

Figure 3. Effects of repeated administration of PCP on $\alpha 7$ nicotinic receptor ($\alpha 7$ nAChR) protein in the mouse brain. Saline (10 mL/kg/day) or PCP (10 mg/kg/day) was administered SC for 10 days (once daily on days 1–5, 8–12). Three days after the last administration of saline or PCP (i.e., on day 15), the mice were killed by decapitation. Western blot analysis with $\alpha 7$ nAChR antibody was performed as described in Methods. The levels of $\alpha 7$ nAChRs in the PCP-treated mice were expressed as percentages of those of the saline-treated mice. Values are the means \pm SEM ($n = 8$). * $p < .05$, ** $p < .01$ as compared with the saline-treated group (control). Other abbreviations as in Figure 1.

reduction of the exploratory preference in mice after repeated administration of PCP (Figure 1B).

In contrast, PCP-induced cognitive deficits were significantly improved after subsequent subchronic (2-week) administration of the higher dose (3.0 mg/kg/day) but not of the lower dose (.3 mg/kg/day) of SSR180711. In the training session, the exploratory preferences of the six groups were not significantly different [$F(5,74) = .762$, $p = .580$] (Figure 2A). However, in the retention session, ANOVA analysis revealed that the exploratory preferences of the six groups were significantly different [$F(5,74) = 12.11$, $p < .001$] (Figure 2B). A post hoc Bonferroni test indicated that the exploratory preference of the PCP-treated group was significantly ($p < .001$) increased after subchronic (2-week) administration of SSR180711 (3.0 mg/kg/day) but not SSR180711 (.3 mg/kg/day) (Figure 2B). Furthermore, the effect of SSR180711 (3.0 mg/kg) on the PCP-induced cognitive deficits was significantly ($p < .001$) antagonized by the co-administration of MLA (3 mg/kg/day) (Figure 2B). Moreover, subchronic (2-week) administration of MLA (3.0 mg/kg/day) alone did not alter PCP-induced cognitive deficits in mice (Figure 2B).

Effects of Repeated PCP Administration on the Levels of $\alpha 7$ nAChRs in the Mouse Brain

Western blot analysis revealed that the levels of $\alpha 7$ nAChRs in the frontal cortex ($t = 2.589$, $p = .021$) and hippocampus ($t = 3.024$, $p = .009$) of the PCP-treated (10 mg/kg/day for 10 days) mice were significantly lower than those of saline-treated mice (Figure 3). Furthermore, immunohistochemistry revealed that the immunoreactivity of $\alpha 7$ nAChRs in the frontal cortex ($t = 3.182$, $p = .005$) and hippocampus ($t = 5.820$, $p < .001$) of mice treated with PCP (10 mg/kg/day 10 days) was significantly lower than that of the saline-treated group (Figure 4).

Next, we examined whether subsequent subchronic (2-week) administration of SSR180711 (3 mg/kg/day) alters the reduction of $\alpha 7$ nAChRs in the mouse brain after repeated PCP administration. In this study, we found that subchronic administration of SSR180711 (3 mg/kg/day) did not alter the reduction of $\alpha 7$

nAChRs in the frontal cortex and hippocampus after repeated PCP administration (Figure 5). These findings suggest that repeated PCP administration caused a long-term reduction of $\alpha 7$ nAChRs in the mouse brain (more than 2 weeks after the final administration of PCP).

HPLC Determination of PCP and SSR180711 Levels in the Mouse Brain

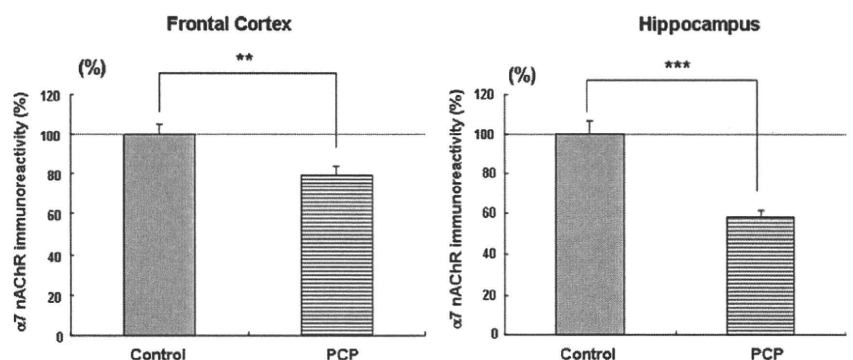
To ascertain whether the behavioral effects of SSR180711 are due to the stimulation at $\alpha 7$ nAChRs in the mouse brain or due to another effect (residual PCP) in the mouse brain, we measured the PCP levels in the mouse brain at the time of the behavioral NORT test. In this study, we did not detect the compound PCP in the mouse brain 24 hours after the subsequent subchronic (2-week) administration of SSR180711 (3 mg/kg/day). Therefore, it is likely that the behavioral effect of SSR180711 on PCP-induced cognitive deficits might be due to the stimulation at $\alpha 7$ nAChRs in the mouse brain but not to residual PCP in the mouse brain.

Next, we measured the levels of SSR180711 in the mouse brain at the time of the behavioral NORT test. We could detect the compound SSR180711 (SSR180711-treated group: 33.04 ± 10.97 ng/mg tissue [$n = 6$]; vehicle-treated group: not detected) in the mouse brain at 1 hour after a single acute administration of SSR180711 (3 mg/kg). However, we did not detect the compound SSR180711 in the mouse brain at 24 hours after the subchronic (2-week) administration of SSR180711 (3 mg/kg/day). These findings suggest that the behavioral effect of SSR180711 on PCP-induced cognitive deficits might be due to the subchronic stimulation at $\alpha 7$ nAChRs in the mouse brain but not to residual SSR180711 in the mouse brain.

