Structural disconnectivity in schizophrenia: a diffusion tensor magnetic resonance imaging study


**Background** There is growing evidence that schizophrenia is a disorder of cortical connectivity. Specifically, frontotemporal and frontoparietal connections are thought to be functionally impaired. Diffusion tensor magnetic resonance imaging (DT-MRI) is a technique that has the potential to demonstrate structural disconnectivity in schizophrenia.

**Aims** To investigate the structural integrity of frontotemporal and frontoparietal white matter tracts in schizophrenia.

**Method** Thirty patients with DSM-IV schizophrenia and thirty matched control subjects underwent DT-MRI and structural MRI. Fractional anisotropy — an index of the integrity of white matter tracts — was determined in the uncinate fasciculus, the anterior cingulum and the arcuate fasciculus and analysed using voxel-based morphometry.

**Results** There was reduced fractional anisotropy in the left uncinate fasciculus and left arcuate fasciculus in patients with schizophrenia compared with controls.

**Conclusions** The findings of reduced white matter tract integrity in the left uncinate fasciculus and left arcuate fasciculus suggest that there is frontotemporal and frontoparietal structural disconnectivity in schizophrenia.

**Declaration of interest** The study was supported by a grant from the Stanley Medical Research Institute.

Many studies have demonstrated abnormal brain structure and function in the frontal and temporal lobes of patients with schizophrenia (Lawrie & Abukmeil, 1998; Wright et al, 2000). Functional imaging studies show abnormal frontotemporal activations on various tasks (Frith, 1995; Fletcher et al, 1999), lending support to the hypothesis that the core feature of schizophrenia is a disruption of frontotemporal integration (Friston & Frith, 1995). A recent negative study does, however, raise doubt as to whether this is a trait marker of the disorder (Spence et al, 2000). The parietal lobes have been studied less in schizophrenia, but there are suggestions that frontoparietal integration may be similarly abnormal (Spence et al, 1997; Lawrie & Abukmeil, 1998; Honey et al, 2002). It would be of considerable interest to establish whether functional disconnectivity (see Friston & Frith, 1995) in schizophrenia is associated with structural abnormalities in specific frontotemporal and frontoparietal white matter tracts, such as the uncinate and arcuate fasciculi and the anterior cingulum (Dejerine, 1895; Petrides & Pandya, 1988). New magnetic resonance imaging (MRI) methodologies, such as diffusion tensor magnetic resonance imaging (DT-MRI), which measures the mobility of water molecules in vivo (Basser et al, 1994), may have the potential to identify structural correlates of impaired functional connectivity in schizophrenia. In this technique, the deviation from pure isotropic diffusion of water molecules along white matter axons is measured and described in terms of the fractional anisotropy. This parameter is thought to provide a useful marker of white matter fibre tract integrity, with high values of fractional anisotropy indicating intact healthy neurons (O’Sullivan et al, 2001).

**METHOD**

**Study participants** Thirty patients with DSM-IV (American Psychiatric Association, 1994) schizophrenia were recruited from the hospital and community services of the Royal Edinburgh Hospital, Scotland. They included equal numbers of men and women, most of whom were on anti-psychotic medication. Control subjects were recruited from the community and were well matched to the patients (Table 1). Full ethical approval was obtained from the relevant Ethics Committee and all subjects gave informed consent for all aspects of the study.

**Procedures** Subjects underwent whole-brain structural MRI and DT-MRI using a GE Signa LX 1.5 T (General Electric, Milwaukee, WI, USA) clinical scanner. The structural MRI imaging consisted of a T1-weighted gradient-echo volumetric sequence followed by a dual-echo fast spin-echo sequence designed to give contiguous axial proton density and T2-weighted magnetic resonance images. In the whole-brain DT-MRI examination, sets of axial diffusion-weighted single-shot echo-planar (DW-EP) images (b_min=0 and b_max=1000 s/mm^2) were collected with diffusion gradients applied sequentially along six non-collinear directions (Basser & Pierpaoli, 1998). Five acquisitions consisting of a baseline T2-weighted echo-planar image and six DW-EP images – a total of 35 images – were collected per slice position. Other acquisition parameters were 31 contiguous axial slices of 5 mm thickness, a field of view of 240 x 240 mm, an acquisition matrix of

