Highly localized alterations of white matter in fixation-off sensitivity: a study using DTI.

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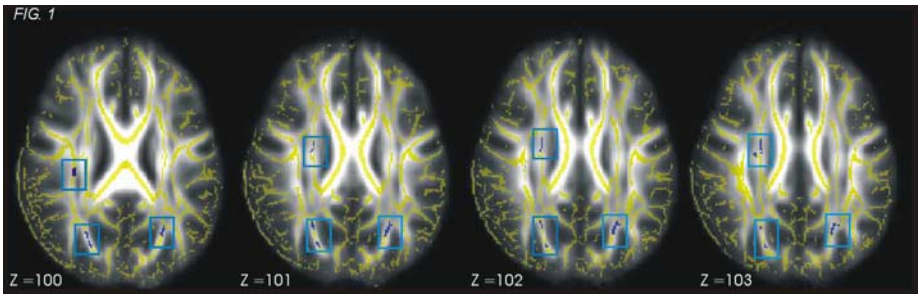
Introduction: Fixation-off-sensitivity (FOS) refers to a rare form of epileptic seizures induced by the elimination of central vision or fixation [1]. FOS is distinguished by sustained paroxysmal EEG activity with parieto-occipital spike-and-waves complexes that desynchronize with eyes opening and monocular or binocular visual fixation. FOS has been defined as an ideal human model to study the pathophysiologic mechanisms underlying continuous epileptic activity, its interictal state and acquired chronic outcome. This form of epyleptic discharges can in fact be predictably triggered by asking patients to close their eyes and are usually not associated with severe clinical symptoms impeding EEG or MRI protocols. Few cases of FOS have been described in the literature. Using concurrent EEG and fMRI measures, previous studies have identified FOS epileptogenic regions with a main bilateral or monolateral activation cluster in the temporo-occipital areas. Yet, FOS activity have never been associated with any type of relevant congenital, aquired, or progressive morphological brain lesion or abnormality. Recently, different clinical trials have shown that DTI appears to be a sensitive method to identify occult damages of white matter (WM) in epilepsy, not otherwise visible on FLAIR and T2 images. Generally, conventional MRimaging and tractography cannot highlight alterations of white matter microanatomy localized in specific tracts with limited extension. Here we combined DTI with the TBSS (Tract-Based Spatial Statistics)[2] method in a FOS patient and a group of healthy volunteers. A focal damage of the white matter in the parieto-occipital WM tracts was found in the FOS patient, suggesting highly localized alterations of the white matter microanatomy.

Methods: A 39-year-old woman affected by cryptogenic partial epilepsy and FOS discharges and a group of 27 healthy control subjects (11 female, 16 male, age) were scanned with conventional MRI at 1.5T and DWI on a 3T MR scanner (Siemens Allegra). The patients neurological and radiological (T2 weighted MRI and FLAIR) examinations, as well as the visual field perimetry were normal, except for slight strabismus on the Goldmann test. Diffusion-weighted data were acquired using echo planar imaging (52 interleaved axial slices, field of view 192x192 mm^2, voxel size of 1.5x1.5x2mm^3). The diffusion weighting was distributed along 12 directions with a b value of 1000 s/mm^2. For each subject we acquired 8 sets of diffusion-weighted data, and for each of those sets we acquired two volumes with no diffusion weighting. Image analysis was carried out using tools from the FMRIB Software Library (Diffusion Toolbox). For each brain voxel in the diffusion data, a diffusion tensor was fitted and for the fractional anisotropy (FA) was calculated. From the second and third eigenvalues (λ_2 and λ_3) of the diffusion tensor the values for "perpendicular diffusivity" $D_{perp}=(\lambda_2+\lambda_3)/2$, a parameter which have been shown to be related with myelin degradation [3] and parallel diffusivity ($D_{paral}=\lambda_1$) were generated. Voxelwise statistical analysis of diffusivity and anisotropy maps were computed using TBSS. First, the FA images of each subject were aligned into a common space using a non-linear registration procedure. The resulting mean FA image was then thinned to create a mean FA skeleton which represented the centres of all tracts common to the group. Each subject's aligned FA data was then projected onto this skeleton and the resulting data was fed into a voxelwise non-parametric cross-subject statistics using a Montecarlo permutation test. Statistically significant differences between patient and control group ($p<0.05$, with a cluster-based correction for multiple comparisons) were assessed by using the null distribution of the max (across the image). Likewise, statistical testing for changes in the Parallel and Perpendicular diffusivity images were also compared using TBSS and statistical comparisons based on permutation tests.

Results: Areas of significant abnormal diffusion in WM tracts were detected in our FOS patient compared to the healthy control group. The patient showed reduced anisotropy and increased perpendicular diffusivity ($p=0.03$, for both FA and D_{perp}) accompanied by bilateral adjacent areas of increased anisotropy and increased parallel diffusivity ($p=0.03$, for both FA and D_{paral}). These alterations, suggesting occult WM micro-structural disorganization, were found adjacent to areas where previous electroclinical and fMRI data had localized FOS activity (BA 19, 37) [1]. Fig 1 shows the mean FA skeleton superimposed on a MNI template, with the WM voxels (higlighted in blue squares) resulting significantly different in our patient compared to healthy controls. The WM tracts are located in areas with MNI coordinates corresponding to bilateral occipito-parietal regions adjacent to the Pre-Cuneus Area and BA 19. Images are in the radiological convention.

Discussion: Diffusion and fractional anisotropy abnormalities in bilateral parieto-occipital regions seem to suggest a loss of structural organization secondary to occult WM damage in our patient. It is known that hyperactivity in the glutamatergic system is one of the main pathophysiological factors of neuronal paroxysms. In a recent paper, a transient linear increase of glutamate during FOS activity has been reported. This finding supports the idea that a cumulative increase of glutamate during sustained FOS discharges is a potential factor for neurotoxicity in these patients. Axonal degeneration and anatomical damages to the WM microstructural enviroment are a common consequence of neuronal injury. Recent animal and human studies show that the increase of perpendicular diffusivity is the underlying reason for the low diffusion anisotropy usually related to chronic axonal damage and Wallerian degeneration in the central nervous system. In our study, we identified a decrease of FA values in the parieto-occipital WM tracts with a concurrent increase of perpendicular diffusivity. The above alteration is also coupled witht an increase of FA and parallel diffusivity values in bilateral adjacent WM tracts. These spatially-dependent abnormalities may respectively represent axonal degeneration and the displacement of WM bundles into areas of low anisotropy. It is likely that the discribed structural disruption is due to white matter gliosis and myelin degradation associated to the highly repetitive and toxic metabolic changes of FOS phenomena.

Conclusions: Our finding suggests that neuronal tissue subject to prolonged FOS paroxysmal activity result in alterations detectable by DTI and TBSS based approaches, suggesting cellular gliosis and WM damage. At this regard, DTI appears to be a sensitive technique for a non-invasive detection of structural abnormalities that standard MRI cannot afford.



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