Discussion

The major findings of the present study are that repeated PCP administration significantly decreased the density of $\alpha 7$ nAChRs in the mouse brain and that PCP-induced cognitive deficits could be improved by subsequent subchronic (2-week) administration of the

Figure 4. Effects of repeated administration of PCP on the distribution of $\alpha 7$ nAChR immunoreactivity in the mouse brain. Saline (10 mL/kg/day) or PCP (10 mg/kg/day) was administered SC for 10 days (once daily on days 1–5, 8–12). Three days after the last administration of saline or PCP (i.e., on day 15), the mice were perfused. Immunohistochemistry was performed as described in Methods. Values are the means \pm SEM ($n = 11$). ** $p < .01$, *** $p < .001$ as compared with the saline-treated group (control). Other abbreviations as in Figure 1.



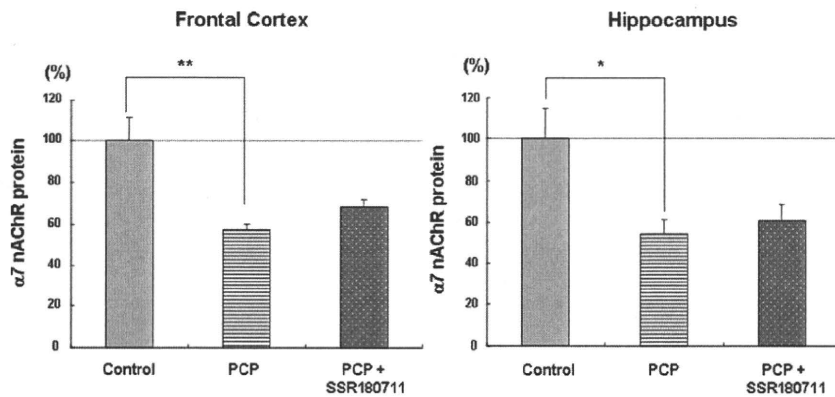


Figure 5. Effects of subsequent subchronic administration of SSR180711 on the reduction of $\alpha 7$ nAChR immunoreactivity in the mouse brain after the repeated administration of PCP. Saline (10 mL/kg/day) or PCP (10 mg/kg/day) was administered SC for 10 days (once daily on days 1–5, 8–12). Three days after the last administration of saline or PCP (i.e., on day 15), vehicle (10 mL/kg/day; saline) or SSR180711 (3.0 mg/kg/day) was administered IP to the mice for 2 consecutive weeks (once daily on days 15–28). Twenty-four hours after the last administration of vehicle or SSR180711, the mice were killed by decapitation. Western blot analysis with $\alpha 7$ nAChR antibody was performed as described in Methods. The levels of $\alpha 7$ nAChRs in the PCP-treated mice were expressed as percentages of those of the saline-treated mice. Values are the means \pm SEM ($n = 8$). * $p < .05$, ** $p < .01$ as compared with the saline-treated group (control). Other abbreviations as in Figure 1.

novel selective $\alpha 7$ nAChR agonist SSR180711. We reported recently that, in the NORT, PCP-induced cognitive deficits could be improved by subsequent subchronic (2-week) administration of clozapine but not of haloperidol, suggesting that the reversal of PCP-induced cognitive deficits with the NORT might be a potential animal model of atypical antipsychotic activity related to the amelioration of cognitive deficits in schizophrenia (14). Very recently, Pichat *et al.* (35) reported that SSR180711 significantly reversed dizocilpine-induced deficits in the retention of episodic memory in rats (object recognition test). SSR180711 was co-administered with dizocilpine (1 mg/kg, IP) in that study (35), whereas SSR180711 was administered after repeated PCP administration in the present study. Taken together, these findings suggest that SSR180711 could ameliorate cognitive deficits after the administration of NMDA receptor antagonists (PCP and dizocilpine), although the treatment schedules differed between the two studies. Nonetheless, it is likely that SSR180711 can be used as a therapeutic drug in the treatment of cognitive deficits in schizophrenia.

In the present study, we found that repeated PCP administration caused the reduction of $\alpha 7$ nAChRs in the mouse brain. This is the first report demonstrating that the administration of PCP significantly decreased the density of $\alpha 7$ nAChRs in the brain. The precise mechanism(s) underlying how repeated PCP administration could modulate $\alpha 7$ nAChRs in the brain are currently unknown. A postmortem human brain study demonstrated decreased expression of hippocampal $\alpha 7$ nAChRs in schizophrenic patients (37), suggesting that schizophrenic patients have fewer $\alpha 7$ nAChRs in the hippocampus, a condition that might lead to the failure of cholinergic activation of the inhibitory interneurons, manifesting clinically as decreased gating of responses to sensory stimulation (18,37). Furthermore, it has been reported that the immunoreactivity of $\alpha 7$ nAChRs in the prefrontal cortex of schizophrenia was significantly decreased as compared with normal control subjects (38). Interestingly, $\alpha 7$ nAChR agonists can increase the release of glutamate from the presynaptic terminals, resulting in stimulation of the NMDA receptors on the postsynaptic neurons, suggesting that stimulation at $\alpha 7$ nAChRs might potentiate the NMDA receptors (11,25). Taken together, these findings suggest that $\alpha 7$ nAChRs might interact with the NMDA receptors in the brain (11,25), although further study on the cross-talk between $\alpha 7$ nAChRs and NMDA receptors in the brain is necessary (39).