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<th>Table 1</th>
<th>Demographics (mean (s.d.))</th>
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<tr>
<td></td>
<td>Average age&lt;br&gt;(years)</td>
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<tr>
<td>Schizophrenia (n=30)</td>
<td>36.4 (12.2)</td>
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<tr>
<td>Controls (n=30)</td>
<td>35.7 (12.4)</td>
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is a technique where one can perform a region-of-interest analysis in SPM99 (with all the associated benefits of the statistical parametric map method). Based upon the a priori hypothesis, coordinates were selected that represented the midpoints of the structures that we wished to investigate. In this case, coordinates for the three tracts were selected from the Talairach Atlas and converted to Montreal Neurological Institute (MNI) coordinates. The MNI coordinates for the small-volume correction were: 11.0 mm radius spheres centred at $[\pm 32, +5, -21]$ for the uncinate fasciculus, $[\pm 31, +11, -23]$ for the arcuate fasciculus and $[\pm 10, +5, -34]$ for the anterior cingulum. In other words, three spheres of 11.0-mm radius were centred on these coordinates, and mean functional anisotropy values for each voxel within the spheres were compared between the two study groups. The 11.0-mm radius rendered the smallest spheres possible for a valid statistical inference in this particular statistical parametric map analysis.

**DISCUSSION**

This is a hypothesis-driven study using a novel means of imaging white matter to identify structural disconnectivity in schizophrenia. The results are in keeping with the hypothesis that specific frontotemporal and frontoparietal white matter tracts, namely the uncinate fasciculus and the arcuate fasciculus, are abnormal in schizophrenia. This is consistent with the findings of functional imaging studies, which have demonstrated abnormalities in the functional relationship between frontal and temporal (Frith, 1995; Fletcher et al., 1999) and frontal and parietal (Spence et al., 1997; Honey et al., 2002) lobes in schizophrenia. Furthermore, our finding of structural changes lateralised to the left hemisphere may be consistent with the cerebral asymmetry hypothesis (Crow, 1995), although it should be noted that we did not specifically test this.

**RESULTS**

We found a trend towards significantly reduced functional anisotropy values on comparing patients with schizophrenia with controls within the small-volume correction placed over the left uncinate fasciculus ($P=0.06$). In addition, we found significantly reduced fractional anisotropy in two voxels in the left arcuate fasciculus ($P<0.05$). These results are shown graphically in Fig. 1 and separately in Table 2 (left uncinate fasciculus) and Table 3 (left arcuate fasciculus). In Table 2 the coordinates of the voxel showing the maximal point of fractional anisotropy reduction in the schizophrenia group is reported. This voxel lies on the border of the left uncinate and left inferior longitudinal fasciculus and shows a trend towards significance. In Table 3, the coordinates of two voxels showing significantly reduced fractional anisotropy values in the schizophrenia group are reported. Both voxels are within the white matter of the left arcuate fasciculus and both are located anteriorly in the tract.

No significant differences were detected in the small-volume corrections placed over the right arcuate fasciculus, the right uncinate fasciculus or the right and left anterior cingulum. There were no volumetric differences between the groups in the white matter segments derived from the T2-weighted images.

**Diffusion tensor MRI**

Diffusion tensor MRI is a relatively new structural imaging modality that measures the three-dimensional mobility of brain water molecules in vivo (Basser et al., 1994). In this technique, the apparent diffusion tensor of water ($D$) is calculated for each voxel in an image set of diffusion-weighted magnetic resonance images. Owing to the presence of axonal membranes, myelin sheaths and microfilaments, water molecules diffuse preferentially along axons rather than across them. Thus, within coherent, ordered white matter structures, the mobility of water is greatest in the principal direction of the fibre tract. This directional dependence of water diffusion is termed ‘diffusion anisotropy’ and can be represented by a range of scalar parameters, or diffusion anisotropy indices, derived from $D$ (Basser, 1995). The most common diffusion anisotropy index is the fractional anisotropy, which varies from zero (diffusion equal in all directions) to unity (diffusion purely unidirectional). Extensive in vivo and in vitro experiments on various non-myelinated neuronal fibres, axons with large axoplasmic spaces and neurons in which fast axonal transport has been inhibited indicate that the primary determinant of white matter anisotropic diffusion is the...
Previous DT–MRI studies in schizophrenia

Previous studies have reported reduced fractional anisotropy in both frontal white matter and the splenium of the corpus callosum on exploratory analyses (Buchsbaum et al., 1998; Lim et al., 1999; Agartz et al., 2001; Foong et al., 2002). Some have used statistical parametric mapping methods of analysis and the results are varied (Buchsbaum et al., 1998; Agartz et al., 2001; Foong et al., 2002). None has used the small-volume correction tool and future studies may benefit from using this technique. A study by Kubicki (Kubicki et al., 2002) is interesting in terms of our own findings and indeed the asymmetry hypothesis (Crow, 1995). Presumably motivated by a similar interest in frontotemporal connections, they looked at diffusion anisotropy in the uncinate fasciculus and found a group-by-side interaction in the patient group, although the fractional anisotropy was reduced on the left side and their smaller number of subjects may have reduced the power to find statistically significant differences.

