Combined functional magnetic resonance imaging and diffusion tensor imaging demonstrate widespread modified organisation in malformation of cortical development

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Abstract
A patient with a mild left hemiparesis and a malformation of cortical development in the right hemisphere was investigated using fMRI (functional magnetic resonance imaging) and DTI (diffusion tensor imaging). The motor cortex was studied using a finger tapping fMRI experiment. The fibre orientation was studied by displaying the principal eigenvector of the diffusion tensor in the spatially normalised brain of the patient and of control subjects. In addition, the anisotropy (directionality) of water diffusion of the patient was statistically compared with control subjects.

The malformation was located in the right central region in the expected position of the motor cortex. fMRI showed activation anterior and posterior to the malformation. DTI disclosed that fibres with rostrocaudal orientation, presumably representing the pyramidal tract, were deviating from their normal orientation and passing around the malformation. There were widespread regions of reduced anisotropy affecting both hemispheres.

In conclusion, fMRI and DTI provided concordant information showing widespread modified functional and structural organisation including regions which appeared normal on standard imaging.

Keywords: diffusion tensor imaging; functional magnetic resonance imaging; malformation of cortical development; epilepsy

Brains with malformations of cortical development may differ from normal brains in both functional and structural organisation. Microstructural abnormalities may be present in regions which appear normal on standard MRI. Modern MR techniques allow study of both function and structure in vivo. Functional MRI (fMRI) using the blood oxygen concentration dependent (BOLD) contrast mechanism allows the identification of activated brain areas during specific tasks and is therefore a tool to study the functional organisation of the cortex. Diffusion imaging provides an opportunity to study microstructure, in particular the orientation of fibres in the white matter. In the white matter of the brain diffusion is directional (anisotropic) because water molecules diffuse predominantly parallel to tracts. Diffusion tensor imaging (DTI) provides quantitative measures of the magnitude and directionality of water in a three dimensional space and can be used for accurate studies of fibre orientation in vivo.

The principal eigenvector represents the principal direction of diffusion and can be used to display the direction of the fibre tract axis. Maps of the anisotropy of water diffusion give information about the degree of directionality. Highly directionally organised tissues have high anisotropy. In this study, we combined functional MRI and diffusion tensor imaging (DTI) to study functional and structural organisation of the brain in a patient with a cerebral malformation.

Methods
We studied a 22 year old right handed man who had had epilepsy since the age of 1 year and 20 control subjects. The patient had simple partial seizures with jerking and numbness of the left arm, complex partial seizures, and secondary generalised seizures. On examination, he had a mild left hemiparesis. An EEG disclosed frequent focal spikes and sharp waves over the temporal and parasagittal region of the right hemisphere. Standard MR imaging with T1 weighted and T2 weighted sequences showed the MR signs of subcortical nodular heterotopia in the right hemisphere with a large nodule in the central region and a smaller one in the medial parietal lobe.

IMAGING PARAMETERS
All scans were performed on a 1.5T GE Scanner (GE, Milwaukee, USA) using single shot EPI sequences. We have previously described the method for tractography and fMRI. In addition we created a norm fractional

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anisotropy brain by averaging the spatially normalised anisotropy maps of 20 control subjects and generated maximum intensity projections (MIPs) of the fractional anisotropy using ANALYZE 7.5 software. We overlaid the MIP of the normal anisotropy brain with pixels with significantly (>mean −2 SD) reduced anisotropy of the patient.

**Results**

The subcortical nodular heterotopia in the right hemisphere visible on standard MR images was located in the central region in the expected position of the motor cortex (fig 1A). However, during finger tapping there was no activation in pixels inside the heterotopic grey matter but it occurred in pixels adjacent to the heterotopic grey matter (fig 1B). Maps of the principle eigenvector showed that fibres were deviating from their usual rostral caudal orientation (in control subjects the angle between the AC-PC line and the pyramidal tract ranged from 50° to 80°) passing around the malformation, which explained the unusual findings of the fMRI experiments (fig 1C). This also implies that the fibres are terminating in a different place.

The fractional anisotropy was reduced (values around 0.4) and the mean diffusivity (values around 1.0×10⁻³mm²/s) increased in the area of nodular heterotopia. In addition, there was reduced anisotropy throughout the brain, including normal appearing white matter (mean diffusivity in white matter of normal control subjects: mean 0.75×10⁻³mm²/s (SD 0.05×10⁻³mm²/s), fractional anisotropy in control subjects: mean 0.76 (SD 0.05) (fig 1D).

**Discussion**

The pattern of cortical activation in our patient during finger tapping differed from the pattern found in subjects without neurological disease. The activation was widespread, but spared the malformation of cortical development. We could not exclude the possibility that some cortical activation below the threshold of fMRI occurred within the heterotopic grey matter. However, the fMRI study indicated...
an abnormal functional organisation of the cortex involving large regions in the right hemisphere consistent with previous PET studies. Maps of the principal eigenvector of the diffusion tensor showed that fibres with rostral caudal orientation (presumably reflecting the pyramidal tract) deviated “avoiding” the malformation. Comparing the anisotropy of water diffusion of the patient with a normal control group we also demonstrated widespread regions of reduced anisotropy in the white matter not only affecting the malformation but also the normal appearing white matter in the contralateral hemisphere, consistent with a loss of directional organisation of white matter.

New MR imaging techniques are now increasingly able to detect abnormalities which have been previously invisible on standard MRI. With DTI structural abnormalities in normal appearing white matter can be detected in multiple sclerosis and blunt head trauma. Displaying the principal eigenvector to study the direction of fibres allows the identification of displacement of fibres by tumours in the normal appearing white matter and has the prospect of guiding neurosurgical interventions. Several different diffusion parameters and display techniques have been used to visualise the directionality of white matter and quantitative methods to assess displacement are currently being developed. Studies with fMRI are increasingly used in patients with neurological disease where normal anatomical organisation cannot be assumed. The technique of DTI can provide additional information which may assist the interpretation of fMRI in such patients. In our patient the combined use of fMRI and DTI showed widespread modified functional and structural organisation including regions which appeared normal on standard imaging. The combined use of these techniques will enhance our understanding of brain function in such patients and is likely to be important in the context of epilepsy surgery.

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