Deficient inhibitory processing of the P50 auditory evoked potential is a pathophysiological feature of schizophrenia (17,18,40). Several lines of evidence suggest that $\alpha 7$ nAChRs play a critical role in this phenomenon (17–19,22). Similar to schizophrenic patients, DBA/2 mice (decreased levels of $\alpha 7$ nAChRs) spontaneously exhibit a deficit in the inhibitory processing of the P20-N40 auditory evoked potential, which is thought to be a

rodent analogue of the human P50 auditory evoked potential (41). We reported that the administration of tropisetron, a partial agonist at $\alpha 7$ nAChRs, improved the deficient inhibitory processing of the P20-N40 auditory evoked potential in DBA/2 mice and that the co-administration of MLA (3 mg/kg) blocked the normalizing effect of tropisetron, suggesting that $\alpha 7$ nAChRs play a role in the mechanism of action of tropisetron (15). In addition, we also reported that tropisetron improved the deficits of P50 suppression in schizophrenic patients (32). Recently, we also reported that, via $\alpha 7$ nAChRs, tropisetron could improve PCP-induced cognitive deficits in mice (31). Furthermore, it has been reported that the selective $\alpha 7$ nAChR agonist PNU-282987 restores auditory gating deficits in rats after the administration of amphetamine (42) and that the selective $\alpha 7$ nAChR agonists, (R)-3'-(5-chlorothiophen-2-yl)spiro-1-azabicyclo[2.2.2]octane-3,5'-[1',3']oxazolidin-2'-one (25,43) and W-56203, (R)-3'-(3-methylbenzob[thiophen-5-yl]spiro[1-azabicyclo[2.2.2]octane-3,5'-oxazolidin-2'-one (25,44), significantly improved dizocilpine-induced auditory gating deficits in rats. Therefore, it might be of interest to study the P20-N40 auditory evoked potential in mice with the repeated PCP administration, because repeated PCP administration decreased the density of $\alpha 7$ nAChRs in the mouse brain.

In conclusion, the present findings suggest that repeated administration of PCP decreased the density of $\alpha 7$ nAChRs in the mouse brain and that SSR180711 could improve the cognitive deficits that occur in mice after the repeated administration of PCP. These findings suggest that $\alpha 7$ nAChR agonists such as SSR180711 could be used as potential therapeutic drugs in the treatment of cognitive deficits in schizophrenia.

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

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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" disturbance¹ and a pathological process in "late neurodevelopment" occurring during the initial stage of illness.²⁻⁵ Previous magnetic resonance (MR) imaging studies have demonstrated progressive brain changes in the years following illness onset,^{4,6-11} 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.¹²⁻¹⁵

In our previous voxel-based morphometric (VBM) study in ultrahigh-risk (UHR) individuals, those who had devel-

oped psychosis within 12 months (30%-40% of UHR subjects)^{16,17} showed progressive gray matter reductions in temporal, orbitofrontal, and cingulate regions¹³ over the transition phase, although there was no significant group \times 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,¹⁸ genetically high-risk individuals with transient or isolated psychosis or who later developed schizophrenia showed progressive changes mainly in the left temporal lobe regions.¹² Despite the lack of a comparison cohort of patients with first-episode psychosis (FEP) and potential methodologic problems of brain registration,¹⁹ these VBM findings provide evidence that brain abnormalities associated with psychotic disorders predate the on-

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set of frank symptoms and are not due to medication. Our recent study based on cortical pattern matching,²⁰ which allows more sensitive analysis of the lateral cortical surface than does VBM, demonstrated increased brain surface contraction in prefrontal regions during illness transition.¹⁴ This approach cannot examine the medial brain surface or detailed cortical regions in deep sulci such as Heschl gyrus (HG).

Morphologic abnormalities of the superior temporal gyrus (STG)²¹⁻²³ and its functionally relevant subregions such as the primary auditory cortex (HG)^{24,26} and planum temporale (PT),^{24,26-29} a neocortical language region,³⁰ 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.^{26,31-34} 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 perception³⁵ or mentalizing tasks,³⁶ 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.^{8,9} These changes were highly correlated with progressive impairments of the normal neurophysiologic response of the region, specifically mismatch negativity.³⁷ However, progressive gray matter changes of other STG subregions are not well documented. Borgwardt et al³⁸ 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.³⁹ 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^{40,41} 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 own¹³ and other^{8,9} 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.^{17,42} The UHR identification criteria (**Table 1**) and the rationale for these cri-

Table 1. Ultrahigh-Risk Intake and Exit Criteria^a

| Criteria | |
|--|--|
| Intake criteria | |
| Group 1: attenuated psychotic symptoms | Presence of ≥ 1 of following symptoms: idea of reference, magical thinking, perceptual disturbance, paranoid ideation, and odd thinking and speech (score of 2-3 on unusual thought content subscale, 1-2 on hallucinations subscale, 2-3 on suspiciousness subscale, or 1-3 on conceptual disorganization subscale of BPRS) Held with reasonable degree of conviction, as defined by score of 2 on CASH rating scale for delusions Frequency of symptoms is several times a wk Change in mental state present for ≥ 1 wk but not longer than 5 y |
| Group 2: BLIPS | Transient psychotic symptoms: presence of ≥ 1 of following symptoms: idea of reference, magical thinking, perceptual disturbance, paranoid ideation, and odd thinking and speech (score of ≥ 4 on unusual thought content subscale, ≥ 3 on hallucinations subscale, ≥ 4 on suspiciousness subscale [or it is held with strong conviction, as defined by score of ≥ 3 on CASH rating scale for delusions], or ≥ 4 on conceptual disorganization subscale of BPRS) Duration of episode of < 1 wk Symptoms resolve spontaneously BLIPS must have occurred within past year |
| Group 3: trait and state risk factors | First-degree relative with psychotic disorder or schizotypal personality disorder or individual has schizotypal personality disorder Significant decrease in mental state or functioning maintained for ≥ 1 mo (reduction in GAF scale of 30 points from premorbid level) Decrease in functioning occurred within past year |
| Exit criteria: acute psychosis | Presence of ≥ 1 of following symptoms: hallucinations (defined by score of ≥ 3 on hallucinations subscale of BPRS), delusions (defined by score of ≥ 4 on unusual thought content subscale of BPRS or ≥ 4 on suspiciousness subscale of BPRS), or it is held with strong conviction, as defined by score of ≥ 3 on CASH rating scale for delusions or formal thought disorder (defined by score of ≥ 4 on conceptual disorganization subscale of BPRS) Frequency of symptoms is at least several times a week to daily Duration of mental state change is > 1 wk |

