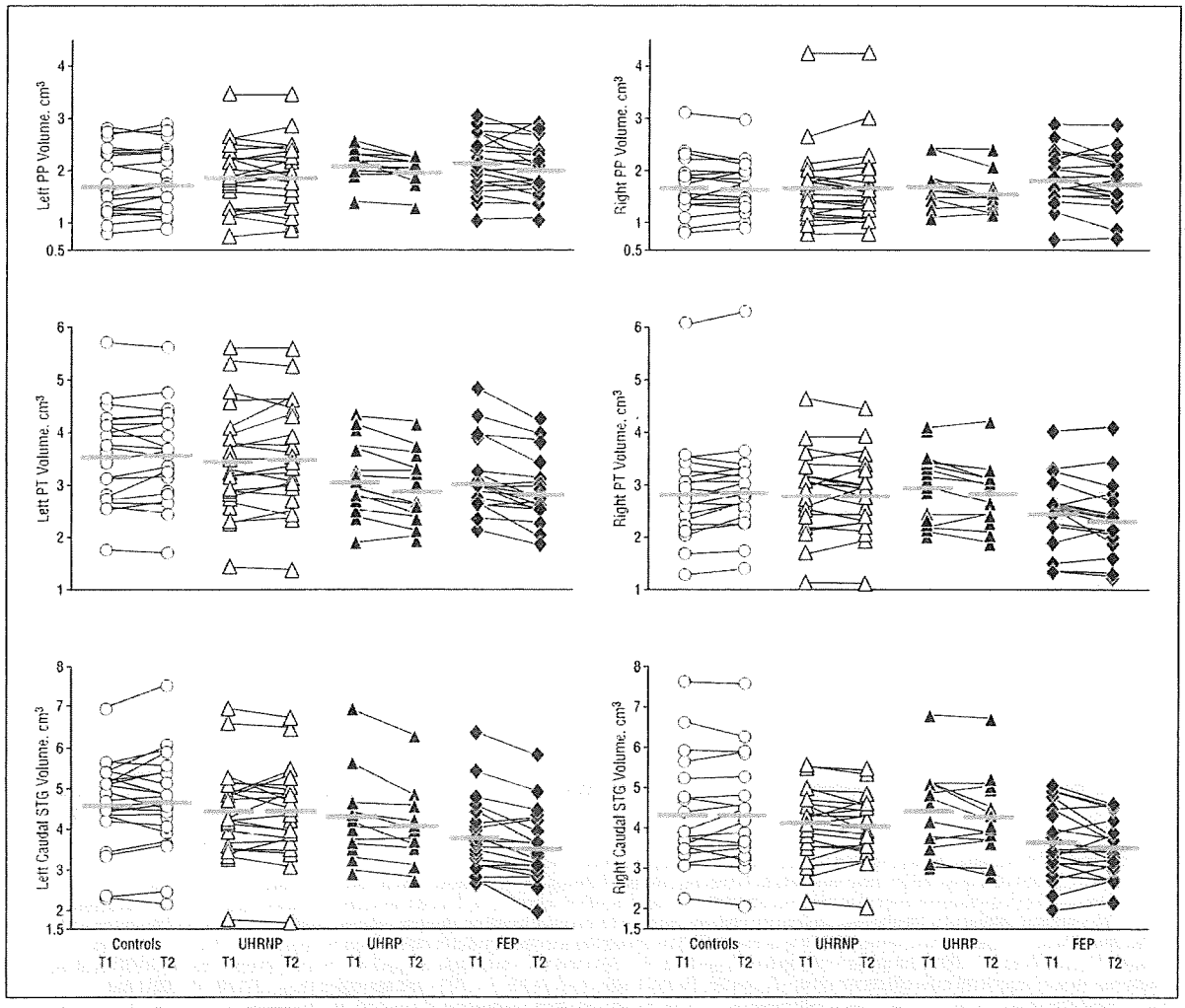

Figure 2. Scatterplots of absolute volumes of the planum polare (PP), planum temporale (PT), and caudal superior temporal gyrus (STG) in healthy control subjects, ultrahigh-risk nonpsychotic (UHRNP) subjects, ultrahigh-risk psychotic (UHRP) subjects, and patients with first-episode psychosis (FEP). Values 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

correlation between medication dosage and baseline or follow-up STG volumes, but dosage at follow-up was correlated with greater reduction in the left HG (ρ=0.45, P=.03) and left rostral STG (ρ=0.59, P=.003). The PANSS delusions score in FEP patients was correlated with medication dosage at follow-up (ρ=0.49, P=.02).

COMMENT

This is, to our knowledge, the first volumetric MR imaging study to report progressive gray matter reduction of STG subregions during the prodromal phase and after the onset of frank psychosis in a high-risk cohort. Compared with controls or UHRNP subjects, both UHRP and FEP subjects showed significant gray matter reduction over time in the PP, PT, and caudal STG, whereas the rate of progressive gray matter loss of the left HG and rostral region after the onset was significantly correlated with the severity of delusions. These longitudinal changes were not evident in healthy comparison subjects or UHRNP subjects for any STG subregions. For cross-sectional comparison, only FEP patients, especially males, had a smaller caudal STG and PT than did the other groups at baseline, but male UHRP subjects also exhibited a smaller PT at follow-up. These findings suggest that a regional progressive pathological process in the STG precedes the first expression of florid psychosis, and its extent may reflect the severity of positive symptomatology during the early course of psychosis.

These findings are in line with previous longitudinal VBM studies that demonstrated that high-risk subjects who later developed psychosis exhibited progressive gray matter reduction in left temporal lobe regions.[12,13] Our previous UHR studies[13,14] demonstrated gray matter changes in the cingulate and/or prefrontal regions but not in the superior temporal region. The STG findings of the current study are similar to those identified in the Edinburgh High Risk Study[12] and indicate that these changes are unlikely to have prominent subregional effects because the HG and rostral STG showed nonsignificant but considerable volume changes during the transition (Table 3). These differences across studies may be explained by differences in sample characteristics (genetic vs clinical high-risk subjects) or methods (VBM vs ROI approach).[5,19] Nevertheless, these findings support the naturalistic observations of schizophrenia, that the neurobiological deterioration commences 2 to 3 years before the onset of psychosis and appears to diminish in activity during the first few years after illness onset.[58]

The rate of reduction in the HG and PT in our FEP sample was comparable to that in an earlier study in first-episode schizophrenia (left HG, −4.8% per year; right HG, 1.5% per year; left PT, −5.1% per year; right PT, −0.6% per year).[9] Our findings further indicated that the volumes of the other STG subregions were also comparably reduced over time. In our FEP sample, however, we did not find highly lateralized (left > right) progressive changes of the PT as in the sample of Kasai et al,[9] and absolute volume differs considerably among the reports including our group's own study in a Japanese sample, where patients with chronic schizophrenia had up to a 20% smaller PT than the current sample.[26] These discrepancies could be the result of different parcellation strategies or different groups (race, sex ratio, first episode vs long-term medication treatment, and established schizophrenia vs psychosis in general) being examined. Although we cannot directly address the issue of diagnostic heterogeneity (eg, schizophrenia spectrum vs affective psychosis)[56,59-61] for our FEP cohort, which included a rather diverse population with psychotic symptoms but only 1 patient with affective psychosis, the STG gray matter reduction in UHRP patients who developed schizophrenia spectrum (n=7; left, −5.3% per year; right, −2.7% per year) and affective psychosis (n=5; left, −4.5% per year; right, −5.5% per year) might imply that left-lateralized STG changes are specific to patients with schizophrenia-spectrum disorders (eTable 2 and eFigure 1). Although brain structural changes in schizophrenia may be nonlinear,[62] with a period of intense gray matter reduction occurring during the initial years around the onset,[63] patients with chronic schizophrenia also exhibit progressive gray matter loss in the STG that exceeds the normal aging changes.[64] In this study, we demonstrated the STG gray matter changes during the earliest phases of psychosis with a mean interimaging interval of about 2 years, but further longitudinal follow-up of UHRP or FEP patients and additional patients with chronic disease would be required to examine the nature, timing, and course of the morphologic brain changes associated with psychosis.

A major aim of high-risk studies has been to identify a significant neurobiological predictor of future transition to psychosis, which allows specific and targeted preventive strategies.[65,66] We found no differences in baseline STG gray matter volume between UHRP and UHRNP subjects. In comparison, previous VBM studies in UHR[13] and other clinical high-risk cohorts[38] have demonstrated that high-risk subjects who later developed psychosis had less gray matter in frontotemporolimbic-paralimbic regions, including the right anterior part of the STG, than subjects who did not. The reason for this discrepancy is unclear, but it might be related to marked

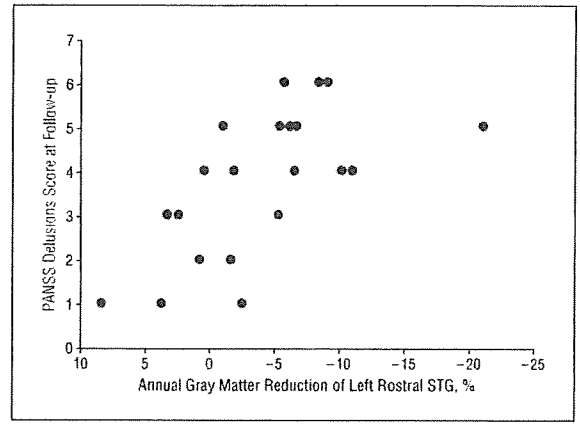

Figure 3. Correlation between annual gray matter reduction of the left rostral superior temporal gyrus (STG) and score for delusions on the Positive and Negative Syndrome Scale (PANSS) in 21 patients with first-episode psychosis at follow-up imaging (ρ=0.67, P< .001). Annual gray matter reduction was calculated as follows: (100 × [absolute volume at second imaging − absolute volume at baseline]/absolute volume at baseline)/interimaging interval (in years). Negative values indicate decreases in volume.

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 HG[71] 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-naive schizophrenia showed that left STG volume reduction tended to normalize after neuroleptic medication,[40] and there is evidence that atypical antipsychotics ameliorate the structural brain changes in schizophrenia.[78-80] These observations suggest that the regional progressive pathological process in the left STG in schizophrenia could be at least partly mitigated by antipsychotic medication and that intervention before expression of frank psychotic symptoms may reduce neurobiological deterioration as well as the transition rate to psychosis.[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-naive at baseline, but most of the UHRP patients were taking antipsychotics at follow-up imaging. However, the effects of medication alone could not explain the marked gray matter reduction in our UHRP subjects who were treated with low doses of atypical antipsychotics,[78-80] as also suggested in neuroleptic-naive genetically high-risk cohorts.[12,82] 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 VBM[13] 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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REFERENCES

