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Auditory cortex asymmetry, altered minicolumn spacing and absence of ageing effects in schizophrenia

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The superior temporal gyrus, which contains the auditory cortex, including the planum temporale, is the most consistently altered neocortical structure in schizophrenia (Shenton ME, Dickey CC, Frumin M, McCarley RW. A review of MRI findings in schizophrenia. Schizophr Res 2001; 49: 1–52). Auditory hallucinations are associated with abnormalities in this region and activation in Heschl's gyrus. Our review of 34 MRI and 5 post-mortem studies of planum temporale reveals that half of those measuring region size reported a change in schizophrenia, usually consistent with a reduction in the left hemisphere and a relative increase in the right hemisphere. Furthermore, female subjects are under-represented in the literature and insight from sex differences may be lost. Here we present evidence from post-mortem brain ($N = 21$ patients, compared with 17 previously reported controls) that normal age-associated changes in planum temporale are not found in schizophrenia. These age-associated differences are reported in an adult population (age range 29–90 years) and were not found in the primary auditory cortex of Heschl's gyrus, indicating that they are selective to the more plastic regions of association cortex involved in cognition. Areas and volumes of Heschl's gyrus and planum temporale and the separation of the minicolumns that are held to be the structural units of the cerebral cortex were assessed in patients. Minicolumn distribution in planum temporale and Heschl's gyrus was assessed on Nissl-stained sections by semi-automated microscope image analysis. The cortical surface area of planum temporale in the left hemisphere (usually asymmetrically larger) was positively correlated with its constituent minicolumn spacing in patients and controls. Surface area asymmetry of planum temporale was reduced in patients with schizophrenia by a reduction in the left hemisphere ($F = 7.7$, df 1,32, $P < 0.01$). The relationship between cortical asymmetry and the connecting, interhemispheric callosal white matter was also investigated; minicolumn asymmetry of both Heschl's gyrus and planum temporale was correlated with axon number in the wrong subregions of the corpus callosum in patients. The spacing of minicolumns was altered in a sex-dependent manner due to the absence of age-related minicolumn thinning in schizophrenia. This is interpreted as a failure of adult neuroplasticity that maintains neuropil space. The arrested capacity to absorb anomalous events and cognitive demands may confer vulnerability to schizophrenic symptoms when adult neuroplastic demands are not met.

Keywords: auditory processing; neuroplasticity; cerebral asymmetry; corpus callosum; language processing; schizophrenia

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Introduction

The planum temporale (particularly on the left) has been found to be smaller and even to reduce over time in schizophrenia (Kasai *et al.*, 2003) and its reduced size has been correlated with the degree of thought disorder in patients (Shenton *et al.*, 1992). Another common symptom, the perception of auditory hallucinations, is accompanied by increased blood flow (functional MRI—Shergill *et al.*, 2000) and neural activity (magnetoencephalographzy—Ropohl *et al.*, 2004) in the planum temporale and the primary auditory cortex in Heschl's gyrus. Enlargement of the ventricles has also been found correlated with reduced superior temporal gyrus volume (Chance *et al.*, 2003).

Reductions or reversals of asymmetry of the planum temporale have been reported in schizophrenia (Rossi *et al.*, 1992; Petty *et al.*, 1995; Barta *et al.*, 1997). Although it has not been found in a number of subsequent studies (Kulynych *et al.*, 1993, 1995; Kleinschmidt *et al.*, 1994; Rossi *et al.*, 1994; O'Leary *et al.*, 1995; Ward *et al.*, 1995; Frangou *et al.*, 1997), meta-analyses (Shapleske *et al.*, 1999; Sommer *et al.*, 2001) confirm a loss of

asymmetry in patients relative to controls in the literature as a whole.

The developmental expansion of the cortical surface depends on the proliferation of minicolumnar units of cells according to the radial unit hypothesis (Rakic, 1995). During embryogenesis, the columns are formed as cells migrate radially towards the brain's surface. Consequently, the nature of the pathophysiology underlying altered region size in schizophrenia may be reflected in minicolumn organization. Cortical minicolumnar structure is visible in axonal and dendritic bundles and, most commonly, cell body distribution. In adult cortex, these usually have a periodicity of 20–90 μm, depending on region and method.

We previously reported region and minicolumn size asymmetries in the superior temporal lobe in normal subjects as a putative substrate of language processing (Chance *et al.*, 2006a). Following the principle that language lateralization involves an interaction between the auditory cortices of the two hemispheres mediated by the corpus callosum, we identified asymmetries in minicolumn number in the normal auditory cortex that related to variation in the number of axons passing through the connecting regions of the corpus callosum; the posterior midbody contains the connections between the primary auditory regions of Heschl's gyri in both hemispheres and the isthmus contains the connections between the plana temporale (Chance *et al.*, 2006a). It has been suggested that cortical misconnections underlie the symptoms of schizophrenia (Friston and Frith, 1995) and that the corpus callosum may be particularly vulnerable (Crow *et al.*, 1998).

Minicolumn organization, little investigated in schizophrenia, therefore offers an approach to cytoarchitectural anomalies relating to abnormal region size and deficits in speech perception in schizophrenia. For example, reduced electrophysiological auditory mismatch responses have been associated with altered lateralization in the planum temporale in schizophrenia (Kircher *et al.*, 2004). Sex-dependent, asymmetric alteration in the evoked activation of auditory cortex has also been reported (Rojas *et al.*, 1997).

Given previous reports of grey matter reduction and reduced asymmetry, we hypothesized that schizophrenia patients would have reduced asymmetry of auditory cortex including PT, with smaller cortical surface area associated with smaller minicolumn spacing. Furthermore, based on the misconnectiviy hypotheses of Crow, Friston and Frith, we predicted that patients would have lost correlations between minicolumn asymmetry and axon numbers (measured previously in these brains) in the posterior midbody and isthmus of the corpus callosum.

Material and Methods

Subjects

Formalin-fixed brain tissue was sampled from 21 patients with schizophrenia (11 female, 10 male) conforming to DSM IV criteria, for comparison with a group of 17 control subjects (10 female, 7 male) for which minicolumn and callosal data have been reported previously using the same methods (Chance *et al.*, 2006a). Although control data were analysed separately to address independent scientific questions of cerebral lateralization in normal humans (Chance *et al.*, 2006a), the data for both patients and controls were originally gathered by the same raters at the same time while blind to diagnosis. Tissue was collected with consent in accordance with standard neuropathological practice and is registered with UK national investigations on organ retention. Cases were selected to yield comparable group mean fixation times and ages at death as far as possible, although a close match was not possible. Causes of death are listed in Table 1. Patients were included on the basis of the assessment of clinical notes by a consultant psychiatrist (T.J.C. or Dr S.J. Cooper, Belfast). Assessment of tissue sample pathology was carried out by a consultant neuropathologist (M.M. Esiri or B. McDonald, Oxford) and cases with significant pathology, such as Alzheimer's disease or cerebrovascular disease, were excluded using CERAD criteria. Control subjects had no history of neuropsychiatric illness. Demographic details and potentially confounding variables, including age at death, post-mortem interval and fixation time, were subjected to statistical analysis (see below).

No comorbidity of alcohol or illicit drug misuse was detected in our sample's records. Patients had received long-term anti-psychotic medication. Unfortunately, insufficient detail on lifetime medication was available for subsequent statistical analysis; however, we note that Benes *et al.* (2001) found no structural changes in cortical areas when comparing patients who had been exposed to neuroleptics with drug-naive patients.

Tissue samples

The brains had been supported by the basilar artery in 10% formalin for fixation and assigned a randomized code by a third party, so that measurements could be made by persons blind to sex, diagnosis and age. Five millimeter thick blocks of temporal lobe were cut orthogonal to the long axis of the lobe, systematically random with respect to the anterior boundary of Heschl's gyrus, sampling exhaustively through HG and PT, as defined below. Blocks were cut by hand using a calibrated metal guide. All blocks were used for the assessment of gross volume and area measurements. For the analysis of minicolumns, two 25 μm thick paraffin sections were cut from separate blocks within each region of interest (ROI), spaced to preserve the systematic random nature of the sample so that the entire ROI had a chance of being sampled. This was done in each hemisphere and the sections were Cresyl violet Nissl stained. Each ROI from each hemisphere was therefore analysed on two slides. Cortical tissue shrinkage due to embedding in these brains has been estimated with a mean of 23.7% (measurements on the 5 mm thick blocks were taken before embedding and afterwards and a measure of shrinkage was calculated) and no systematic difference was found between groups. The corpus callosum was not sampled in this study and the data used here were drawn from a previous study on the brains of the same subjects reported in Highley *et al.* (1999a). The material used in the present study was removed from formalin and tissue blocks were placed in embedding medium at the same time as in the previous studies that have been reported for these brains. Consequently, the comparison between recent minicolumn measures in the cortex and axon measures previously reported is not confounded by the time between studies.

