Morphological abnormalities of the superior temporal gyrus, and its functionally relevant subregions such as Heschl’s gyrus and planum temporale, in schizophrenia appear to be already present at onset of overt psychosis, but the time course of their occurrence remains unclear. Magnetic resonance imaging (MRI) studies have demonstrated that among participants at ultra-high risk of psychosis, those who subsequently developed psychosis had less grey matter than those who did not in frontotemporolimbic–paralimbic regions, including the right anterior part of the superior temporal gyrus, prior to psychosis onset. However, the conclusions that can be drawn from these analyses are limited by the potential methodological problems of voxel-based morphometry (VBM), and the inclusion of people taking medication such as antipsychotics or antidepressants. One MRI study investigating regions of interest in individuals at high genetic risk demonstrated smaller superior temporal gyrus volumes bilaterally compared with controls, but this study did not examine diagnostic outcome (i.e. later transition) and subregional specificity of the superior temporal gyrus. Our longitudinal region-of-interest study did not detect baseline superior temporal gyrus changes in the individuals who went on to develop psychosis, but was limited by a small sample size. We sought to address these limitations by conducting a region-of-interest analysis of the superior temporal gyrus subregions in a relatively large sample of antipsychotic-naive individuals at ultra-high risk who did and did not later develop a psychotic disorder, and healthy controls. Based on previous work, we predicted that the high-risk group who developed psychosis would have a smaller superior temporal gyrus at baseline compared with controls.

**Method**

**Participants**

Antipsychotic-naive individuals at ultra-high risk of psychosis (n=97) were recruited between 1995 and 2001 from admissions to the Personal Assessment and Crisis Evaluation clinic, Melbourne, Australia, which was established to identify young people at clinical risk of developing a first psychotic episode within a short follow-up period. Those recruited were aged 14–30 years, had not experienced a previous psychotic episode, had never received antipsychotic medication (antipsychotics, antidepressants, mood stabilisers or benzodiazepines) and had an IQ score above 70, assessed with the National Adult Reading Test. At intake, the Comprehensive Assessment of At Risk Mental States (CAARMS), a structured clinical interview designed to assess prodromal symptoms and risk of psychosis, was administered. General psychopathology was assessed using the Brief Psychiatric Rating Scale (BPRS), negative symptoms were rated with the Scale for the Assessment of Negative Symptoms (SANS), and family history of psychosis in a first- or second-degree relative was assessed using the Family Interview for Genetic Studies, as well as interviews with a family member. The CAARMS-defined risk identification criteria and their rationale have been fully described elsewhere. Briefly, individuals considered to be at ultra-high risk are characterised by one or more of the following:

(a) attenuated psychotic symptoms, defined by subthreshold intensity or frequency;

(b) brief limited intermittent psychotic symptoms with spontaneous resolution within 1 week;

(c) family history of psychosis (first-degree relative) or a personal history of schizotypal personality disorder, accompanied by a decline in general functioning.

The group at risk were monitored regularly over a minimum 12-month period (mean 1.1 years, maximum 3.7 years) for the onset of full-blown psychosis and were then divided into subgroups based on operationalised criteria for psychosis onset using CAARMS and the Structured Clinical Interview for DSM–IV Axis I disorders. In total, 31 (32%) of this ultra-high risk...
risk group developed a psychotic illness (UHR–P) and 66 (68%) did not (UHR–NP) during follow-up. Of those who developed psychosis, 19 developed schizophrenia-spectrum disorder (17 schizophrenia, 2 schizoaffective disorder), 10 an affective psychosis (5 major depressive disorder with psychotic features, 5 bipolar disorder with psychotic features) and 2 other psychoses (1 psychosis not otherwise specified, 1 brief psychosis). Fifty of the at-risk sample had a positive family history of psychosis.