1. Weinberger DR. Implications of normal brain development for the pathogenesis of schizophrenia. *Arch Gen Psychiatry.* 1987;44(7):660-669.
2. Cannon TD, van Erp TG, Bearden CE, Loewy R, Thompson P, Toga AW, Huttunen MO, Keshavan MS, Seidman LJ, Tsuang MT. Early and late neurodevelopmental influences in the prodrome to schizophrenia: contributions of genes, environment, and their interactions. *Schizophr Bull.* 2003;29(4):653-669.
3. Pantelis C, Velakoulis D, Wood SJ, Yücel M, Yung AR, Phillips LJ, Sun DQ, McGorry PD. Neuroimaging and emerging psychotic disorders: the Melbourne ultra-high risk studies. *Int Rev Psychiatry.* 2007;19(4):371-381.
4. Pantelis C, Yucel M, Wood SJ, Velakoulis D, Sun D, Berger G, Stuart GW, Yung A, Phillips L, McGorry PD. Structural brain imaging evidence for multiple pathological processes at different stages of brain development in schizophrenia. *Schizophr Bull.* 2005;31(3):672-696.
5. Wood SJ, Pantelis C, Velakoulis D, Yucel M, Fornito A, McGorry PD. Progressive changes in the development toward schizophrenia: studies in subjects at increased symptomatic risk. *Schizophr Bull.* 2008;34(2):322-329.
6. Gur RE, Cowell P, Turetsky BI, Gallacher F, Cannon T, Bilker W, Gur RC. A follow-up magnetic resonance imaging study of schizophrenia: relationship of neuroanatomical changes to clinical and neurobehavioral measures. *Arch Gen Psychiatry.* 1998;55(2):145-152.
7. Ho BC, Andreasen NC, Nopoulos P, Arndt S, Magnotta V, Flaum M. Progressive structural brain abnormalities and their relationship to clinical outcome: a longitudinal magnetic resonance imaging study early in schizophrenia. *Arch Gen Psychiatry.* 2003;60(6):585-594.
8. Kasai K, Shenton ME, Salisbury DF, Hirayasu Y, Lee CU, Ciszewski AA, Yurgelun-Todd D, Kikinis R, Jolesz FA, McCarley RW. Progressive decrease of left superior temporal gyrus gray matter volume in patients with first-episode schizophrenia. *Am J Psychiatry.* 2003;160(1):156-164.
9. Kasai K, Shenton ME, Salisbury DF, Hirayasu Y, Onitsuka T, Spencer MH, Yurgelun-Todd DA, Kikinis R, Jolesz FA, McCarley RW. Progressive decrease of left Heschl gyrus and planum temporale gray matter volume in first-episode schizophrenia: a longitudinal magnetic resonance imaging study. *Arch Gen Psychiatry.* 2003;60(8):766-775.
10. Sun D, Stuart GW, Jenkinson M, Wood SJ, McGorry PD, Velakoulis D, van Erp TG, Thompson PM, Toga AW, Smith DJ, Cannon TD, Pantelis C. Brain surface contraction mapped in first-episode schizophrenia: a longitudinal magnetic resonance imaging study [published online July 8, 2008]. *Mol Psychiatry.* doi:10.1038/mp.2008.34.
11. Wood SJ, Velakoulis D, Smith DJ, Bond D, Stuart GW, McGorry PD, Brewer WJ, Bridle N, Eritaia J, Desmond P, Singh B, Copolov D, Pantelis C. A longitudinal study of hippocampal volume in first episode psychosis and chronic schizophrenia. *Schizophr Res.* 2001;52(1-2):37-46.
12. Job DE, Whalley HC, Johnstone EC, Lawrie SM. Grey matter changes over time in high risk subjects developing schizophrenia. *Neuroimage.* 2005;25(4):1023-1030.
13. Pantelis C, Velakoulis D, McGorry PD, Wood SJ, Suckling J, Phillips LJ, Yung AR, Bullmore ET, Brewer W, Soulsby B, Desmond P, McGuire PK. Neuroanatomical abnormalities before and after onset of psychosis: a cross-sectional and longitudinal MRI comparison. *Lancet.* 2003;361(9354):281-288.
14. Sun D, Phillips L, Velakoulis D, Yung A, McGorry PD, Wood SJ, van Erp TG, Thompson PM, Toga AW, Cannon TD, Pantelis C. Progressive brain structural changes mapped as psychosis develops in "at risk" individuals (abstract). *Schizophr Bull.* 2007;33(2):356-357.
15. Walterfang M, McGuire PK, Yung A, Phillips LJ, Velakoulis D, Wood SJ, Suckling J, Bullmore ET, Brewer W, Soulsby B, Desmond P, McGorry PD, Pantelis C. White matter volume changes in people who develop psychosis. *Br J Psychiatry.* 2008;193(3):210-215.
16. Yung AR, Phillips LJ, Yuen HP, Francey SM, McFarlane CA, Hallgren M, McGorry PD. Psychosis prediction: 12-month follow up of a high-risk ("prodromal") group. *Schizophr Res.* 2003;60(1):21-32.
17. Yung AR, Phillips LJ, Yuen HP, McGorry PD. Risk factors for psychosis in an ultra high-risk group. *Schizophr Res.* 2004;67(2-3):131-142.
18. Johnstone EC, Abukmeil SS, Byrne M, Clafferty R, Grant E, Hodges A, Lawrie SM, Owens DG. Edinburgh High Risk Study—findings after four years: demographic, attainment and psychopathological issues. *Schizophr Res.* 2000;46(1):1-15.
19. Giuliani NR, Calhoun VD, Pearlson GD, Francis A, Buchanan RW. Voxel-based morphometry versus region of interest. *Schizophr Res.* 2005;74(2-3):135-147.
20. Thompson PM, Giedd JN, Woods RP, MacDonald D, Evans AC, Toga AW. Growth patterns in the developing brain detected by using continuum mechanical tensor maps. *Nature.* 2000;404(6774):190-193.
21. Honea R, Crow TJ, Passingham D, Mackay CE. Regional deficits in brain volume in schizophrenia. *Am J Psychiatry.* 2005;162(12):2233-2245.
22. Shenton ME, Dickey CC, Frumin M, McCarley RW. A review of MRI findings in schizophrenia. *Schizophr Res.* 2001;49(1-2):1-52.
23. Suzuki M, Nohara S, Hagino H, Kurokawa K, Yotsutsuji T, Kawasaki Y, Takahashi T, Matsui M, Watanabe N, Seto H, Kurachi M. Regional changes in brain gray and white matter in patients with schizophrenia demonstrated with voxel-based analysis of MRI. *Schizophr Res.* 2002;55(1-2):41-54.
24. Hirayasu Y, McCarley RW, Salisbury DF, Tanaka S, Kwon JS, Frumin M, Snyderman D, Yurgelun-Todd D, Kikinis R, Jolesz FA, Shenton ME. Planum temporale and Heschl gyrus volume reduction in schizophrenia: a magnetic resonance imaging study of first-episode patients. *Arch Gen Psychiatry.* 2000;57(7):692-699.
25. Rojas DC, Teale P, Sheeder J, Simon J, Reite M. Sex-specific expression of Heschl's gyrus functional and structural abnormalities in paranoid schizophrenia. *Am J Psychiatry.* 1997;154(12):1655-1662.
26. Takahashi T, Suzuki M, Zhou SY, Tanino R, Hagino H, Kawasaki Y, Matsui M, Seto H, Kurachi M. Morphologic alterations of the parcellated superior temporal gyrus in schizophrenia spectrum. *Schizophr Res.* 2006;83(2-3):131-143.
27. Kwon JS, McCarley RW, Hirayasu Y, Anderson JE, Fischer IA, Kikinis R, Jolesz FA, Shenton ME. Left planum temporale volume reduction in schizophrenia. *Arch Gen Psychiatry.* 1999;56(2):142-148.
28. Sumich A, Chitnis XA, Fannon DG, O'Ceallaigh S, Doku VC, Falrowicz A, Marshall N, Matthew VM, Potter M, Sharma T. Temporal lobe abnormalities in first-episode psychosis. *Am J Psychiatry.* 2002;159(7):1232-1235.
29. Yamasue H, Yamada H, Yumoto M, Kamio S, Kudo N, Uetsuki M, Abe O, Fukuda R, Aoki S, Ohtomo K, Iwanami A, Kato N, Kasai K. Abnormal association between reduced magnetic mismatch field to speech sounds and smaller left planum temporale volume in schizophrenia. *Neuroimage.* 2004;22(2):720-727.
30. Pearlson GD. Superior temporal gyrus and planum temporale in schizophrenia: a selective review. *Prog Neuropsychopharmacol Biol Psychiatry.* 1997;21(8):1203-1229.
31. Barta PE, Pearlson GD, Powers RE, Richards SS, Tune LE. Auditory hallucinations and smaller superior temporal gyral volume in schizophrenia. *Am J Psychiatry.* 1990;147(11):1457-1462.
32. Shenton ME, Kikinis R, Jolesz FA, Pollak SD, LeMay M, Wible CG, Hokama H, Martin J, Metcalf D, Coleman M, McCarley RW. Abnormalities of the left temporal lobe and thought disorder in schizophrenia: a quantitative magnetic resonance imaging study. *N Engl J Med.* 1992;327(9):604-612.
33. Sumich A, Chitnis XA, Fannon DG, O'Ceallaigh S, Doku VC, Faldrowicz A, Sharma T. Unreality symptoms and volumetric measures of Heschl's gyrus

and planum temporal in first-episode psychosis. *Biol Psychiatry*. 2005;57(8):947-950.
34. Rajarethinam RP, DeQuardo JR, Nalepa R, Tandon R. Superior temporal gyrus in schizophrenia. *Schizophr Res*. 2000;41(2):303-312.
35. Price C. An overview of speech comprehension and production. In: Frackowiak RSJ, Friston KJ, Frith CD, Dolan RJ, Price CJ, eds. *Human Brain Function*. 2nd ed. San Diego, CA: Elsevier Academic Press; 2004:517-545.
36. Gallagher HL, Frith CD. Functional imaging of "theory of mind." *Trends Cogn Sci*. 2003;7(2):77-83.
37. Salisbury DF, Kuroki N, Kasai K, Shenton ME, McCarley RW. Progressive and interrelated functional and structural evidence of post-onset brain reduction in schizophrenia. *Arch Gen Psychiatry*. 2007;64(5):521-529.
38. Borgwardt SJ, Riecher-Rossler A, Dazzan P, Chitnis X, Aston J, Drewe M, Gschwandtner U, Haller S, Pflüger M, Rechsteiner E, D'Souza M, Stieglitz RD, Radü EW, McGuire PK. Regional gray matter volume abnormalities in the at risk mental state. *Biol Psychiatry*. 2007;61(10):1148-1156.
39. Rajarethinam R, Sahni S, Rosenberg DR, Keshavan MS. Reduced superior temporal gyrus volume in young offspring of patients with schizophrenia. *Am J Psychiatry*. 2004;161(6):1121-1124.
40. Keshavan MS, Haas GL, Kahn CE, Aguilar E, Dick EL, Schooler NR, Sweeney JA, Pettegrew JW. Superior temporal gyrus and the course of early schizophrenia: progressive, static, or reversible? *J Psychiatr Res*. 1998;32(3-4):161-167.
41. Takahashi T, Suzuki M, Tanino R, Zhou SY, Hagino H, Niu L, Kawasaki Y, Seto H, Kurachi M. Volume reduction of the left planum temporale gray matter associated with long duration of untreated psychosis in schizophrenia: a preliminary report. *Psychiatry Res*. 2007;154(3):209-219.
42. McGorry PD, Yung AR, Phillips LJ, Yuen HP, Francey S, Cosgrave EM, Germano D, Bravin J, McDonald T, Blair A, Adlard S, Jackson H. Randomized controlled trial of interventions designed to reduce the risk of progression to first-episode psychosis in a clinical sample with subthreshold symptoms. *Arch Gen Psychiatry*. 2002;59(10):921-928.
43. Rhoades HM, Overall JE. The semistructured BPRS interview and rating guide. *Psychopharmacol Bull*. 1988;24(1):101-104.
44. Andreasen NC. *The Scale for the Assessment of Negative Symptoms (SANS)*. Iowa City: University of Iowa; 1983.
45. Yung AR, Phillips LJ, McGorry PD. *Treating Schizophrenia in the Prodromal Phase*. London, England: Taylor & Francis; 2004.
46. McGorry PD, Edwards J, Mihalopoulos C, Harrigan SM, Jackson HJ. EPPIC: an evolving system of early detection and optimal management. *Schizophr Bull*. 1996;22(2):305-326.
47. Velakoulis D, Pantelis C, McGorry PD, Dudgeon P, Brewer W, Cook M, Desmond P, Bridle N, Tierney P, Murrie V, Singh B, Copolov D. Hippocampal volume in first-episode psychoses and chronic schizophrenia: a high-resolution magnetic resonance imaging study. *Arch Gen Psychiatry*. 1999;56(2):133-141.
48. First MB, Spitzer RL, Gibbon M, Williams JB. *Structured Clinical Interview for DSM-IV Axis I Disorders*. Washington, DC: American Psychiatric Press; 1997.
49. McGorry PD, Kaplan I, Dossetor C, Herrman H, Copolov D, Singh B. *Royal Park Multidiagnostic Instrument for Psychosis*. Melbourne, Australia: National Health and Medical Research Council; 1989.
50. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull*. 1987;13(2):261-276.
51. Nelson HE, O'Connell A. Dementia: the estimation of premorbid intelligence levels using the New Adult Reading Test. *Cortex*. 1978;14(2):234-244.
52. American Psychiatric Association. *Diagnostic Criteria From* DSM-IV. Washington, DC: American Psychiatric Association; 1994.
53. Alpert NM, Berdichevsky D, Levin Z, Morris ED, Fischman AJ. Improved methods for image registration. *Neuroimage*. 1996;3(1):10-18.
54. Takahashi T, Kawasaki Y, Kurokawa K, Hagino H, Nohara S, Yamashita I, Nakamura K, Murata M, Matsui M, Suzuki M, Seto H, Kurachi M. Lack of normal structural asymmetry of the anterior cingulate gyrus in female patients with schizophrenia. *Schizophr Res*. 2002;55(1-2):69-81.
55. Eritaia J, Wood SJ, Stuart GW, Bridle N, Dudgeon P, Maruff P, Velakoulis D, Pantelis C. An optimized method for estimating intracranial volume from magnetic resonance images. *Magn Reson Med*. 2000;44(6):973-977.
56. Velakoulis D, Wood SJ, Wong MT, McGorry PD, Yung A, Phillips L, Smith D, Brewer W, Proffitt T, Desmond P, Pantelis C. Hippocampal and amygdala volumes according to psychosis stage and diagnosis: a magnetic resonance imaging study of chronic schizophrenia, first-episode psychosis, and ultra-high-risk individuals. *Arch Gen Psychiatry*. 2006;63(2):139-149.
57. Kim JJ, Crespo-Facorro B, Andreasen NC, O'Leary DS, Zhang B, Harris G, Magnotta VA. An MRI-based parcellation method for the temporal lobe. *Neuroimage*. 2000;11(4):271-288.
58. McGlashan TH. Duration of untreated psychosis in first-episode schizophrenia: marker or determinant of course? *Biol Psychiatry*. 1999;46(7):899-907.
59. Crow TJ. Nature of the genetic contribution to psychotic illness: a continuum viewpoint. *Acta Psychiatr Scand*. 1990;81(5):401-408.
60. Maier W, Zobel A, Wagner M. Schizophrenia and bipolar disorder: differences and overlaps. *Curr Opin Psychiatry*. 2006;19(2):165-170.
61. Murray RM, Sham P, Van Os J, Zanelli J, Cannon M, McDonald C. A developmental model for similarities and dissimilarities between schizophrenia and bipolar disorder. *Schizophr Res*. 2004;71(2-3):405-416.
62. Weinberger DR, McClure RK. Neurotoxicity, neuroplasticity, and magnetic resonance imaging morphometry: what is happening in the schizophrenic brain? *Arch Gen Psychiatry*. 2002;59(6):553-558.
63. van Haren NE, Hulshoff Pol HE, Schnack HG, Cahn W, Brans R, Carati I, Rais M, Kahn RS. Progressive brain volume loss in schizophrenia over the course of the illness. *Biol Psychiatry*. 2008;63(1):106-113.
64. Mathalon DH, Sullivan EV, Lim KO, Pfefferbaum A. Progressive brain volume changes and the clinical course of schizophrenia in men: a longitudinal magnetic resonance imaging study. *Arch Gen Psychiatry*. 2001;58(2):148-157.
65. Johnstone EC, Ebmeier KP, Miller P, Owens DG, Lawrie SM. Predicting schizophrenia. *Br J Psychiatry*. 2005;186:18-25.
66. McGorry PD, Hickie IB, Yung AR, Pantelis C, Jackson HJ. Clinical staging of psychiatric disorders. *Aust N Z J Psychiatry*. 2006;40(8):616-622.
67. Cahn W, Hulshoff Pol HE, Lems EB, van Haren NE, Schnack HG, van der Linden JA, Schothorst PF, van Engeland H, Kahn RS. Brain volume changes in first-episode schizophrenia. *Arch Gen Psychiatry*. 2002;59(11):1002-1010.
68. Nakamura M, Salisbury DF, Hirayasu Y, Bouix S, Pohl KM, Yoshida T, Koo MS, Shenton ME, McCarley RW. Neocortical gray matter volume in first-episode schizophrenia and first-episode affective psychosis: a cross-sectional and longitudinal MRI study. *Biol Psychiatry*. 2007;62(7):773-783.
69. van Haren NE, Cahn W, Hulshoff Pol HE, Schnack HG, Caspers E, Lemstra A, Sitskoorn MM, Wiersma D, van den Bosch RJ, Dingemans PM, Schene AH, Kahn RS. Brain volumes as predictor of outcome in recent-onset schizophrenia: a multicenter MRI study. *Schizophr Res*. 2003;64(1):41-52.
70. Sweet RA, Pierri JN, Auh S, Sampson AR, Lewis DA. Reduced pyramidal cell somal volume in auditory association cortex of subjects with schizophrenia. *Neuropsychopharmacology*. 2003;28(3):599-609.
71. Cotter D, Mackay D, Frangou S, Hudson L, Landau S. Cell density and cortical thickness in Heschl's gyrus in schizophrenia, major depression and bipolar disorder. *Br J Psychiatry*. 2004;185:258-259.
72. Beasley CL, Chana G, Honavar M, Landau S, Everall IP, Cotter D. Evidence for altered neuronal organisation within the planum temporale in major psychiatric disorders. *Schizophr Res*. 2005;73(1):69-78.
73. Coyle JT, Tsai G, Goff D. Converging evidence of NMDA receptor hypofunction in the pathophysiology of schizophrenia. *Ann N Y Acad Sci*. 2003;1003:318-327.
74. Stone JM, Morrison PD, Pilowsky LS. Glutamate and dopamine dysregulation in schizophrenia. *J Psychopharmacol*. 2007;21(4):440-452.
75. Marshall M, Lewis S, Lockwood A, Drake R, Jones P, Croudace T. Association between duration of untreated psychosis and outcome in cohorts of first-episode patients: a systematic review. *Arch Gen Psychiatry*. 2005;62(9):975-983.
76. Perkins DO, Gu H, Boteva K, Lieberman JA. Relationship between duration of untreated psychosis and outcome in first-episode schizophrenia: a critical review and meta-analysis. *Am J Psychiatry*. 2005;162(10):1785-1804.
77. Schmitz N, Malla A, Norman R, Archie S, Zipursky R. Inconsistency in the relationship between duration of untreated psychosis (DUP) and negative symptoms: sorting out the problem of heterogeneity. *Schizophr Res*. 2007;93(1-3):152-159.
78. Dazzan P, Morgan KD, Orr K, Hutchinson G, Chitnis X, Suckling J, Fearon P, McGuire PK, Mallett RM, Jones PB, Leff J, Murray RM. Different effects of typical and atypical antipsychotics on grey matter in first episode psychosis: the AESOP study. *Neuropsychopharmacology*. 2005;30(4):765-774.
79. Lieberman JA, Tollefson GD, Charles C, Zipursky R, Sharma T, Kahn RS, Keefe RS, Green AI, Gur RE, McEvoy J, Perkins D, Hamer RM, Gu H, Tohen M; HGDH Study Group. Antipsychotic drug effects on brain morphology in first-episode psychosis. *Arch Gen Psychiatry*. 2005;62(4):361-370.
80. Molina V, Reig S, Sanz J, Palomo T, Benito C, Sánchez J, Sarramea F, Pascau J, Desco M. Increase in gray matter and decrease in white matter volumes in the cortex during treatment with atypical neuroleptics in schizophrenia. *Schizophr Res*. 2005;80(1):61-71.
81. McGlashan TH, Zipursky RB, Perkins D, Addington J, Miller T, Woods SW, Hawkins KA, Hoffman RE, Preda A, Epstein I, Addington D, Lindborg S, Trzaskoma Q, Tohen M, Breier A. Randomized, double-blind trial of olanzapine versus placebo in patients prodromally symptomatic for psychosis. *Am J Psychiatry*. 2006;163(5):790-799.
82. Gogtay N, Greenstein D, Lenane M, Clasen L, Sharp W, Gochman P, Butler P, Evans A, Rapoport J. Cortical brain development in nonpsychotic siblings of patients with childhood-onset schizophrenia. *Arch Gen Psychiatry*. 2007;64(7):772-780.
83. Moore GJ, Bebchuk JM, Wilds IB, Chen G, Manji HK, Manji HK. Lithium-induced increase in human brain grey matter [published correction appears in *Lancet*. 2000;356(9247):2104]. *Lancet*. 2000;356(9237):1241-1242.
84. Crum WR, Griffin LD, Hill DL, Hawkes DJ. Zen and the art of medical image registration: correspondence, homology, and quality. *Neuroimage*. 2003;20(3):1425-1437.