Abbreviations: BLIPS, brief limited intermittent psychotic symptoms; BPRS, Brief Psychiatric Rating Scale; CASH, Comprehensive Assessment of Symptoms and History; GAF, Global Assessment of Function.

^aPeople were included if they met criteria for 1 or more of the 3 groups.

teria have been previously described.^{16,17} The UHR subjects were assessed with the Brief Psychiatric Rating Scale,⁴³ the Scale for the Assessment of Negative Symptoms,⁴⁴ and the Comprehensive Assessment of At Risk Mental States.⁴⁵ 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 onset¹⁷ 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

Table 2. Demographic and Clinical Data of Healthy Control Subjects, UHR Individuals, and Patients With FEP^a

| | Control Subjects (n=22) | UHR Subjects | | Patients With FEP (n=23) | Group Comparisons |
|---|----------------------------|---------------------------|---------------------------|-----------------------------|----------------------------|
| | | Nonpsychotic (n=23) | Psychotic (n=12) | | |
| Sex, No. M/F | 12/10 | 12/11 | 7/5 | 16/7 | $\chi^2=1.68, P=.64$ |
| Handedness, No. right/mixed/left ^b | 22/0/0 | 18/1/4 | 10/0/2 | 18/0/5 | $\chi^2=7.70, P=.26$ |
| Height, cm ^c | 175.3 (12.0) | 169.0 (10.1) | 173.2 (9.2) | 171.3 (7.8) | $F_{3,69}=1.43, P=.24^d$ |
| Premorbid IQ ^e | 102.7 (9.6) | 93.3 (13.7) | 94.3 (13.6) | 92.8 (15.0) | $F_{3,61}=2.30, P=.09^d$ |
| Age at baseline imaging, y | 22.0 (4.7) [16.2 to 32.8] | 20.2 (4.0) [14.3 to 27.5] | 19.5 (5.1) [13.9 to 29.1] | 21.6 (3.5) [16.8 to 28.3] | $F_{3,76}=1.28, P=.29^d$ |
| Age at second imaging, y | 24.1 (4.9) [18.1 to 35.7] | 21.6 (4.0) [15.4 to 28.5] | 20.7 (5.2) [15.4 to 30.9] | 23.6 (4.0) [17.7 to 32.3] | $F_{3,76}=2.29, P=.08^d$ |
| Days between images | 780 (312) [313 to 1428] | 511 (289) [329 to 1361] | 443 (186) [237 to 826] | 739 (279) [294 to 1527] | $F_{3,76}=6.39, P<.001^d$ |
| Age at onset, y | NA | NA | 20.1 (5.0) [15.3 to 29.5] | 21.4 (3.6) [15.6 to 28.3] | $F_{1,33}=0.78, P=.38^d$ |
| Days between baseline image and onset | NA | NA | 211 (141) [84 to 538] | NA | NA |
| Days between onset and baseline image | NA | NA | NA | 64 (102) [-2 to 429] | NA |
| Days between onset and second image | NA | NA | 232 (144) [15 to 534] | 803 (266) [345 to 1676] | $F_{1,33}=47.46, P<.001^d$ |
| BPRS score at intake | NA | 18.0 (7.7) | 20.1 (8.7) | NA | $F_{1,33}=0.53, P=.47^d$ |
| SANS score at intake | NA | 18.7 (10.7) | 29.3 (16.1) | NA | $F_{1,33}=6.43, P=.03^d$ |
| PANSS positive at follow-up ^f | NA | NA | NA | 20.6 (7.8) | NA |
| PANSS negative at follow-up ^f | NA | NA | NA | 18.7 (7.9) | NA |
| PANSS general at follow-up ^f | NA | NA | NA | 40.7 (10.3) | NA |
| Intracranial volume, cm ³ | 1401.7 (149.9) | 1415.3 (154.3) | 1485.6 (135.8) | 1402.0 (137.4) | $F_{3,75}=1.12, P=.35^d$ |

Abbreviations: 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.

^aData are presented as mean (SD) [range].

^bEffect of handedness on the laterality of the superior temporal gyrus in patients with FEP was tested by means of a laterality index (eTable 1, <http://www.archgenpsychiatry.com>).

^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.

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.⁴² Most UHRP subjects received 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.⁴⁶ 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).⁴⁷ The DSM-IV diagnoses were based on medical record review, Structured Clinical Interview for DSM-IV,⁴⁸ and the Royal Park Multidiagnostic Instrument for Psychosis⁴⁹ administered during the initial treatment episode (median illness duration, 29.0 days). All patients were neuroleptic-naïve 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.⁴⁷ 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 fol-

low-up were as follows: schizophrenia (n=16; 3 paranoid, 3 disorganized, 3 undifferentiated, and 7 residual subtypes), schizoaffective disorder (n=3), schizophreniform 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.⁴⁷

Clinical information including handedness, illness onset, premorbid IQ (where available) as assessed by the National Adult Reading Test,⁵¹ and medication data was obtained from patient interview and medical record review. All participants were screened for comorbid medical and psychiatric conditions by clinical assessment and physical and neurologic examination. Exclusion criteria were a history of significant head injury, neurologic diseases, impaired thyroid function, corticosteroid use, or DSM-IV criteria for alcohol or substance abuse or dependence.⁵² Comparison subjects with a personal or family history of psychiatric illness were excluded. This study was approved by local research and ethics committees. Written informed consent was obtained from all subjects.

