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


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 (magnetoencephalography—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 planum 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 misconnectivity 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. Controls 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 antipsychotic 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.
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

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

F = female; M = male; C = control; S = schizophrenia. Age at death is given in years (in ascending order within diagnosis × sex groups).
repeated for 10 hemispheres to determine reliability—intraclass correlation coefficient for all measures was good \((\geq 0.9)\). 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 model is method 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 \(\mu m\) resolution and tessellated. Two resulting photomicrographs (each about 1.5 mm² 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 \(\mu m\)—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 \(((\text{left}-\text{right})/(\text{left+right})/2)\times 100\).

**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, r-statistics or Pearson’s r coefficients have been reported, as appropriate.

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 x 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 x diagnosis groups and was not subjected to separate tests.

Table 2 Demographic variables and covariates

<table>
<thead>
<tr>
<th>Group</th>
<th>Age at death (years)</th>
<th>PMI (h)a</th>
<th>Fixation time (months)b</th>
<th>Age of illness onset (years)b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male controls</td>
<td>599 ± 11.9</td>
<td>36.4 ± 15.9</td>
<td>209 ± 9.8</td>
<td>NA</td>
</tr>
<tr>
<td>Female controls</td>
<td>73.2 ± 12.4</td>
<td>36.9 ± 19.0</td>
<td>26.9 ± 13.3</td>
<td>NA</td>
</tr>
<tr>
<td>Male schizophrenia</td>
<td>593 ± 15.8</td>
<td>35.4 ± 21.2</td>
<td>32.8 ± 20.1</td>
<td>24.4 ± 6.4</td>
</tr>
<tr>
<td>Female schizophrenia</td>
<td>71.6 ± 14.5</td>
<td>35.0 ± 23.6</td>
<td>58.2 ± 20.2</td>
<td>38.4 ± 15.5</td>
</tr>
</tbody>
</table>

aInaccurate information for six cases (see text for details).
bInaccurate 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.

Table 3 Cortical volume and surface area

<table>
<thead>
<tr>
<th>Group</th>
<th>Volume (mm³)</th>
<th>Area (mm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Planum</td>
<td>Heschl’s</td>
</tr>
<tr>
<td></td>
<td>Left</td>
<td>Right</td>
</tr>
<tr>
<td>Male controls</td>
<td>2170.4 ± 553.5</td>
<td>1590.3 ± 2599</td>
</tr>
<tr>
<td>Female controls</td>
<td>1910.4 ± 421.1</td>
<td>1486.5 ± 584.9</td>
</tr>
<tr>
<td>Male patients</td>
<td>2186.5 ± 600.4</td>
<td>1536.4 ± 756.0</td>
</tr>
<tr>
<td>Female patients</td>
<td>1715 ± 610.5</td>
<td>1517.5 ± 526.7</td>
</tr>
</tbody>
</table>

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

Table 4 Minicolumn spacing and number

<table>
<thead>
<tr>
<th>Group</th>
<th>Heschl’s minicolumn spacing (μm)</th>
<th>Planum minicolumn spacing (μm)</th>
<th>Heschl’s minicolumn number</th>
<th>Planum minicolumn number</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Left</td>
<td>Right</td>
<td>Left</td>
<td>Right</td>
</tr>
<tr>
<td>Male control</td>
<td>794 ± 11.3</td>
<td>777 ± 10.1</td>
<td>85.8 ± 12.6</td>
<td>83.8 ± 8.5</td>
</tr>
<tr>
<td>Female control</td>
<td>740 ± 5.72</td>
<td>73.2 ± 13.2</td>
<td>80.8 ± 7.6</td>
<td>79.3 ± 10.2</td>
</tr>
<tr>
<td>Male schizophrenia</td>
<td>75.0 ± 17.6</td>
<td>72.0 ± 8.1</td>
<td>85.7 ± 10.6</td>
<td>77.4 ± 14.0</td>
</tr>
<tr>
<td>Female schizophrenia</td>
<td>79.7 ± 13.9</td>
<td>80.5 ± 10.5</td>
<td>86.3 ± 12.8</td>
<td>88.1 ± 11.7</td>
</tr>
</tbody>
</table>