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An MRI study of the superior temporal subregions in first-episode patients with various psychotic disorders

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ABSTRACT

Morphologic abnormalities of the superior temporal gyrus (STG) have been reported in schizophrenia, but have not been extensively studied in other psychotic disorders such as affective psychosis. In the present study, magnetic resonance imaging was used to examine the volumes of the STG and its subregions [planum polare (PP), Heschl gyrus (HG), planum temporale (PT), rostral STG, and caudal STG] in 162 first-episode patients with various psychotic disorders [46 schizophrenia (31 schizophrenia and 15 schizoaffective disorder), 57 schizophreniform disorder, 34 affective psychosis, and 25 other psychoses] and 62 age- and sex-matched healthy controls. The first-episode schizophrenia patients had significantly less gray matter in HG, PT, and caudal STG bilaterally compared with all other groups, but there was no difference between the controls and affective psychosis, schizophreniform disorder, or other psychoses for any STG subregion. The STG white matter volume did not differ between groups. Our findings indicate that morphologic abnormalities of the STG gray matter are specific to schizophrenia among various psychotic disorders, implicating its role in the underlying pathophysiology of schizophrenia.

1. Introduction

Morphologic abnormalities of the superior temporal gyri (STG), which play a crucial role in auditory processing and language- and sociality-related functions (Gallagher and Frith, 2003; Pearlson, 1997), have been repeatedly described in previous magnetic resonance imaging (MRI) studies of schizophrenia (reviewed by Shenton et al., 2001). Gray matter reductions of the STG (Hirayasu et al., 1998; Kasai et al., 2003b; Keshavan et al., 1998; Kim et al., 2003) and its functionally relevant subregions [e.g., primary auditory cortex (Heschl gyrus, HG) or a neocortical language region (planum temporale, PT)] (Hirayasu et al., 2000; Kasai et al., 2003a) appear to be already present at first-episode of schizophrenia accompanied by further progressive changes during the early stages of illness (Kasai et al., 2003a,b; Takahashi et al., 2007), and these morphologic changes have been implicated in various psychotic symptoms such as auditory hallucinations or thought disorder (Barta et al., 1990; Rajarethinam et al., 2000; Shenton et al., 1992; Sumich et al., 2005; Takahashi et al., 2006). On the other hand, white matter findings of the STG in schizophrenia have been controversial; some MRI studies reported smaller STG white matter volume (O'Daly et al., 2007; Spalletta et al., 2003), whereas others found no changes (Antonova et al., 2005; Matsumoto et al., 2001; Sanfilipo et al., 2002; Suzuki et al., 2002) or even enlargement (Taylor et al., 2005). In addition, given the recent findings of smaller STG in schizotypal personality disorder (Goldstein et al., 2009; Takahashi et al., 2006), it remains unclear

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whether the STG changes reported in schizophrenia are diagnostically specific or common to various psychotic disorders.

Several lines of evidence suggest that affective disorder with psychotic features is similar to schizophrenia genetically and neurobiologically, with more pronounced cognitive and structural brain abnormalities being evident in schizophrenia, although this view remains controversial (Maier et al., 2006; Murray et al., 2004). Although not consistently replicated (e.g., Morgan et al., 2007), previous MRI studies that directly compared brain morphology in these two major psychotic disorders have identified more gray matter deficits in schizophrenia, predominantly in fronto-temporolimbic-paralimbic regions (Hirayasu et al., 1998, 2001; Kasai et al., 2003c; Koo et al., 2008; McDonald et al., 2005). On the other hand, some brain changes, such as ventricular enlargement, might be common to both disorders (Elkis et al., 1995; Nakamura et al., 2007; Strasser et al., 2005). Less is known about the white matter changes in psychotic disorders, but McDonald et al. (2004, 2005) reported white matter reduction in the frontal and temporo-parietal regions for both disorders. Regarding the STG changes, previous studies suggested that schizophrenia but not affective psychosis exhibited gray matter reduction compared with controls (Hirayasu et al., 1998, 2000; Kasai et al., 2003a,b), but these studies might be partly limited by lack of white matter investigation and relatively small sample size. Furthermore, to our knowledge, no MRI studies have specifically examined the STG changes in schizophreniform disorder, in which the psychotic episode has a duration of less than 6 months [DSM-III-R and -IV (American Psychiatric Association, 1987, 1994)].

The present study aimed to address the disease specificity of the STG morphologic changes within various psychotic disorders. We used MRI to measure the volumes of the STG (both gray and white matter) and its gray matter subregions [planum polare (PP), HG, PT, rostral STG, and caudal STG] in patients with first-episode psychoses (i.e., schizophrenia, affective psychosis, schizophreniform disorder, and other psychoses) and healthy controls. Based on previous MRI findings (Goldstein et al., 2009; Hirayasu et al., 2000; Kasai et al., 2003a,b) and the potential role of the STG in clinical characteristics associated with schizophrenia spectrum (Rajarethinam et al., 2000), we hypothesized that only schizophrenia and schizophreniform patients would have STG gray matter reduction compared with controls.

2. Methods

2.1. Subjects

Patients with first-episode psychosis (FEP) ($n=162$) and healthy controls ($n=62$) participated in this study (Table 1). All participants in this study were screened for comorbid medical and psychiatric conditions by clinical assessment and physical and neurological examination (excluding a urine toxicology screen), although the healthy controls did not receive a structured diagnostic interview. Exclusion criteria were a lifetime history of serious head trauma, neurological illness, serious medical or surgical illness, or DSM-III-R criteria of alcohol or substance abuse or dependence (American Psychiatric Association, 1987).

Inclusion criteria and demographic characteristics of the FEP sample, recruited from the Early Psychosis Prevention and Intervention Centre (EPPIC; McGorry et al., 1996) between 1994 and 1999, have been described previously (Velakoulis et al., 2006). Briefly, the FEP patients were: (1) age at onset between 16 and 30 years, (2) current psychosis as reflected by the presence of at least one of; (a) delusions, (b) hallucinations, (c) disorder of thinking or speech other than simple acceleration or retardation, (d) disorganized, bizarre, or markedly inappropriate behavior. DSM-III-R diagnoses were based on chart review and either the Structured Clinical Interview for DSM-III-R (SCID; Spitzer et al., 1990) or the Royal Park Multidiagnostic Instrument for Psychosis (RPMIP), which allows SCID-based DSM diagnoses (McGorry et al., 1989). Since the current study started at the time when the Structured Clinical Interview for DSM-IV (First et al., 1997)

Table 1
Demographic characteristics of the participants.

	Controls ($n=62$)	Sz ($n=46$)	Szform ($n=57$)	Aff ($n=34$)	Other ($n=25$)	Group comparisons
Age (years)	21.8 ± 4.4 (range, 13–34)	21.5 ± 3.6 (range, 16–29)	21.0 ± 3.0 (range, 16–29)	22.0 ± 3.1 (range, 15–31)	21.7 ± 4.2 (range, 16–29)	$F(4, 219)=0.58$, $p=0.68$
Male/female	38/24	34/12	42/15	18/16	14/11	Chi-square = 6.95, $p=0.14$
Handedness (right/mixed/left) [a]	58/1/3	38/1/7	51/2/4	28/0/5	22/1/1	$p=0.48$, Fisher's exact test
Height (cm) [a]	175.8 ± 9.2	172.9 ± 9.5	174.1 ± 8.2	169.8 ± 9.8	173.7 ± 9.8	$F(4, 218)=2.32$, $p=0.06$
Premorbid IQ [a, b]	101.6 ± 10.0	92.4 ± 16.4	94.0 ± 11.7	95.5 ± 13.0	94.6 ± 12.6	$F(4, 180)=3.73$, $p<0.01$; controls>Sz
Duration of illness (days) [c]	–	82 ± 136 (median = 30)	53 ± 67 (median = 36)	32 ± 24 (median = 24)	38 ± 42 (median = 16)	$F(3, 155)=2.56$, $p=0.06$
Drug (mg/day, CP equivalent) [d]	–	195.5 ± 167.0	209.0 ± 193.8	158.7 ± 124.4	136.5 ± 104.0	$F(3, 152)=1.48$, $p=0.22$
Medication type (typical/atypical/no medication) [d]	–	23/20/1	6/48/0	11/20/3	2/20/2	Chi-square = 32.60, $p<0.01$
Intracranial volume(cm^3)	1449 ± 150	1391 ± 134	1447 ± 118	1433 ± 151	1409 ± 135	$F(4, 218)=0.58$, $p=0.18$ [e]

The values represent means ± SDs. Aff, affective psychosis; CP, chlorpromazine; other, other psychoses; Sz, schizophrenia; Szform, schizophreniform.
[a] Data missing for some participants.
[b] Estimated using the National Adult Reading Test (NART).
[c] Data on 3 patients were not available.
[d] 6 patients had incomplete medication data. Atypical antipsychotic dosages were converted into CP equivalents using the guideline by Woods (2003).
[e] ANCOVAwith age as a covariate and group as a between-subject factor was used.

was not available, the FEP patients were diagnosed using the DSM-III-R criteria. Based on these assessments, which were administered during the initial treatment episode (median duration of illness = 27 days), and clinical follow-up, the 162 FEP patients were further divided into 4 subgroups: (1) 46 schizophrenia (31 schizophrenia and 15 schizoaffective disorder), (2) 57 schizophreniform disorder (who had a psychotic episode of <6 months' duration), (3) 34 affective psychosis (22 bipolar and 12 major depressive psychoses), and (4) 25 other psychoses (3 delusional disorder, 6 brief psychosis, 4 substance-induced psychosis, and 12 psychosis not otherwise specified). Because the diagnostic status of schizoaffective disorder remains under debate (Averill et al., 2004), and given evidence that this disorder may be a variant of schizophrenia (Evans et al., 1999), schizoaffective disorder and schizophrenia patients, who had no significant group difference in demographic or clinical variables, were categorized together (Velakoulis et al., 2006). All FEP patients were neuroleptic-naïve prior to admission but 150 had received antipsychotic medication for a short period prior to scanning, of which 42 patients were treated with typical antipsychotics and 108 patients received atypical ones. Accurate values for duration of medication were not available, but mean duration of such a period in our centre was about 30 days (Velakoulis et al., 1999). Seventeen patients (1 schizophrenia, 5 schizophreniform, 9 affective, and 2 other psychoses patients) were also receiving lithium carbonate at the time of scanning. Illness duration and medication dosage did not differ significantly between the FEP subgroups (Table 1).

Healthy volunteers, who had no personal or family history of psychiatric illness, were recruited from similar sociodemographic areas as the patients by approaching ancillary hospital staff and through advertisements (Velakoulis et al., 1999, 2006). There was no significant group difference in age, sex, handedness and height (Table 1), but pair-wise comparison showed that the schizophreniform group had a larger proportion of males compared with affective psychosis group (chi-square = 4.08, $p = 0.043$). Premorbid IQ was higher in control subjects than in schizophrenia patients. This study was approved by the regional ethics committee while written informed consent was obtained from all subjects prior to study participation.

2.2. Magnetic resonance imaging procedures

MR scans were acquired with a 1.5-T GE Signa scanner (General Electric Medical Systems, Milwaukee, Wisconsin). A 3D volumetric spoiled gradient recalled echo in the steady state sequence generated 124 contiguous 1.5 mm coronal slices (TR = 14.3 ms, TE = 3.3 ms, Flip = 30°, FOV = 24 × 24 cm, Matrix = 256 × 256, voxel dimension = 0.938 × 0.938 × 1.5 mm). The scanner was calibrated fortnightly with the same phantom to ensure the stability of measurements.

