Superior temporal gyrus volume in antipsychotic-naive people at risk of psychosis

Tsutomu Takahashi, Stephen J. Wood, Alison R. Yung, Mark Walterfang, Lisa J. Phillips, Bridget Soulsby, Yasuhiro Kawasaki, Patrick D. McGorry, Michio Suzuki, Dennis Velakoulis and Christos Pantelis

Background
Morphological abnormalities of the superior temporal gyrus have been consistently reported in schizophrenia, but the timing of their occurrence remains unclear.

Aims
To determine whether individuals exhibit superior temporal gyral changes before the onset of psychosis.

Method
We used magnetic resonance imaging to examine grey matter volumes of the superior temporal gyrus and its subregions (planum polare, Heschl's gyrus, planum temporale, and rostral and caudal regions) in 97 antipsychotic-naive individuals at ultra-high risk of psychosis, of whom 31 subsequently developed psychosis and 66 did not, and 42 controls.

Results
Those at risk of psychosis had significantly smaller superior temporal gyri at baseline compared with controls bilaterally, without any prominent subregional effect; however, there was no difference between those who did and did not subsequently develop psychosis.

Conclusions
Our findings indicate that grey matter reductions of the superior temporal gyrus are present before psychosis onset, and are not due to medication, but these baseline changes are not predictive of transition to psychosis.

Declaration of interest
None.

Morphological abnormalities of the superior temporal gyrus,[1–3] and its functionally relevant subregions such as Heschl's gyrus and planum temporale,[4,5] 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,[6,7] 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.[8,9] However, the conclusions that can be drawn from these analyses are limited by the potential methodological problems of voxel-based morphometry (VBM),[10] 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 gyral volumes bilaterally compared with controls,[11] 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,[12] 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,[8,9] 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.[7] 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.[13] At intake, the Comprehensive Assessment of At Risk Mental States (CAARMS),[14] 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),[15] negative symptoms were rated with the Scale for the Assessment of Negative Symptoms (SANS),[16] and family history of psychosis in a first- or second-degree relative was assessed using the Family Interview for Genetic Studies,[17] as well as interviews with a family member. The CAARMS-defined risk identification criteria and their rationale have been fully described elsewhere.[18] 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.[19] In total, 31 (32%) of this ultra-high

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.[20] 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,[8] and 31 (11 UHR–P and 20 UHR–NP) had taken part in our longitudinal superior temporal gyrus study.[12] 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 fortnightly 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 T_1-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.[21]

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 traced on 0.938 mm consecutive coronal slices as described in detail elsewhere.[12,22] Briefly, the first coronal plane showing the temporofrontal junction and the coronal plane containing the posterior end of the posterior horizontal limb of the sylvian fissure were chosen as the anterior and posterior boundaries respectively of the whole superior temporal gyrus. On each coronal slice the whole superior temporal gyrus was bounded superiorly by the sylvian fissure and inferiorly by the superior temporal sulcus. The gyrus was then segmented into supratemporal and lateral portions by the lateral limb of the supratemporal plane. Heschl's gyrus was traced from posterior to anterior, beginning with the

first slice containing Heschl's sulcus and ending anteriorly with the slice containing the most anterior point of Heschl's sulcus or the sulcus intermedius if it existed. On each coronal slice, 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).

<div align="center">Results</div>

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 ($F_{(2,132)} = 3.36$, $P = 0.038$), 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 ×