Healthy volunteers (N = 42) with sociodemographic characteristics similar to the high-risk group were recruited by approaching ancillary hospital staff and through advertisements; those with a personal or family history of psychiatric illness were excluded. All participants were screened for comorbid medical and psychiatric conditions by clinical assessment and by physical and neurological examination. Exclusion criteria were a history of significant head injury, seizures, neurological disease, impaired thyroid function, diabetes, corticosteroid use, or alcohol or substance misuse or dependence meeting DSM–IV criteria. Of the 97 at-risk participants in this study, 64 (22 UHR–P and 42 UHR–NP) had taken part in our earlier VBM study, and 31 (11 UHR–P and 20 UHR–NP) had taken part in our longitudinal superior temporal gyrus study. The study reported here was approved by local research and ethics committees, and written informed consent was obtained from the participants or their parents/guardians where appropriate.

**Imaging procedure**

Magnetic resonance scans were acquired with a 1.5 T GE Signa scanner (General Electric Medical Systems, Milwaukee, Wisconsin, USA). A three-dimensional volumetric spoiled gradient recalled echo sequence generated 124 contiguous 1.5 mm coronal slices (repetition time (TR) = 14.3 ms, time to echo (TE) = 3.3 ms, flip angle = 30°, field of view = 24 cm × 24 cm, matrix = 256 × 256, voxel dimensions = 0.938 mm × 0.938 mm × 1.5 mm). The scanner was calibrated fortuitously with the same phantom to ensure stability of measurements.

On a Unix workstation the image data were coded randomly and analysed with the software package Dr View version 5 (AJS, Tokyo, Japan). Brain images were realigned in three dimensions and reconstructed into contiguous coronal images, with a 0.938 mm thickness, perpendicular to the anterior–posterior commissural line. The whole cerebrum was manually separated from the brain stem and cerebellum. The signal-intensity histogram distributions from the T1-weighted images across the whole cerebrum were used to segment the voxels semi-automatically into grey matter, white matter and cerebrospinal fluid. The intracranial volume was measured to correct for differences in head size as previously described.

**Volumetric analyses of superior temporal subregions**

The grey matter of the superior temporal gyrus subregions (planum polare, Heschl's gyrus, planum temporale, rostral and caudal superior temporal gyrus; online Fig. DS1) was manually chosen as the anterior and posterior boundaries respectively by the lateral limb of the supratemporal plane. Heschl’s gyrus was bounded medially by the sylvian fissure, inferior circular insular sulcus or the first transverse sulcus and laterally by Heschl’s sulcus. After tracing the Heschl’s gyrus that takes a diagonal course on the supratemporal plane, the regions lying anteromedial and posterolateral to the gyrus within the remaining grey matter of the supratemporal plane were regarded as planum polare and planum temporale respectively. The lateral superior temporal gyrus was divided into rostral and caudal portions by the plane including the anterior tip of Heschl’s gyrus.

All volumetric data reported here were measured by one rater (T.T.) masked to the participants’ identities. Intra-rater (T.T.) and interrater (T.T., Y.K.) intraclass correlation coefficients in eight randomly selected brains exceeded 0.88 for all subregions.

**Statistical analysis**

Clinical and demographic differences between groups were examined with one-way analysis of variance (ANOVA) or chi-squared tests. The relative volume of the superior temporal gyrus, calculated as (absolute volume/intracranial volume) × 100, was assessed using a repeated-measures analysis of covariance (ANCOVA) with age as a covariate, with group (control, UHR–NP and UHR–P) and gender as between-participant factors, and subregion (planum polare, Heschl’s gyrus, planum temporale, rostral superior temporal gyrus, caudal superior temporal gyrus) and side (left, right) as within-participant variables. For the at-risk group, the effects of family history (n = 50 with history v. n = 47 without history) and type of psychosis developed (schizophrenia-spectrum disorder n = 19 v. affective psychosis n = 10) on relative superior temporal gyrus volume were also examined by ANCOVA. The post hoc Tukey’s test was employed to follow up the significant main effects or interactions. We performed a Cox regression analysis to examine whether superior temporal gyrus volume would predict later transition, using transition to psychosis as the status variable, time to onset (UHR–P) or follow-up period (UHR–NP) as the time variable, and relative superior temporal gyrus volume and intake BPRS and SANS scores as covariates. The relationships between the relative superior temporal gyrus volumes and demographic or clinical variables were examined with Pearson’s r (time between scan and psychosis onset was log-transformed because of skewed distributions). Owing to the lack of prominent subregional effects, we used the whole superior temporal gyrus volume for the regression and correlational analyses. Statistical significance was defined as P < 0.05 (two-tailed).