The image data were coded randomly and analyzed with the Dr View software (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 AC-PC line. The whole cerebrum was manually separated from the brainstem and cerebellum. The signal-intensity histogram distributions from the T1-weighted images across the whole cerebrum were used to automatically segment the voxels into gray matter, white matter, and cerebrospinal fluid. Intracranial volume (ICV) was measured on a sagittal reformat of the original 3-dimensional data to correct for differences in head size (Eritaia et al., 2000); the groups did not differ significantly in their ICVs (Table 1).

2.3. Volumetric analyses of superior temporal subregions

The STG (gray and white matter) and its gray matter subregions [planum polare (PP), Heschl gyrus (HG), planum temporale (PT), rostral STG, and caudal STG] were manually traced on 0.938-mm consecutive coronal slices (Fig. 1). The detailed procedures for delineation of these structures were described previously (Takahashi et al., 2006, 2009a). Briefly, based on the established tracing guidelines (Kim et al., 2000),

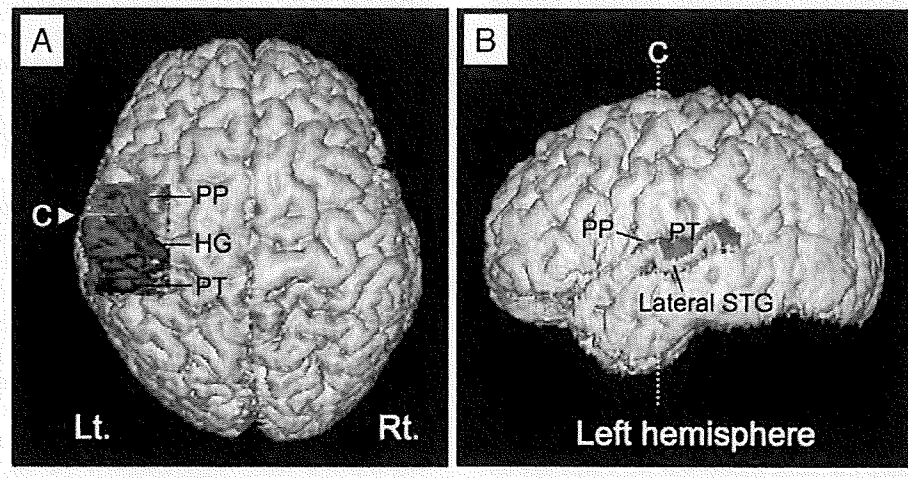

Fig.1. Three-dimensional reconstructed images of superior temporal sub-regions presenting top-down (A) and lateral (B) views of the brain. The frontal and parietal lobes in panel A are partially cut off to disclose the regions examined. The lateral superior temporal gyrus (STG) was further subdivided into rostral STG and caudal STG by a plane containing the anterior end of the Heschl gyrus (arrowhead C on panel A, dotted line C on panel B). Abbreviations: HG = Heschl gyrus; PP = planum polare; PT = planum temporale; STG = superior temporal gyrus.

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 anterior and posterior boundaries of the whole STG, respectively. On each coronal slice, the whole STG was bounded superiorly by the sylvian fissure and inferiorly by the superior temporal sulcus. The deepest recesses of these sulci were connected to each other with a straight line as a medial boundary. The gray and white matter components of the whole STG were segmented automatically as described above, and the whole STG gray matter was then parcellated into supratemporal and lateral portions by the lateral limb of the supratemporal plane. HG was traced from posterior to anterior, beginning with the first slice containing Heschl sulcus (HS) and ending anteriorly with the slice containing the most anterior point of HS or the sulcus intermedius if it existed. On each coronal slice, the HG was bounded medially by the sylvian fissure, inferior circular insular sulcus, or the first transverse sulcus and laterally by HS. When two convolutions oriented separately from the retroinsular regions, the most anterior gyrus was regarded as the HG. When they oriented medially from the common stem, however, both were defined as the HG. After tracing the HG that 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 (Fig. 1A). The lateral STG was divided into rostral and caudal STG portions by the plane including the anterior tip of HG (Fig. 1B).

All volumetric data reported here were measured by one rater (TT), who was blinded to subjects' identities. The volumes of the whole STG and its subregions in a subset of eight randomly selected brains were measured independently by two raters (TT and YK), and each volume was then remeasured after at least 4 weeks by the first-rater; intra- and inter-rater intraclass correlation coefficients for each region were over 0.88.

2.4. Statistical analysis

Clinical and demographic differences between groups were examined with one-way analysis of variance (ANOVA) or chi-square test.

The absolute volume of the STG was analyzed using repeated measures multivariate analysis of covariance (MANCOVA) with age and ICV as covariates, group (schizophrenia, schizophreniform psychosis, affective psychosis, other psychoses, and healthy controls) and sex as between-subject factors, and hemisphere (left, right) and tissue class (gray and white matter) as within-subject variables. We then investigated subregional effects of the STG gray matter changes using the same MANCOVA model but with hemisphere and subregion (PP, HG, PT, rostral STG, and caudal STG) as within-subject variables. Finally, each subregion was analyzed separately based on a significant group × subregion interaction. The relative STG volume [(absolute volume/ICV) × 100] was also analyzed using the same model but with only age as a covariate. The statistical analyses for group comparisons reported here are based on the absolute volumes, but these MANCOVA results were considered significant only when the results with both absolute and relative volumes reached significance. Even when we used only group as a between-subject factor, these results remained the same (except the effect involving sex). The post-hoc Neuman-Keuls tests were employed to follow up the significant main effects or interactions.

Spearman's rho was calculated to examine relationships between the relative STG volumes and clinical variables because of skewed distribution of these variables (i.e., illness duration, medication dose). Statistical significance was defined as $p<0.05$ (two tailed). To prevent a possible type I error due to multiple comparisons, a Bonferroni correction was applied for correlational analyses.

3. Results

3.1. Superior temporal gyrus volumes

MANCOVA of the absolute STG volume showed significant main effects for group [$F(4, 212)=8.43$, $p<0.001$] and tissue class [$F(1, 214)=4745.14$, $p<0.001$] and a significant interaction between them [$F(4, 214)=7.45$, $p<0.001$], with the schizophrenia patients having a smaller gray matter volume compared to all other groups (post hoc test, all $p<0.001$), while white matter did not differ between the groups (post hoc test, all $p>0.319$). There was also a significant tissue class × hemisphere interaction [$F(1, 214)=411.58$, $p<0.001$]; the STG gray and white matter volumes had left-greater-than-right ($p<0.001$) and right-greater-than-left ($p<0.001$) asymmetries, respectively. However, there was no tissue class × hemisphere × group interaction [$F(4, 214)=1.10$, $p=0.359$].

MANCOVA of the STG gray matter subregions revealed significant main effects for group [$F(4, 212)=8.88$, $p<0.001$], hemisphere [$F(1, 214)=146.34$, $p<0.001$], and subregion [$F(4, 856)=837.98$, $p<0.001$] and significant group × subregion [$F(16, 856)=3.97$, $p<0.001$], hemisphere × subregion [$F(4, 856)=18.94$, $p<0.001$], sex × hemisphere [$F(1, 214)=9.68$, $p=0.002$], and sex × subregion [$F(4, 856)=3.55$, $p=0.007$] interactions. MANCOVAs for each subregion and post hoc comparisons showed that the schizophrenia patients had significantly smaller HG, PT, and caudal STG volumes than all other groups bilaterally, but there was no difference between the controls and affective psychosis, schizophreniform disorder, or other psychoses groups for any STG subregion (Tables 2, and 3). All the subregions (HG, PT, and PP, $p<0.001$; rostral STG, $p=0.005$; and caudal STG, $p=0.015$) had a significant asymmetrical pattern (left > right) and the left HG was larger in males than in females ($p<0.001$).

There was no significant difference in the STG gray matter volume between the schizophrenia subgroups [schizoaffective disorder ($n=15$) and schizophrenia ($n=31$)] [$F(1, 42)=2.19$, $p=0.147$] (Table 4) or between the affective psychosis subgroups [bipolar disorder ($n=22$) and major depression ($n=12$)] [$F(1, 30)=6.89$, $p=0.014$; post hoc test, $p=0.120$]. Exclusion of schizoaffective disorder patients did not change the MANCOVA results of the PT [$F(4, 197)=3.16$, $p=0.015$] and cSTG [$F(4, 197)=4.41$, $p=0.002$], while group difference of the HG did not reach significance [$F(4, 197)=1.60$, $p=0.177$] possibly due to reduced statistical power.

The STG gray matter volume in the patients on lithium treatment ($n=17$) did not differ significantly from that in the other patients ($n=145$) [$F(1, 158)=0.01$, $p=0.905$]. More

Table 2
Absolute volume of the superior temporal gyrus (STG).

Brain region (mm^3)	Controls ($n=62$)		Sz ($n=46$)		Szform ($n=57$)		Aff ($n=34$)		Other ($n=25$)		Analysis of covariance[a] Group		Hemisphere		Group × hemisphere	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	$F(4,212)$	p	$F(1,214)$	p	$F(4,214)$	p
Whole STG WM											0.62	0.649	463.92	<0.001	1.31	0.267
Left	3495	1051	3089	667	3446	991	3642	991	3397	883						
Right	5143	1389	4602	1007	5013	1215	4964	1121	4642	1155						
Whole STG GM											9.00	<0.001	144.10	<0.001	0.41	0.805
Left	14696	2729	12291[b]	1927	14772	2288	14115	2360	13868	2263						
Right	12725	2242	10755[b]	1567	13072	1684	12384	1864	12333	1441						
Planum polare											0.42	0.796	19.24	<0.001	0.11	0.979
Left	1964	535	1861	584	1952	493	1852	488	1801	412						
Right	1777	488	1644	467	1764	474	1721	464	1657	364						
Heschl gyrus											2.66	0.034	125.23	<0.001	1.31	0.269
Left	2509	733	2025[c]	610	2445	746	2280	680	2300	634						
Right	1830	503	1596[c]	462	1934	501	1788	400	1729	255						
Planum temporale											7.16	<0.001	124.21	<0.001	0.48	0.748
Left	3662	892	2952[b]	678	3568	813	3550	837	3394	918						
Right	2899	783	2340[b]	555	2999	658	2815	610	2804	543						
Rostral STG											0.13	0.973	6.31	0.013	0.28	0.982
Left	1550	672	1458	747	1571	722	1499	724	1487	609						
Right	1450	674	1285	514	1400	801	1329	625	1430	533						
Caudal STG											7.18	<0.001	4.81	0.029	0.25	0.909
Left	4974	1198	3960[b]	865	5199	1252	4945	1386	4852	1383						
Right	4735	1189	3873[b]	858	4944	1031	4701	1149	4678	734						

Aff, affective psychosis; GM, gray matter; other, other psychoses; Sz, schizophrenia; Szform, schizophreniform; WM, white matter.

[a] Main effect of sex was not significant for any regions. Sex-by-hemisphere interaction was significant for the whole STG white matter [$F(1, 214)=46.41$, $p<0.001$], whole STG gray matter [$F(1, 214)=9.24$, $p=0.003$], and HG[$F(1, 214)=19.24$, $p<0.001$]. For the results of post hoc group comparisons (Neuman-Keuls tests), see below.

[b] $p<0.01$: smaller than all other groups.

[c] $p<0.01$: smaller than Controls and Szform; $p<0.05$: smaller than Aff and Other.

schizophrenia patients were taking typical antipsychotics compared with other patient groups (Table 1), but no difference in the STG gray matter volume was found between the schizophrenia patients taking typical ($n=23$) and atypical ($n=20$) antipsychotics [$F(1, 39)=0.00$, $p=0.987$].

Table 3
Percent volume differences of the superior temporal subregions from the controls.[a]

Brain region (%)	Sz ($n=46$)		Szform ($n=57$)		Aff ($n=34$)		Other ($n=25$)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Planum polare								
Left	−1.6	28.3	−0.5	23.7	−4.1	25.1	−5.3	20.6
Right	−4.1	26.7	−0.8	26.6	−2.4	25.4	−4.7	19.4
Heschl gyrus								
Left	−15.4	25.3	−2.0	29.7	−8.4	23.0	−6.0	24.1
Right	−9.3	25.1	6.3	29.5	−0.9	22.4	−2.2	16.9
Planum temporale								
Left	−15.7	19.7	−2.3	21.3	−1.9	21.8	−5.0	23.4
Right	−15.6	20.1	3.4	21.3	−1.6	20.8	−0.6	18.1
Rostral STG								
Left	−2.5	47.8	1.2	44.6	−2.2	47.0	−0.6	40.4
Right	−8.0	37.0	−4.2	53.2	−7.9	43.1	−0.4	33.2
Caudal STG								
Left	−16.7	17.9	4.8	24.4	0.9	29.3	0.1	25.1
Right	−14.5	18.2	4.8	20.5	0.7	23.3	2.6	18.8

Aff, affective psychosis; Other, other psychoses; STG, superior temporal gyrus; Sz, schizophrenia; Szform, schizophreniform.

[a] Calculated by the following formula: 100 × (relative volume of the patients − mean relative volume of the controls)/mean relative volume of the controls.

3.2. Correlational analyses

Correlational analyses in the FEP subgroups did not reveal any significant correlation between the whole STG gray and white matter volumes and medication dosage (rho = −0.263 to 0.253, $p=0.066$ to 0.950) or illness duration (rho = −0.218 to 0.307, $p=0.068$ to 0.913). Also, each STG subregion was not correlated with these variables after Bonferroni correction. We then separately analyzed the schizophrenia patients taking typical ($n=23$) and atypical ($n=20$) antipsychotics, but there was no significant correlation between their STG volumes (white matter and gray matter subregions) and medication dosage or illness duration. Pearson's partial correlation analyses controlling for age did not reveal any significant correlation between the relative STG gray and white matter volumes and premorbid IQ for any group.

4. Discussion

This region of interest (ROI)-based MRI study examined the volumes of the STG and its functionally relevant subregions in first-episode patients with various psychotic disorders. The schizophrenia patients had significantly smaller STG gray matter in bilateral HG, PT, and caudal STG compared with healthy controls, whereas the affective and schizophreniform psychosis patients as well as the 'other psychoses' group, which included small numbers of patients with less common diagnoses (e.g., delusional disorder, brief psychosis), had normal STG gray matter volumes. However, no group difference was found in the STG white matter volume. Our findings thus indicate that bilateral gray matter

Table 4
Absolute volume of the superior temporal gyrus (STG) in schizophrenia subgroups.