There is overlap between the subjects in this study and those in our previous longitudinal MR imaging studies. Of the 35 UHR subjects, 20 subjects also participated in our VBM study.¹³ All

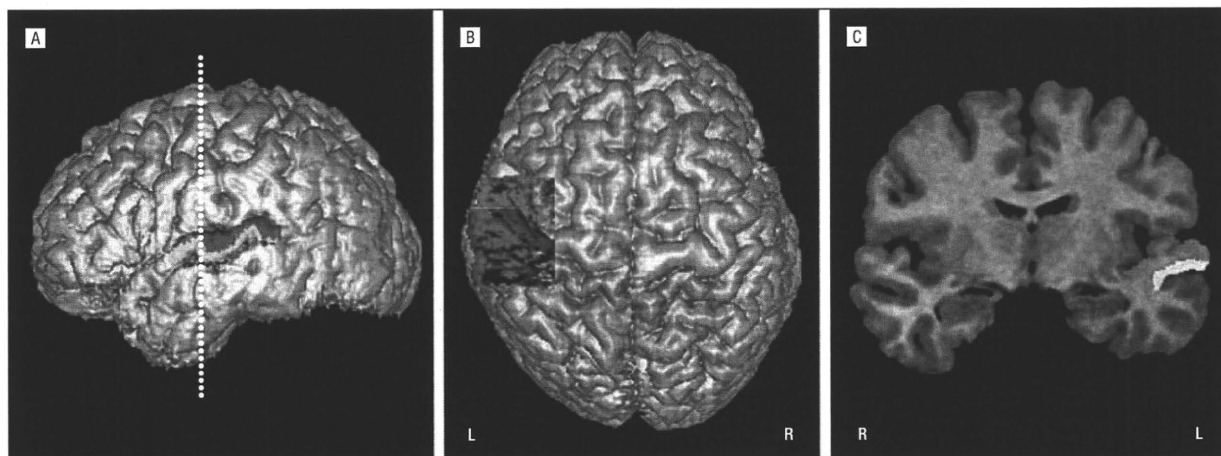


Figure 1. Three-dimensional reconstructed images presenting lateral (A) and top-down (B) views and a sample coronal image (C) of superior temporal subregions of the left hemisphere. The frontal and parietal lobes in B are partially cut away to disclose the regions examined. The lateral superior temporal 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-recalled 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.⁵⁴ 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, dorsum sellae, clivus, and C1 vertebra as major landmarks to correct for differences in head size^{55,56}; 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,⁵⁷ the first coronal plane showing the temporo-frontal 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)^{26,57} 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 anteriorly 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 oriented medially from the common stem, however, both were defined as the HG. After tracing of the HG, which takes a diagonal course on the supratemporal plane, the regions lying anteromedial and posterolateral to the HG within the remaining 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 portions 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 χ^2 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-

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^a

| Brain Region | Mean (SD) | | | |
|------------------|------------------|------------------|---------------------------|------------------------------|
| | Control Subjects | UHR Subjects | | Patients With FEP |
| | | Nonpsychotic | Psychotic | |
| Whole brain | | | | |
| Baseline | 724 263 (84 307) | 710 743 (95 937) | 759 148 (78 830) | 710 584 (63 151) |
| 2nd image | 701 540 (88 796) | 706 167 (89 854) | 738 340 (82 330) | 685 085 (68 399) |
| % Change | -1.7 (2.4) | -0.5 (4.2) | -2.1 (5.0) | -1.5 (2.3) |
| Whole STG | | | | |
| Left | | | | |
| Baseline | 13 461 (2587) | 13 564 (3008) | 13 475 (1902) | 12 645 (2134) |
| 2nd image | 13 601 (2676) | 13 606 (3134) | 12 772 (1736) | 11 714 ^{b,c} (1900) |
| % Change | 0.4 (1.8) | 0.1 (4.8) | -5.0 ^{b,c} (4.4) | -3.6 ^{b,c} (2.9) |
| Right | | | | |
| Baseline | 11 801 (2390) | 11 538 (2022) | 12 221 (1930) | 10 807 (1627) |
| 2nd image | 11 880 (2355) | 11 473 (1970) | 11 656 (1778) | 10 404 ^{b,c} (1391) |
| % Change | 0.4 (2.1) | -0.5 (4.9) | -3.9 ^b (5.7) | -1.5 (4.1) |
| Planum polare | | | | |
| Left | | | | |
| Baseline | 1725 (580) | 1874 (616) | 2089 (302) | 2130 (537) |
| 2nd image | 1754 (572) | 1869 (632) | 1958 (269) | 2010 (529) |
| % Change | 1.0 (4.3) | 0.1 (7.9) | -5.6 ^b (6.1) | -2.6 ^b (4.5) |
| Right | | | | |
| Baseline | 1666 (509) | 1664 (705) | 1686 (389) | 1817 (508) |
| 2nd image | 1658 (451) | 1675 (738) | 1559 (349) | 1741 (508) |
| % Change | 0.6 (4.1) | 0.2 (5.9) | -6.3 ^c (7.4) | -1.5 (4.6) |
| Heschl gyrus | | | | |
| Left | | | | |
| Baseline | 2226 (585) | 2135 (666) | 2252 (908) | 1804 (869) |
| 2nd image | 2242 (589) | 2118 (691) | 2150 (864) | 1688 (787) |
| % Change | -0.1 (3.6) | -1.2 (5.4) | -4.3 (6.0) | -3.0 ^b (3.6) |
| Right | | | | |
| Baseline | 1619 (483) | 1655 (478) | 1796 (587) | 1470 (433) |
| 2nd image | 1632 (478) | 1631 (490) | 1728 (609) | 1423 (365) |
| % Change | 0.5 (3.9) | -1.3 (7.5) | -3.5 (8.3) | -0.7 (9.3) |
| Planum temporale | | | | |
| Left | | | | |
| Baseline | 3519 (865) | 3439 (989) | 3096 (711) | 3059 ^{b,c,d} (627) |
| 2nd image | 3554 (836) | 3474 (995) | 2934 ^{b,d} (678) | 2845 ^{b,c,d} (575) |
| % Change | 0.9 (4.3) | 0.9 (5.0) | -5.2 ^{b,c} (5.2) | -3.3 ^{b,c} (2.5) |
| Right | | | | |
| Baseline | 2846 (921) | 2820 (750) | 2974 (630) | 2435 ^{b,c,d} (614) |
| 2nd image | 2924 (918) | 2819 (717) | 2851 ^{b,d} (616) | 2331 ^{b,c,d} (623) |
| % Change | 2.1 (4.2) | 0.3 (5.9) | -3.9 ^b (4.9) | -2.2 ^b (4.4) |

