups (vs controls, $P = .004$; UHRNP, $P = .03$; and UHRP, $P = .046$). An ANCOVA of the PT showed a significant group $\times$ sex interaction ($F_{3,71} = 3.05, \ P = .03$), where male FEP patients had a smaller PT than did male controls ($P = .02$) and male UHRNP subjects ($P = .03$). All STG subregions except the caudal STG had a significant left-greater-than-right asymmetry for all groups (PP: $F_{1,72} = 14.85, \ P < .001$; HG: $F_{1,72} = 40.68, \ P < .001$; PT: $F_{1,72} = 37.42, \ P < .001$; and rostral STG: $F_{1,72} = 9.46, \ P = .003$).

At the second imaging, ANCOVAs for the PT ($F_{1,72} = 4.23, \ P = .008$) and caudal STG ($F_{1,72} = 7.18, \ P < .001$) showed a significant main effect for group. An ANCOVA of the PT showed a group $\times$ sex interaction ($F_{3,71} = 3.37, \ P = .02$). Post hoc tests indicated that FEP patients had a significantly smaller caudal STG than did the controls ($P < .001$), UHRNP subjects ($P = .003$), and UHRP subjects ($P = .04$). For male subjects only, the PT of the FEP patients was smaller than that of the controls ($P < .001$) or UHRNP subjects ($P = .002$), and UHRP subjects had a smaller PT than did controls ($P = .04$). The volumes of the PP ($F_{1,72} = 16.94, \ P < .001$), HG ($F_{1,72} = 35.45, \ P < .001$), PT ($F_{1,72} = 34.52, \ P < .001$), and rostral STG ($F_{1,72} = 9.28, \ P < .001$), HG ($F_{1,72} = 35.45, \ P < .001$), PT ($F_{1,72} = 34.52, \ P < .001$), and rostral STG ($F_{1,72} = 9.28, \ P < .001$), and other imaging procedures (vs controls, $P = .004$; UHRNP, $P = .03$; and UHRP, $P = .046$). An ANCOVA of the PT showed a significant group $\times$ sex interaction ($F_{3,71} = 3.05, \ P = .03$), where male FEP patients had a smaller PT than did male controls ($P = .02$) and male UHRNP subjects ($P = .03$). All STG subregions except the caudal STG had a significant left-greater-than-right asymmetry for all groups (PP: $F_{1,72} = 14.85, \ P < .001$; HG: $F_{1,72} = 40.68, \ P < .001$; PT: $F_{1,72} = 37.42, \ P < .001$; and rostral STG: $F_{1,72} = 9.46, \ P = .003$).

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had a significant asymmetrical pattern (left/right) in all groups.

**LONGITUDINAL GRAY MATTER CHANGES**

The ANCOVA results of gray matter reduction over time and the percentage of volume change values of the STG subregions are given in Table 3. The ANCOVAs of the PP (left: \(F_{3,74}=3.45, P=.02\); right: \(F_{3,74}=3.79, P=.01\)), left HG (\(F_{3,74}=5.10, P=.003\)), PT (left: \(F_{3,74}=12.19, P<.001\); right: \(F_{3,74}=5.10, P=.003\)), left rostral STG (\(F_{3,74}=3.14, P=.03\)), and caudal STG (left: \(F_{3,74}=7.95, P<.001\); right: \(F_{3,74}=2.83, P=.04\)) showed a significant main effect for diagnosis, with the UHRP group having significant gray matter reduction in the left PP (\(P=.04\)), PT (left, \(P=.02\); right, \(P=.01\)), and left rostral STG (\(P=.02\)) compared with controls and in the right PP (\(P=.02\)) and left PT (\(P=.02\)) compared with the UHRNP group (Figure 2). Compared with controls, FEP patients had significant gray matter loss in the left PP (\(P=.02\)), left HG (\(P=.01\)), PT (left, \(P=.02\); right, \(P=.01\)), left rostral STG (\(P=.02\)), and left caudal STG (\(P<.001\)). The gray matter reduction of the PT (\(P<.001\)), rostral STG (\(P=.006\)), and caudal STG (\(P=.009\)) in FEP patients was larger than that in UHRNP subjects in the left hemisphere.

