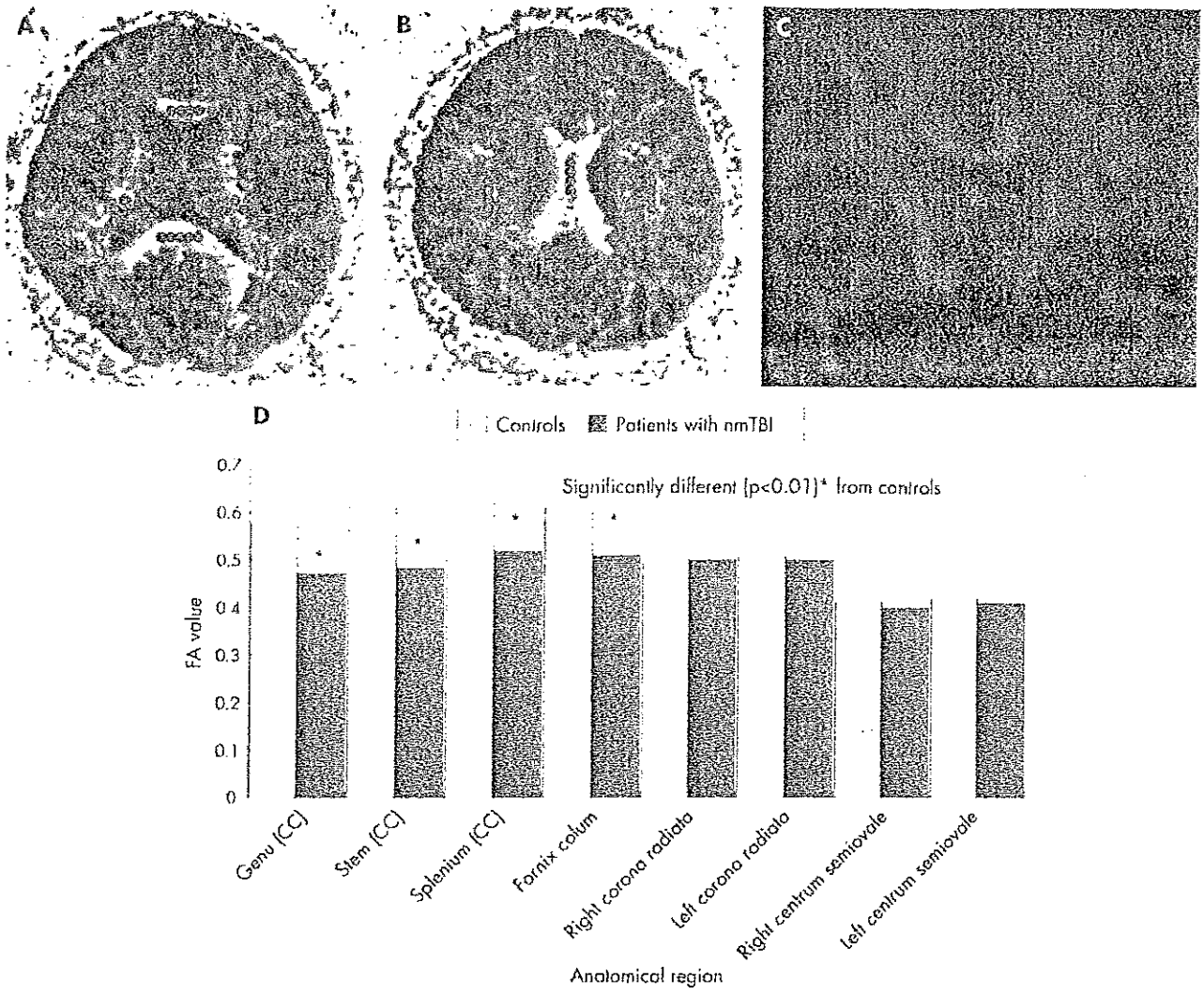

Figure 3 (A–C) Axial and coronal fractional anisotropy (FA) maps. Several circular regions of interest with a diameter of 2 mm are placed in the corpus callosum (CC; the genu, stem and splenium), column of the fornix, corona radiata and centrum semiovale. (D) FA values in the CC, fornix, corona radiata and centrum semiovale of patients with traumatic brain injury. nmTBI, non-missile traumatic brain injury.