Brain region (mm^3)	Schizophrenia (23 males, 8 females)		Schizoaffective (11 males, 4 females)		Analysis of covariance [a]					
					Group		Hemisphere		Group × hemisphere	
	Mean	SD	Mean	SD	F (1,42)	p	F (1,44)	p	F (1,44)	p
Whole STG WM					0.52	0.473	80.29	<0.001	3.79	0.058
Left	3063	723	3141	554						
Right	4775	1026	4242	892						
Whole STG GM					2.10	0.155	38.10	<0.001	3.73	0.060
Left	12668	1972	11512	1625						
Right	10849	1722	10561	1215						
Planum polare					0.08	0.775	5.97	0.019	5.08	0.029
Left	1909	627	1762	489						
Right	1593 [b]	416	1750	561						
Heschl gyrus					1.12	0.296	33.11	<0.001	0.05	0.818
Left	2073	600	1925	638						
Right	1656	459	1472	459						
Planum temporale					5.47	0.024	25.5	<0.001	3.58	0.065
Left	3130	678	2583 [c]	527						
Right	2383	587	2244 [c]	487						
Rostral STG					0.35	0.557	1.72	0.197	0.78	0.382
Left	1467	854	1440	482						
Right	1232	538	1394	457						
Caudal STG					1.40	0.243	0.46	0.500	0.01	0.927
Left	4053	944	3769	661						
Right	3973	907	3665	729						

GM, gray matter; WM, white matter.

[a] Sex was not used as a between-subject factor due to small sample size especially for females. MANCOVA of the STG gray matter subregions showed no group-by-subregion interaction [F (4, 176) = 1.23, p = 0.299], but the results of lower order analyses for each subregion are also reported here.

[b] p<0.01: smaller than left hemisphere in schizophrenia.

[c] p<0.05: smaller than schizophrenia. Not significant when analyzed using relative volume.

reduction of the STG (especially its posterior portion), which is unlikely due to chronic illness or medication, is diagnostically specific to schizophrenia among various disorders with psychotic features.

Consistent with previous MRI findings (Hirayasu et al., 2000; Kasai et al., 2003a), our results of PT and HG volume reductions in first-episode schizophrenia support the notion that schizophrenia involves disruption to regions subserving primary auditory, speech, and language processes (Kasai et al., 2003a; Sumich et al., 2005). In contrast, as in previous observations in chronic schizophrenia (Crespo-Facorro et al., 2004; Takahashi et al., 2006), we found no volume changes in the PP, an area of auditory association cortex located anterior to HG. We also replicated findings of marked gray matter reduction of the caudal STG in schizophrenia (Kim et al., 2003; Takahashi et al., 2006), a region activated during auditory speech perception (Price, 2004) or mentalizing tasks (Gallagher and Frith, 2003), supporting the notion that impairments in mentalizing (interpretation of the mental states of others) abilities may account for the varying range of clinical presentations in schizophrenia (Brüne, 2005; Frith and Frith, 1999). White matter abnormalities in schizophrenia may represent a neural substrate of impaired connectivity (reviewed by Walterfang et al., 2006), but the present and a previous (Whitford et al., 2007) MRI study in first-episode schizophrenia did not identify any STG white matter changes. However, other studies have identified STG white matter volume reductions in chronic schizophrenia (O'Daly et al., 2007; Spalletta et al., 2003), while enlargement has been reported in childhood onset schizophrenia (Taylor et al., 2005). These controversial findings of the STG white matter might be related to longitudinal volume changes in the course of illness, effect of medication, and/or disease heterogeneity.

In this study, we found no STG changes in either affective or schizophreniform psychosis as contrasted with schizophrenia, suggesting that morphologic abnormalities of the STG gray matter at first-episode are specific to schizophrenia. Previous ROI-based (Hirayasu et al., 1998, 2000; Kasai et al., 2003a,b) and voxel-based morphometric (McDonald et al., 2005) MRI studies have also demonstrated STG gray matter reduction in schizophrenia but not in affective psychosis. Although schizophrenia and affective psychosis may have common pathophysiological and clinical features (Maier et al., 2006; Murray et al., 2004), these STG findings may represent neurobiological differences between these disorders, which could underlie more pronounced cognitive impairments in schizophrenia (Bertrand et al., 2008; Bora et al., in submission; Kim et al., 2009). On the other hand, assuming that the schizophreniform group only differs from schizophrenia on duration of symptoms, the lack of STG changes in this group raises the possibility that the STG abnormalities are related to persistent psychosis or chronic course observed in schizophrenia. Reduced STG volume reported in individuals with schizotypal personality disorder (Goldstein et al., 2009; Takahashi et al., 2006) might be related to the effects of medication and/or chronicity of the illness.

Our studies using the same FEP sample as in this study have found that volume reductions of bilateral insula (Takahashi et al., 2009b) and left hippocampus are specific to schizophrenia, while only non-schizophrenic psychoses exhibited amygdala enlargement (Velakoulis et al., 2006). Another group comparing the brain morphology between

first-episode samples of schizophrenia and affective psychosis (mainly manic) reported specific gray matter reduction of prefrontal cortex (Hirayasu et al., 2001), STG (Hirayasu et al., 1998, 2000; Kasai et al., 2003a,b), insula (Kasai et al., 2003c), and fusiform gyrus (Lee et al., 2002) in schizophrenia, but both psychoses had smaller volumes of left posterior amygdala-hippocampal complex (non-significant in affective psychosis) (Hirayasu et al., 1998), temporal pole (Kasai et al., 2003c) and subgenual cingulate cortex (Koo et al., 2008). Although the data are not entirely consistent, possibly due to different methodologies (e.g., anatomical definitions of amygdala and hippocampus), these observations provide evidence that these two psychoses are characterized by distinctive patterns of brain morphologic changes (McDonald et al., 2005); abnormalities in cortical regions related to affect regulation appear to underlie the pathophysiology of affective psychosis, whereas schizophrenia exhibits more widespread alterations involving primary sensory processing cortex and cortical regions specialized for other functions (e.g., language and speech processes) (Kasai et al., 2003c).

The nature of the morphologic change in schizophrenia remains unclear. Postmortem studies by Sweet et al. (2003, 2004) described somal volume reductions of PT and HG pyramidal cells in schizophrenia, but others have demonstrated preservation of normal cytoarchitecture in these regions (Beasley et al., 2005; Cotter et al., 2004). Recent longitudinal MRI studies have reported marked gray matter loss in posterior STG in schizophrenia but not in affective psychosis during the initial years after the onset (Kasai et al., 2003a,b), implicating ongoing regional pathological mechanisms in the context of 'late neurodevelopment' (Pantelis et al., 2005, 2007) specific to schizophrenia. In contrast, while our own data identified progressive changes in the STG from the earliest stages of illness, no significant difference in STG gray matter reduction over time was found between clinical high-risk subjects who later developed schizophrenia spectrum ($n=7$) and those who developed affective psychosis ($n=5$) (Takahashi et al., 2009a). We also failed to detect significant difference in the STG volume between the high-risk subjects with and without future transition to psychosis (unpublished data). Thus, further examination in a larger longitudinal sample at different stages and diagnoses is required to clarify the timing and course of the STG abnormalities in various psychotic disorders.

A few possible confounding factors in the present study should be taken into account. First, most patients had a brief exposure to neuroleptics, with more schizophrenia patients being treated with typical antipsychotics compared with other FEP subgroups. Typical and atypical antipsychotic agents may differentially affect brain morphology in schizophrenia (Lieberman et al., 2005; Scherk and Falkai, 2006; Thompson et al., 2009), while lithium may increase gray matter volume (Moore et al., 2000). However, no significant medication effect (type, daily dosage) on the STG volume was identified in the FEP subgroups, and the STG gray matter volume did not differ between the FEP patients with and without lithium treatment. Second, detailed clinical data of the patients such as the symptomatology and clinical course were not available, representing a limitation of the study. Lower IQ in the schizophrenia patients might have also biased our results, but their STG gray matter volume did not correlate with premorbid IQ for any subregion. Finally, we included schizoaffective disorder patients in the schizophrenia group despite the debate on it as a separate diagnostic entity (Averill et al., 2004; Evans et al., 1999). The possibility also exists that bipolar and depressive psychoses have different STG changes. In fact, exclusion of the schizoaffective patients changed the results of the HG, although the STG gray matter volume did not significantly differ between the schizophrenia and affective psychosis subgroups. Thus, potential biological differences of these subgroups need to be further tested in a larger sample.

In summary, our findings indicate that volume reduction of the STG gray matter, but not white matter, is specific to first-episode schizophrenia among various first-episode psychotic disorders especially in its posterior subregions (HG, PT, and caudal STG). These findings implicate the specific role of the STG gray matter in the pathophysiology of schizophrenia, but further studies are needed to explore its association with the cognitive and clinical characteristics reported in schizophrenia.

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Contributors

MS, DV, and CP conceived the idea and methodology of the study. TT conducted the statistical analyses and wrote the manuscript. SJW, PDM, DV, and CP recruited subjects, were involved in clinical and diagnostic assessments and for MRI scanning. TT and YK analyzed magnetic resonance imaging. BS provided technical support (data processing). All authors contributed in writing of the manuscript and have approved the final manuscript.

Conflict of interest

There are no conflicts of interest for any of the authors.

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References

American Psychiatric Association, 1987. Diagnostic and Statistical Manual of Mental Disorders. American Psychiatric Association, Washington, DC. Revised Third Edition.

American Psychiatric Association, 1994. Diagnostic criteria from DSM-IV. American Psychiatric Association, Washington, DC.

Antonova, E., Kumari, V., Morris, R., Halari, R., Anilkumar, A., Mehrotra, R., Sharma, T., 2005. The relationship of structural alterations to cognitive deficits in schizophrenia: a voxel-based morphometry study. Biol. Psychiatry 58, 457–467.

Averill, P.M., Reas, D.L., Shack, A., Shah, N.N., Cowan, K., Krajewski, K., Kopecky, C., Guynn, R.W., 2004. Is schizoaffective disorder a stable diagnostic category: a retrospective examination. Psychiatr. Q 75, 215–227.