Table 1 Demographic characteristics of the participants

	Controls ($n = 42$)	UHR–NP ($n = 66$)	UHR–P ($n = 31$)	Group comparisons
Age, years: mean (s.d.)	20.0 (2.8)	20.2 (3.3)	19.1 (3.6)	$F(2,136) = 1.34$, $P = 0.265$
Male/female, n/n	28/14	39/27	20/11	$\chi^2 = 0.69$, $P = 0.71$
Handedness, n (right/mixed/left)[a]	38/1/2	54/2/9	28/0/3	$P = 0.52$, Fisher's exact test
Height, cm: mean (s.d.)[a]	175.7 (9.7)	171.2 (8.5)	172.3 (8.9)	$F(2,132) = 3.20$, $P = 0.044$; controls > UHR–NP
Premorbid IQ, mean (s.d.)[a]	97.9 (8.9)	95.7 (13.5)	93.9 (13.6)	$F(2,118) = 0.77$, $P = 0.464$
Time between scan and onset, days				
Mean (s.d.)	–	–	199 (199)	–
Median	–	–	104	–
BPRS score at intake, mean (s.d.)	–	17.9 (7.1)	18.9 (7.2)	$F(1,95) = 0.36$, $P = 0.551$
SANS score at intake, mean (s.d.)	–	19.7 (14.2)	29.0 (15.7)	$F(1,95) = 8.37$, $P = 0.005$; UHR–P > UHR–NP
Intracranial volume, cm³: mean (s.d.)	1453 (152)	1416 (146)	1470 (129)	$F(2,144) = 1.86$, $P = 0.160$[b]

BPRS, Brief Psychiatric Rating Scale; SANS, Scale for the Assessment of Negative Symptoms; UHR–NP, ultra-high risk group who did not develop psychosis; UHR–P, ultra-high risk group who did develop psychosis.
a. Data missing for some participants.
b. Analysis of covariance with age as covariate and group as between-participant factor.

subregion ($F_{(8,532)} = 1.07$, $P = 0.384$) or group × side × subregion ($F_{(8,532)} = 0.54$, $P = 0.821$) interaction, implying that group difference in superior temporal gyrus volume was not highly localised to a particular subregion. These ANCOVA results remained the same when we analysed the absolute superior temporal gyrus 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 ($P = 0.031$), but there was no difference between the UHR–NP and control groups ($P = 0.133$), or the UHR–NP and UHR–P groups ($P = 0.576$). 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, $P = 0.014$).

No difference in superior temporal gyral volume was found between the at-risk participants with and without a family history of psychosis ($F_{(1,94)} = 1.00$, $P = 0.319$), 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, β = 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 gyrus 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 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 diagnoses,[6,7] and also had experienced subthreshold psychotic symptoms, supporting the hypothesis that such superior temporal gyrus changes represent a vulnerability marker.[9] 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.[8,9]

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 gyral 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

Table 2 Absolute grey matter volume of the superior temporal subregions

	Grey matter volume, mm³: mean (s.d.)			Analysis of covariance[a,b]					
				Group		Side		Group × side	
	Controls (n=42)	UHR–NP (n=66)	UHR–P (n=31)	F(2,135)	P	F(1,136)	P	F(2,136)	P
Whole STG				3.87	0.023	118.65	<0.001	3.11	0.048
Left	15053 (2582)	13903 (2599)	13573[c] (1875)						
Right	12746 (1959)	12183 (2181)	12417[c] (1776)						
Planum polare				0.63	0.533	18.05	<0.001	0.13	0.883
Left	1984 (466)	1969 (615)	1912 (428)						
Right	1804 (508)	1754 (573)	1721 (445)						
Heschl's gyrus				1.12	0.331	99.86	<0.001	2.82	0.063
Left	2609 (842)	2282 (624)	2293 (806)						
Right	1846 (474)	1759 (490)	1921 (534)						
Planum temporale				2.20	0.115	103.70	<0.001	2.34	0.100
Left	3772 (837)	3393 (864)	3351 (818)						
Right	2875 (671)	2756 (712)	2851 (667)						
Rostral STG				2.13	0.122	7.39	0.007	0.40	0.669
Left	1598 (636)	1718 (781)	1446 (480)						
Right	1421 (632)	1490 (700)	1349 (591)						
Caudal STG				3.34	0.038	1.26	0.264	0.798	0.452
Left	5054 (1124)	4507 (1061)	4523 (976)						
Right	4760 (1050)	4394 (1001)	4601 (1027)						

STG, superior temporal gyrus; UHR–NP, ultra-high risk group with no psychosis; UHR–P, ultra-high risk group with psychosis.
a. Result of statistical analyses based on relative STG volumes.
b. Whole STG and its subregions were separately analysed with age as a covariate, group as between-participant factor and side as within-participant variable.
c. Significantly different from controls (*post hoc* Tukey's test).