Several round ROIs with a diameter of 2 mm were placed in the corpus callosum, the column of the fornix, the corona radiata bilaterally and the centrum semiovale bilaterally on individual fractional anisotropy maps (figs 3A–C). The mean values of fractional anisotropy from several round ROIs were used. Examination of group differences by study of ROIs confirmed the marked differences in fractional anisotropy, noted in the voxel-based analysis. We found considerable differences between the group with nmTBI group and controls in the fractional anisotropy values of the genu ($p = 0.0008$), stem ($p = 0.006$) and splenium of the corpus callosum ($p = 0.009$), and the column of the fornix ($p = 0.009$; fig 3D). Average values generated from the ROI placed in the corticospinal tract did not differ between the two groups.

Figure 4 compares individual magnetic resonance tractography of the corpus callosum and the fornix from some nmTBI cases with controls. In cases with nmTBI, the tracking lines through the genu and the splenium of the corpus callosum were different from those in controls, with the connecting fibres not reaching the cortex. The volume and the connecting fibres from the splenium in patients with nmTBI were relatively retained. Compared with controls, the tracking lines through the column of the fornix in patients with nmTBI did not pass along the fimbria of the hippocampus, although tractography around the mamillary body to the column of the fornix was relatively retained.

DISCUSSION

Our results suggest that DTI was able to objectively show abnormalities in patients with nmTBI with cognitive impairments but without macroscopically detectable lesions. To our knowledge, this is the first report of white matter disruption of the corpus callosum and fornix to evaluate nmTBI without macroscopically detectable lesions by using DTI. Voxel-based fractional anisotropy analysis and tractography study objectively showed the vulnerability of the corpus callosum and fornix in patients with nmTBI. The parasagittal subcortical white matter, internal capsules, cerebellar folia dorsal to the dentate nuclei and brain stem, but not corpus callosum and fornix, are susceptible to diffuse axonal injury.[9] Our study showed the specific vulnerability of the corpus callosum and fornix, because our patients with nmTBI had cognitive impairments but no physical problems. The corpus callosum and fornix are thought to be the structures at the core of neural networks in cognition and memory. Changes in the anterior white matter, including the corpus callosum, were strongly related to age-related cognitive decline.[10 11] The fornix is the major limbic white matter pathway interconnecting the hippocampus and the mamillary bodies. The