**CORRELATIONAL ANALYSIS**

For the FEP patients, greater annual gray matter reductions of the left rostral STG (\(p=0.67, P<.001\)) and left HG (\(p=0.56, P=.008\)) were correlated with higher score for delusions on the PANSS at follow-up. The correlation of the left rostral STG and the severity of delusions remained significant even after Bonferroni correction (5 ROIs for each hemisphere by 4 symptom ratings; \(P<.00125 [.05/40]\)) (Figure 3). The score for hallucinatory behavior was not correlated with the progressive changes in the left STG subregions (\(p=-0.28\) to 0.44, \(P=.046\) to .86). Right STG changes did not correlate with these symptom ratings (\(p=-0.27\) to 0.34, \(P=.13\) to .99). There was no significant
The rate of reduction in the HG and PT in our FEP sample was comparable to that in an earlier study in first-episode schizophrenia (left HG, −4.8% per year; right HG, 1.5% per year; left PT, −5.1% per year; right PT, −0.6% per year). Our findings further indicated that the volumes of the other STG subregions were also comparatively reduced over time. In our FEP sample, however, we did not find highly lateralized (left > right) progressive changes of the PT as in the sample of Kasai et al., and absolute volume differs considerably among the reports including our group’s own study in a Japanese sample, where patients with chronic schizophrenia had up to a 20% smaller PT than the current sample. These discrepancies could be the result of different parcellation strategies or different groups (race, sex ratio, first episode vs long-term medication treatment, and established schizophrenia vs psychosis in general) being examined. Although we cannot directly address the issue of diagnostic heterogeneity (eg, schizophrenia spectrum vs affective psychosis) for our FEP cohort, which included a rather diverse population with psychotic symptoms but only 1 patient with affective psychosis, the STG gray matter reduction in UHRP patients who developed schizophrenia spectrum (n = 7; left, −5.3% per year; right, −2.7% per year) and affective psychosis (n = 5; left, −4.5% per year; right, −5.5% per year) might imply that left-lateralized STG changes are specific to patients with schizophrenia-spectrum disorders (eTable 2 and eFigure 1). Although brain structural changes in schizophrenia may be nonlinear, with a period of intense gray matter reduction occurring during the initial years around the onset, patients with chronic schizophrenia also exhibit progressive gray matter loss in the STG that exceeds the normal aging changes. In this study, we demonstrated the STG gray matter changes during the earliest phases of psychosis with a mean interimaging interval of about 2 years, but further longitudinal follow-up of UHRP or FEP patients and additional patients with chronic disease would be required to examine the nature, timing, and course of the morphologic brain changes associated with psychosis.

A major aim of high-risk studies has been to identify a significant neurobiological predictor of future transition to psychosis, which allows specific and targeted preventive strategies. We found no differences in baseline STG gray matter volume between UHRP and UHRNP subjects. In comparison, previous VBM studies in UHR and other clinical high-risk cohorts have demonstrated that high-risk subjects who later developed psychosis had less gray matter in frontotemporolimbic-paralimbic regions, including the right anterior part of the STG, than subjects who did not. The reason for this discrepancy is unclear, but it might be related to marked...
progressive gray matter loss in the right PP (−6.3% per year) in UHRP patients. Alternatively, the issue of ROI definition could partly explain the discrepancy between reports; the anterior PP and rostral STG boundaries were defined by an external landmark and, as presented as a large variation among individuals in the number of coronal sections (eFigure 2), these volumes could be substantially influenced by the course of Heschl sulcus.