−15.5%).[24] 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 gyral 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 changes might at least partly underpin prodromal symptoms such as subthreshold psychotic symptoms or increasing social withdrawal,[7] although we found no correlation
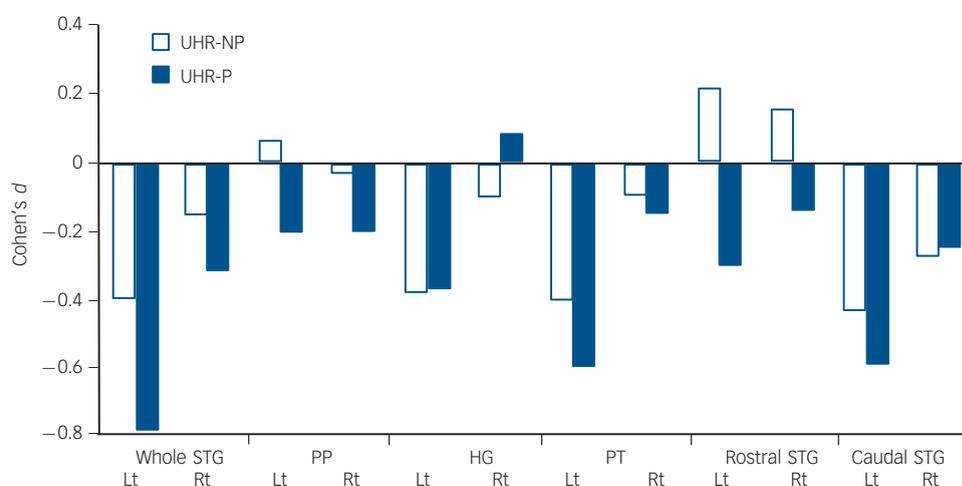
Fig. 1 Effect sizes (Cohen's *d*) based on relative superior temporal gyrus (STG) volumes for ultra-high risk participants who did (UHR–P) and did not (UHR–NP) develop psychosis relative to healthy controls. HG, Heschl's gyrus; PP, planum polare; PT, planum temporale.
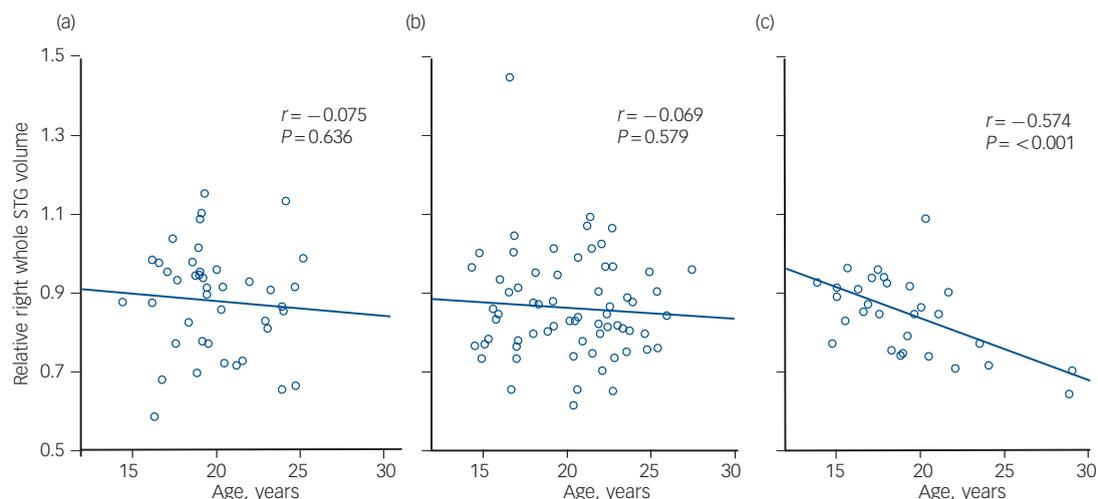
Fig. 2 Correlations between age and relative volumes of the right whole superior temporal gyrus (STG) in a healthy control group (a) and in individuals at ultra-high risk who did not (b) and did (c) later develop psychosis.

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.[12] 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.