Table 1 Causes of death

Diagnosis	Sex	Age	Cause of death
C	F	53	Carcinomatosis due to carcinoma of kidney
C	F	59	Multi-organ failure in a patient with myelodysplastic syndrome
C	F	63	Acute pulmonary oedema due to myocardial infarction due to coronary artery atheroma
C	F	71	Ruptured abdominal aortic aneurysm due to atherosclerosis
C	F	72	Pulmonary embolus, carcinomatosis (cancer of left lower lobe)
C	F	73	Haemothorax
C	F	80	Carcinomatosis (primary tumour probably lung), ulceration and haemorrhage of oesophagus
C	F	82	Pulmonary oedema due to brown atrophy to heart due to coronary artery atherosclerosis
C	F	89	Cardiac failure
C	F	90	Acute myocardial ischaemia due to coronary artery atheroma
C	M	40	Pulmonary oedema due to myocardial infarction and fibrosis due to coronary artery atherosclerosis with myocardial hypertrophy
C	M	53	Acute coronary insufficiency, coronary atherosclerosis
C	M	54	Ischaemic heart disease due to coronary artery atheroma
C	M	62	Congestive cardiac failure due to acute myocardial ischaemia due to coronary artery atheroma (operated)
C	M	66	Myocardial infarction due to coronary artery occlusion
C	M	68	Congestive cardiac failure due to coronary artery atheroma
C	M	76	Retroperitoneal haemorrhage due to ruptured abdominal aortic aneurysm due to aortic atherosclerosis
S	F	44	Sudden, other
S	F	48	Acute pulmonary oedema, hypertensive heart disease, Hodgkin's disease
S	F	66	Probably from bleeding duodenal ulcer and dehydration
S	F	70	Other, unknown
S	F	71	Suppurative bronchopneumonia, aspiration
S	F	73	Coronary thrombosis; septicaemia
S	F	79	Bilateral bronchopneumonia
S	F	80	Perforated duodenal ulcer and peritonitis
S	F	83	Pulmonary embolism
S	F	84	Other, unknown
S	F	90	Pulmonary embolus
S	M	29	Chest injuries (suicide)
S	M	41	Pulmonary oedema due to left ventricular failure and renal failure
S	M	58	Pulmonary oedema, ischaemic heart disease
S	M	59	Myocardial ischaemia, coronary occlusion, atherosclerosis, bronchopneumonia
S	M	60	Chest infection following carcinoma
S	M	65	Bronchopneumonia
S	M	66	Haemopericardium, cardiac infarction, coronary atherosclerosis
S	M	67	Respiratory infection
S	M	76	Acute myocardial ischaemia due to coronary artery atheroma
S	M	87	Other, non-acute

F = female; M = male; C = control; S = schizophrenia. Age at death is given in years (in ascending order within diagnosis × sex groups).

Anatomical measurements

Gross anatomical measurements

HG was defined as Heschl's gyrus, bounded by Heschl's sulcus posteriorly, the First Transverse sulcus anteriorly (Kim *et al.*, 2000) and laterally by the superolateral margin of the STG (Zetzsche *et al.*, 2001) containing cytoarchitectural regions TC and TBC following the definitions of von Economo and Koskinas (1925). The lower bank of the Sylvian fissure, posterior to HG was measured as PT. This consisted of the planum temporale bounded anteriorly by Heschl's sulcus, including regions TB and TA1, excluding the posterior ascending ramus. The PT was painted while still intact to clearly identify the beginning of the ascending ramus as the posterior border of the PT.

The callosal subregion boundaries, as reported in Highley *et al.* (1999a), were defined as proportions of the total length of the corpus callosum. Cortical volume was estimated by point counting within the grey matter of each region. Surface area was estimated by counting intersections between the cortical surface and cycloidal test lines (with changing orientation through 180° and known dimensions). Images of tissue slices were superimposed over the probe grids. A parallel slice design was used, as reported by Pakkenberg and Gundersen (1997). It should be noted that the present study was not strictly stereological since the identification of STG anatomy and minicolumnar organization requires a non-random orientation of tissue. Although probes were used that reduce the bias otherwise incurred by subjective outlining of structures, the parallel slice design (coronal slicing) does not satisfy the random orientation criteria to be strictly unbiased as discussed in Pakkenberg and Gundersen (1997).

Each structure was sampled twice by replacement of the point grid or test lines on each count of every slice, random with respect to the boundaries of the ROI, to generate a mean estimate. Estimation of PT and HG surface area and cortical volume was

repeated for 10 hemispheres to determine reliability—intraclass correlation coefficient for all measures was good ($\geqslant 0.9$). Across the entire final dataset, strong correlations were found between volume and surface area (Pearson correlations 0.87–0.94 for the four ROIs), indicating good agreement between the methods. To validate the surface area measured by cycloids, a comparison was made on a subgroup (10 plana) with an area measure based on manual surface outlining using the CortexTrace software (S.A.C., University of Oxford). Although surface outlining constitutes a more biased method as it depends on entirely user-guided tracing and was therefore undesirable for the main study, the agreement between methods was high (correlation 0.96, $P < 0.01$), indicating that the cycloid sampling was in good agreement with outlining methods such as those employed by many MRI analyses.

Columnar measurements

Minicolumn width and peripheral neuropil width were quantified using semi-automated computerized image analysis so that user bias is minimal. The method is model based and has been reported in detail with stereological validation and discussion of assumptions by Casanova and Switala (2005). The tissue sections were a systematically spaced subset that preserved randomization with respect to the anterior and posterior boundaries of the ROIs and therefore maintained systematic random sampling of the full extent of the regions while retaining coronal orientation. Minicolumns are clearest in lamina III, so minicolumn detection was optimized for lamina III. In summary, photographs of cortical lamina III were taken at 100× magnification, in coronal view, and the photographs were digitized at 0.48 µm resolution and tessellated. Two resulting photomicrographs (each about 1.5 mm^2 in area) were generated from each slide. Fields were selected systematically, randomly from the section, although regions of high cortical curvature such as the fundi of sulci or the apices of gyri were excluded since, while minicolumns are still clearly visible, high curvature affects cell distribution (Chance *et al.*, 2004). A mean of 261.6 minicolumns were sampled per brain (65.4 minicolumns per region, per hemisphere).

The image was automatically segmented to select neurons and nearest neighbour measurements of clustering were applied to determine the periodicity of columnar distribution. Segmentation was based on grey level intensity of the digitized image, with automated shape and size thresholds for cell identification, as validated previously (Casanova and Switala, 2005). The software is able to recognize minicolumns despite variations in stain, as long as cell object size and background contrast pass a threshold of acceptability for inclusion. Every image was studied for quality control by the user and artefacts were manually selected for exclusion from the analysis. A minicolumn is composed of the cell dense core and the cell sparse periphery of the cell column where local circuits, synapses and dendritic branches predominate. Centre-to-centre minicolumn spacing is calculated from the combination of the core and peripheral space.

The potential confounds of over-projection and lost caps are prevented by the thickness of sections—25 µm—being approximately matched to the spacing of minicolumns (taking into account *z*-axis shrinkage); therefore, a single plane of minicolumns is in view—for detailed discussion see Casanova and Switala (2005).

Tissue quality from one hemisphere did not pass the confidence threshold for automatic minicolumn segmentation in three cases for HG (1 male left, 1 female left and 1 female right) and once for PT (1 female right), so minicolumn measures were obtained only from the remaining hemisphere in these cases. To relate minicolumn spacing to regional surface area for the calculation of regional minicolumn number, the surface area per column was estimated based on a hexagonal distribution [as indicated by other researchers (Gabbott, 2003; Favorov and Kelly, 1994a, b)]. Asymmetry coefficients of minicolumn spacing were calculated as the magnitude of difference between hemispheres, expressed as a percentage of the bihemispheric mean ((left−right)/((left+right)/2)) × 100.

Statistical analysis

The four key measures, surface area, cortical volume, minicolumn spacing and minicolumn number, were analysed by repeated measures analysis of variance (rmANOVA). Statistical analyses were conducted using SPSS software (version 12.0) to apply rmANOVAs with diagnosis and gender as between-subject factors and either one level (hemisphere) or two levels (hemisphere and region) of within-subject factors. The influence of potential confounding factors in the rmANOVAs, including age at death, post-mortem interval and fixation time, was accounted for—*t*-tests were used to identify differences between groups.

The influence of age on columnar organization (Chance *et al.*, 2006b) was controlled by including age at death as a covariate in all rmANOVAs of columnar variables. It was also retained in rmANOVAs of region size variables, if it was a significant covariate. *t*-tests of post-mortem interval showed no differences between groups (and six cases had missing values, see Table 2, where the time since death was uncertain and not recorded in hours), so it was not included as a covariate in rmANOVAs. Fixation time was found to differ between groups and so was subjected to covariate analysis. However, fixation time data for one case was found to be an approximation (inaccurate by up to 6 months), so this covariate was only retained in rmANOVAs if found to be a significant covariate. All groups passed Kolmogorov–Smirnov tests, indicating a normal distribution, on all measured parameters. All repeated measures analyses also passed Box's M-test for equality of variance except Heschl's gyrus volume, which was corrected as reported below.

Three Pearson correlation analyses were performed—the first examined the relationship between minicolumn spacing and region size (surface area) for each region and the second considered the relationship between minicolumn number asymmetry and callosal axon number. A correlation analysis of age and minicolumn spacing was also performed.

Several unique tests were performed in this analysis. Due to the undesirability of multiple testing, data were compressed into single tests (i.e. rmANOVAs) wherever possible. The rmANOVA tests for inter-subject differences while also modelling an additional level of contrasts between intra-subject repeated measures (i.e. left and right hemispheres, or HG and PT). Mean values are reported for diagnosis, sex and hemisphere in Tables 3 and 4. In the main text, only statistically significant results are reported. Lateralized hemisphere differences are described only when there is an explicit statistical interaction depending on hemisphere. Where a main result did not involve a difference between hemispheres, a mean of left and right has been reported in the text.