(continued)

gion separately on the basis of a significant group × subregion interaction for both time points (Table 3).

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 × 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-

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^a (continued)

| Brain Region | Mean (SD) | | | |
|--------------------|------------------|--------------|-------------------------|-----------------------------|
| | Control Subjects | UHR Subjects | | Patients With FEP |
| | | Nonpsychotic | Psychotic | |
| Lateral STG | | | | |
| Left | | | | |
| Baseline | 5951 (1257) | 6071 (1426) | 5986 (828) | 5599 (1020) |
| 2nd image | 6021 (1386) | 6083 (1507) | 5669 (713) | 5119 ^{b,c} (877) |
| % Change | 0.2 (2.9) | -0.1 (5.5) | -5.0 (4.2) | -4.2 ^{b,c} (3.8) |
| Right | | | | |
| Baseline | 5632 (1320) | 5364 (959) | 5736 (996) | 5047 (840) |
| 2nd image | 5646 (1323) | 5308 (892) | 5497 (844) | 4871 ^{b,c} (688) |
| % Change | 0.0 (3.2) | -0.8 (4.9) | -3.2 (6.0) | -1.4 (4.3) |
| Rostral STG | | | | |
| Left | | | | |
| Baseline | 1335 (776) | 1654 (945) | 1721 (418) | 1868 (808) |
| 2nd image | 1339 (775) | 1675 (967) | 1631 (365) | 1675 (581) |
| % Change | 0.0 (5.2) | 0.8 (10.5) | -4.3 (7.1) | -3.8 ^{b,c} (6.2) |
| Right | | | | |
| Baseline | 1356 (685) | 1290 (744) | 1343 (625) | 1490 (600) |
| 2nd image | 1344 (641) | 1277 (751) | 1282 (571) | 1451 (596) |
| % Change | 0.0 (3.7) | -1.6 (7.2) | -2.6 (7.5) | -1.5 (3.8) |
| Caudal STG | | | | |
| Left | | | | |
| Baseline | 4616 (1055) | 4416 (1095) | 4264 (1073) | 3730 ^{b,c,e} (885) |
| 2nd image | 4682 (1161) | 4408 (1079) | 4038 (902) | 3444 ^{b,c,e} (829) |
| % Change | 0.3 (3.2) | -0.1 (5.1) | -4.8 ^d (5.3) | -3.9 ^{b,c} (3.2) |
| Right | | | | |
| Baseline | 4276 (1264) | 4074 (830) | 4394 (1068) | 3557 ^{b,c,e} (802) |
| 2nd image | 4302 (1263) | 4031 (763) | 4215 (1051) | 3420 ^{b,c,e} (640) |
| % Change | 0.1 (3.7) | -0.6 (5.4) | -3.6 (6.2) | -1.2 (6.1) |

Abbreviations: FEP, first-episode psychosis; STG, superior temporal gyrus; UHR, ultrahigh-risk.

^aValues indicate absolute volumes (in cubic millimeters) except percentage of change per year values, which were calculated as follows: $(100 \times [\text{absolute volume at second imaging} - \text{absolute volume at baseline}] / \text{absolute volume at baseline}) / \text{interimaging interval (in years)}$. Negative values indicate decreases in volume. The statistical analyses for longitudinal gray matter changes reported herein were based on absolute volume changes covarying for interimaging interval and baseline volume. Analysis of covariance (ANCOVA) of the whole STG at baseline showed significant main effects for side ($F_{1,72} = 77.51, P < .001$) and subregion ($F_{4,288} = 265.42, P < .001$) and group \times subregion ($F_{12,288} = 2.93, P < .001$) and sex \times subregion ($F_{4,288} = 2.47, P = .045$) interactions. An ANCOVA of the STG at follow-up showed significant main effects for group ($F_{3,71} = 4.36, P = .007$), side ($F_{1,72} = 81.18, P < .001$), and subregion ($F_{4,288} = 271.08, P < .001$) and group \times subregion ($F_{2,288} = 3.76, P < .001$), sex \times subregion ($F_{4,288} = 2.59, P = .04$), and side \times subregion ($F_{4,288} = 2.59, P = .04$) interactions. For the lower-order ANCOVAs and post hoc tests of each subregion, see the "Results" section. An ANCOVA of the absolute STG volume change over time demonstrated significant main effects for group ($F_{3,70} = 6.83, P < .001$) and subregion ($F_{4,288} = 2.84, P = .03$) and group \times side ($F_{3,72} = 3.40, P = .02$) and group \times subregion ($F_{12,288} = 2.02, P = .02$) interactions. For the lower-order ANCOVAs and post hoc tests of each subregion, see text.

