# Investigating structural abnormalities in adolescent-onset schizophrenic patients: a combined T1-weighted and diffusion-weighted study.

**G. Douaud[1], S. M. Smith[1], J. Vickers[1], N. Voets[1,2], S. James[3], M. Jenkinson[1], P. M. Matthews[2], and A. James[3]**
[1]FMRIB Centre, Oxford, United Kingdom, [2]GSK, London, [3]Highfield Adolescent Unit, Warneford Hospital, Oxford

## Introduction

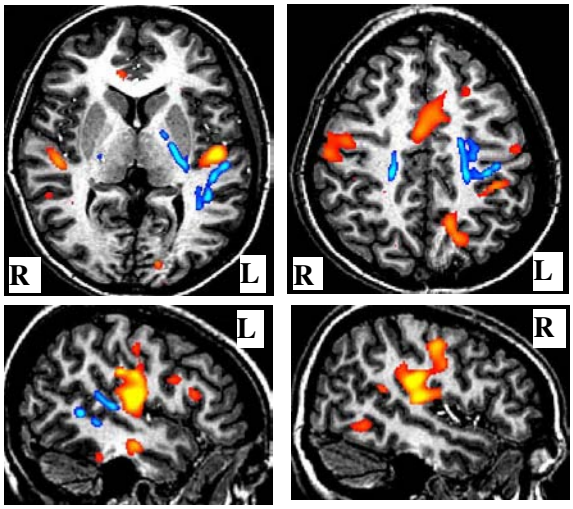
The neuropathology of schizophrenia, which is one of the most debilitating of the mental illnesses, with a prevalence of around 1% across all countries and ethnic groups, remains largely unknown. There is now however accumulating evidence for grey and white matter abnormalities, investigated with both T1-weighted and diffusion tensor imaging (DTI) (Shenton et al., Schizophr Res 2001; Honea et al., Am J Psychiatry 2005; Kubicki et al., Ann N Y Acad Sci 2005). Yet, as most cases are first diagnosed between the ages of 20 and 25, the majority of DTI studies in schizophrenia have been confined to adult subjects. Few studies have explored grey matter changes and white matter integrity in adolescent-onset schizophrenia. The aim of this study was to investigate differences in the topographic distribution of grey matter (GM) between adolescent-onset schizophrenic patients and control subjects, and to examine whether the GM pattern relates to microstructural alteration or disorganisation of the white matter.

## Methods

25 (7f, 18m, aged 13-18) adolescent-onset schizophrenic patients were recruited for this study. All were diagnosed as having DSM-IV schizophrenia using the Kiddie SADS-PL. Age at onset of symptoms ranged from 11 to 17. T1-weighted images were acquired on a 1.5 T Siemens Sonata with a high-resolution 3D FLASH acquisition ($1\times1\times1$ mm$^3$ resolution, TE/TR= 5.6/12 ms, $\alpha$=19°). Diffusion images were acquired on the same scanner: 60 directions, b = 1000 s/mm$^2$, $2.5\times2.5\times2.5$ mm$^3$ resolution, TE/TR=80/8500 ms, 3 NEX. 25 control subjects matched for age and gender with the patient group underwent the same imaging.

To assess differences in the distribution of GM between patients and controls, an optimised VBM analysis (Good et al., Neuroimage 2001) using FSL tools for brain extraction and segmentation (www.fmrib.ox.ac.uk/fsl/) and non-rigid registration using free-form deformations (Rueckert et al., IEEE Trans Med Imaging 1999) was carried out. Differences in FA maps were investigated using TBSS (Smith et al., Neuroimage 2006). Changes in the distribution of GM and FA between both groups were analysed using permutation-based non-parametric inference, and were considered significant for $P<0.05$ (after initial cluster-based thresholding at $t=2$), fully corrected for multiple comparisons.

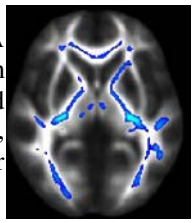
## Results




GM analysis (red) revealed bilateral loss of GM (or different patterns of gyrification) for the patients in the sensorimotor and premotor areas (S1, M1, SMA, FEF, BA 44, 45), in the anterior cingulate, in the right prefrontal cortex (BA 9), in the opercular cortex, the left posterior insula, in both Heschl gyri, in the temporal lobe (BA 37, 20) and in the occipital lobe (pre/cuneus).

Analysis of the FA maps showed a decrease of anisotropy (blue) in schizophrenic patients in the pyramidal/corticopontine tracts (more significant on the left), in the left posterior superior longitudinal fasciculi and in the left posterior superior temporal white matter (contiguous to the left planum temporale).

Furthermore, at $P<0.05$ uncorrected (figure on the right), FA was seen to be lower in patients in the genu and the splenium of the corpus callosum, and bilaterally in the anterior and posterior internal capsule, the anterior pillars of the fornix, the inferior fronto-occipital fasciculi and in the posterior superior temporal white matter.



## Discussion

GM changes found in the bilateral sensorimotor and premotor cortices seem consistent with a decrease in FA in the pyramidal and the cortico-pontine tracts. The decrease in the degree of anisotropy found in theses tracts may suggest that GM differences in the sensorimotor and premotor areas found in patients are related to an effective GM loss. It is unclear whether the insular and prefrontal GM changes are a result of atrophy or reflect a difference in the gyrification in the patients, as we found no significant changes of FA in the white matter tracts coming from/to these areas (Harris et al., Biol Psychiatry 2004; Falkai et al., J Psychiatr Res 2006). Work is being undertaken to explore the relationship between these various findings and the motor, cognitive and behavioural deficits seen in the schizophrenic patients included in this study. In conclusion, voxel-wise analyses of GM and FA changes provide complementary information on the neuropathology of adolescent-onset schizophrenia, and may therefore represent a sensitive surrogate marker. Strikingly, turning these specific GM and FA patterns into a global discriminant analysis, GM data permits to correctly categorise 92% of the 50 subjects as belonging to the control or the patient group, while combined GM and FA information raises this discrimination accuracy to 96%.

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