Tests refer to specific separable elements of the study: (i) altered minicolumn configuration (Casanova *et al.*, 2005), (ii) altered

gross regional morphometry (area and volume) (Kawasaki *et al.*, 2007), (iii) the relationship between region size and minicolumn spacing (Chance *et al.*, 2006a), (iv) the relationship between minicolumn asymmetry and corpus callosum (compared with Chance *et al.*, 2006a) and (v) different effects of age on minicolumn spacing (Chance *et al.*, 2006b). *F*-statistics, *t*-statistics or Pearson's *r* coefficents have been reported, as appropriate.

Table 2 Demographic variables and covariates

Group	Age at death (years)	PMI (h)[a]	Fixation time (months)[b]	Age of illness onset (years)[b]
Male controls	59.9 ± 11.9	36.4 ± 15.9	20.9 ± 9.8	NA
Female controls	73.2 ± 12.4	36.9 ± 19.0	26.9 ± 13.3	NA
Male schizophrenia	59.5 ± 15.8	35.4 ± 21.2	32.8 ± 20.1	24.4 ± 6.4
Female schizophrenia	71.6 ± 14.5	35.0 ± 23.6	58.2 ± 20.2	38.4 ± 15.5

[a]Inaccurate information for six cases (see text for details).
[b]Inaccurate information for one case (fixation time uncertain by up to 6 months in one case, age of onset not recorded for one case).
NA = Not applicable.

Results

Minicolumn spacing

In the planum temporale, centre-to-centre minicolumn spacing was altered in schizophrenia in a sex-dependent manner, with a decrease in males (control mean = 86.2 μm, patient mean = 81.6 μm) and an increase in females (control mean = 80.1 μm, patient mean = 87.2 μm) (sex × diagnosis $F = 4.5$, df 1,29, $P = 0.04$). No other main effects of diagnosis, sex or hemisphere were observed. Age at death and fixation time were not significant covariates.

As there was a difference in the number of cases for which successful measurements were possible in each region, minicolumn data for Heschl's gyrus were treated separately from the planum temporale (Table 4). In Heschl's gyrus, there was no effect of diagnosis, sex, hemisphere or their interactions on minicolumn spacing. Age was not a significant covariate although it was included in the ANOVA, as described in the methods (above) and fixation was also included due to a significant interaction with hemisphere ($F = 5.5$, df 1,17, $P = 0.03$).

The cell sparse, peripheral region of minicolumns was found to constitute a mean 29% of minicolumn spacing in all sex × diagnosis groups and was not subjected to separate tests.

Table 3 Cortical volume and surface area

Group	Volume (mm^3)				Area (mm^2)			
	Planum		Heschl's		Planum		Heschl's	
	Left	Right	Left	Right	Left	Right	Left	Right
Male controls	2170.4 ± 553.5 (0.13)	1590.3 ± 259.9 (0.06)	2593.6 ± 600.4 (0.08)	2180.6 ± 316.8 (0.06)	902.5 ± 280. 8 (0.1)	609.7 ± 95.7 (0.07)	1052.2 ± 209.5 (0.09)	908.2 ± 123.9 (0.06)
Female controls	1910.4 ± 421.1 (0.08)	1486.5 ± 584.9 (0.11)	2041.4 ± 600.8 (0.09)	1648.5 ± 333.8 (0.08)	709.5 ± 173.2 (0.07)	544.5 ± 191.2 (0.12)	946.9 ± 257.8 (0.09)	748.4 ± 196.5 (0.06)
Male patients	2186.5 ± 600.4 (0.12)	1536.4 ± 756.0 (0.15)	2279.5 ± 849.2 (0.11)	2014.8 ± 694.6 (0.08)	840.9 ± 310.9 (0.09)	615.1 ± 293.9 (0.16)	1007.8 ± 350.4 (0.12)	890.9 ± 239.2 (0.11)
Female patients	1715 ± 610.5 (0.11)	1517.5 ± 526.7 (0.11)	1707.5 ± 406.3 (0.09)	1783.4 ± 355.4 (0.07)	636 ± 240.3 (0.11)	606.2 ± 212.5 (0.1)	758.3 ± 220.0 (0.07)	847. 4 ± 196.4 (0.06)

Means, SD and co-efficients of error of measurements.

Table 4 Minicolumn spacing and number

Group	Heschl's minicolumn spacing (μm)		Planum minicolumn spacing (μm)		Heschl's minicolumn number		Planum minicolumn number	
	Left	Right	Left	Right	Left	Right	Left	Right
Male control	79.4 ± 11.3	77.7 ± 10.17	88.5 ± 12.6	83.8 ± 8.5	184 024 ± 59 505	177 980 ± 48 627	122 397 ± 29 949	100 926 ± 25 454
Female control	74.0 ± 7.52	73.2 ± 13.2	80.8 ± 7.6	79.3 ± 10.2	210 923 ± 51 557	183 143 ± 68 440	129 785 ± 51 483	108 530 ± 51 759
Male schizophrenia	75.0 ± 17.6	72.0 ± 8.1	85.7 ± 10.6	77.4 ± 14.0	162 520 ± 37 750	219 999 ± 66 735	137 530 ± 56 826	134 214 ± 74 075
Female schizophrenia	79.7 ± 13.9	80.5 ± 10.5	86.3 ± 12.8	88.1 ± 11.7	152 654 ± 46 574	164 490 ± 29 945	96 498 ± 20 811	90 440 ± 37 137

Means and SD of measurements.
Fewer cases [*N* = 10 schizophrenia (5M, 5F), 16 controls (7M, 9F)] were sampled for Heschl's gyrus due to tissue exclusion, for example by damage during post-mortem brain extraction. (CEs are not included since minicolumn measures were by non-stereological automated method, previously validated).

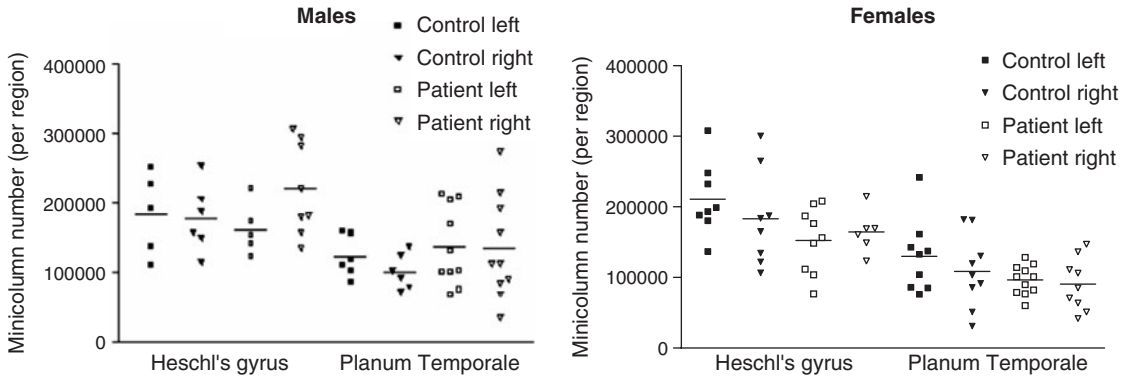

Fig. 1 Minicolumn number in HG and PT is increased in males and decreased in females with schizophrenia. (Males are shown in the graph on the left, females are shown in the graph on the right. Control subjects are indicated by solid shapes, patients by unfilled shapes. HG is represented by the four columns of data on the left of each graph and PT by the four columns on the right. The left hemisphere is represented by squares, the right hemisphere by triangles.)

Minicolumn number

A decrease in total minicolumn number per region was found in the PT in female patients (control mean = 119 158, patient mean = 93 469 [although note that values for the female right hemisphere fall within the normal control range)] and an increase in male patients compared with controls (control mean = 111 662, patient mean = 135 872) (sex × diagnosis $F = 5.9$, df 1,28, $P = 0.02$) (Fig. 1). No other significant effects were observed and neither fixation nor age was a significant covariate.

Tested separately in HG, minicolumn number was not changed, although there was a non-significant trend for a sex × diagnosis interaction that echoed the finding in planum temporale of a decrease in female patients and an increase in male patients ($F = 3.9$, df 1,17, $P = 0.065$). This result was not significant partly because the left hemisphere in males did not conform to this pattern. Neither fixation nor age was a significant covariate.

Region size

Reduced surface areas of both PT and HG were found in patients relative to controls in the left hemisphere (two-level analysis, diagnosis × hemisphere $F = 7.7$, df 1,32, $P < 0.01$) (Table 3). (This hemisphere effect is also emphasized by a small increase in the right hemisphere, particularly in female patients compared with controls.) Furthermore, surface areas were less in females than males (two-level analysis, sex effect $F = 7.2$, df 1,32, $P = 0.01$), particularly in the left hemisphere in both patients and controls, resulting in overall less asymmetry in females (two-level analysis, sex × hemisphere $F = 6.6$, df 1,32, $P = 0.02$). Fixation time, with a strong trend for an interaction, was included as a covariate (hemisphere × fixation, $F = 3.8$, df 1,32, $P = 0.06$). Age was not a significant covariate and therefore not included.