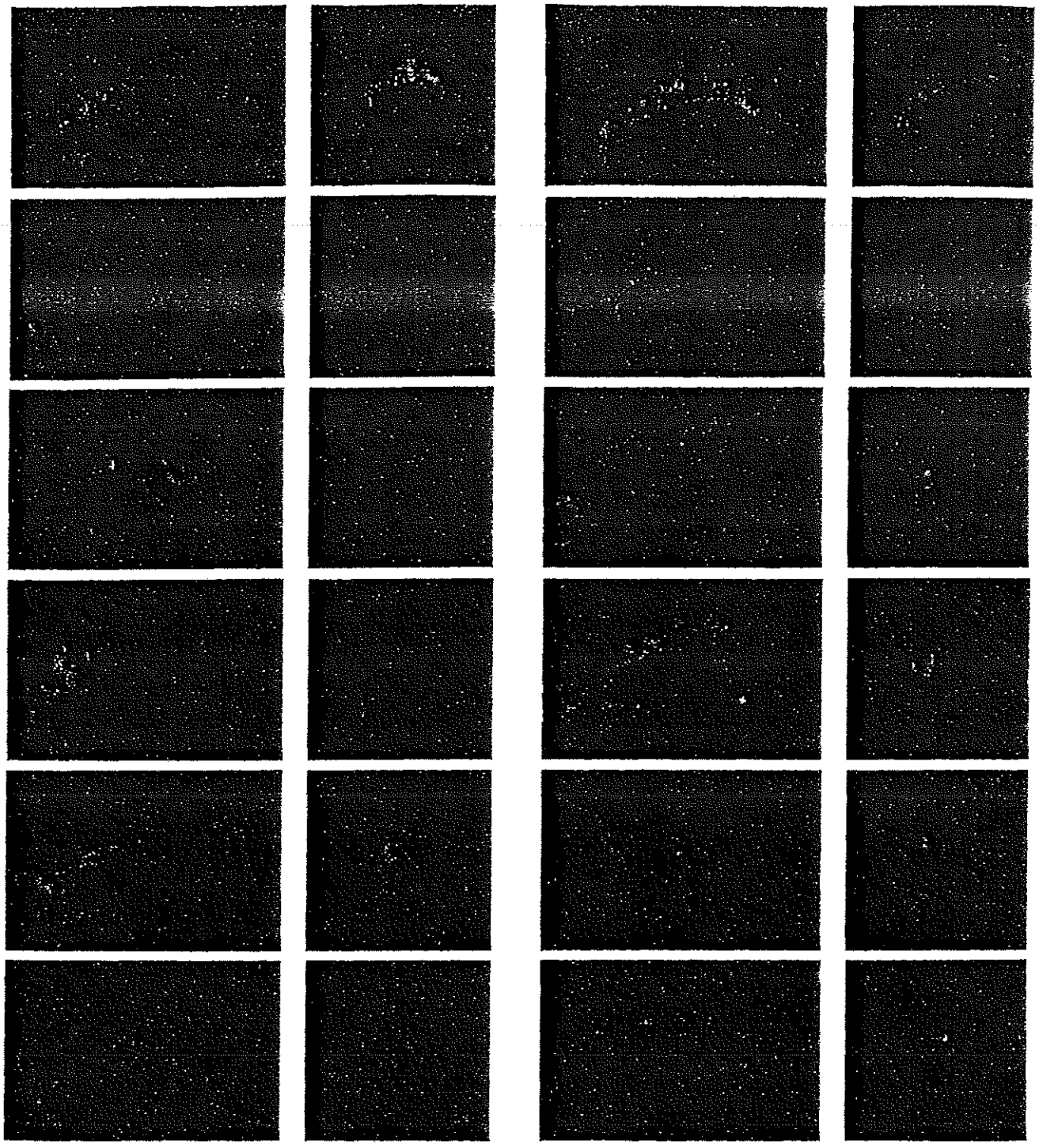

Figure 4 Lateral view for the tractography of the corpus callosum (left column) and fornix (right column) in a control (left upper) and in 11 patients with traumatic brain injury. The tractographs are overlaid on T2-weighted MRI.

limbic circuitry of the hippocampus–fornix–mamillary body interaction has been the focus of extensive research on memory function. Damage to any of these limbic structures results in various memory disorders.[21]

Limitations exist in assessing fractional anisotropy value by ROI techniques, especially in the case of very small ROI with a diameter of 2 mm. ROI techniques depend either on subjective assessment or on the relatively arbitrary size, shape and placement of the ROIs. As a result, some areas of the brain may not be explored. SPM analysis is an alternative voxel-by-voxel analysis method that can avoid subjectivities. In this study, a marked decrease in values of fractional anisotropy in the column of the fornix was not obvious with SPM. The SPM may not have been successful because of the small size of the fornix. Its location in stereotactic space may have been displaced between subjects because of normalisation errors and smeared out during smoothing with a gaussian low-pass filter of an 8-mm full-width at half-maximum, making differences harder to detect. Because it was relatively easy to detect on the native fractional anisotropy images, the manual ROI values, especially in the small size, may be more accurate, resulting in greater statistical power.

