Apparent Fibre Density shows tract-specific white matter changes in Temporal Lobe Epilepsy

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TARGET AUDIENCE: Clinicians investigating patients with epilepsy. Researchers who perform diffusion-weighted imaging analysis.

PURPOSE: White matter abnormalities in temporal lobe epilepsy may indicate the effect of seizures or changes due to the underlying epileptogenic process. Changes in scalar white matter parameters, derived from the diffusion tensor model, have previously been shown in both the affected temporal lobe and extra-temporal regions[1]. However, such group analyses do not consider the directionality of the information, and cannot identify the orientation of affected fibres. The Apparent Fibre Density (AFD) measure is derived from diffusion imaging data via calculation of the Fibre Orientation Distribution (FOD)[2]. It can be interpreted as proportional to the intra-axonal volume of axons aligned to a given orientation[2]. Each AFD measurement is associated with a specific direction within a single voxel (herein called a *dixel*). Therefore AFD differences can be attributed to a single fibre bundle, even within regions containing multiple crossing fibres. Here we apply the AFD technique to demonstrate tract-specific changes in both lesional and lesion-negative temporal lobe epilepsy.

METHODS: Patients with mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE-HS: 19 patients, 13 female, 7 left epileptic focus, mean age 39.0, range 24-55 years) were compared to healthy non-epileptic controls (36 participants, 24 female, mean age 30.4, range 17-55 years). Additional patients with unilateral temporal lobe epilepsy and normal structural MRI (TLE-N: 19 patients, 9 female, 10 left epileptic focus, mean age 36.6, range 21-63 years) were also compared to a matched control group (46 participants, 22 female, mean age 31.2, range 17-52 years). The diagnosis of temporal lobe epilepsy was confirmed on clinical assessment and video-EEG monitoring, and no other relevant lesion was reported on T1- or T2-weighted images. Diffusion weighted images were acquired on a 3T Siemens Trio (60 directions, b=3000 s/mm^2, 2.5mm). Pre-processing involved motion and bias field correction[2], intensity normalisation[2], and up-sampling[2] by a factor of 2. FODs were computed by Constrained Spherical Deconvolution[3] using MRtrix[4]. Individual FOD images were flipped left-right to align the epileptic side and registered towards a symmetrical population-specific FOD template[2]. Final transforms were applied with AFD modulation[2]. The AFD was sampled along 300 equally distributed directions within each voxel, and anisotropic smoothing was performed[2]. AFD was compared across subjects within corresponding dixels, with age, gender and epileptic side as covariates of no interest. Multiple comparison correction was performed using threshold-free cluster enhancement (TFCE)[5], with clusters formed using dixel neighbours defined in both space and orientation[2]. Corrected p-values were assigned to each dixel using permutation testing (5000 permutations). To visualise significant dixels, one million streamlines were generated using the iFOD2 probabilistic tractography algorithm[6] on the population-specific FOD template. Every point along each streamline was colour-coded according to the associated dixel TFCE t-value, and non-significant streamline points were excluded from the visualisation (p>0.05).

RESULTS: A significant decrease in AFD was seen in MTLE-HS compared to controls, at regions and directions corresponding to white matter tracts arising from the ipsilateral temporal lobe (figure 1a). These were the uncinate fasciculus, anterior commissure, inferior longitudinal fasciculus, crus of the fornix extending to the hippocampal commissure and stria terminalis, and tapetum extending to the splenium of the corpus callosum. Abnormalities were greatest (peak t-value 5.7) in the anterior temporal lobe and temporal stem (figure 1d), and decreased away from these regions. Significant changes affected the contralateral hemisphere in all three commissural tracts. Additional AFD decreases were seen in the ipsilateral corticospinal tract. No regions of increased AFD were detected. In TLE-N significant decreases in AFD were seen extensively throughout white matter tracts bilaterally.

DISCUSSION & CONCLUSIONS: Decreased AFD is seen in multiple tracts radiating from the affected temporal lobe in MTLE-HS, with greatest change closer to the epileptogenic zone. This can be interpreted as a decrease in the axonal volume of these specific tracts. The extensive bilateral AFD decrease found in TLE-N suggests that these patients may form a distinct group from MTLE-HS, with differing pathological mechanisms and implications for treatment. This technique identifies specific tracts in a way that has not been possible previously, and further extends understanding of white matter abnormalities in focal epilepsy.

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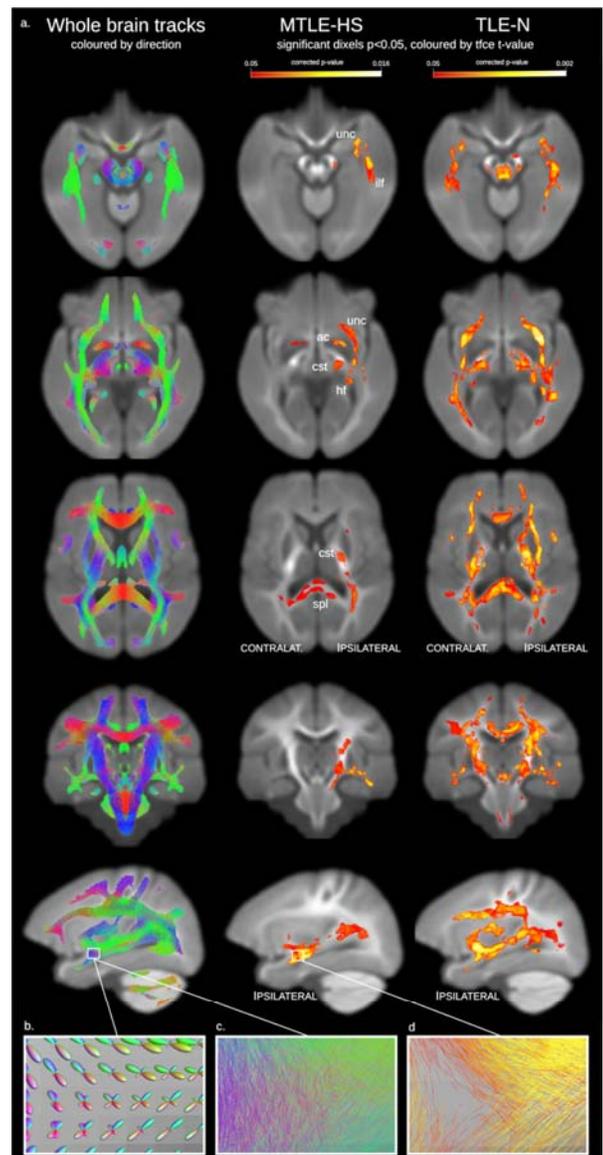
Fig. 1a) Significant dixels in MTLE-HS and TLE-N. b&c) FODs and crossing tracks at the temporal stem, coloured by direction. d) Significant dixels in this region are crossed, indicating changes in both tracts seen in this image. Legend: unc-uncinate fasciculus, ilf-inferior longitudinal fasciculus, ac-anterior commissure, cst-cortico-spinal tract, hf-hippocampal fornix, spl-splenium of the corpus callosum.