For the analysis of cortical volume, a two-level analysis including region as a factor failed Box's M-test for homogeneity of variance and so HG was analysed independently from PT since both structures passed Box's M-test independently. For HG no change was found in schizophrenia, although the gyrus was larger on the left (hemisphere effect $F = 7.1$, df 1,33, $P = 0.01$) and larger in males than females (sex effect $F = 8.4$, df 1,33, $P < 0.01$). Fixation and age were not significant covariates and therefore not included in the ANOVA. In the separate test of PT, volume was also unchanged in schizophrenia ($F = 0.1$, df 1,33, $P = 0.75$), while the usual left > right volume asymmetry persisted (hemisphere effect, $F = 16.1$, df 1,33, $P < 0.01$), with no differences dependent on sex. Age and fixation were not significant covariates and therefore not included in ANOVA.

Correlations

Region size and minicolumn spacing

In HG, minicolumn spacing was independent of surface area (correlations between surface area and minicolumn spacing were $r = 0.2$, $P = 0.31$ for the left hemisphere and $r = 0.3$, $P = 0.12$ for the right hemisphere). However, in PT, minicolumn spacing in the left hemisphere was positively correlated with surface area ($r = 0.37$, $P = 0.03$). The right hemisphere, which has smaller minicolumn spacing, did not show this correlation ($r = 0.04$, $P = 0.82$).

Mean minicolumn spacing asymmetry of PT is more than that of HG in normal control subjects (Chance *et al.*, 2006a). In schizophrenia, by contrast, the asymmetry was less in PT (mean asymmetry coefficient = 3.4% of bihemispheric mean) than in HG (mean asymmetry coefficient = 6.7% of bihemispheric mean).

Minicolumn asymmetry and callosal axons

The relationship of minicolumn number asymmetry in HG and PT to axonal fibre number in the five middle and posterior subregions of the corpus callosum was tested. In patients, the correlation values did not have clear peaks

selective to the appropriate regions of the corpus callosum. Instead, the data showed poor selectivity for the expected callosal subregions, with similar correlations for several different subregions (Fig. 2).

Minicolumn spacing and age

Due to normal age-associated thinning, Pearson's correlation analysis found a negative correlation between minicolumn spacing and age for the PT in Controls ($r = -0.51$, $P = 0.04$). As seen in Fig. 3A, both males and females show a negative correlation. In contrast, patients did not show a negative ageing effect ($r = 0.4$, $P = 0.09$). This trend for a positive correlation depended on the combination of males and females, including a single female outlier. More rigorous statistical consideration suggested that the sexes should be separated and the outlier excluded. Following this, the regression lines were horizontal, still showing no effect of age (Fig. 3B).

HG did not show an effect of age in controls (as reported previously, $r = -0.21$, $P = 0.46$) or patients ($r = 0.05$, $P = 0.89$).

Discussion

Literature review

Our review of previous imaging studies (Table 5) identified several features of the literature. Overall, half of the studies

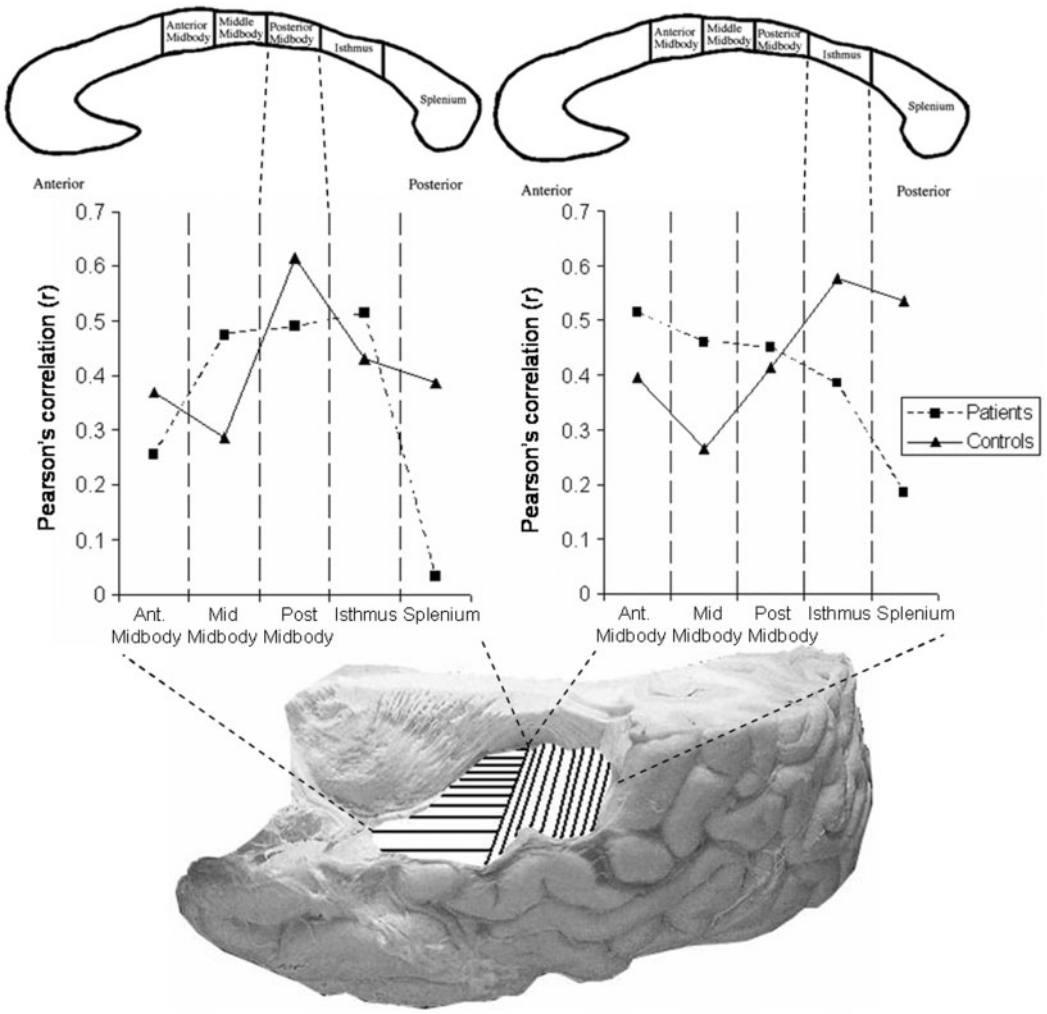

Fig. 2 Bottom: Image of the superior surface of the left temporal lobe. HG (horizontal shading) and PT (vertical shading) project through different subregions of the corpus callosum. Top: Two images of the corpus callosum. For HG the key subregion (upper left) is identified, by dotted lines linking it to the graph on the left, as the posterior midbody, for PT the key subregion (upper right) is the isthmus, linked by dotted lines to the graph on the right. Middle: The middle graphs show correlations between minicolumn number asymmetry and axonal fibre number for subregions of the corpus callosum. Middle left: Pearson *r*-values are plotted for HG primary auditory cortex against the five subregions. Middle right: Pearson *r*-values are plotted for PT association cortex against the five subregions. For both graphs, control subject data are represented by triangles (solid line) and patient data by squares (dashed line). [*r*-Values are directionless ($\sqrt{r^2}$) to ease comparison, indicating a correlation between increasing axon number and either increasing leftwards asymmetry (for HG) or decreasing leftwards asymmetry (for PT).] In controls, a clear peak correlation is seen for the subregions through which the respective cortical regions (HG and PT) are known to project. However, this peak correlation is not clear and is not selective to the appropriate subregion in patients.

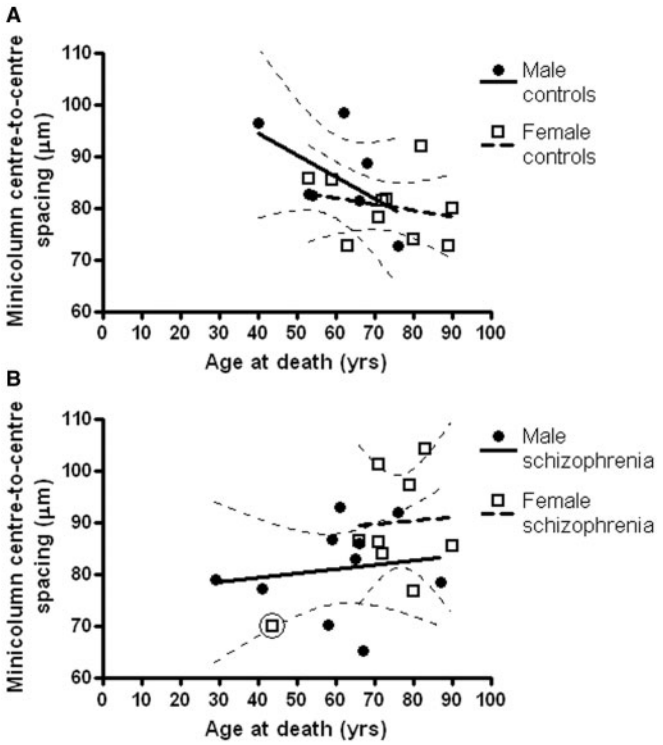

Fig. 3 Age-associated minicolumn shrinkage is found in the Planum Temporale in controls but this is absent in patients. Graphs show the bihemispheric mean minicolumn spacing in the planum temporale for male and female groups, with linear regression lines and 95% CIs. Overall, the negative correlation for control subjects (**A**) is significant ($r = -0.51$, $P = 0.04$) but there was no negative relationship for patients (**B**). (One outlier in the female patient group has been ringed and was excluded from linear regression due to its disproportionate effect on the result, see Results section).