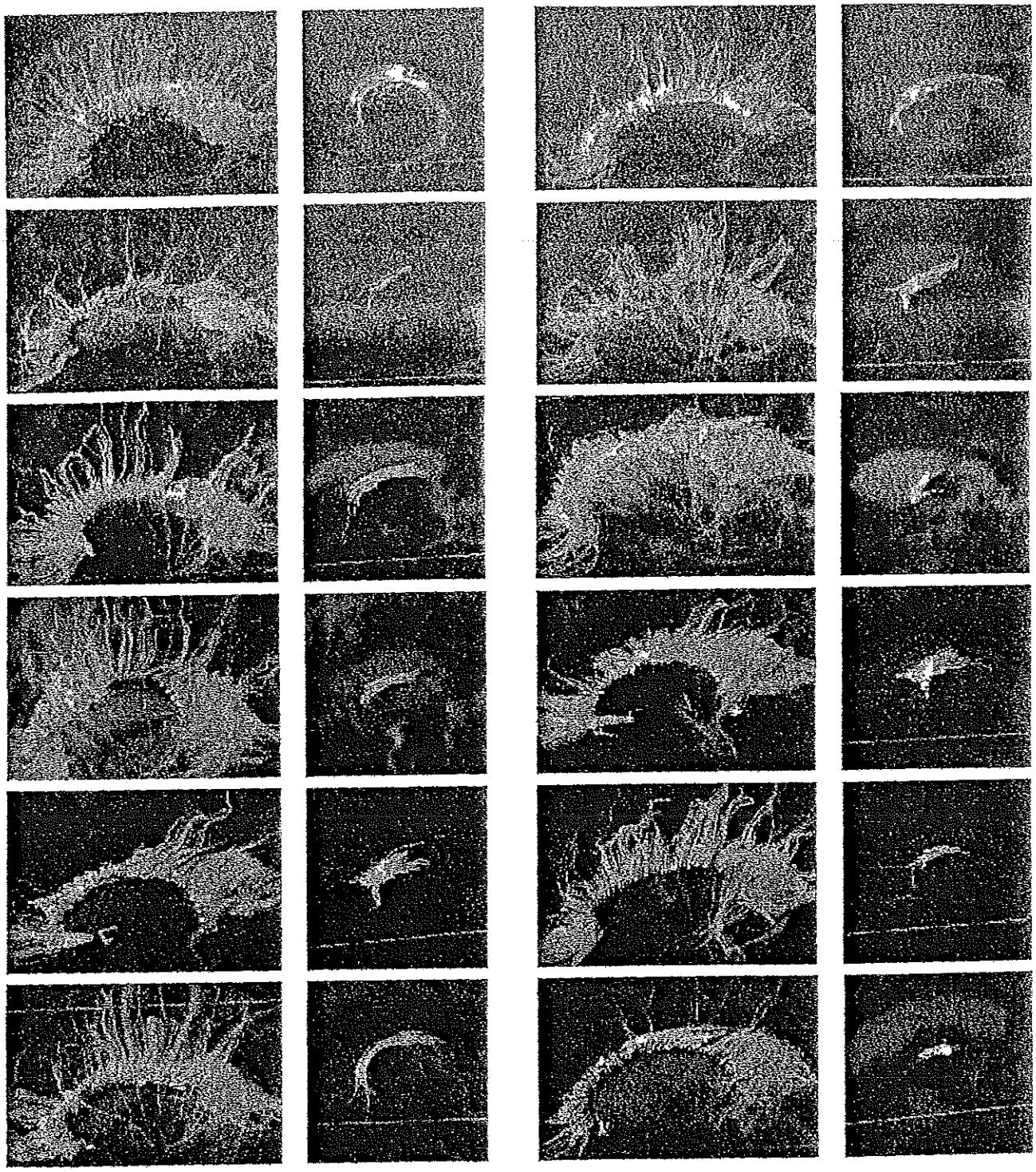

Figure 4 Lateral view for the tractography of the corpus callosum (left column) and fornix (right column) in a control (left upper) and in 11 patients with traumatic brain injury. The tractographs are overlaid on T2-weighted MRI.