Structural basis of functional disconnectivity

Although there is evidence for a disturbance of the functional relationship between frontal and temporal and frontal and parietal lobes in schizophrenia, it is not clearly understood whether white matter connections between these regions are structurally abnormal. With DT–MRI, however, it was possible to investigate this hypothesis. Data from both human and primate dissection studies suggested that these association tracts may include the uncinate fasciculus, the anterior cingulum and the superior longitudinal or arcuate fasciculus (Dejerine, 1895; Petrides & Pandya, 1988). In this study we applied current analysis techniques to fractional anisotropy maps obtained from DT–MRI data to test the hypothesis that these specific frontotemporal and frontoparietal white matter tracts would be disrupted in patients with schizophrenia. Such a disruption would manifest itself as a reduction in fractional anisotropy values in patients with schizophrenia compared with controls.

The arcuate fasciculus is a major association tract connecting large parts of the frontal association cortices with parietal and temporal association areas (Dejerine, 1895). It also forms the main connection between Wernicke’s and Broca’s language areas. Our finding of reduced neuronal integrity in the left arcuate fasciculus supports the notion that schizophrenia is a disorder of large-scale neurocognitive
networks rather than specific regions and, as others suggest, pathological changes in this disorder should be sought at the supra-regional rather than regional level (Sigmundsson et al, 2001). Both structural and functional abnormalities of frontotemporal networks have been described in schizophrenia (Schlaepfer et al, 1994; Honey et al, 2002), and may constitute a basis for the wide range of cognitive functions impaired in the disorder, such as selective attention, language processing and attribution of agency.

The uncinate fasciculus is the largest of the three fibre tracts connecting the frontal and temporal lobes, and dissection studies have demonstrated that the bulk of these fibres connect the orbital and medial prefrontal cortex (including anterior cingulate cortex) to the amygdala, entorhinal cortex and rostral superior temporal gyrus (Petrides & Pandya, 1988; Morris et al, 1999). These frontal and temporal cortical regions show grey matter volume changes in many structural imaging studies of schizophrenia (Lawrie & Abukmeil, 1998; Wright et al, 2000) and possibly the greatest structural decrements. During early brain development, ingrowing association fibres linking these frontal and temporal cortices could encounter abnormal termination sites and form aberrant connections in the superficial layers. Pruning of aberrant connections during the second and third decades of life could lead to impoverished dendritic arborisation rather than neuronal depopulation (Harrison, 1999). Such a mechanism may possibly account for grey and white matter loss and reduced intercorrelations of these volumes (Wible et al, 1995; Woodruff et al, 1997), as well as our findings of reduced neuronal integrity in the uncinate fasciculus. A recent post-mortem study of the uncinate fasciculus in schizophrenia merits particular consideration (Highley et al, 2002). Right-greater-than-left asymmetry of the uncinate fasciculus was demonstrated in both patients and controls, with no significant differences in asymmetry between the two groups. A possible interpretation, in terms of our own findings, is that the different techniques are examining different aspects of uncinate morphology. The study by Highley et al (2002) may yield information about fibre number and density, whereas our study is detecting differences in neuronal integrity as the uncinate tracts disperse near their termination in the temporal lobe.

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**CLINICAL IMPLICATIONS**

- There appear to be structural abnormalities in frontotemporal and frontoparietal white matter tracts in schizophrenia.
- Novel imaging techniques, such as diffusion tensor magnetic resonance imaging, can be used to investigate the structural integrity of white matter tracts in psychiatric disorders in vivo.
- We provide further support for the notion that schizophrenia is a disorder of cortical connectivity.

**LIMITATIONS**

- Most of our patients were on psychotropic medication at the time of scanning, and this may be a confounder.
- Smoothing with a 12-mm Gaussian filter promotes the detection of 12-mm differences in spatial extent but may miss smaller differences.
- The anterior cingulum is a particularly slender tract and therefore more liable to partial volume effects in statistical parametric map analysis of this structure.

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disconnectivity in schizophrenia and also, we would argue, suggest that aberrant connectivity is a wider feature of fibre tracts linking the prefrontal to posterior cortices. Future studies might seek to elucidate further the exact relationship between the anatomical findings of disconnectivity and the clinical symptoms of schizophrenia.

ACKNOWLEDGEMENTS

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