report a change in PT in schizophrenia, 13 report a decrease, 9 of which are selective to the left hemisphere, and 3 report an increase, 2 of which are selective to the right hemisphere. Most studies investigated Heschl's gyrus as well and since changes occur in both HG and PT, their interaction deserves attention. Structural changes in these areas are among the most frequent to be associated with functional deficits. Change in Heschl's gyrus has been associated with hallucinations, semantics, mismatch negativity, illness duration and auditory sensory memory. Asymmetry or left hemispheric size of PT has been correlated with delusions, positive symptoms, phonetic mismatch strength, hallucinatory behaviour, social withdrawal, stereotyped thinking, memory deficits, P300 amplitude, suspiciousness, left ear advantage, phonology, psychosis duration and thought disorder. Of this wide range, the most consistent relationship is that of PT size with auditory mismatch responses (McCarley *et al.*, 1993, 2002; Yamasue *et al.*, 2004; Salisbury *et al.*, 2007). From the 34 studies reviewed, the male–female ratio among patients was approximately 5:2. For the majority of studies, the numbers of female subjects were too small to analyse sex differences (only 41% of studies had more than five females in the patient group of which three studies found sex differences) that should be addressed in future work. Although there are far fewer post-mortem studies, some sex differences are also reported (Table 6).

Neuropathological study

Region size

The surface areas of both Heschl's gyrus and the planum temporale in the left hemisphere were reduced in schizophrenia. The change in cortical volume was less. Consistent with a meta-analysis of MRI studies, the volume of planum temporale cortex on the left was not reduced significantly. Thus, loss of asymmetry of the planum temporale reflects a greater change in surface area than volume.

The findings relate to a problem outstanding in the imaging literature. Some authors (e.g. Kulynych *et al.*, 1995; Frangou *et al.*, 1997; Meisenzahl *et al.*, 2002) have failed to find the losses of asymmetry of the planum temporale reported by others [for meta-analyses see Shapleske *et al.* (1999) and Sommer *et al.* (2001)]. Barta *et al.* (1997) suggested that measurements of the surface area of the planum temporale were more important than those of volume and reported reversal of surface area asymmetry but an absence of asymmetry of volume. Our findings are in agreement with this suggestion. The significance of surface area as a measurement is brought into focus by the findings of Harasty *et al.* (2003) that asymmetry of the planum temporale in normal individuals is due to expansion ('ballooning') of the cortex on the left side relative to the right. A change in surface area implies a change in minicolumn number and spacing. We have shown that this is the case not only in the planum temporale, which shows the greatest change, but also in Heschl's gyrus, which may relate to early auditory perceptual abnormalities in patients.

Differences between HG and PT

Given that there are surface area differences of HG but no accompanying minicolumn spacing differences and that HG minicolumn spacing was not correlated with surface area, variation in HG size appears to be more dependent on the early established proliferation in number rather than spacing of minicolumns. In PT, in contrast, both surface area and minicolumn spacing differences were found in schizophrenia and minicolumn spacing in the left hemisphere was positively correlated with surface area, consistent with Harasty *et al.* (2003), indicating that the size and asymmetry of this region is linked more closely to the spacing of its minicolumns. Surface area, therefore, depends partly on proliferation of minicolumns, but also, particularly in association cortex, on later expansion of minicolumn spacing. These are the variables (proliferation and spacing) that are altered in schizophrenia and most of all in the latest maturing, most asymmetric cortex (thus alteration of the size of the left PT was correlated most closely to the spacing of minicolumns).

Table 5 Summary table of MRI studies examining the Planum Temporale (and Heschl's gyrus) in schizophrenia

Focus of study	References	Sample size		Finding	Asymmetry	Sex difference	Functional correlates	Notes
		Controls	Patients					
Volume	Kawasaki *et al*. (2007)	60 (30 M, 30 F)	60 (30 M, 30 F)	PT reduced asymmetry due to left PT ↓	PT L > R in controls and patients	No	Clinical variables did not correlate	
Cortical thickness	Qiu *et al*. (2007)	20 (10M, 10F)	20 (10M, 10F)	Anterior left PT thinner, posterior thicker	Not quantified	Not tested	No	
Volume	Salisbury *et al*. (2007)	32 (22M, 10F)	20 (17M, 3F)	Left HG grey matter ↓	Grey matter L > R all subjects. Asymmetric HG reduction	Not tested	Asymmetric HG reduction correlated with MMN reduction	First episode, longitudinal
Volume correlates	Weinstein *et al*. (2007)	0	12 (7M, 5F)	No comparison with controls	Only left hemisphere measured	No	PT grey matter correlated with thought disorder and fMRI activation	
Volume correlates	Takahashi *et al*. (2007)	0	38 (20M, 18F)	No comparison with controls	PT and HG L > R but not statistically significant	Not tested	Correlation between untreated psychosis duration and left PT volume	
Volume	Yamasaki *et al*. (2007)	17	22	HG no change PT ↓ bilateral	PT and HG L > R but not statistically significant	All males	PT reduction correlated with delusional behaviour	
Volume correlates	(2007) Walder *et al*. (related to Goldstein *et al*. (2002))	15 (6M, 9F)	19 (11M, 8F)	(See Goldstein *et al*. (2002))	(See Goldstein *et al*. (2002))	PT: L > R in males	All: left PT associated with phonology. Females: right HG associated with semantics and phonology	
Volume	Takahashi *et al*. (2006)	72 (38M, 34F)	65 (35M, 30F)	STG↓, HG↓, PT↓	Controls: L > R in STG, HG, PT, Scz: PT left sided reduction	No	No	
Volume	Sumich *et al*. (2005)	0 (no control group)	25	–	See functional correlates	All males	Left HG vol associated with hallucinations, Left PT associated with delusions	
Volume	Crespo-Facorro *et al*. (2004)	30	30	Right HG↓	All groups: L > R PT and HG. Scz: Right HG↓(volume and surface area)	All males	HG↓: Longer illness duration, PT↓: positive symptoms	
Spatial probability	Park *et al*. (2004)	21 (up to 5 female)	17 (up to 4 female)	Greater structural variation of HG and PT in scz	No	Not tested	No	First episode
Volume	Yamasue *et al*. (2004)	19 (13M, 6F)	13 (7M, 6F)	Left PT↓	Controls: no clear asymmetry, Scz: left PT↓	Not tested	Left PT reduction associated with phonetic mismatch strength	

Volume	Kasai *et al*. (2003)	22 (20M, 2F)	13 (10M, 3F)	Left HG↓, left PT↓	All groups: L > R HG, Scz: left HG↓, left PT↓	Not tested	No	First episode, longitudinal change over time
Volume	Sallet *et al*. (2003)	20 (12M, 8F)	40 (24M, 16F)	No difference	No clear asymmetry	None reported	Left PT vol associated: hallucinatory behaviour, social withdrawal and stereotyped thinking. Reversed asymmetry: memory deficits and judgement of NSRS	
Volume	Sumich *et al*. (2002)	16	25	Left PT↓	Controls: no clear asymmetry, Scz: left PT↓	All males	No	
Volume	Meisenzahl *et al*. (2002)	30	30	No difference	All groups: L > R PT	All males	No	First episode
Volume	McCarley *et al*. (2002)	18 (15M, 3F)	15 (12M, 3F)	Bilateral HG↓, left PT↓	Controls: L > R in HG, PT, Scz: PT left sided reduction	Not tested	Left post. STG↓: left temporal P300 amplitude↓	First episode
Volume	Goldstein *et al*. (2002)	48 (27M, 21F)	40 (27M, 13F)	HG↓ in males, right PT↑ in females	Scz: right PT↑ in females	Controls: L > R PT. Scz: HG↓ in males, right PT↑ in females, left PT↓ in males	No	
Volume	Shapleske *et al*. (2001)	32	74	No difference	All groups: L > R PT	All males	No correlations with symptom clusters	
Volume	Hirayasu *et al*. (2000)	22 (20M, 2F)	20 (16M, 4F)	Bilateral HG↓, left PT↓	All groups: L > R HG, Scz: left PT↓	Not tested	No	First episode
Volume	Kwon *et al*. (1999)	16	16	Left PT↓	All groups: HG no clear asymmetry, Controls: L > R PT, Scz: left PT↓	All males	Suspiciousness/persecution correlated with left PT volume	
Volume	Frangou *et al*. (1997)	39 (19M, 20F)	32 (21M, 11F)	No difference	All groups: L > R PT	No	No	
Volume/surface area	Barta *et al*. (1997) (also Pearlson *et al*. 1996)	32	28	Scz: right PT thickness↓	No clear asymmetry	Reversed PT surface area in male and female patients	No	
Surface area	Kulynych *et al*. (1995)	12	12	No difference	All groups: L > R PT, no asymmetry HG	All males	No	
Surface area	Mosnik *et al*. (1995)	10	10	Scz: PT surface smaller	All groups: L > R PT	All males	PT asym↑: left ear advantage↑	
Volume	O'Leary *et al*. (1995)	10	10	No difference	All groups L > R PT		PT rCBF greater individual variability during language tests	
Surface area	Ward *et al*. (1995)	30	30	PT no difference, HG↓	All groups: L > R	None reported	HG↓: auditory sensory memory↓	
Surface area	Petty *et al*. (1995)	14 (9M, 5F)	14 (9M, 5F)	PT reversed asymmetry	Controls: PT L > R, Scz: PT R > L	No	Greater thought disorder: greater reversal of asymmetry	
Surface area	Shenton *et al*. (1995)	15	15	PT surface↑ (L > R)	All groups: PT L > R	All males	No	
Surface area	Rossi *et al*. (1994)	23 (13M, 10F)	22 (13M, 9F),	No difference	All groups: L > R	Not tested	PT asymmetry↓: thought disorder↑	
Surface area	Kleinschmidt *et al*. (1994)	26 (13M, 13F)	26 (13M, 13F),	No difference	All groups: L > R	No	No	First episode