**Results**

Comparison of the control, UHR–P and UHR–NP groups revealed no significant difference in age, gender, handedness or IQ score (Table 1). Participants in the control group were taller than those in the UHR–NP group, but the groups did not differ significantly in their intracranial volume. Baseline SANS score, but not BPRS score, was higher in the UHR–P group.

**Superior temporal gyrus volumes**

Analysis of covariance of the relative superior temporal gyral volumes revealed significant main effects for group (F(2,532) = 3.36, P = 0.038), side (F(1,133) = 99.13, P < 0.001) and subregion (F(4,532) = 599.56, P < 0.001), and a significant side × subregion interaction (F(4,532) = 14.54, P < 0.001). There was no group ×
subregion ($F_{1,8,533} = 1.07$, $P = 0.384$) or group $\times$ side $\times$ subregion ($F_{1,8,533} = 0.54$, $P = 0.821$) interaction, implying that group difference in superior temporal gyral volume was not highly localised to a particular subregion. These ANCOVA results remained the same when we analysed the whole superior temporal gyral volume with intracranial volume and age as covariates.

Post hoc tests showed that the superior temporal gyral volume was significantly smaller in the UHR–P group compared with the control group ($F = 0.031$), but there was no difference between the UHR–NP and control groups ($F = 0.133$), or the UHR–NP and UHR–P groups ($F = 0.576$). Heschl’s gyrus ($P < 0.001$) and planum temporale ($P < 0.001$) had a significant asymmetrical pattern (left $> $ right) for all groups. No group difference was found for any superior temporal gyrus subregion (Table 2, Fig. 1). When the UHR–P and UHR–NP groups were categorised together, the group as a whole had a significantly smaller whole superior temporal gyrus compared with controls bilaterally (group effect, $F_{1,134} = 5.48$, $P = 0.021$; post hoc test, $F = 0.014$).

No difference in superior temporal gyral volume was found between the at-risk participants with and without a family history of psychosis ($F_{1,94} = 1.08$, $P = 0.319$), or between those in the UHR–P group who later developed schizophrenia-spectrum disorder ($n = 19$) and those who developed affective psychosis ($n = 10$; $F_{1,26} = 0.61$, $P = 0.443$).

Regression and correlational analyses

The SANS ratings predicted time to transition (Wald test $= 5.784$, $\beta = 1.034$, 95% CI 1.01–1.06, $P = 0.016$), but the superior temporal gyrus volume (left, $P = 0.123$; right, $P = 0.658$) and BPRS score ($P = 0.819$) were not predictive of later transition. The relative whole superior temporal gyral volumes were not correlated with height and IQ score for all groups. There was a negative correlation between age and right superior temporal gyral volume only for the UHR–P group ($r = -0.574$, $P < 0.001$); this correlation was significantly different from that in the other groups (v. UHR–NP, $P = 0.010$; v. controls, $P = 0.020$) (Fig. 2). Correlational analyses did not reveal any significant correlation between the superior temporal gyral volumes and intake BPRS and SANS scores in either UHR group ($r$ values $-0.033$ to $0.109$, all $P > 0.388$) or time to the psychosis onset (log) in the UHR–P group.

Discussion

Compared with healthy controls, the ultra-high risk cohort, especially the UHR–P group, showed diffuse (not highly localised to a particular subregion) grey-matter reductions of bilateral superior temporal gyrus, whereas there was no difference in superior temporal gyral volumes between the UHR–NP and control or UHR–P groups. We also demonstrated that the superior temporal gyral volume did not predict who would develop psychosis.