One major aim of high-risk group studies has been to identify neurobiological and clinical predictors of future transition to psychosis, such as high level of depression, poor functioning and negative symptoms,[7] which would allow specific and targeted preventive strategies.[32] A series of our MRI studies has identified such predictive markers, including pituitary volume, thickness of the anterior cingulate cortex and corpus callosum shape.[33–35] The study reported here replicated the predictive validity of the SANS score,[7] but did not support the role of pre-existing superior temporal gyrus volume reduction as a significant predictor of future transition. However, the onset-related ongoing superior temporal gyral changes, which could affect subsequent course of the illness,[12] and potential ameliorating effects of antipsychotics,[36] may implicate the potential role of the superior temporal gyrus changes as a therapeutic target during the early phases or an outcome marker after the onset of psychosis.

Limitations

Some limitations of this study should be taken into account. First, although all participants tested were antipsychotic-naive at the time of scanning, 11 individuals (UHR–P $n = 3$, UHR–NP $n = 6$, control $n = 2$) had records of a significant degree of cannabis use, which could affect brain morphology.[37] However, exclusion of these participants did not change the statistical conclusions. Second, the superior temporal gyrus findings in the ultra-high risk group are partly inconsistent with our previous investigations despite considerable sample overlap. Our VBM study found smaller superior temporal gyral volumes in the UHR–P group only for the right hemisphere,[8] but it should be noted that this VBM study used T_2-weighted and proton density images in 3 mm thick slices that might hinder detection of subtle changes, and that the use of VBM has been criticised because of its inadequacy in dealing with problems of brain registration.[10] Although our longitudinal region-based analysis failed to detect

baseline superior temporal gyrus changes in the at-risk group,[12] this could be explained by limited statistical power due to small sample size (UHR–P $n = 12$, UHR–NP $n = 23$). The study reported here thus complements and extends our previous findings in suggesting that those at ultra-high risk of psychosis exhibit bilateral superior temporal gyrus reductions. Finally, our cohort included a rather diverse population with psychotic symptoms, and the findings could be relevant to psychoses in general. Neurobiological similarities and differences between schizophrenia and other psychoses such as bipolar disorder remain controversial.[38] Although no difference in superior temporal gyrus volume was found between participants who later developed schizophrenia-spectrum disorders ($n = 19$) and those who developed affective psychosis ($n = 10$), further work will be required to clarify the diagnostic specificity of our findings in a larger sample.

Future research

Although we have demonstrated that superior temporal gyral 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.

Tsutomu Takahashi, MD, PhD, Melbourne Neuropsychiatry Centre, Department of Psychiatry, University of Melbourne, Australia, Department of Neuropsychiatry, University of Toyama, Japan, and CREST, JST, Japan; **Stephen J. Wood**, PhD, Melbourne Neuropsychiatry Centre, Department of Psychiatry, Univeristy of Melbourne; **Alison R. Yung**, MBBS, MD, MPM, FRANZCP, ORYGEN Research Centre, PACE Clinic and Department of Psychiatry, University of Melbourne; **Mark Walterfang**, FRANZCP, ORYGEN Research Centre, PACE Clinic and Department of Psychiatry, University of Melbourne; **Lisa J. Phillips**, PhD, Department of Psychology, University of Melbourne; **Bridget Soulsby**, BSc, Melbourne Neuropsychiatry Centre, Department of Psychiatry, University of Melbourne; **Yasuhiro Kawasaki**, MD, PhD, Department of Neuropsychiatry, University of Toyama and CREST, JST; **Patrick D. McGorry**, MD, PhD, FRCP, FRANZCP, ORYGEN Research Centre, PACE Clinic and Department of Psychiatry, University of Melbourne; **Michio Suzuki**, MD, PhD, Department of Neuropsychiatry, University of Toyama and CREST, JST; **Dennis Velakoulis**, MBBS, FRANZCP, **Christos Pantelis**, MD, MRCPsych, FRANZCP, Melbourne Neuropsychiatry Centre, Department of Psychiatry, University of Melbourne

Correspondence: Dr Tsutomu Takahashi, Melbourne Neuropsychiatry Centre, c/o National Neuroscience Facility, 161 Barry Street, Carlton South, Victoria 3053, Australia. E-mail: tsutomu@med.u-toyama.ac.jp

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