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).
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](https://academic.oup.com/brain/article-abstract/131/12/3178/291338/3184)
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 nega-
tivity, 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 with-
drawal, 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 schizo-
phrenia. 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 mini-
column 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 hemi-
sphere was positively correlated with surface area, consist-
tent 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, particu-
larly in association cortex, on later expansion of mini-
column 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>
<thead>
<tr>
<th>Focus of study</th>
<th>References</th>
<th>Sample size</th>
<th>Finding</th>
<th>Asymmetry</th>
<th>Sex difference</th>
<th>Functional correlates</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume</td>
<td>Kawasaki et al. (2007)</td>
<td>60 (30M, 30F)</td>
<td>PT reduced asymmetry due to left PT ↓</td>
<td>PT L &gt; R in controls and patients</td>
<td>No</td>
<td>Clinical variables did not correlate</td>
<td></td>
</tr>
<tr>
<td>Cortical thickness</td>
<td>Qiu et al. (2007)</td>
<td>20 (10M, 10F)</td>
<td>PT L &gt; R in controls and patients</td>
<td>Not quantified</td>
<td>Not tested</td>
<td>Asymmetric HG reduction correlated with MMN reduction</td>
<td></td>
</tr>
<tr>
<td>Volume</td>
<td>Salisbury et al. (2007)</td>
<td>32 (22M, 10F)</td>
<td>Anterior left PT thinner, posterior thicker</td>
<td>Not quantified</td>
<td>Not tested</td>
<td>First episode, longitudinal PT grey matter correlated with thought disorder and fMRI activation</td>
<td></td>
</tr>
<tr>
<td>Volume correlates</td>
<td>Weinstein et al. (2007)</td>
<td>0</td>
<td>Only left hemisphere measured</td>
<td>No</td>
<td>No</td>
<td>Correlation between untreated psychosis duration and left PT volume</td>
<td></td>
</tr>
<tr>
<td>Volume correlates</td>
<td>Takahashi et al. (2007)</td>
<td>0</td>
<td>No comparison with controls</td>
<td>PT and HG L &gt; R but not statistically significant</td>
<td>Not tested</td>
<td>PT reduction correlated with delusional behaviour</td>
<td></td>
</tr>
<tr>
<td>Volume</td>
<td>Yamasaki et al. (2007)</td>
<td>17</td>
<td>HG no change PT ↓ bilateral</td>
<td>PT and HG L &gt; R but not statistically significant</td>
<td>All males</td>
<td>PT: L &gt; R in males</td>
<td></td>
</tr>
<tr>
<td>Volume correlates</td>
<td>(2007) Walder et al.</td>
<td>15 (6M, 9F)</td>
<td>(See Goldstein et al. (2002))</td>
<td>(See Goldstein et al. (2002))</td>
<td>PT: L &gt; R in males</td>
<td>All: left PT associated with phonology Females: right HG associated with semantics and phonology</td>
<td></td>
</tr>
<tr>
<td>Volume</td>
<td>Takahashi et al. (2006)</td>
<td>72 (38M, 34F)</td>
<td>STG ↓, HG ↓, PT ↓</td>
<td>Controls: L &gt; R in STG, HG, PT, Scz: PT left sided reduction</td>
<td>No</td>
<td>Left HG vol associated with hallucinations, Left PT associated with delusions</td>
<td></td>
</tr>
<tr>
<td>Volume</td>
<td>Sumich et al. (2005)</td>
<td>0 (no control group)</td>
<td>–</td>
<td>See functional correlates</td>
<td>All males</td>
<td>HG ↓: Longer illness duration, PT ↓: positive symptoms</td>
<td></td>
</tr>
<tr>
<td>Volume</td>
<td>Crespo-Facorro et al.</td>
<td>30</td>
<td>Right HG ↓</td>
<td>All groups: L &gt; R PT and HG, All males</td>
<td>All males</td>
<td>First episode</td>
<td></td>
</tr>
<tr>
<td>Spatial probability</td>
<td>Park et al. (2004)</td>
<td>21 (up to 5 female)</td>
<td>Greater structural variation of HG and PT in scz</td>
<td>No</td>
<td>Not tested</td>
<td>Left PT reduction associated with phonetic mismatch strength</td>
<td></td>
</tr>
<tr>
<td>Volume</td>
<td>Yamasue et al. (2004)</td>
<td>19 (13M, 6F)</td>
<td>Left PT ↓</td>
<td>Controls: no clear asymmetry, Scz: left PT ↓</td>
<td>Not tested</td>
<td>Left PT reduction associated with phonetic mismatch strength</td>
<td></td>
</tr>
</tbody>
</table>