Changes in superior temporal gyrus as a vulnerability marker

Consistent with previous VBM studies,8,9 our results suggest that the superior temporal gyrus changes in individuals at ultra-high risk of psychosis who subsequently develop full-blown psychosis are present before illness onset. Our findings indicate that these changes are not due to the effect of medication. The UHR–NP group also exhibited non-significant but mild grey matter reductions relative to the control group (effect size > 0.2), especially in left posterior regions (Heschl’s gyrus, planum temporale and caudal superior temporal gyrus). Furthermore, the ultra-high risk group as a whole (regardless of later transition) demonstrated significant grey matter reduction of the bilateral superior temporal gyrus compared with controls, consistent with previous MRI studies in clinically or genetically predisposed high-risk individuals.9,11,23 These findings are in line with the fact that those in the at-risk group who did not progress to psychosis were not asymptomatic, as evidenced by the range of non-psychotic diagnostics,6,7 and also had experienced subthreshold psychotic symptoms, supporting the hypothesis that such superior temporal gyrus changes represent a vulnerability marker.3 However, given the issue of region-of-interest definition in this study (e.g. an external landmark for the anterior boundary of the superior temporal gyrus),12 the possibility also exists that anterior reductions in the superior temporal gyrus are more prominent in the individuals with future transition.6,9

Onset-related superior temporal gyrus change

These cross-sectional findings are in line with our recent longitudinal region of interest analysis in a small ultra-high risk sample,12 which demonstrated progressive grey matter reduction of the superior temporal gyrus in the UHR–P group during the transition phase (left $-5.0%$ per year, right $-3.9%$ per year). The current UHR–P cohort exhibited lesser reductions in superior temporal gyrus grey matter (left $-9.8%$, right $-2.6%$) relative to controls compared with those in our previous region-of-interest study in first-episode schizophrenia (left $-16.4%$, right
The results of a cross-sectional VBM study by Borgwardt et al were similar to ours: the superior temporal gyrus in high-risk participants with later transition was significantly larger than that in first-episode psychosis, but was smaller (at a less stringent statistical threshold) in the right hemisphere than in controls.25 Taken together, these superior temporal gyrus observations support the model of psychosis that morphological abnormalities seen in patients reflect a combination of pre-existing vulnerability and changes associated with the first expression of psychotic symptoms.26

We found no effect of family history of psychosis on superior temporal gyrus volume in our at-risk sample, consistent with a previous negative finding for this region in a large genetically high-risk sample (n = 146).27 These findings suggest that the superior temporal gyrus volume changes related to psychosis are more likely to be acquired, e.g. due to environmental influences later in development,26,28 than genetic in origin. A significant effect of age on superior temporal gyrus volume only in the UHR–P group may be consistent with the notion that the transition to psychosis is associated with an acceleration of normal brain maturational processes.27,28

**Clinical implications**

Given the role of the superior temporal gyrus in manifesting psychotic symptoms such as hallucinations or thought disorder,29,30 as well as relevance to social cognitive function,31 pre-onset superior temporal gyral volume changes might at least partly underpin prodromal symptoms such as subthreshold psychotic symptoms or increasing social withdrawal,7 although we found no correlation

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**Table 2** Absolute grey matter volume of the superior temporal subregions