(continued)

Table 5 Continued

Focus of study	References	Sample size		Finding	Asymmetry	Sex difference	Functional correlates	Notes
		Controls	Patients					
Surface area	DeLisi *et al.* (1994)	40 (24M, 16F)	85 (50M, 24F).	No difference	Diagnosis difference dependent on antero–posterior boundary	Female PT asymmetry reduced	No relationship to thought disorder or hallucinations	First episode
Surface area	Vladar *et al.* (1993)	8 (discordant twins)	8 (discordant twins)	No difference	All groups: L > R	Not tested	No	
Surface area	Rossi *et al.* (1992)	12	20	Scz: left PT↓, right PT↑	Controls: PT L > R, Scz: PT R > L	No		
Approximately 60% studies report volume as primary measure	Summary:	772 (F : M ratio ~2 : 5)	907 (F : M ratio ~2 : 5)	13/29 studies report decrease of PT, 9 selective to left	21/30 studies report L > R in controls	3/11 studies report sex difference, most underpowered	Correlations replicated with auditory mismatch and thought disorder	First episode $N = 226$. 5/8 studies positive

Studies since 1992 were identified on the basis of a PubMed search in October 2007 using the search terms 'Planum Temporale' and 'schizophrenia' or inclusion in the previous meta-analyses of Sommer *et al.* (2001) or Shapleske *et al.* (1999). 32 of 34 studies report region size; ↓ = reduction, ↑ = increase.

Regional differences may relate to the hierarchical relationship between PT and HG in which PT is the recipient of feed-forward projections from the primary auditory area of HG and plays a role in more integrative, associative processing than HG. The two regions differ in maturation (Guillery, 2005; Chance, 2006; Toga *et al.*, 2006), dendritic arborization (Elston *et al.*, 1999), asymmetry and neuroplasticity (Arendt, 2004).

For minicolumn spacing in HG, there was a statistical interaction between fixation and hemisphere. Effects of fixation time are of greater concern for methods such as immunohistochemistry for which antigen retrieval techniques may be necessary but the Nissl stains used here are relatively robust and unlikely to be systematically affected by fixation. Given that shrinkage due to formalin fixation stabilizes after a few weeks and all of the brains in the present study were fixed for longer than that and furthermore both hemispheres were in formalin for identical periods, the interaction between fixation time and hemisphere seems unlikely to be causal. Any suggestion that the neuropil is more vulnerable to shrinkage in one hemisphere is contradicted by the absence of an equivalent, asymmetric fixation effect in PT. Similarly, the longer fixation time in female patients did not result in a sex-dependent fixation effect.

Callosal interaction

In schizophrenia, among the middle and posterior callosal subregions, the strongest correlation for area PT was with fibre number in the anterior midbody, forward of the appropriate subregion, the isthmus, through which posterior auditory association cortex projects (Pandya and Seltzer, 1996). However, the direction of the relationship was the same as for controls (Chance *et al.*, 2006a) indicating that a larger number of minicolumns in the right PT (reduced leftwards asymmetry) was associated with increased axon number. For HG, the strongest correlation was with fibre number in the isthmus, which is posterior to the expected subregion—the posterior midbody—through which primary auditory cortex is known to project. In this case, increasing number of minicolumns in the left HG (increased leftwards asymmetry) was associated with increased axon number (Fig. 2), also similar to controls.

The results indicate different relationships between minicolumn asymmetry and callosal axon number for HG and PT. The PT data show that less leftwards asymmetry is correlated with increasing axon number, consistent with predictions that greater leftwards, typical cortical asymmetry is associated with fewer interhemispheric connections. The relationship for HG is the reverse. A further interpretation is that an increased number of interhemispheric axons is associated with a more rightward bias for PT and a leftward bias for HG. This is of interest given that auditory processing that varies in the temporal domain is processed preferentially by HG in the left hemisphere whereas variation in the spectral domain is

Table 6 Post mortem studies are few compared to MRI

Focus of study	References	Sample size		Finding	Asymmetry	Sex difference	Functional correlates	Notes
		Control	Patients					
Cell density	Chance *et al.* (2005)	12 (5M, 7F)	12 (7M, 5F)	Calbindin interneuron density↓	No	Scz: Male calbindin interneuron size↑, Female size↓	No	PM cell density
Cell distribution	Beasley *et al.* (2005)	15 (9M, 6F)	15 (9M, 6F)	Neuron clustering↓, no change in density	Both hemispheres not tested	No		PM cell distribution
Cell size	Sweet *et al.* (2003)	18 (10M, 8F)	18 (10M, 8F)	Pyramidal neuron size↓	Only left hemisphere tested	No	No	PM cell size
5-HT receptors	Pralong *et al.* (2000)	20 (3F, 17M)	20 (3F, 17M)	5-HT2a receptor binding density reduced	Only left hemisphere tested	Not tested		PM receptors
Cortical volume	Falkai *et al.* (1995)	24	24	Left PT↓	Controls: L > R, Scz: R > L	Scz: Male right PT size↑, Female right PT size↓	No	PM cortical volume

Overall neuron density is not clearly altered but more subtle reductions of interneuron subpopulations, neuron size and clustering appear to contribute to the altered cortical volume reported in MRI. There is some evidence for sex differences but in general asymmetries and sex differences have not been adequately investigated.

preferentially processed by the auditory belt areas in the right hemisphere (Jamison *et al.*, 2006). Therefore, it is possible that the domain-sensitive processing bias for each region depends on callosal interaction.

Sex differences and minicolumn changes

There were sex differences in the present study. In summary, surface area (and volume in HG) was generally larger and more asymmetrical in males—a common sex difference. For minicolumn measures (number and spacing) in PT, the values for patients resembled those of the control group of the opposite sex. A similar effect was not significant in HG.

The peculiar reversal of the effect of schizophrenia in each sex in the minicolumn measures may imply a different pathology in each sex. However, the age difference between sexes here raised the possibility of a more parsimonious interpretation that the direction of change in schizophrenia was dependent on age. Further investigation supported this unifying view, although it revealed that there are slight differences between the sexes in the normal trajectory of age-related changes that should be taken into account. Therefore, the apparent reversal of the effect of schizophrenia in PT may be understood in terms of normal sex differences in the proliferation and neuropil basis of minicolumn spacing, over which is superimposed a failure of age-associated, neuroplastic processes in schizophrenia.

The normally faster maturing female brain (Kretschmann *et al.*, 1979) is associated with more narrow minicolumns relative to the male brain. It appears that the prolonged development in males contributes to wider minicolumns, larger region size and greater asymmetries in the mature brain compared with that of females.

Neuroplasticity and disease course

Normal dendritic remodelling and age-associated changes in minicolumn spacing are associated with neuroplasticity that persists into adult life (Arendt, 2004; Chance *et al.*, 2006b). In schizophrenia, there is an absence of ageing changes in minicolumn spacing, as reported here, that is consistent with loss of plasticity. The greater dependence in males on a longer period of maturation confers vulnerability to a greater deficit in schizophrenia. In males the greater deficit results in greater loss of Minicolumn spacing. In females the deficit is less so that in old age, and in the absence of the normal age-associated thinning, minicolumn spacing in patients is actually greater than that of controls.

Other sex differences have been found in this series of brains in the asymmetrical volumes of the superior temporal (Highley *et al.*, 1999b), fusiform and parahippocampal (McDonald *et al.*, 2000) gyri. These differences are potentially relevant to a sex difference in the manifestation of the disease: onset is earlier in males than females (Penrose, 1991; Hafner, 2003) and in general earlier onset is

a predictor of poor outcome (Eaton *et al.*, 1992), particularly in males. Therefore, it is paradoxical that onsets of psychosis are earlier in males although the female brain usually matures faster than that of the male (Kretschmann *et al.*, 1979).

We draw attention to the fact that the corpus callosum goes on developing in size later in females than in males (Cowell *et al.*, 1992; Pujol *et al.*, 1993) continuing through the third and fourth decades of life, providing a close correlate of age of onset. The sex-dependent findings in the planum temporale here parallel those of the corpus callosum reported previously (Highley *et al.*, 1999a): the densities of minicolumns in PT and axons in corpus callosum are decreased in females with schizophrenia and increased in males.