Barta, P.E., Pearlson, G.D., Powers, R.E., Richards, S.S., Tune, L.E., 1990. Auditory hallucinations and smaller superior temporal gyral volume in schizophrenia. Am. J. Psychiatry 147, 1457–1462.
Beasley, C.L., Chana, G., Honavar, M., Landau, S., Everall, I.P., Cotter, D., 2005. Evidence for altered neuronal organisation within the planum temporale in major psychiatric disorders. Schizophr. Res. 73, 69–78.
Bertrand, M.C., Achim, A.M., Harvey, P.O., Sutton, H., Malla, A.K., Lepage, M., 2008. Structural neural correlates of impairments in social cognition in first episode psychosis. Soc. Neurosci. 3, 79–88.
Brüne, M., 2005. "Theory of mind" in schizophrenia: a review of the literature. Schizophr. Bull. 31, 21–42.
Cotter, D., Mackay, D., Frangou, S., Hudson, L., Landau, S., 2004. Cell density and cortical thickness in Heschl's gyrus in schizophrenia, major depression and bipolar disorder. Br. J. Psychiatry 185, 258–259.
Crespo-Facorro, B., Kim, J.J., Chemerinski, E., Magnotta, V., Andreasen, N.C., Nopoulos, P., 2004. Morphometry of the superior temporal plane in schizophrenia: relationship to clinical correlates. J. Neuropsychiatry. Clin. Neurosci. 16, 284–294.
Elkis, H., Friedman, L., Wise, A., Melzer, H.Y., 1995. Meta-analyses of studies of ventricular enlargement and cortical sulcal prominence in mood disorders. Comparisons with controls or patients with schizophrenia. Arch. Gen. Psychiatry 52, 735–746.
Eritaia, J., Wood, S.J., Stuart, G.W., Bridle, N., Dudgeon, P., Maruff, P., Velakoulis, D., Pantelis, C., 2000. An optimized method for estimating intracranial volume from magnetic resonance images. Magn. Reson. Med. 44, 973–977.
Evans, J.D., Heaton, R.K., Paulsen, J.S., McAdams, L.A., Heaton, S.C., Jeste, D., 1999. Schizoaffective disorder: a form of schizophrenia or affective disorder? J. Clin. Psychiatry 60, 874–882.
First, M.B., Spitzer, R.L., Gibbon, M., Williams, J.B., 1997. Structured clinical interview for DSM-IV Axis I disorders. American Psychiatric Press, Washington, DC.
Frith, C.D., Frith, U., 1999. Interacting minds—a biological basis. Science 286, 1692–1695.
Gallagher, H.L., Frith, C.D., 2003. Functional imaging of 'theory of mind'. Trends Cogn. Sci. 7, 77–83.
Goldstein, K.E., Hazlett, E.A., New, A.S., Haznedar, M.M., Newmark, R.E., Zelmanova, Y., Passarelli, V., Weinstein, S.R., Canfield, E.L., Meyerson, D.A., Tang, C.Y., Buchsbaum, M.S., Siever, L.J., 2009. Smaller superior temporal gyrus volume specificity in schizotypal personality disorder. Schizophr. Res. 112, 14–23.
Hirayasu, Y., Shenton, M.E., Salisbury, D.F., Dickey, C.C., Fischer, I.A., Mazzoni, P., Kisler, T., Arakaki, H., Kwon, J.S., Anderson, J.E., Yurgelun-Todd, D., Tohen, M., McCarley, R.W., Hirayasu, Y., Shenton, M.E., Salisbury, D.F., Dickey, C.C., Fischer, I.A., Mazzoni, P., Kisler, T., Arakaki, H., Kwon, J.S., Anderson, J.E., Yurgelun-Todd, D., Tohen, M., McCarley, R.W., 1998. Lower left temporal lobe MRI volumes in patients with first-episode schizophrenia compared with psychotic patients with first-episode affective disorder and normal subjects. Am. J. Psychiatry 155, 1384–1391.
Hirayasu, Y., McCarley, R.W., Salisbury, D.F., Tanaka, S., Kwon, J.S., Frumin, M., Snyderman, D., Yurgelun-Todd, D., Kikinis, R., Jolesz, F.A., Shenton, M.E., 2000. Planum temporale and Heschl gyrus volume reduction in schizophrenia: a magnetic resonance imaging study of first-episode patients. Arch. Gen. Psychiatry 57, 692–699.
Hirayasu, Y., Tanaka, S., Shenton, M.E., Salisbury, D.F., DeSantis, M.A., Levitt, J.J., Wible, C., Yurgelun-Todd, D., Kikinis, R., Jolesz, F.A., McCarley, R.W., 2001. Prefrontal gray matter volume reduction in first episode schizophrenia. Cereb. Cortex 11, 374–381.
Kasai, K., Shenton, M.E., Salisbury, D.F., Hirayasu, Y., Onitsuka, T., Spencer, M.H., Yurgelun-Todd, D.A., Kikinis, R., Jolesz, F.A., McCarley, R.W., 2003a. Progressive decrease of left Heschl gyrus and planum temporale gray matter volume in first-episode schizophrenia. Arch. Gen. Psychiatry 60, 766–775.
Kasai, K., Shenton, M.E., Salisbury, D.F., Hirayasu, Y., Lee, C.U., Ciszewski, A.A., Yurgelun-Todd, D., Kikinis, R., Jolesz, F.A., McCarley, R.W., 2003b. Progressive decrease of left superior temporal gyrus gray matter volume in patients with first-episode schizophrenia. Am. J. Psychiatry 160, 156–164.
Kasai, K., Shenton, M.E., Salisbury, D.F., Onitsuka, T., Toner, S.K., Yurgelun-Todd, D., Kikinis, R., Jolesz, F.A., McCarley, R.W., 2003c. Differences and similarities in insular and temporal pole MRI gray matter volume abnormalities in first-episode schizophrenia and affective psychosis. Arch. Gen. Psychiatry 60, 1069–1077.
Keshavan, M.S., Haas, G.L., Kahn, C.E., Aguilar, E., Dick, E.L., Schooler, N.R., Sweeney, J.A., Pettegrew, J.W., 1998. Superior temporal gyrus and the course of early schizophrenia: progressive, static, or reversible? J. Psychiatr. Res. 32, 161–167.
Kim, D.I., Mathalon, D.H., Ford, J.M., Mannell, M., Turner, J.A., Brown, G.G., Belger, A., Gollub, R., Lauriello, J., Wible, C., O'Leary, D., Lim, K., Toga, A., Potkin, S.G., Birn, F., Calhoun, V.D., 2009. Auditory oddball deficits in schizophrenia: an independent component analysis of the fMRI multisite function BIRN study. Schizophr. Bull. 35, 67–81.
Kim, J.J., Crespo-Facorro, B., Andreasen, N.C., O'Leary, D.S., Zhang, B., Harris, G., Magnotta, V.A., 2000. An MRI-based parcellation method for the temporal lobe. Neuroimage 11, 271–288.
Kim, J.J., Crespo-Facorro, B., Andreasen, N.C., O'Leary, D.S., Magnotta, V., Nopoulos, P., 2003. Morphology of the lateral superior temporal gyrus in neuroleptic naive patients with schizophrenia: relationship to symptoms. Schizophr. Res. 60, 173–181.
Koo, M.S., Levitt, J.J., Salisbury, D.F., Nakamura, M., Shenton, M.E., McCarley, R.W., 2008. A cross-sectional and longitudinal magnetic resonance imaging study of cingulate gyrus gray matter volume abnormalities in first-episode schizophrenia and first-episode affective psychosis. Arch. Gen. Psychiatry 65, 746–760.
Lee, C.U., Shenton, M.E., Salisbury, D.F., Kasai, K., Onitsuka, T., Dickey, C.C., Yurgelun-Todd, D., Kikinis, R., Jolesz, F.A., McCarley, R.W., 2002. Fusiform gyrus volume reduction in first-episode schizophrenia: a magnetic resonance imaging study. Arch. Gen. Psychiatry 59, 775–781.
Lieberman, J.A., Tollefson, G.D., Charles, C., Zipursky, R., Sharma, T., Kahn, R.S., Keefe, R.S., Green, A.I., Gur, R.E., McEvoy, J., Perkins, D., Hamer, R.M., Gu, H., Tohen, M., HGDH Study Group, 2005. Antipsychotic drug effects on brain morphology in first-episode psychosis. Arch. Gen. Psychiatry 62, 361–370.
Matsumoto, H., Simmons, A., Williams, S., Hadjulis, M., Pipe, R., Murray, R., Frangou, S., 2001. Superior temporal gyrus abnormalities in early-onset schizophrenia: similarities and differences with adult-onset schizophrenia. Am. J. Psychiatry 158, 1299–1304.
Maier, W., Zobel, A., Wagner, M., 2006. Schizophrenia and bipolar disorder: differences and overlaps. Curr. Opin. Psychiatry 19, 165–170.
McDonald, C., Bullmore, E.T., Sham, P.C., Chitnis, X., Wickham, H., Bramon, E., Murray, R.M., 2004. Association of genetic risks for schizophrenia and bipolar disorder with specific and generic brain structural endophenotypes. Arch. Gen. Psychiatry 61, 974–984.
McDonald, C., Bullmore, E., Sham, P., Chitnis, X., Suckling, J., MacCabe, J., Walshe, M., Murray, R.M., 2005. Regional volume deviations of brain structure in schizophrenia and psychotic bipolar disorder: computational morphometry study. Br. J. Psychiatry 186, 369–377.
McGorry, P.D., Kaplan, I., Dossetor, C., Herrman, H., Copolov, D., Singh, B., 1989. Royal park multidiagnostic instrument for psychosis. National Health and Medical Research Council, Melbourne, Australia.
McGorry, P.D., Edwards, J., Mihalopoulos, C., Harrigan, S.M., Jackson, H.J., 1996. EPPIC: an evolving system of early detection and optimal management. Schizophr. Bull. 22, 305–326.
Moore, G.J., Bebchuk, J.M., Wilds, I.B., Chen, G., Manji, H.K., 2000. Lithium-induced increase in human brain grey matter. Lancet 356, 1241–1242.
Morgan, K.D., Dazzan, P., Orr, K.G., Hutchinson, G., Chitnis, X., Suckling, J., Lythgoe, D., Pollock, S.J., Rossell, S., Shapleske, J., Fearon, P., Morgan, C., David, A., McGuire, P.K., Jones, P.B., Leff, J., Murray, R.M., 2007. Grey matter abnormalities in first-episode schizophrenia and affective psychosis. Br. J. Psychiatry 51, s111–116.
Murray, R.M., Sham, P., Van Os, J., Zanelli, J., Cannon, M., McDonald, C., 2004. A developmental model for similarities and dissimilarities between schizophrenia and bipolar disorder. Schizophr. Res. 71, 405–416.
Nakamura, M., Salisbury, D.F., Hirayasu, Y., Bouix, S., Pohl, K.M., Yoshida, T., Koo, M.S., Shenton, M.E., McCarley, R.W., 2007. Neocortical gray matter volume in first-episode schizophrenia and first-episode affective psychosis: a cross-sectional and longitudinal MRI study. Biol. Psychiatry 62, 773–783.
O'Daly, O.G., Frangou, S., Chitnis, X., Shergill, S.S., 2007. Brain structural changes in schizophrenia patients with persistent hallucinations. Psychiatry Res. 156, 15–21.
Pantelis, C., Yücel, M., Wood, S.J., Velakoulis, D., Sun, D., Berger, G., Stuart, G.W., Yung, A., Phillips, L., McGorry, P.D., 2005. Structural brain imaging evidence for multiple pathological processes at different stages of brain development in schizophrenia. Schizophr. Bull. 31, 672–696.
Pantelis, C., Velakoulis, D., Wood, S.J., Yücel, M., Yung, A.R., Phillips, L.J., Sun, D.Q., McGorry, P.D., 2007. Neuroimaging and emerging psychotic disorders: the Melbourne ultra-high risk studies. Int. Rev. Psychiatry 19, 371–381.
Pearlson, G.D., 1997. Superior temporal gyrus and planum temporale in schizophrenia: a selective review. Prog. Neuropsychopharmacol. Biol. Psychiatry 21, 1203–1229.
Price, C., 2004. An overview of speech comprehension and production, In: Frackowiak, R.S.J., Friston, K.J., Frith, C.D., Dolan, R.J., Price, D.J., Zeki, S., Ashburner, J., Penny, W. (Eds.), Human brain function, 2nd ed. Elsevier academic press, California, pp. 517–545.
Rajarethinam, R.P., DeQuardo, J.R., Nalepa, R., Tandon, R., 2000. Superior temporal gyrus in schizophrenia: a volumetric magnetic resonance imaging study. Schizophr. Res. 41, 303–312.
Sanfilipo, M., Lafargue, T., Rusinek, H., Arena, L., Loneragan, C., Lautin, A., Rotrosen, J., Wolkin, A., 2002. Cognitive performance in schizophrenia: relationship to regional brain volumes and psychiatric symptoms. Psychiatry Res. 116, 1–23.

Scherk, H., Falkai, P., 2006. Effects of antipsychotics on brain structure. Curr. Opin. Psychiatry 19, 145–150.
Shenton, M.E., Kikinis, R., Jolesz, F.A., Pollak, S.D., LeMay, M., Wible, C.G., Hokama, H., Martin, J., Metcalf, D., Coleman, M., McCarley, R.W., 1992. Abnormalities of the left temporal lobe and thought disorder in schizophrenia. A quantitative magnetic resonance imaging study. N. Engl. J. Med. 327, 604–612.
Shenton, M.E., Dickey, C.C., Frumin, M., McCarley, R.W., 2001. A review of MRI findings in schizophrenia. Schizophr. Res. 49, 1–52.
Spalletta, G., Tomaiuolo, F., Marino, V., Bonaviri, G., Trequattrini, A., Caltagirone, C., 2003. Chronic schizophrenia as a brain misconnection syndrome: a white matter voxel-based morphometry study. Schizophr. Res. 64, 15–23.
Spitzer, R.L., Williams, J.B., Gibbon, M., First, M.B., 1990. Structured clinical interview for DSM-III-R, patient edition (SCID-P). American Psychiatric Press, Washington, DC.
Strasser, H.C., Lilyestrom, J., Ashby, E.R., Honeycutt, N.A., Schretlen, D.J., Pulver, A.E., Hopkins, R.O., Depaulo, J.R., Potash, J.B., Schweizer, B., Yates, K.O., Kurian, E., Barta, P.E., Pearlson, G.D., 2005. Hippocampal and ventricular volumes in psychotic and nonpsychotic bipolar patients compared with schizophrenia patients and community control subjects: a pilot study. Biol. Psychiatry 57, 633–639.
Sumich, A., Chitnis, X.A., Fannon, D.G., O'Ceallaigh, S., Doku, V.C., Faldrowicz, A., Sharma, T., 2005. Unreality symptoms and volumetric measures of Heschl's gyrus and planum temporal in first-episode psychosis. Biol. Psychiatry 57, 947–950.
Suzuki, M., Nohara, S., Hagino, H., Kurokawa, K., Yotsutsuji, T., Kawasaki, Y., Takahashi, T., Matsui, M., Watanabe, N., Seto, H., Kurachi, M., 2002. Regional changes in brain gray and white matter in patients with schizophrenia demonstrated with voxel-based analysis of MRI. Schizophr. Res. 55, 41–54.
Sweet, R.A., Pierri, J.N., Auh, S., Sampson, A.R., Lewis, D.A., 2003. Reduced pyramidal cell somal volume in auditory association cortex of subjects with schizophrenia. Neuropsychopharmacology 28, 599–609.
Sweet, R.A., Bergen, S.E., Sun, Z., Sampson, A.R., Pierri, J.N., Lewis, D.A., 2004. Pyramidal cell size reduction in schizophrenia: evidence for involvement of auditory feedforward circuits. Biol. Psychiatry 55, 1128–1137.
Takahashi, T., Suzuki, M., Zhou, S.Y., Tanino, R., Hagino, H., Kawasaki, Y., Matsui, M., Seto, H., Kurachi, M., 2006. Morphologic alterations of the parcellated superior temporal gyrus in schizophrenia spectrum. Schizophr. Res. 83, 131–143.
Takahashi, T., Suzuki, M., Tanino, R., Zhou, S.Y., Hagino, H., Niu, L., Kawasaki, Y., Seto, H., Kurachi, M., 2007. Volume reduction of the left planum temporale gray matter associated with long duration of untreated psychosis in schizophrenia: a preliminary report. Psychiatry Res. 154, 209–219.
Takahashi, T., Wood, S.J., Yung, A.R., Soulsby, B., McGorry, P.D., Suzuki, M., Kawasaki, Y., Phillips, L.J., Velakoulis, D., Pantelis, C., 2009a. Progressive gray matter reduction of the superior temporal gyrus during transition to psychosis. Arch. Gen. Psychiatry 66, 366–376.
Takahashi, T., Wood, S.J., Soulsby, B., Tanino, R., Wong, M.T., McGorry, P.D., Suzuki, M., Velakoulis, D., Pantelis, C., 2009b. Diagnostic specificity of the insular cortex abnormalities in first-episode psychotic disorders. Prog. Neuropsychopharmacol. Biol. Psychiatry 33, 651–657.
Taylor, J.L., Blanton, R.E., Levitt, J.G., Caplan, R., Nobel, D., Toga, A.W., 2005. Superior temporal gyrus differences in childhood-onset schizophrenia. Schizophr. Res. 73, 235–241.
Thompson, P.M., Bartzokis, G., Hayashi, K.M., Klunder, A.D., Lu, P.H., Edwards, N., Hong, M.S., Yu, M., Geaga, J.A., Toga, A.W., Charles, C., Perkins, D.O., McEvoy, J., Hamer, R.M., Tohen, M., Tollefson, G.D., Lieberman, J.A., HGDH Study Group, 2009. Time-lapse mapping of cortical changes in schizophrenia with different treatments. Cereb. Cortex 19, 1107–1123.
Velakoulis, D., Pantelis, C., McGorry, P.D., Dudgeon, P., Brewer, W., Cook, M., Desmond, P., Bridle, N., Tierney, P., Murrie, V., Singh, B., Copolov, D., 1999. Hippocampal volume in first-episode psychoses and chronic schizophrenia: a high-resolution magnetic resonance imaging study. Arch. Gen. Psychiatry 56, 133–141.
Velakoulis, D., Wood, S.J., Wong, M.T., McGorry, P.D., Yung, A., Phillips, L., Smith, D., Brewer, W., Proffitt, T., Desmond, P., Pantelis, C., 2006. Hippocampal and amygdala volumes according to psychosis stage and diagnosis: a magnetic resonance imaging study of chronic schizophrenia, first-episode psychosis, and ultra-high-risk individuals. Arch. Gen. Psychiatry 63, 139–149.
Walterfang, M., Wood, S.J., Velakoulis, D., Pantelis, C., 2006. Neuropathological, neurogenetic and neuroimaging evidence for white matter pathology in schizophrenia. Neurosci. Biobehav. Rev. 30, 918–948.
Whitford, T.J., Grieve, S.M., Farrow, T.F., Gomes, L., Brennan, J., Harris, A.W., Gordon, E., Williams, L.M., 2007. Volumetric white matter abnormalities in first-episode schizophrenia: a longitudinal, tensor-based morphometry study. Am. J. Psychiatry 164, 1082–1089.
Woods, S.W., 2003. Chlorpromazine equivalent doses for the newer atypical antipsychotics. J. Clin. Psychiatry 64, 663–667.