^bSignificantly different from controls.

^cSignificantly different from UHR nonpsychotic subjects.

^dSignificant only for males.

^eSignificantly different from UHR psychotic subjects.

tween imaging sessions (Table 2), with the interimaging interval being shorter in UHR subjects than in controls (UHRNP, $P = .01$; UHRP, $P = .007$) or FEP patients (UHRNP, $P = .04$; UHRP, $P = .02$). Mean interimaging interval of the whole sample was 1.8 years.

CROSS-SECTIONAL VOLUME COMPARISON

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 sub-

regions 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 ($F_{3,71} = 4.23, P = .008$) and caudal STG ($F_{3,71} = 7.18, P < .001$) 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 ($F_{1,72} = 9.28$,

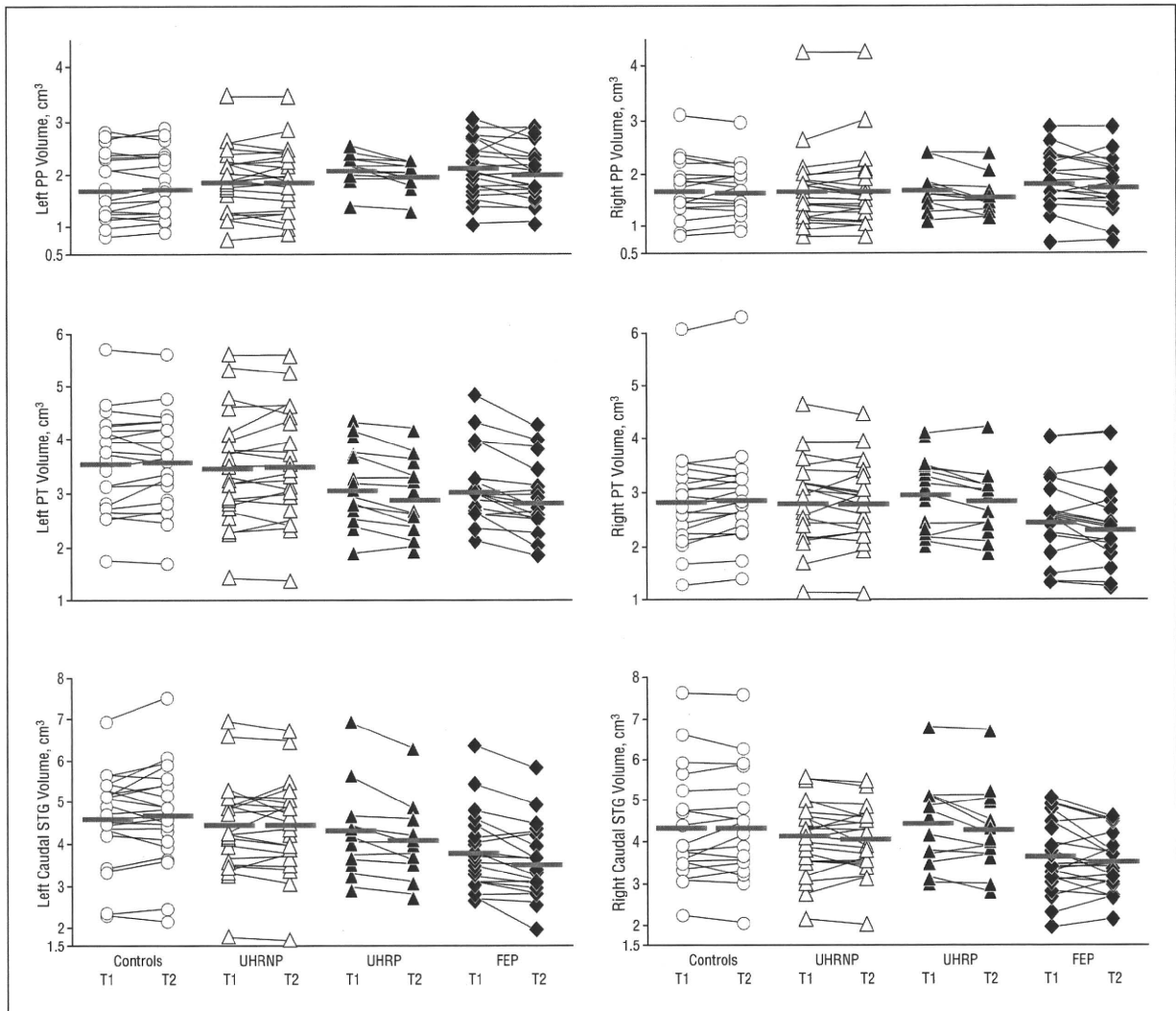


Figure 2. Scatterplots of absolute volumes of the planum polare (PP), planum temporale (PT), and caudal superior temporal gyrus (STG) in healthy control subjects, ultrahigh-risk nonpsychotic (UHRNP) subjects, ultrahigh-risk psychotic (UHRP) subjects, and patients with first-episode psychosis (FEP). Values of baseline (T1) and follow-up (T2) images in each subject are connected with a straight line. Horizontal bars indicate the means of each group. The interimaging interval was significantly shorter in UHR individuals than in patients with FEP or controls.