<table>
<thead>
<tr>
<th></th>
<th>Controls (n=42)</th>
<th>UHR–NP (n=66)</th>
<th>UHR–P (n=31)</th>
<th>Analysis of covariance&lt;sup&gt;ab&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group</td>
<td>Side</td>
<td>Group x side</td>
<td>F(2,135)</td>
</tr>
<tr>
<td>Whole STG</td>
<td>3.87</td>
<td>0.023</td>
<td>118.65</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Left</td>
<td>15053 (2582)</td>
<td>13903 (2599)</td>
<td>13573&lt;sup&gt;)&lt;/sup&gt; (1875)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>12746 (1959)</td>
<td>12183 (2181)</td>
<td>12417&lt;sup&gt;)&lt;/sup&gt; (1774)</td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>1984 (466)</td>
<td>1969 (615)</td>
<td>1912 (428)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1804 (508)</td>
<td>1754 (573)</td>
<td>1721 (445)</td>
<td></td>
</tr>
<tr>
<td>Planum polare</td>
<td>0.63</td>
<td>0.533</td>
<td>18.05</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Left</td>
<td>2609 (842)</td>
<td>2282 (624)</td>
<td>2293 (806)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1846 (474)</td>
<td>1759 (490)</td>
<td>1721 (534)</td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>3772 (837)</td>
<td>3393 (864)</td>
<td>3351 (818)</td>
<td></td>
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<tr>
<td></td>
<td>2875 (671)</td>
<td>2756 (712)</td>
<td>2851 (667)</td>
<td></td>
</tr>
<tr>
<td>Heschl’s gyrus</td>
<td>1.12</td>
<td>0.331</td>
<td>99.86</td>
<td>&lt;0.001</td>
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<tr>
<td>Left</td>
<td>1598 (636)</td>
<td>1718 (781)</td>
<td>1446 (480)</td>
<td></td>
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<td></td>
<td>1421 (632)</td>
<td>1490 (700)</td>
<td>1349 (591)</td>
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<td>Right</td>
<td>5054 (1124)</td>
<td>4507 (1061)</td>
<td>4523 (976)</td>
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<td></td>
<td>4760 (1050)</td>
<td>4394 (1001)</td>
<td>4601 (1027)</td>
<td></td>
</tr>
<tr>
<td>Planum temporale</td>
<td>2.13</td>
<td>0.122</td>
<td>7.39</td>
<td>0.007</td>
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<tr>
<td>Left</td>
<td>3772 (837)</td>
<td>3393 (864)</td>
<td>3351 (818)</td>
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<td>1421 (632)</td>
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<tr>
<td>Rostral STG</td>
<td>3.34</td>
<td>0.038</td>
<td>1.26</td>
<td>0.264</td>
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<tr>
<td>Left</td>
<td>5054 (1124)</td>
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<td>4523 (976)</td>
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<tr>
<td>Caudal STG</td>
<td>3.34</td>
<td>0.038</td>
<td>1.26</td>
<td>0.264</td>
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<td>1421 (632)</td>
<td>1490 (700)</td>
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</table>

STG, superior temporal gyrus; UHR–NP, ultra-high risk group with no psychosis; UHR–P, ultra-high risk group with psychosis.

<sup>a</sup> Result of statistical analyses based on relative STG volumes.

<sup>b</sup> Whole STG and its subregions were separately analysed with age as a covariate, group as between-participant factor and side as within-participant variable.

<sup>c</sup> Significantly different from controls (post hoc Tukey’s test).
between superior temporal gyrus volumes and symptom measures in our ultra-high risk group. However, our own work has demonstrated a significant relationship between ongoing superior temporal gyrus reduction and subsequent positive symptoms in people with first-episode psychosis. These findings suggest that it is the progressive superior temporal gyrus changes during early phases of the illness that are relevant to clinical manifestations of psychosis.

Future research

Although we have demonstrated that superior temporal gyrus changes are already present in people at ultra-high risk of psychosis, the most active and marked abnormalities of this brain region occur predominantly during the transition phase to active psychosis. This implies that this is a time of dynamic or even accelerated brain changes, which could be a target for intervention and preventive strategies.

Fig. 2 Correlations between age and relative volumes of the right whole superior temporal gyrus (STG) in a healthy control group (a) and in individuals at ultra-high risk who did not (b) and did (c) later develop psychosis.
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Data supplement

**Fig. DS1** Three-dimensional reconstructed images of superior temporal subregions presenting top-down (a) and lateral (b) views of the brain. The frontal and parietal lobes in (a) are partially cut off to disclose the regions examined. The lateral superior temporal gyrus was further subdivided into rostral and caudal regions by a plane containing the anterior end of Heschl's gyrus, shown as dotted line in (b). Lt, left; Rt, right.

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Supplementary Material
Supplementary material can be found at:
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