# Evidence for typical and atypical gray and white matter pathology in frontal lobe epilepsy and different types of temporal lobe epilepsy

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**Background:** Unbiased voxel-based image analysis approaches, e.g. as implemented in SPM, demonstrated different, characteristic patterns of gray matter atrophy or white matter damage in group comparisons of different types of non-lesional partial epilepsy, e.g. in temporal lobe epilepsy with (TLE-MTS) and without (TLE-no) mesial temporal sclerosis or frontal lobe epilepsy (FLE) with controls. It is unknown though, to what degree these patterns exist in individual patients. Traditionally, thresholding approaches, e.g. z-scores, or highly unbiased single subject comparisons in tools such as SPM are used to generate individual abnormality maps to address this question. However, these approaches not only violate basic assumptions of parametric statistics and require the subjective selection of thresholds for significance but also do also not allow the combination of information from different imaging modalities. Here we propose a two-level multi-modality imaging Bayesian network approach with the following aims: 1. to characterize the subtype specific structural abnormalities in non-lesional TLE-MTS, TLE-no and FLE using Graphical-Model-based Morphometric Analysis (GAMMA (Cheng and Hershkovits, 2005)). GAMMA uses a Bayesian network and a Markov random field based contextual clustering method to map clusters of voxels with similar associations with a function variable, e.g. group. Compared to SPM, GAMMA has the advantage that it can detect linear and non-linear associations between clusters of voxels and a function variable and that it is based on a probabilistic model and can encode uncertainty, e.g., due to data noise, group membership etc. 2. to use the resulting abnormality maps to develop the second-level Bayesian network which allows for a robust imaging based subtype classification of single subjects by combining the information obtained at the first level. 3. to identify typical, e.g. FLE gray matter and FA abnormality pattern, and atypical pattern, e.g. FLE with TLE features.

**Methods**: 94 subjects (25 controls, 27 non-lesional TLE-MTS, 26 non-lesional TLE-no, 15 non-lesional FLE, mean age: 35.7±11.1 years) were studied on a Bruker Med Spec 4T magnet and the following sequences acquired: 1. T1-weighted whole brain MPrage TR/TE/TI = 2300/3/950 ms, 1.0x1.0x1.0 $mm^3$ resolution. 2. EPI-based DTI (TR/TE = 6000/77, 2x2x3 $mm^3$ resolution, 6 directions, b = 800 s/ $mm^2$. The T1 images were segmented into tissue maps and the DT images were motion/distortion corrected and FA maps calculated. Symmetrical gray matter (GM) and (FA) population atlases were generated from the t original and left/right flipped control GM and FA maps using the DARTEL high dimensional non-linear co-registration algorithm as implemented in SPM 8 and each subject's images warped onto the corresponding template. The images of patients with right-sided seizure onset were side-flipped before warping so that the hemisphere generating the seizures was on the same (left) side in all patients. The spatially normalized GM maps were multiplied with the Jacobian determinants of the warping step and corrected for differences in intracranial volume (ICV). All images were smoothed with an 8 mm FWMH kernel. A voxel-wise mean and standard deviation (SD) map was calculated from the smoothed processed original and side flipped control images. Each subject's smoothed image was compared against this mean map and binary maps with voxels with intensities of at least one SD below the mean generated. These maps were used as input for GAMMA. GAMMA produces a label map (binary map of sub-threshold voxels distinguishing between groups) and a belief map (label map weighted by the confidence in the voxel/group association). The degree of correspondence between the individual sub-threshold maps and the label and belief maps is used to determine the presence/absence (yes/no) of the characteristic GM loss/FA decrease in each subject. The following whole brain comparisons were performed for each modality: TLE-MTS vs controls, FLE vs. controls, TLE-no vs. controls, TLE-MTS vs. TLE-no, FLE vs. TLE (FA), FLEvs.TLE (GM). In order to obtain more detailed information about the presence of medial temporal and/or hippocampal atrophy, a hippocampal-entorhinal region of interest was generated and a comparison Hippo-ERC controls vs TLE-MTS performed. This resulting individual yes/no labels were used to build a second-level Bayesian network which combined the information from all the labels of both modalities to determine A. the probability to be FLE or TLE, and B. if TLE, probability to be TLE-MTS or TLE-no. Subjects correctly identified by the Bayesian network were considered to represent the typical GM and FA abnormalities for that epilepsy subtype, e.g. typical TLE-MTS. Misclassified subjects were considered to represent atypical abnormalities, e.g., a TLE-MTS classified as FLE was considered to be a TLE-MTS with FLE features

**Results:** 15 (58%)TLE-no were classified as TLE-no, the remainder as TLE-MTS or TLE-no with MTS features. Even though all but one of the TLE-no with MTS features had normal hippocampal volumes in the standard hippocampal volumetry, 66% had evidence for mesial temporal atrophy based on the GAMMA Hippo-ERC comparison. None of the typical TLE-no had evidence for Hippo-ERC atrophy. 8 (53%) of the FLE subjects were correctly classified as FLE, the remaining 7 were classified as TLE (2 TLE-no, 5 TLE-MTS). Typical FLE differed from FLE with TLE features by having evidence for diffuse FA abnormalities based on the findings in the DTI FLEvsControl comparison (100%) and FLEvsTLE comparison (100%) which were practically absent in FLE with TLE features (0% in DTI FLEvsControls, 14% in DTI FLEvsTLE comparison). 23 (85%)of the TLE-MTS subjects were classified as TLE-MTS. 3 (11%) were classified as FLE, i.e. are considered to be TLE-MTS with FLE features. Atypical TLE-MTS subjects had evidence for diffuse FA abnormalities similarly as typical FLE (100% in DTI FLEvsControls comparison and DTI FLEvsTLE comparison) which was far less pronounced in typical TLE-MTS (54% in DTI FLEvsControls comparison and 5% in DTI FLEvsTLE comparison) One TLE-MTS with a contralateral MTS was classified as TLE-no. Atypical patients did not differ from their corresponding typical counterparts regarding age at exam or duration of epilepsy.

**Conclusions:** A two-level Bayesian network approach was used to identify brain regions showing characteristic gray and white matter abnormalities in TLE with and without MTS and FLE at the group level and at the single subject level. The latter information was used to identify subjects with typical and at least one form of atypical manifestion of gray and white matter abnormalities in each epilepsy type. The nature of the different patterns is unknown but it is likely that they represent clinically important different entities, e.g., different propagation patterns of the epileptogenic activity, and thus could have consequences for presurgical evaluation and chances of postoperative seizure freedom in candidates for epilepsy surgery.