Biophysical Microstructure Markers Are Correlated with Disease Severity in Medial Temporal Lobe Epilepsy

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<u>**Target audience:**</u> This study investigates diffusion MRI (dMRI)-derived biophysical markers in medial temporal lobe epilepsy (MTLE). The target audience includes basic and clinical epilepsy researchers.

Purpose: dMRI has shown limbic and extra-limbic gray and white matter (WM) abnormalities in MTLE.^{1,2} However, the precise biophysical tissue characteristics responsible for these findings remain to be defined. Moreover, little is known regarding the clinical relevance of the observed alterations. The goals of this study are to investigate the biophysical tissue characteristics responsible for diffusion changes in MTLE and to determine whether these characteristics could serve as markers of disease severity. A newly developed cerebral microenvironment modeling (CMM) method compatible with diffusional kurtosis imaging (DKI)³ was used to obtain the biophysical measures.

Methods: Cerebral microenvironment modeling: CMM extends a recently developed WM modeling (WMM) method.⁴ The model is predicated on the assumption that brain water is housed in two non-exchanging microscopic compartments, where the confined compartment (CC) represents water restricted inside neurites (i.e., dendrites and myelinated axons), while the open compartment (OC) corresponds primarily to less restricted water in glial cells, extracellular spaces, and very thin unmyelinated axons. CMM differs from WMM in that it allows the CC diffusion to be non-Gaussian, enabling the model to account for complex neurite arrangements. This is achieved by including a CC kurtosis term $K_{\rm CC}$ in the diffusion signal model. The signal $S_{\rm CMM}(b, \mathbf{n})$ is then given as

$$\mathbf{S}_{\text{CMM}}(b,\mathbf{n}) = f \exp\left[-b\mathbf{n}^{T}\mathbf{D}_{\text{CC}}\mathbf{n} + \frac{1}{6}(b\mathbf{n}^{T}\mathbf{D}_{\text{CC}}\mathbf{n})^{2}K_{\text{CC}}\right] + (1-f)\exp\left[-b\mathbf{n}^{T}\mathbf{D}_{\text{CC}}\mathbf{n}\right]$$
(1)

where *b* denotes the b-value, **n** is a gradient direction vector, *f* is CC water proton fraction, and \mathbf{D}_{CC} and \mathbf{D}_{OC} are the CC and OC diffusion tensors.

Participants, imaging, and data analysis: DKI scans were obtained from 19 patients with MTLE (10 left, 9 right) (mean age \pm std dev = 31.9 ± 8.5 years; 11 female) and 28 age- and sex-matched healthy volunteers (mean age \pm std dev = 33.0 ± 7.4 years; 17 female). The patients were divided into two subgroups based on their response to antiepileptic drug therapy. Six patients were well-controlled (≤ 4 seizures a year) and 13 patients were poorly-controlled (> 4 seizures a year). The two subgroups did not significantly differ in

(a) Increased MD Ipsi Contra (b) Decreased FA (c) Decreased MK (d) Decreased f

t > 3.4: Two-sided p < 0.001 (uncorrected) 3.0 4.0 5.0 **Figure 1.** Voxelwise analysis of dMRI metrics in patients with MTLE and age- and sex-matched healthy volunteers. Structures ipsilateral to seizure focus are shown on the left. All metrics were age-corrected.

terms of age, age of seizure onset, or duration of disease. MTLE diagnosis was based on a history of partial epilepsy and presence of unilateral hippocampal sclerosis on conventional diagnostic MRI or ictal video-electroencephalography demonstrating unilateral temporal seizure onset. Diffusion-weighted images (DWIs) were obtained on a Siemens 3T Verio scanner using a twice-refocused echo planar sequence with three diffusion weightings (b = 0, 1000, and 2000 s/mm²) along 30 diffusion encoding directions with NEX = 1 (NEX = 10 for b = 0). Other imaging parameters were TR = 8500 ms, TE = 98 ms, FOV = 222×222 mm², matrix size = 74×74 , parallel imaging factor of 2, no partial Fourier encoding, slice thickness = 3 mm, and 40 axial slices. Diffusion and diffusional kurtosis tensors were obtained from DWIs using methods described elsewhere.⁵ Diffusivity, kurtosis, and CMM parametric maps were then calculated from the tensors. Fractional anisotropy (FA) maps were spatially normalized to standard space using the FMRIB Software Library (FSL)⁶ and the resulting transformation was applied to normalize the other maps. Following spatial normalization, voxelwise and region-of-interest analyses were performed with in-house scripts.

<u>Results:</u> Figure 1 shows voxelwise analysis of mean diffusivity (MD), FA, mean kurtosis (MK), and f in patients and healthy individuals. MD identified very small areas of abnormalities clustered around the hippocampus and in the peri-hippocampal WM. FA identified larger regions of reduced WM integrity in the peri-hippocampal, temporal, and peri-thalamic WM. Conversely, MK showed widespread limbic and extra-limbic abnormalities, with a higher intensity around peri-hippocampal and peri-limbic regions. CC water fraction f identified the largest areas of compromised microstructure, essentially reflecting the MK findings. Figure 2(a, b) shows regional comparisons of CMM metrics between the well- and poorly-controlled patients. The parahippocampal cortex (PHC) showed bilaterally increased f and K_{cc} in poorly-controlled patients, with the ipsilateral findings being statistically significant. MD and FA did not show a significant group difference in the PHC. Figure 2(c) shows reduced OC FA in ipsilateral inferior longitudinal fasciculus (ILF), cingulum, and fornix. We observed similar group differences with FA.

Discussion and conclusion: We applied the newly developed CMM to provide biophysical interpretation of diffusion abnormalities observed in MTLE. The extensive reduction of MK in patients was primarily associated with reduced f, consistent with the cerebral neurite loss known to occur in MTLE.⁷ We also investigated the association between CMM metrics and frequency of seizures. Our results suggest that poorly-controlled MTLE is associated with reduced OC FA in several ipsilateral peri-hippocampal WM tracts. This may be attributed to a possible increase in the degree of gliosis and/or myelin degradation in these patients. We also observed increased apparent f and K_{cc} in the ipsilateral PHC. Contralateral PHC, bilateral hippocampi and thalami showed largely similar trends, although these were not

significant. Our conjecture is that a combination of morphological (e.g., aberrant axonal sprouting) and/or permeability changes between the OC and CC may underlie these changes. In summary, CMM may improve biophysical interpretation of dMRI markers in MTLE. Moreover, the association of CMM measures with disease severity suggests a potential clinical role for these markers in disease monitoring and treatment planning.

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Figure 2. (a, b) Regional comparison of f and $K_{\rm CC}$ in the PHC between well- and poorly-controlled patients with MTLE. (c) Regional comparison of OC FA in the ipsilateral peri-hippocampal WM tracts. All metrics were corrected for age and the Wilcoxon rank-sum test was used.