There may be an association between the arrest of axodendritic plasticity seen in the minicolumn data and the peak of callosal maturation (i.e. myelination). In male patients an early arrest means that neuropil expansion is low compared with controls, leading to more dense minicolumns. In females with a relatively late arrest in schizophrenia, the deficit is smaller.

Conclusions

The effect of illness on auditory cortex region size and asymmetry can be understood in terms of the lifetime trajectory of neuropil change in the underlying cytoarchitecture. The absence of ageing effects in schizophrenia supports the concept of failure of axo-dendritic plasticity, which is most acute in those areas of the brain that go on developing longest (asymmetric association cortex). Schizophrenia can be conceived to involve transcallosal misconnection with timing of onset that reflects the sex difference in maturation of the corpus callosum. We propose that altered auditory perception in schizophrenia is related to differences in maturation and asymmetry of language cortex and its interhemispheric connections.

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References

Arendt T. Neurodegeneration and plasticity. Int J Dev Neurosci 2004; 22: 507–14.

Barta PE, Pearlson GD, Brill LB 2nd, Royall R, McGilchrist IK, Pulver AE, et al. Planum temporale asymmetry reversal in schizophrenia: replication and relationship to gray matter abnormalities. Am J Psychiatry 1997; 154: 661–7.

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: 69–78.

Benes FM, Vincent SL, Todtenkopf M. The density of pyramidal and nonpyramidal neurons in anterior cingulate cortex of schizophrenic and bipolar subjects. Biol Psychiatry 2001; 50: 395–406.

Casanova MF, de Zeeuw L, Switala A, Kreczmanski P, Korr H, Ulfig N, et al. Mean cell spacing abnormalities in the neocortex of patients with schizophrenia. Psychiatry Res 2005; 133: 1–12.

Casanova MF, Switala AE. Minicolumnar morphometry: computerized image analysis. In: Casanova MF, editor. Neocortical modularity and the cell minicolumn. New York: Nova Biomedical; 2005. p. 161–80.

Chance SA. Subtle changes in the ageing human brain. Nutr Health 2006; 18: 217–24.

Chance SA, Casanova MF, Switala AE, Crow TJ. Minicolumnar structure in Heschl's gyrus and Planum temporale: asymmetries in relation to sex and callosal fibre number. Neuroscience 2006a; 143: 1041–50.

Chance SA, Casanova MF, Switala AE, Crow TJ, Esiri MM. Minicolumn thinning in temporal lobe association cortex but not primary auditory cortex in normal human ageing. Acta Neuropathol (Berl) 2006b; 111: 459–64.

Chance SA, Esiri MM, Crow TJ. Ventricular enlargement in schizophrenia: a primary change in the temporal lobe? Schizophrenia Res 2003; 62: 123–31.

Chance SA, Tzotzoli PM, Vitelli A, Esiri MM, Crow TJ. The cytoarchitecture of sulcal folding in Heschl's sulcus and the temporal cortex in the normal brain and schizophrenia: lamina thickness and cell density. Neurosci Lett 2004; 367: 384–8.

Chance SA, Walker M, Crow TJ. Reduced density of calbindin immunoreactive interneurons in the planum temporale in schizophrenia. Brain Res 2005; 1046: 32–7.

Cowell PE, Allen LS, Zalatimo NS, Denenberg VH. A developmental study of sex and age interactions in the human corpus callosum. Brain Res Dev Brain Res 1992; 66: 187–92.

Crespo-Facorro B, Kim JJ, Chemerinski E, Magnotta V, Andreasen NC, Nopoulos P. Morphometry of the superior temporal plane in schizophrenia: relationship to clinical correlates. J Neuropsychiatry Clin Neurosci 2004; 16: 284–94.

Crow TJ, Crow LR, Done DJ, Leask S, Crow TJ. Schizophrenia as a transcallosal misconnection syndrome. Schizophr Res 1998; 30: 111–4.

DeLisi LE, Hoff AL, Neale C, Kushner M. Asymmetry in the superior temporal lobe in men and women first schizophrenic patients. Measure of the planum temporale and superior temporal gyrus in MRI. Schizophr. Res. 1994; 12: 19–28.

Eaton WW, Bilker W, Haro JM, Herrman H, Mortensen PB, Freeman H, et al. Long-term course of hospitalization for schizophrenia: part II. Change with passage of time. Schizophr Bull 1992; 18: 229–41.

Elston GN, Tweedale R, Rosa MG. Cellular heterogeneity in cerebral cortex: a study of the morphology of pyramidal neurones in visual areas of the marmoset monkey. J Comp Neurol 1999; 415: 33–51.

Falkai P, Bogerts B, Schneider T, Greve B, Pfeiffer U, Pilz K, et al. Disturbed planum temporale asymmetry in schizophrenia. A quantitative post-mortem study. Schizophr Res 1995; 14: 161–76.

Favorov OV, Kelly G. Minicolumnar organization within somatosensory cortical segregates I: development of afferent connections. Cereb Cortex 1994a; 4: 408–27.

Favorov OV, Kelly G. Minicolumnar organization within somatosensory cortical segregates II: emergent functional properties. Cereb Cortex 1994b; 4: 428–42.

Frangou S, Sharma T, Sigmundsson T, Barta P, Pearlson GE, Murray RM. The Maudsley family study: IV. Normal planum temporale asymmetry in familial schizophrenia: a volumetric MRI study. Br J Psychiatry 1997; 170: 328–33.

Friston KJ, Frith CD. Schizophrenia: a disconnection syndrome? Clin Neurosci 1995; 3: 89–97.

Gabbott PL. Radial organisation of neurons and dendrites in human cortical areas 25, 32, and 32'. Brain Res 2003; 992: 298–304.

Goldstein JM, Seidman LJ, O'Brien LM, Horton NJ, Kennedy DN, Makris N, et al. Impact of normal sexual dimorphisms on sex differences in structural brain abnormalities in schizophrenia assessed by magnetic resonance imaging. Arch Gen Psychiatry 2002; 59: 154–64.

Guillery RW. Is postnatal neocortical maturation hierarchical? Trends Neurosci 2005; 28: 512–7.

Hafner H. Gender differences in schizophrenia. Psychoneuroendocrinology 2003; 28 (Suppl 2): 17–54.

Harasty J, Seldon HL, Chan P, Halliday G, Harding A. The left human speech-processing cortex is thinner but longer than the right. Laterality 2003; 8: 247–60.

Highley JR, Esiri MM, McDonald B, Cortina-Borja M, Herron BM, Crow TJ The size and fibre composition of the corpus callosum with respect to gender and schizophrenia: a post-mortem study. Brain 1999a; 122: 99–110.

Highley JR, McDonald B, Walker MA, Esiri MM, Crow TJ. Schizophrenia and temporal lobe asymmetry. A post-mortem stereological study of tissue volume. Br J Psychiatry 1999b; 175: 127–34.

Hirayasu Y, McCarley RW, Salisbury DF, Tanaka S, Kwon JS, Frumin M, et al. Planum temporale and Heschl gyrus volume reduction in schizophrenia: a magnetic resonance imaging study of first-episode patients. Arch Gen Psychiatry 2000; 57: 692–9.

Jamison HL, Watkins KE, Bishop DVM, Matthews PM. Hemispheric specialization for processing auditory nonspeech stimuli. Cereb Cortex 2006; 16: 1266–75.

Kasai K, Shenton ME, Salisbury DF, Hirayasu Y, Onitsuka T, Spencer MH, et al. 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: 766–75.

Kawasaki Y, Suzuki M, Takahashi T, Nohara S, McGuire PK, Seto H, et al. Anomalous cerebral asymmetry in patients with schizophrenia demonstrated by voxel-based morphometry. Biol Psychiatry 2007; October 13 [Epub ahead of print].

Kim JJ, Crespo-Facorro B, Andreasen NC, O'Leary DS, Zhang B, Harris G, et al. An MRI-based parcellation method for the temporal lobe. Neuroimage 2000; 11: 271–88.

Kircher TT, Rapp A, Grodd W, Buchkremer G, Weiskopf N, Lutzenberger W, et al. Mismatch negativity responses in schizophrenia: a combined fMRI and whole-head MEG study. Am J Psychiatry 2004; 161: 294–304.

Kleinschmidt A, Falkai P, Huang Y, Schneider T, Furst G, Steinmetz H. In vivo morphometry of planum temporale asymmetry in first episode schizophrenics. Schizophr Res 1994; 12: 9–18.

Kretschmann HJ, Schleicher A, Wingert F, Zilles K, Loblich HJ. Human brain growth in the 19th and 20th century. J Neurol Sci 1979; 40: 169–88.

Kulynych JJ, Vladar K, Fantie BD, Jones DW, Weinberger DR. Normal asymmetry of the planum temporale in patients with schizophrenia: three dimensional cortical morphometry with MRI. Br J Psychiatry 1995; 166: 742–9.

Kulynych JJ, Vladar K, Jones DW, Weinberger DR. A 3D surface rendering in MRI morphometry: a study of the planum temporale. J Comput Assisted Tomogr 1993; 17: 529–35.

Kwon JS, McCarley RW, Hirayasu Y, Anderson JE, Fischer IA, Kikinis R, et al. Left planum temporale volume reduction in schizophrenia. Arch Gen Psychiatry 1999; 56: 142–8.