*Table 5 Summary table of MRI studies examining the Planum Temporale (and Heschl’s gyrus) in schizophrenia*
<table>
<thead>
<tr>
<th>Volume</th>
<th>Authors (Year)</th>
<th>Sample</th>
<th>Controls</th>
<th>Diagnosis</th>
<th>Asymmetry</th>
<th>Associated ( PT ) volume associated: hallucinatory behaviour, social withdrawal and stereotyped thinking. Reversed asymmetry: memory deficits and judgement of NSRS</th>
<th>First episode, longitudinal change over time</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Volume</strong></td>
<td>Kasai et al. (2003)</td>
<td>22 (20M, 2F)</td>
<td>13 (10M, 3F)</td>
<td>Left HG↓, left PT↓</td>
<td>All groups: L &gt; R HG, Scz: left HG↓, left PT↓</td>
<td>Not tested</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Sallet et al. (2003)</td>
<td>20 (12M, 8F)</td>
<td>40 (24M, 16F)</td>
<td>No difference</td>
<td>No clear asymmetry</td>
<td>None reported</td>
<td>Left PT vol associated: hallucinatory behaviour, social withdrawal and stereotyped thinking. Reversed asymmetry: memory deficits and judgement of NSRS</td>
</tr>
<tr>
<td></td>
<td>Sumich et al. (2002)</td>
<td>16</td>
<td>25</td>
<td>Left PT↓</td>
<td>Controls: no clear asymmetry, Scz: left PT↓</td>
<td>All groups: L &gt; R PT</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Goldstein et al. (2002)</td>
<td>48 (27M, 2F)</td>
<td>40 (27M, 13F)</td>
<td>HG↓ in males, right PT↑ in females</td>
<td>Scz: right PT↑ in females</td>
<td>Controls: L &gt; R PT, Scz: HG↓ in males, right PT↑ in females, left PT↓ in males</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Shapleske et al. (2001)</td>
<td>32</td>
<td>74</td>
<td>No difference</td>
<td>All groups: L &gt; R PT</td>
<td>All males</td>
<td>No correlations with symptom clusters</td>
</tr>
<tr>
<td></td>
<td>Hirayasu et al. (2000)</td>
<td>22 (20M, 2F)</td>
<td>20 (16M, 4F)</td>
<td>Bilateral HG↓, left PT↓</td>
<td>All groups: L &gt; R HG, Scz: left PT↓</td>
<td>Not tested</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Kwon et al. (1999)</td>
<td>16</td>
<td>16</td>
<td>Left PT↓</td>
<td>All groups: HG no clear asymmetry, Controls: L &gt; R PT, Scz: left PT↓</td>
<td>All males</td>
<td>Suspicousness/persecution correlated with left PT volume</td>
</tr>
<tr>
<td></td>
<td>Frangou et al. (1997)</td>
<td>39 (19M, 20F)</td>
<td>32 (21M, 11F)</td>
<td>No difference</td>
<td>Scz: right PT thickness↓</td>
<td>All groups: L &gt; R PT</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Barta et al. (1997)</td>
<td>32</td>
<td>28</td>
<td>No difference</td>
<td>No clear asymmetry</td>
<td>No Reversed PT surface area in male and female patients</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Kulynych et al. (1995)</td>
<td>12</td>
<td>12</td>
<td>No difference</td>
<td>All groups: L &gt; R PT, no asymmetry HG</td>
<td>All males</td>
<td>PT asym↓: left ear advantage↑</td>
</tr>
<tr>
<td></td>
<td>Mosnik et al. (1995)</td>
<td>10</td>
<td>10</td>
<td>Scz: PT surface smaller</td>
<td>All groups: L &gt; R PT</td>
<td>All males</td>
<td>PT rCBF greater individual variability during language tests</td>
</tr>
<tr>
<td></td>
<td>O'Leary et al. (1995)</td>
<td>10</td>
<td>10</td>
<td>No difference</td>
<td>All groups L &gt; R PT</td>
<td>All males</td>
<td>Greater thought disorder: greater reversal of asymmetry</td>
</tr>
<tr>
<td></td>
<td>Ward et al. (1995)</td>
<td>30</td>
<td>30</td>
<td>PT no difference, HG↓</td>
<td>All groups: L &gt; R</td>
<td>None reported</td>
<td>HG↓: auditory sensory memory↓</td>
</tr>
<tr>
<td></td>
<td>Shenton et al. (1995)</td>
<td>15 (13M, 10F)</td>
<td>15 (13M, 9F)</td>
<td>PT surface↑ (L &gt; R)</td>
<td>All groups: PT L &gt; R</td>
<td>All males</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Rossi et al. (1994)</td>
<td>23 (13M, 10F)</td>
<td>22 (13M, 9F)</td>
<td>No difference</td>
<td>All groups: L &gt; R</td>
<td>Not tested</td>
<td>PT asymmetry↓: thought disorder↑</td>
</tr>
<tr>
<td></td>
<td>Kleinschmidt et al. (1994)</td>
<td>26 (13M, 13F)</td>
<td>26 (13M, 13F)</td>
<td>No difference</td>
<td>All groups: L &gt; R</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

(continued)
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
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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