The PANSS delusions score in FEP patients at follow-up imaging correlated with annual gray matter reduction of the left rostral STG and left HG, consistent with previous reports.35,36 Together with previous MR imaging observations that implicate the left STG in hallucinations or thought disorders,31,32,39 our findings support the notion that schizophrenia involves dysfunction to primary auditory, speech, and language processes.35,36 It is notable that several longitudinal MR imaging studies have identified progressive brain changes, such as ventricular enlargement or global gray matter loss at an early course of schizophrenia, which are associated with clinical deterioration and poor outcome.37,92,93

Our findings have important implications for the treatment of psychotic disorders. It has been suggested by some,75,76 although not all,77 studies that a longer duration of untreated psychosis is associated with poor clinical outcome in schizophrenia, and it is suggested that increased duration of untreated psychosis may be related to gray matter reduction in the left PT.41 An MR imaging study in neuroleptic-naive schizophrenia showed that left STG volume reduction tended to normalize after neuroleptic medication,40 and there is evidence that atypical antipsychotics ameliorate the structural brain changes in schizophrenia.78-80 These observations suggest that the regional progressive pathological process in the left STG in schizophrenia could be at least partly mitigated by antipsychotic medication and that intervention before expression of frank psychotic symptoms may reduce neurobiological deterioration as well as the transition rate to psychosis.32,81

Several limitations of the current study should be taken into account. First, some patients withdrew from their medication or failed to make outpatient consultations during the follow-up interval so that their entire clinical data, especially medication data, were not available. Correlational analysis in our FEP sample raises the possibility that some progressive brain reductions (eg, left HG and left rostral STG) could be related to antipsychotics. In fact, progressive changes of left HG (−0.6% per year) and left rostral STG (0.7% per year) in 8 antipsychotic-free FEP patients at the second imaging were less than those in 15 medicated patients (left HG, −4.2% per year; left rostral STG, −6.2% per year). Our UHR subjects were antipsychotic-naive at baseline, but most of the UHRP patients were taking antipsychotics at follow-up imaging. However, the effects of medication alone could not explain the marked gray matter reduction in our UHRP subjects who were treated with low doses of atypical antipsychotics,78-80 as also suggested in neuroleptic-naive genetically high-risk cohorts.12,81 Although mood stabilizers may increase gray matter volume,58,83 the exclusion of 6 FEP patients who were taking lithium carbonate and/or valproate at either time point did not change the statistical conclusions. As supported by the positive correlation between medication dosage and symptom severity in the FEP patients at follow-up, these observations suggest that the patients requiring higher doses of medication due to their illness showed greater STG changes. Second, our group’s previous UHR studies using VBM13 and cortical pattern matching14 did not find longitudinal STG changes despite considerable sample overlap. It should be noted that our previous VBM study was in a small sample and used T2-weighted and proton density images in 3-mm-thick sections that may hinder detection of subtle changes and that the use of VBM has been criticized because of its inadequacy in dealing with problems of brain registration.94 The cortical pattern matching can detect subtle brain changes at a subvoxel resolution, but it cannot assess detailed cortical regions in deep sulci including STG subregions. The present study, therefore, extends the findings of our recent investigations in suggesting that the STG also shows progressive changes in early psychosis.

In summary, the present study provides evidence that gray matter reduction over time in the STG precedes the first expression of florid psychosis. These progressive changes appear to be prominent during the transition period and persist during the period after psychosis onset. Our findings also suggest that the extent of this process could be implicated in the severity of positive psychotic symptoms in patients with psychotic disorders. Although the underlying pathology of this regional progressive process is unknown, our findings provide an impetus for further studies to prevent or ameliorate these active brain changes by early intervention during or before the first episode of psychosis.

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Author Affiliations: Melbourne Neuropsychiatry Centre, Department of Psychiatry, University of Melbourne and Melbourne Health (Drs Takahashi, Wood, Velakoulis, and Pantelis and Ms Soulsby), ORYGEN Research Centre, Early Psychosis Prevention and Intervention Centre, Personal Assessment and Crisis Evaluation Clinic (Drs Yung and McGorry) and Departments of Psychiatry (Drs Yung and McGorry) and Psychology (Dr Phillips), University of Melbourne, and Howard Florey Institute (Dr Pantelis), Melbourne, Australia; Department of Neuropsychiatry, University of Toyama, Toyama, Japan (Drs Takahashi, Suzuki, and Kawasaki); and Core Re-
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