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Increased pituitary volume in schizophrenia spectrum disorders

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ABSTRACT

While hypothalamic-pituitary-adrenal (HPA) axis hyperactivity has been implicated in psychotic disorders, previous magnetic resonance imaging (MRI) studies of the pituitary gland volume in schizophrenia have yielded controversial results. It is also unknown whether patients with schizophrenia spectrum such as schizotypal disorder exhibit pituitary volume changes. In this study, we investigated the pituitary volume using MRI in 47 schizotypal disorder patients (29 males, mean age=25.0 years), 72 schizophrenia patients (38 males, mean age=26.2 years), and 81 age and gender matched healthy controls (46 males, mean age=24.5 years). Both patient groups had a larger pituitary volume compared with controls, but no difference was found between the schizophrenia and schizotypal patients. The pituitary volume was larger in females than in males for all diagnostic groups. There was no association between the pituitary volume and type (typical versus atypical), daily dosage, or duration of antipsychotic medication in either patient group. These findings are consistent with a stress-diathesis model of schizophrenia and further suggest that the schizotypal patients share HPA axis hyperactivity with young established schizophrenia patients reflecting a common vulnerability to stress within the schizophrenia spectrum.

1. Introduction

Hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis, one of the primary biological systems that mediates the psychological experience of stress by governing the release of steroids (e.g., cortisol), has been implicated in models of the onset and exacerbation of psychotic symptoms in patients with schizophrenia (reviewed by Phillips et al., 2006; Walker et al., 2008). Recent magnetic resonance imaging (MRI) studies in first-episode patients with psychotic disorders (predominantly schizophrenia) demonstrated enlarged volume of the pituitary gland, possibly reflecting activation of the hormonal stress response in the early course of the illness (Pariante et al., 2004, 2005). While antipsychotic medications, especially prolactin-elevating drugs, may increase pituitary volume (MacMaster et al., 2007b; Pariante et al., 2004), Pariante et al. (2005) have identified larger pituitary volume in antipsychotic-naïve patients. In contrast, two MRI studies in chronically medicated schizophrenia patients reported normal (Tournikioti et al., 2007) or smaller (Pariante et al., 2004) pituitary volume compared with healthy controls. These findings could be explained by the notion that pituitary size may reduce during the course of illness as a result of chronic activation of HPA axis (Sassi et al.,

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2001). Not all published studies are consistent with this notion, however, as another MRI study has demonstrated that neuroleptic-naïve schizophrenia patients with relatively recent onset also exhibit smaller pituitary volume (Upadhyaya et al., 2007). Pituitary findings in schizophrenia thus remain inconsistent and more data are needed to evaluate the potential role of HPA axis dysregulation in schizophrenia.

Schizotypal (personality) disorder (SPD) is thought to be a prototypic disorder within the schizophrenia spectrum (Siever et al., 1993; Siever and Davis, 2004), characterized by odd behavior and attenuated forms of schizophrenic features without the manifestation of an overt and sustained psychosis (American Psychiatric Association, 1994; World Health Organization, 1992). SPD is genetically related to schizophrenia and might share biological and psychological commonalities with schizophrenia as a neurobiological basis for vulnerability factors (Siever and Davis, 2004). Higher salivary cortisol level (Mittal et al., 2007; Walker et al., 2001; Weinstein et al., 1999) and blunted cortisol response to an acute metabolic stress (Mitropoulou et al., 2004) reported in SPD suggest that subjects with schizotypal features manifest, at least partly, similar HPA axis dysfunction to patients with established schizophrenia (Phillips et al., 2006; Walker et al., 2008). These findings and an enlarged pituitary volume in individuals during the prodromal phase of psychosis (Garner et al., 2005) suggest that the distress and arousal of the mild or incipient psychotic experience could activate the stress response even without florid psychotic symptoms. Such observations raise the possibility that the schizotypal subjects may exhibit a larger pituitary volume compared to healthy subjects. To our knowledge no brain morphologic studies have specifically examined the size of the pituitary gland in schizotypal subjects.

In the present study, we used MRI to investigate the pituitary volume in schizophrenia patients, schizotypal disorder patients, and healthy comparisons. The aims of the present study were 1) to determine if our schizophrenia sample (median illness duration=3 years) exhibited volume changes of the pituitary gland and 2) to test the hypothesis that the schizotypal disorder patients would have larger pituitary volume compared to healthy comparison subjects. We also examined whether pituitary volume was related to antipsychotic medication or other clinical characteristics in schizophrenia and schizotypal disorder patients.

2. Methods

2.1. Subjects

Forty-seven schizotypal disorder patients (29 males and 18 females; mean age=25.0 years, SD=5.4), 72 schizophrenia patients (38 males and 34 females; mean age=26.2 years, SD=5.6), and 81 control subjects (46 males and 35 females; mean age=24.5 years, SD=5.7) were included in this study. The subjects were right-handed except for one female patient with schizotypal disorder of unknown handedness. Table 1 shows the demographic and clinical data of the subjects. MRI findings of the midline brain abnormalities in the same group of subjects have been reported previously (Takahashi et al., 2008).

The schizotypal disorder patients who met the ICD-10 criteria for research (World Health Organization, 1993) were recruited from among patients who visited the clinics of the Department of Neuropsychiatry, Toyama Medical and Pharmaceutical University Hospital. This patient group exhibited schizotypal features accompanied by distress or associated problems in their lives and required clinical care including low-dose antipsychotics. Since schizotypal subjects rarely present themselves for clinical care, our clinic-based sample was considered to be more severely ill than schizotypal individuals among the general population. The sample characteristics of the clinic-based schizotypal disorder patients in our laboratory have been described previously (Kawasaki et al., 2004; Suzuki et al., 2004, 2005; Takahashi et al., 2006a). The mental condition of each subject was assessed by experienced psychiatrists to check for the emergence of overt psychotic symptoms, and none of the 47 patients has developed overt schizophrenia to date (mean follow-up period after MRI scanning=3.0 years, SD=2.6). All available clinical information and data obtained from a detailed review of the clinical records and structured interviews for Comprehensive Assessment of Symptoms and History (CASH) including the chapter on premorbid or intermorbid personality (Andreasen et al., 1992) were stored in a database. The subjects were diagnosed by consensus reached by at least two psychiatrists based on these data. Although all of the schizotypal subjects in this study also fulfilled the DSM-IV criteria of the SPD on Axis II, 13 subjects had previously experienced transient quasi-psychotic episodes fulfilling a DSM Axis I diagnosis of brief psychotic disorder (American Psychiatric Association, 1994). At the time of MRI scanning, 40 of the 47 patients were treated with low-dose antipsychotics, of which 14 were treated with typical antipsychotics and 26 received atypical antipsychotics (risperidone, $N=14$; others, $N=12$). The remaining seven patients were neuroleptic-naïve.

The schizophrenia patients fulfilled ICD-10 diagnostic criteria for schizophrenia (World Health Organization, 1993). All but one of the schizophrenia patients were on antipsychotic medication; 38 were being treated with typical antipsychotics and 33 were receiving atypical antipsychotics (risperidone, $N=17$; others, $N=16$). Clinical symptoms of schizotypal disorder and schizophrenia patients were rated at the time of scanning using the Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1984a) and the Scale for the Assessment of Positive Symptoms (SAPS; Andreasen, 1984b).

The control subjects consisted of healthy volunteers recruited from members of the community, hospital staff, and university students. They were given a questionnaire consisting of 15 items concerning their family and past histories, as well as present illness. They did not have any personal or family history of psychiatric illness among their first-degree relatives. All controls were interviewed and administered the Minnesota Multiphasic Personality Inventory (MMPI) by experienced psychologists to obtain a rather homogenous control group without eccentric profiles on the MMPI, and were excluded if they had an abnormal profile with any T-score for the validity scales or the clinical scales exceeding 70.

All subjects were physically healthy at the time of the study, and none had a lifetime history of serious head trauma, neurological illness or substance abuse disorder. All

Table 1
Demographic characteristics of healthy controls, patients with schizotypal disorder, and patients with schizophrenia

Variable	Healthy controls		Schizotypal patients		Schizophrenia patients	
	Male	Female	Male	Female	Male	Female
	(*N*=46)	(*N*=35)	(*N*=29)	(*N*=18)	(*N*=38)	(*N*=34)
Age (years)	25.0±5.8	23.8±5.7	25.2±5.8	24.6±4.9	25.6±4.7	27.0±6.5
Height (cm)	172.0±4.4[a]	159.3±4.5	171±5.6[a]	157.7±6.1	170.8±4.7[a]	158.3±4.0
Education (years)	16.9±2.8[b]	14.8±1.6[c]	13.3±1.9	12.8±2.2	13.5±1.8	13.4±1.9
Parental education (years)[d]	13.1±2.4	12.5±2.3	12.4±1.6	12.2±1.9	12.2±1.9	11.9±2.4
Age at onset (years)	–	–	–	–	21.7±4.4	21.7±4.2
Duration of illness (years)	–	–	–	–	3.9±4.0	5.5±5.9
Duration of medication (years)	–	–	1.8±3.5	1.1±1.8	2.9±3.2[e]	4.3±5.1[e]
Drug (mg/day, haloperidol equivalent)	–	–	5.0±5.5	4.5±6.3	11.7±8.7[e]	11.3±10.2[e]
Total SAPS score[d]	–	–	15.5±8.8	16.9±10.1	24.9±22.2[e]	28.7±19.6[e]
Total SANS score[d]	–	–	40.5±21.3	44.0±22.8	50.9±22.1	43.5±23.6

Values represent means±SDs. SANS, scale for the assessment of negative symptoms; SAPS, scale for the assessment of positive symptoms. ANOVA followed by Scheffé's test was used.
[a]$p<0.01$: compared to females.
[b]$p<0.01$: compared to male and female schizophrenia patients, male and female schizolypal patients, and female controls.
[c]$p<0.05$: compared to female schizotypal patients.
[d]Data missing for some participants.
[e]$p<0.01$: compared to schizotypal patients.*

participants were also screened for the gross brain abnormalities by the neuroradiologists. The three groups were matched for age, gender, height, and parental education, but the control subjects had attained a higher mean level of education than had the patients with either disorder (Table 1). The total SAPS score for the schizophrenia patients was significantly higher than that for the schizotypal patients. There were significant differences in medication dosage and duration of antipsychotic medication; the patients with schizotypal disorder took significantly smaller amounts of antipsychotics than did the patients with schizophrenia. This study was approved by the Committee on Medical Ethics of Toyama Medical and Pharmaceutical University. After a complete description of the study, written informed consent was obtained from all subjects.

2.2. Magnetic resonance imaging procedures

Magnetic resonance images were obtained by utilizing a 1.5-T Magnetom Vision (Siemens Medical System, Inc, Erlangen, Germany) with a three-dimensional gradient-echo sequence FLASH (fast low-angle shots) yielding 160–180 contiguous T1-weighted slices of 1.0-mm thickness in the sagittal plane. The imaging parameters were: repetition time=24 ms; echo time=5 ms; flip angle=40°; field of view=256 mm; and matrix size=256×256 pixels. The voxel size was 1.0×1.0×1.0 mm.

Image processing for volumetric analysis has been described in detail elsewhere (Takahashi et al., 2002). Briefly, on a Unix workstation (Silicon Graphics, Inc, Mountain View, CA, USA), the image data were processed using the software package Dr View 5.3 (AJS, Tokyo, Japan). Brain images were realigned in three dimensions to standardize for differences in head tilt during image acquisition and were then reconstructed into entire contiguous coronal images, with a 1-mm thickness, perpendicular to the anterior commissure-posterior commissure line. The signal-intensity histogram distributions from the T1-weighted images across the whole cerebrum were then used to semi-automatically segment the voxels into brain tissue components and cerebrospinal fluid. The intracranial volume (ICV) was measured to correct for differences in head size as previously described (Zhou et al., 2003); the groups did not significantly differ in their ICVs ($F=1.13$; $df=2, 192$; $p=0.324$) (Table 2).

Table 2
Intracranial and pituitaly volumes in healthy controls, patients with schizotypal disorder, and patients with schizophrenia

Variable	Healthy controls		Schizotypal patients		Schizophrenia patients	
	Male	Female	Male	Female	Male	Female
	(*N*=46)	(*N*=35)	(*N*=29)	(*N*=18)	(*N*=38)	(*N*=34)
Intracranial volume (cm^3)	1583±109[a]	1385±108	1587±108[a]	1423±150	1573±129[a]	1393±101
Pituitary Gland (mm^3)	651±122	779±136[b]	708±132[c]	884±123[b,c]	727±102[c]	892±134[b,c]

Values represent means±SDs.
ANCOVA followed by Scheffé's test was used. Age and height were used as covariates for the intracranial volume.
[a]$p<0.01$: compared to females.
[b]$p<0.01$: compared to males.
[c]$p<0.01$: compared to controls.

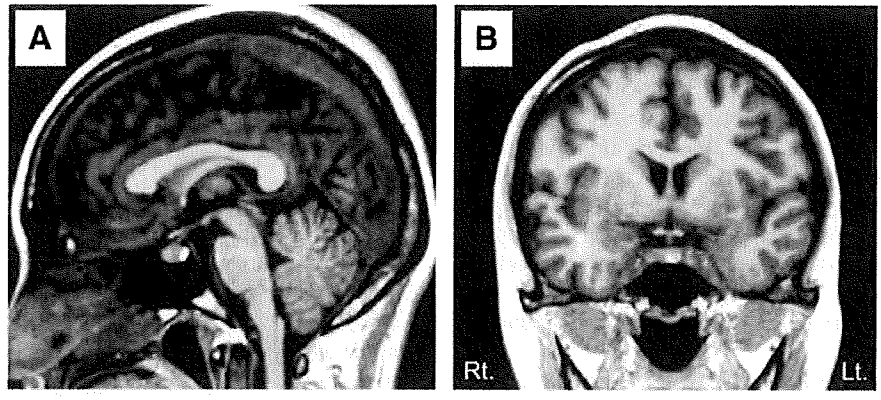

Fig. 1. Sagittal (A) and coronal (B) views of the pituitary gland manually traced in this study (blue). The pituitary stalk was excluded from the tracings, but we included a posterior bright spot.