$P = .003$) 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, $P = .02$), and left caudal STG ($P = .03$) 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,

$P < .001$; 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 ($\rho = 0.67$, $P < .001$) and left HG ($\rho = 0.56$, $P = .008$) 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 ($\rho = -0.28$ to 0.44 , $P = .046$ to $.86$). Right STG changes did not correlate with these symptom ratings ($\rho = -0.27$ to 0.34 , $P = .13$ to $.99$). There was no significant

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.^{26,33} 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.^{9,33} 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.^{7,63,67-69}

The neurobiological basis for STG volume reduction is unknown. The current MR imaging study cannot address the pathological mechanisms underlying the progressive changes, but anomalies of synaptic plasticity, abnormal brain maturation in the context of “late neurodevelopment,” and stress or other environmental factors may be relevant.^{3,4} One postmortem study described PT pyramidal cell somal volume reduction in schizophrenia,⁷⁰ but others demonstrated preservation of normal cytoarchitecture in the HG⁷¹ and PT.⁷² Glutamatergic excess due to hypofunction of the *N*-methyl-D-aspartate receptors on corticolimbic γ -aminobutyric acid-ergic interneurons may also lead to adverse neurotoxic effects in the early stages of psychosis.^{73,74}

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-naïve 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.^{42,81}

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-naïve 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-naïve genetically high-risk cohorts.^{12,82} Although mood stabilizers may increase gray matter volume,^{68,83} 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 matching^{10,14} 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.⁸⁴ 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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Superior temporal gyrus volume in antipsychotic-naive people at risk of psychosis

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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:

- attenuated psychotic symptoms, defined by subthreshold intensity or frequency;
- brief limited intermittent psychotic symptoms with spontaneous resolution within 1 week;
- 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).

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 gyrus 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 ×

| | 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, cm ³ : 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 \times side \times 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, $\beta = 1.034, 95\% \text{ CI } 1.01\text{--}1.06, P = 0.016$), 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 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 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, mm ³ : 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

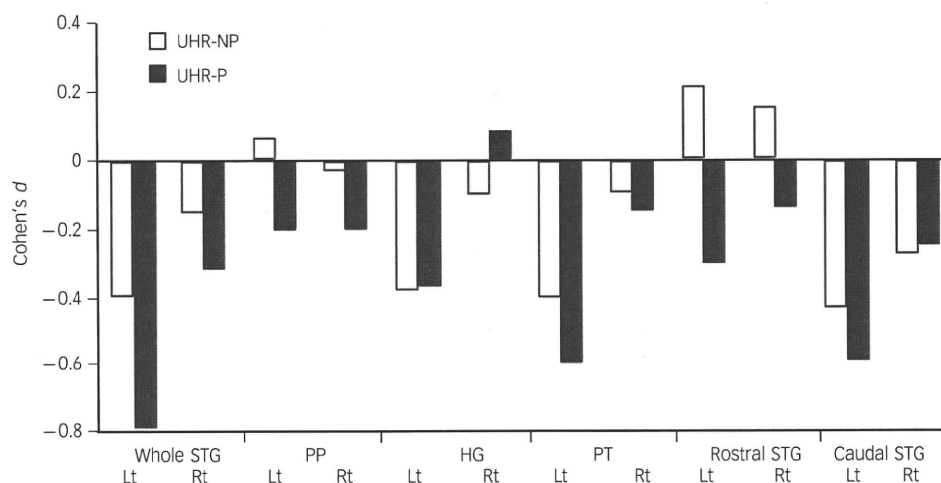


Fig. 1 Effect sizes (Cohen's d) based on relative superior temporal gyrus (STG) volumes for ultra-high risk participants who did (UHR-P) and did not (UHR-NP) develop psychosis relative to healthy controls. HG, Heschl's gyrus; PP, planum polare; PT, planum temporale.

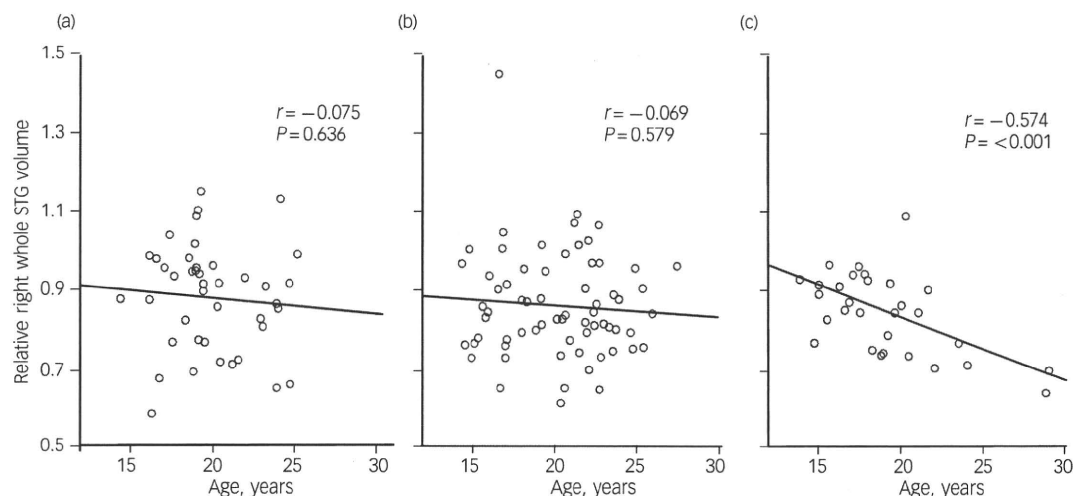


Fig. 2 Correlations between age and relative volumes of the right whole superior temporal gyrus (STG) in a healthy control group (a) and in individuals at ultra-high risk who did not (b) and did (c) later develop psychosis.

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 gyrus 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-naïve 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 gyrus 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 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.

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