vue latérale pour la tractographie du corps calleux (colonne de gauche) et fornix (colonne de droite chez un contrôle sain (à gauche en haut) et chez 11 patients traumatisés crâniens

limbic circuitry of the hippocampus–fornix–mamillary body interaction has been the focus of extensive research on memory function. Damage to any of these limbic structures results in various memory disorders.[7]

Limitations exist in assessing fractional anisotropy value by ROI techniques, especially in the case of very small ROI with a diameter of 2 mm. ROI techniques depend either on subjective assessment or on the relatively arbitrary size, shape and placement of the ROIs. As a result, some areas of the brain may not be explored. SPM analysis is an alternative voxel-by-voxel analysis method that can avoid subjectivities. In this study, a marked decrease in values of fractional anisotropy in the column of the fornix was not obvious with SPM. The SPM may not have been successful because of the small size of the fornix. Its location in stereotactic space may have been displaced between subjects because of normalisation errors and smeared out during smoothing with a gaussian low-pass filter of an 8-mm full-width at half-maximum, making differences harder to detect. Because it was relatively easy to detect on the native fractional anisotropy images, the manual ROI values, especially in the small size, may be more accurate, resulting in greater statistical power.

In this study, a marked correlation was found in the splenium of the corpus callosum between MMSE and fractional anisotropy value. No significant correlation effects of WMS—R and PASAT were, however, detected. Although the condition with threshold at a value of corrected $p<0.05$ in voxel level and at an extent of 60 voxels may cause these results, a positive correlation was shown only in the MMSE may be because of characteristic differences between the MMSE and the others. The MMSE reflects general cognitive function; the others, however, reflect specific cognitive function.

Although a major number of patients with diffuse brain damage and cognitive impairments do not show obvious lesions on conventional neuroimaging, quantitative brain MRI studies conducted at least 6 weeks after injury have shown that moderate to severe traumatic brain injury results in a decrease in the volume of the hippocampus, fornix and corpus callosum.[24–26] These reports point to the vulnerability of the corpus callosum and fornix in patients with nmTBI and the relationship between atrophy and cognitive dysfunction. The results of these morphometric studies and our investigation on abnormalities of the corpus callosum and fornix are consistent. White matter abnormalities in patients with nmTBI can be detected earlier with DTI than with the morphometric methods, because DTI can presume the structure of the white matter, whereas morphometrics may detect secondary, atrophic changes subsequent to primary damage. The altered state of the white matter resulting from acute traumatic brain injury may, however, affect diffusion tensor anisotropy measurements. Oedematous tracts may lose some anisotropy, but retain enough directional organisation to remain identifiable on directional DTI.[27] White matter tracts may be destroyed or disruptured to the point where directional organisation and, consequently, diffusion anisotropy is lost completely. In our study, magnetic resonance tractography of the corpus callosum and fornix disclosed abnormalities in the tracking lines of the individual patients with nmTBI . The magnetic resonance tractography was symbolic and demonstrative of the neural network and may be useful for individual evaluation of patients with nmTBI. The definition of magnetic resonance tractography as a clinical method has, however, not been established. The technical limitations of magnetic resonance tractography must not be overlooked.[28] Studies are under way in our hospital to identify the optimal timing of DTI to identify accurately the presence of white matter abnormalities after nmTBI.

In this study, all participants underwent DTI with the 1.5T MRI system. Although a direct comparison of 3.0T and 1.5T with regard to magnetic resonance tractography has not been reported, the 3.0T MRI system has a higher signal-to-noise ratio than 1.5T. Thin slice images can be obtained with 3.0T owing to a higher signal-to-noise ratio, so z-axis resolution is improved. Therefore, magnetic resonance tractography may be more effective in z axis with 3.0T than with 1.5T. The 3.0T system, however, has a higher susceptibility artefact in DTI. It will be necessary to examine the clinical comparison of 3.0T imaging and 1.5T imaging with regard to magnetic resonance tractography furthermore.

We will apply our findings to each patient with traumatic brain injury in the acute or subacute stage, to obtain an objective index of reliable diagnosis, evaluation, estimation and treatment of cognitive impairments.

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