McCarley RW, Salisbury DF, Hirayasu Y, Yurgelun-Todd DA, Tohen M, Zarate C, et al. Association between smaller left posterior superior temporal gyrus volume on magnetic resonance imaging and smaller left temporal P300 amplitude in first-episode schizophrenia. Arch Gen Psychiatry 2002; 59: 321–31.

McCarley RW, Shenton ME, O'Donnell BF, Faux SF, Kikinis R, Nestor PG, et al. Auditory P300 abnormalities and left posterior superior temporal gyrus volume reduction in schizophrenia. Arch Gen Psychiatry 1993; 50: 190–7.

McDonald B, Highley JR, Walker MA, Herron BM, Cooper SJ, Esiri MM, et al. Anomalous asymmetry of fusiform and parahippocampal gyrus gray matter in schizophrenia: a postmortem study. Am J Psychiatry 2000; 157: 40–7.

Meisenzahl EM, Zetzsche T, Preuss U, Frodl T, Leinsinger G, Moller HJ. Does the definition of borders of the planum temporale influence the results in schizophrenia? Am J Psychiatry 2002; 159: 1198–200.

Mosnik MD, O'Leary DS, Tranel AP, Andreasen NC. Left hemisphere language dominance in schizophrenic patients and normal controls: a study of functional and anatomical asymmetries. Schizophr Res 1995; 2: 30–31.

O'Leary DS, Kesler M, Mosnik DM, Tronel AP, Hurtig R, Hichwa R, et al. Regional cerebral blood flow within Heschl's gyrus and the planum temporale in schizophrenic patients and controls during language tasks: an MRI and PET study. Schizophr Res 1995; 2: 94.

Pakkenberg B, Gundersen HJ. Neocortical neuron number in humans: effect of sex and age. J Comp Neurol 1997; 384: 312–20.

Pandya DN, Seltzer B. The topography of commissural fibers. In: Lepore E, Ptito M, Jasper HH, editors. Neurology and neurobiology, Vol. 17, Two hemispheres-one brain. New York: Liss; 1986. p. 47–73.

Park HJ, Levitt J, Shenton ME, Salisbury DF, Kubicki M, Kikinis R, et al. An MRI study of spatial probability brain map differences between first-episode schizophrenia and normal controls. Neuroimage 2004; 22: 1231–46.

Pearlson GD, Barta PE, Powers RE, Menon RR, Richards SS, Aylward EH, et al. Ziskind-Somerfeld Research Award 1996. Medial and superior temporal gyral volumes and cerebral asymmetry in schizophrenia versus bipolar disorder. Biol Psychiatry 1997; 41: 1–14.

Penrose LS. Survey of cases of familial mental illness. L. S. Penrose, July 1945. Eur Arch Psychiatry Clin Neurosci 1991; 240: 315–24; discussion 314–5.

Petty RG, Barta PE, Pearlson GD, Mcgilchrist IK, Lewis RW, Tein AY, et al. Reversal of asymmetry of planum temporale in schizophrenia. Am J Psychiatry 1995; 152: 715–21.

Pralong D, Tomaskovic-Crook E, Opeskin K, Copolov D, Dean B. Serotonin(2A) receptors are reduced in the planum temporale from subjects with schizophrenia. Schizophr Res 2000; 44: 35–45.

Pujol J, Vendrell P, Junque C, Marti-Vilalta JL, Capdevila A. When does human brain development end? Evidence of corpus callosum growth up to adulthood. Ann Neurol 1993; 34: 71–5.

Qiu A, Vaillant M, Barta P, Ratnanather JT, Miller MI. Region-of-interest-based analysis with application of cortical thickness variation of left planum temporale in schizophrenia and psychotic bipolar disorder. Hum Brain Mapp 2007; August 17 [Epub ahead of print].

Rakic P. A small step for the cell, a giant leap for mankind: a hypothesis of neocortical expansion during evolution. Trends Neurosci 1995; 18: 383–8.

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: 1655–62.

Ropohl A, Sperling W, Elstner S, Tomandl B, Reulbach U, Kaltenhauser M, et al. Cortical activity associated with auditory hallucinations. Neuroreport 2004; 15: 523–6.

Rossi A, Serio A, Stratta P, Petruzzi C, Schiazza G, Mancini F, et al. Planum temporale asymmetry and thought disorder in schizophrenia. Schizophr Res 1994; 12: 1–7.

Rossi A, Stratta P, Mattei P, Cupillari M, Bozzao A, Gullucci M, et al. The planum temporale in schizophrenia: a MRI study. Schizophr Res 1992; 7: 19–22.

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: 521–9.

Sallet PC, Elkis H, Alves TM, Oliveira JR, Sassi E, de Castro CC, et al. Rightward cerebral asymmetry in subtypes of schizophrenia according to Leonhard's classification and to DSM-IV: a structural MRI study. Psychiatry Res 2003; 123: 65–79.

Shapleske J, Rossell SL, Simmons A, David AS, Woodruff PW. Are auditory hallucinations the consequence of abnormal cerebral lateralization? A morphometric MRI study of the sylvian fissure and planum temporale. Biol Psychiatry 2001; 49: 685–93.

Shapleske J, Rossell SL, Woodruff PW, David AS. The planum temporale: a systematic, quantitative review of its structural, functional and clinical significance. Brain Res Brain Res Rev 1999; 29: 26–49.

Shenton ME, Dickey CC, Frumin M, McCarley RW. A review of MRI findings in schizophrenia. Schizophr Res 2001; 49: 1–52.

Shenton ME, Hokama HH, Kikinis R, Dickey C, Lornsen WE, Ballard M, et al. A 3D MRI study of the planum temporale in schizophrenia. Schizophr Res 1995; 15: 98.

Shenton ME, Kikinis R, Jolesz FA, Pollak SD, LeMay M, Wible CG, et al. Abnormalities of the left temporal lobe and thought disorder in schizophrenia. A quantitative magnetic resonance imaging study. N Engl J Med 1992; 327: 604–12.

Shergill SS, Brammer MJ, Williams SC, Murray RM, McGuire PK. Mapping auditory hallucinations in schizophrenia using functional magnetic resonance imaging. Arch Gen Psychiatry 2000; 57: 1033–8.

Sommer I, Ramsey N, Kahn R, Aleman A, Bouma A. Handedness, language lateralisation and anatomical asymmetry in schizophrenia: meta-analysis. Br J Psychiatry 2001; 178: 344–51.

Sumich A, Chitnis XA, Fannon DG, O'Ceallaigh S, Doku VC, Falrowicz A, et al. Temporal lobe abnormalities in first-episode psychosis. Am J Psychiatry 2002; 159: 1232–5.

Sumich A, Chitnis XA, Fannon DG, O'Ceallaigh S, Doku VC, Faldrowicz A, et al. Unreality symptoms and volumetric measures of Heschl's gyrus and planum temporale in first-episode psychosis. Biol Psychiatry 2005; 57: 947–50.

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: 599–609.

Takahashi T, Suzuki M, Tanino R, Zhou SY, Hagino H, Niu L, et al. 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: 209–19.

Takahashi T, Suzuki M, Zhou SY, Tanino R, Hagino H, Kawasaki Y, et al. Morphologic alterations of the parcellated superior temporal gyrus in schizophrenia spectrum. Schizophr Res 2006; 83: 131–43.

Toga AW, Thompson PM, Sowell ER. Mapping brain maturation. Trends Neurosci 2006; 29: 148–59.

Vladar K, Kulynych JJ, Jones DW, Torrey EF, Weinberger DR. An MRI study of the planum temporale in monozygotic twins discordant for schizophrenia. Biol. Psychiatry 1993; 33: 123a.

von Economo C, Koskinas GN. Die Cytoarchitektonik der Hirnrinde des Erwachsenen Menschen. Wien und Berlin: Verlag von Julius Springer; 1925.

Walder DJ, Seidman LJ, Makris N, Tsuang MT, Kennedy DN, Goldstein JM. Neuroanatomic substrates of sex differences in language dysfunction in schizophrenia: a pilot study. Schizophr Res 2007; 90: 295–301.

Ward PB, Loneragon C, Liebert B, Calts SV, Chaturvedi S, Pearson M, et al. MRI measures of auditory cortex area correlate with an ERP index of auditory sensory memory in schizophrenia. Schizophr Res 1995; 15: 102.

Weinstein S, Woodward TS, Ngan ET. Brain activation mediates the association between structural abnormality and symptom severity in schizophrenia. Neuroimage 2007; 36: 188–93.

Yamasaki S, Yamasue H, Abe O, Yamada H, Iwanami A, Hirayasu Y, et al. Reduced planum temporale volume and delusional behaviour in patients with schizophrenia. Eur Arch Psychiatry Clin Neurosci 2007; 257: 318–24.

Yamasue H, Yamada H, Yumoto M, Kamio S, Kudo N, Uetsuki M, et al. Abnormal association between reduced magnetic mismatch field to speech sounds and smaller left planum temporale volume in schizophrenia. Neuroimage 2004; 22: 720–7.

Zetzsche T, Meisenzahl EM, Preuss UW, Holder JJ, Kathmann N, Leinsinger G, et al. In-vivo analysis of the human planum temporale (PT): does the definition of PT borders influence the results with regard to cerebral asymmetry and correlation with handedness? Psychiatry Res 2001; 107: 99–115.