2.3. Pituitary measurements

The volume of the pituitary gland was manually traced on consecutive 1-mm coronal slices based on a method used by Garner et al. (2005). Briefly, we traced around the usually well-defined borders of anterior and posterior pituitary: the diaphragma sellae, superiorly; the sphenoid sinus, inferiorly; and the cavernous sinuses, bilaterally. As presented in Fig. 1, the pituitary stalk was excluded from the tracings, but we included a posterior bright spot, corresponding to the posterior pituitary (the intensity of which is thought to reflect vasopressin concentrations). The number of coronal slices traced per brain varied from 7 to 14 (mean = 10.1 slices, SD = 1.3).

All measurements reported here were carried out by one rater (TT) without knowledge of the subjects' identity, gender, or diagnosis. Inter- (TT and VL) and intra-rater intraclass correlation coefficients in a subset of 10 randomly selected brains were 0.93 and 0.96, respectively.

2.4. Statistical analysis

Statistical difference in the absolute pituitary volume was analyzed using analysis of covariance (ANCOVA) with ICV, age, and duration and dosage of antipsychotic medication as covariates, with diagnosis (schizophrenia patients, schizotypal disorder patients, and controls) and gender (male, female) as between-subject factors. The schizophrenia patients were then divided into short (illness duration ≤12 months, 12 males and 9 females) and long (illness duration >12 months, 26 males and 25 females) duration groups; the pituitary volume of these subgroups was compared with the same ANCOVA model but with illness duration (short, long) and gender as between-subject factors. The pituitary volume of

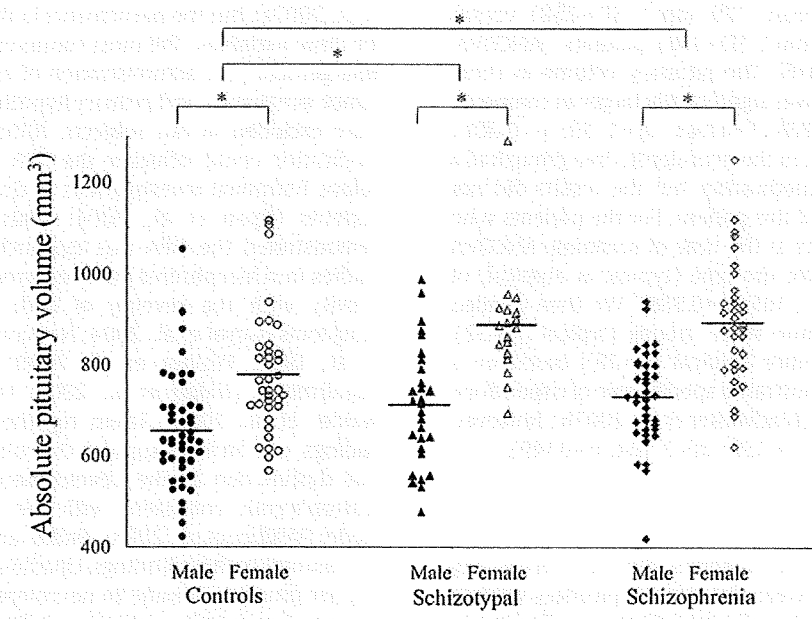

Fig. 2. Absolute volume of the pituitary gland in the healthy controls, patients with schizotypal disorder, and patients with schizophrenia. Horizontal lines indicate mean values. Post hoc Scheffé's test: *$p < 0.01$.

neuroleptic-free patients (seven neuroleptic-naïve schizotypal patients and a neuroleptic-free schizophrenia patient) and those who were receiving antipsychotic medication (71 schizophrenia and 40 schizotypal patients) was analyzed by ANCOVA covarying for age and ICV. For the medicated patients, possible differential effects of typical (N=52) versus atypical (N=59) antipsychotics on pituitary volume was examined by ANCOVA with ICV, age, and duration and dosage of antipsychotics as covariates, with type of medication (typical, atypical) as a between-subject factor. Post hoc Scheffé's tests were carried out to follow up any significant main effects or interactions.

Spearman's rank correlations were calculated to examine relationships between relative pituitary volume [(absolute volume/ICV)×100] and the clinical variables. Statistical significance was defined as $p<0.05$.

3. Results

3.1. Pituitary volumes

ANCOVA of the pituitary volume revealed significant main effects for diagnosis (F=10.63; df=2, 190; $p<0.001$) and gender (F=68.74; df=1, 190; $p<0.001$), but there was no diagnosis-by-gender interaction (F=0.69; df=2, 190; p=0.502). Post hoc analyses showed that the schizophrenia ($p<0.001$) and schizotypal (p=0.002) patients had larger pituitary volumes than control subjects, and that there was a significant gender difference in pituitary size (female > male, $p<0.001$) (Table 2). The statistical conclusions remained the same even when we excluded two outliers (a female schizotypal patient and a female schizophrenia patient with a pituitary gland >1200 mm^3) (Fig. 2).

The short (≤12 months) and long (>12 months) illness duration groups of schizophrenia did not significantly differ for pituitary volume (ANCOVA, F=0.00; df=1, 64; p=0.980).

There was no difference in the pituitary volume between the neuroleptic-free (mean=779 mm^3, SD=258) versus medicated (mean=794 mm^3, SD=138) patients (ANCOVA, F=0.01; df=1, 115; p=0.916). The pituitary volume in these neuroleptic-free patients was significantly larger as compared with the controls (ANCOVA, F=12.43; df=1, 83; $p<0.001$). One schizophrenia patient in the neuroleptic-free group had a history of antipsychotic medication, but the results did not change when we excluded this patient. For the patients who were taking antipsychotics at the time of scanning, ANCOVA revealed no main effect for the type (typical or atypical) of medication (F=0.75; df=1, 105; p=0.388). We then divided the type of medication into three groups [typical (N=52), risperidone (N=31), or other atypical (N=28)] based on a previous report that demonstrated specific role of risperidone on pituitary enlargement (MacMaster et al., 2007b), however, the result did not change (F=1.93; df=2, 104; p=0.149).

3.2. Correlational analyses

Spearman's correlational analyses did not reveal any significant correlation between the relative pituitary volume and daily dosage or duration of antipsychotic medication in either patient group. The pituitary volume was not significantly correlated with age at onset or duration of illness in schizophrenia patients. For both patient groups, there was no significant correlation between the pituitary volume and the total scores for the SAPS or SANS.

4. Discussion

In this study, we demonstrated an enlarged pituitary volume in both schizotypal disorder patients and relatively young patients with established schizophrenia compared with healthy controls. Most patients in this study were on antipsychotic medication, however, no significant medication effect on pituitary size was identified (incl. type, daily dosage, or duration) in either patient group. Pituitary volume changes have been described in psychotic disorders (e.g., Pariante et al., 2004), but the medication effect on the pituitary volume in schizophrenia remains controversial (MacMaster et al., 2007b; Tournikioti et al., 2007). Our findings suggest that the pituitary enlargement reported here is unlikely due to the effect of medication, consistent with previous pituitary findings in antipsychotic-naïve cohorts of psychotic disorders (Pariante et al., 2005) and high-risk individuals (Garner et al., 2005). These findings implicate the role of the HPA axis dysfunction in the pathophysiology of schizophrenia and further suggest that the schizotypal patients share the HPA axis hyperactivity with young schizophrenia patients as a possible indicator of common vulnerability to stress.

Our findings in schizophrenia are consistent with previous MRI findings by Pariante et al. (2004, 2005), who showed that patients with first-episode psychosis had an enlarged pituitary volume in comparison with healthy controls. These pituitary volume changes are considered to reflect HPA axis hyperactivity and a subsequent increase in the size and number of corticotrophs [cells producing adrenocorticotropic hormone (ACTH)], which could be explained by an activation of the hormonal stress response during the psychotic experience (Pariante et al., 2004, 2005). Age and gender have been reported to affect the pituitary volume (MacMaster et al., 2007a), but the participants in this study were matched for these variables. The most common causes of the pituitary enlargement [i.e., administration of estrogens, hypothalamic tumor, pregnancy, and primary hypothyroidism (Elster, 1993)] were excluded in our subjects. Although the antipsychotic medication could influence the HPA activation as discussed below, hormonal investigations in drug-naïve schizophrenia patients (Ryan et al., 2004; Walsh et al., 2005) have demonstrated the HPA axis dysfunction. Moreover, several studies in schizophrenia have reported an association of HPA activity with the severity of both positive and negative symptoms (Goyal et al., 2004; Newcomer et al., 1991; Tandon et al., 1991; Walder et al., 2000) as well as cognitive impairments (Halari et al., 2004; Newcomer et al., 1991; Walder et al., 2000). Taken together with these previous findings, our findings support the role of stress induced HPA axis dysfunction in the development and maintenance of schizophrenia, consistent with the neural diathesis-stress model (Walker et al., 2008; Walker and Diforio, 1997).

Contrary to these findings, Upadhyaya et al. (2007) found a smaller pituitary volume in neuroleptic-naïve schizophrenia patients. Normal (Tournikioti et al., 2007) or smaller (Pariante et al., 2004) pituitary volume in chronic schizophrenia patients with long illness duration (15–20 years) could be

explained by prolonged activation of the HPA axis, which might decrease the pituitary volume by reducing, through negative feedback, the function of the cells producing other pituitary hormones (Pariante et al., 2004; Sassi et al., 2001; Tournikioti et al., 2007). However, the illness duration of the sample of Upadhyaya et al. (2007) [mean=2.3 years (122 weeks)] was rather shorter than that in our schizophrenia patients (mean=4.6 years). Nevertheless, this inconsistency may be partly explained by the differences in sample characteristics; their schizophrenia cohort had relatively mild clinical symptoms, which could be related to mild HPA activation, and large proportion of males (36 of 51 patients), who have a smaller pituitary volume than females (Pariante et al., 2004, 2005; Upadhyaya et al., 2007). The effect of medication is also an important consideration for the discrepancy between studies. Although some antipsychotics may increase pituitary volume possibly by activating prolactin-secreting cells (MacMaster et al., 2007b; Pariante et al., 2004), antipsychotic medication generally dampens HPA activity in schizophrenia (Phillips et al., 2006; Scheepers et al., 2001; Walker et al., 2008). The neuroleptic-naïve patients of Upadhyaya et al. (2007), who had a longer duration of untreated psychosis (DUP) than our schizophrenia sample (median DUP=2 months; Takahashi et al., 2007), might exhibit intense HPA hyperactivity during the initial untreated period over 2 years, which could lead to earlier pituitary reduction in the course of illness. We did not find an effect of medication or illness duration on the pituitary volume in this study, but the possible effect of these and other mediating factors on HPA axis functioning seems worthy of further examination.

One of the primary findings of this study was that patients with schizotypal disorder share the pituitary enlargement with established schizophrenia patients, consistent with previous hormonal investigations showing HPA hyperactivity in individuals with schizotypal personality disorder (SPD) (Mittal et al., 2007; Mitropoulou et al., 2004; Walker et al., 2001; Weinstein et al., 1999). While we did not find a relationship between the clinical symptoms of the schizotypal patients and pituitary volume, Walker et al. (2001) identified an association between elevated cortisol levels in SPD subjects and the severity of their clinical schizotypal signs. Previous MRI studies by our group have demonstrated that the volumes of the brain regions implicated in sociality-related circuits (Kurachi, 2003) including the amygdala were reduced to the same degree in schizotypal disorder patients as in schizophrenia patients (Suzuki et al., 2005; Takahashi et al., 2006a,b). It has been also shown that schizotypal individuals have social and cognitive impairments similar to those observed in schizophrenia and manifest even higher levels of social distress compared with patients with major depression (Dickey et al., 2005; Siever and Davis, 2004; Skodol et al., 2002). Although this is the first MRI study to report pituitary volume changes in schizotypal disorder patients, these subjects might have some overlap in sample characteristics with individuals at ultra-high risk (UHR) of developing psychosis (Yung et al., 2003, 2004), because schizotypal subjects are considered to have a higher incidence of developing psychosis than the general population (Fenton and McGlashan, 1989; Nordentoft et al., 2006). Interestingly, a recent MRI study by Garner et al. (2005) demonstrated that the pituitary enlargement in UHR individuals who subsequently developed psychosis preceded the onset of psychosis. Thus, these previous observations and the present results support the notion that the distress related to social deficits and the level of arousal of an incipient psychotic experience could activate the stress response even without florid psychotic symptoms, implicating a common stress-vulnerability to psychopathology.

A few possible confounding factors in this study should be taken into account. First, our findings of the enlarged pituitary volume in schizophrenia spectrum are thought to reflect HPA axis hyperactivity, but we did not directly assess pituitary function. Although we did not find any association between pituitary volume and antipsychotic medication, the pituitary gland is considered to be sensitive especially to prolactin-elevating antipsychotics. Thus, additional assessment of both pituitary volume and hormonal levels (e.g., cortisol, ACTH, and prolactin) would be required to further examine HPA axis dysfunction in schizophrenia spectrum disorders. Second, the control subjects in this study were not selected to be educationally equivalent to the patients with both disorders. The sociodemographic factors including the educational level may affect stress response in social situations. Although the statistical conclusions in this study remained the same even when we used the educational level as a covariate for all ANCOVAs, this might have influenced the pituitary findings in this study. Regarding the demographic variables, our findings replicated a sexual dimorphism of the pituitary volume previously reported in both healthy subjects and psychosis patients (MacMaster et al., 2007a; Pariante et al., 2004, 2005; Upadhyaya et al., 2007). This study did not support age-related pituitary atrophy after puberty (Lurie et al., 1990; MacMaster et al., 2007a), but this could be related to a relatively narrow age range in the current sample. Finally, HPA axis functioning appears to be affected in various psychiatric populations such as major depressive disorders (Axelson et al., 1992; Krishnan et al., 1991; MacMaster and Kusumakar, 2004) and post-traumatic stress disorder (Yehuda, 2002). Further investigation of the disease specificity of HPA axis dysfunction is warranted.

In summary, the present study demonstrated that patients with schizotypal disorder have an enlarged pituitary volume as compared with healthy comparison subjects, which was similar to the findings in the patients with young established schizophrenia. While the effects of antipsychotic medication on the pituitary volume should be further clarified, our findings suggest that, in conjunction with previous observations regarding hormonal levels, subjects with schizotypal features exhibit the overactivity of the HPA axis as a common stress-vulnerability within the schizophrenia spectrum.

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Contributors

Drs. Suzuki, Kurachi, Velakoulis, and Pantelis conceived the idea and methodology of the study. Dr. Takahashi conducted the statistical analyses and wrote the manuscript. Drs. Takahashi, Suzuki, Nakamura and Kurachi recruited subjects, were involved in clinical and diagnostic assessments. Drs. Takahashi, Lorenzetti, and Zhou analyzed the MRI data. Dr. Seto provided