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A two-level multimodality imaging Bayesian network approach for classification of partial epilepsy: Preliminary data

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ABSTRACT

Background: Quantitative neuroimaging analyses have demonstrated gray and white matter abnormalities in group comparisons of different types of non-lesional partial epilepsy. It is unknown to what degree these type-specific patterns exist in individual patients and if they could be exploited for diagnostic purposes. In this study, a two-level multi-modality imaging Bayesian network approach is proposed that uses information about individual gray matter volume loss and white matter integrity to classify non-lesional temporal lobe epilepsy with (TLE-MTS) and without (TLE-no) mesial-temporal sclerosis and frontal lobe epilepsy (FLE).

Methods: 25 controls, 19 TLE-MTS, 22 TLE-no and 14 FLE were studied on a 4 T MRI and T1 weighted structural and DTI images acquired. Spatially normalized gray matter (GM) and fractional anisotropy (FA) abnormality maps (binary maps with voxels 1 SD below control mean) were calculated for each subject. At the first level, each group's abnormality maps were compared with those from all the other groups using Graphical-Model-based Morphometric Analysis (GAMMA). GAMMA uses a Bayesian network and a Markov random field based contextual clustering method to produce maps of voxels that provide the maximal distinction between two groups and calculates a probability distribution and a group assignment based on this information. The information was then combined in a second level Bayesian network and the probability of each subject to belong to one of the three epilepsy types calculated.

Results: The specificities of the two level Bayesian network to distinguish between the three patient groups were 0.87 for TLE-MTS and TLE-no and 0.86 for FLE, the corresponding sensitivities were 0.84 for TLE-MTS, 0.72 for TLE-no and 0.64 for FLE.

Conclusion: The two-level multi-modality Bayesian network approach was able to distinguish between the three epilepsy types with a reasonably high accuracy even though the majority of the images were completely normal on visual inspection.

Introduction

Quantitative unbiased whole brain neuroimaging analyses have demonstrated subtle but widespread gray and white matter abnormalities in different types of non-lesional partial epilepsy even in the absence of macroscopic lesions. It is generally assumed that the structural abnormalities in the focus are caused by microscopic malformations and/or excitotoxic neuronal damage while abnormalities beyond the focus are the result of excitotoxic damage due to spreading epileptogenic discharges and/or deafferentation (Bernhardt et al., 2008; Bonilha et al., 2006; Concha et al., 2009; Mueller et al., 2009a). The distribution of these abnormalities is determined by the location of the focus and the brain regions connected to it and therefore will be different for different epilepsy types. For example, temporal lobe epilepsy with mesial temporal sclerosis (TLE-MTS) is characterized by bilateral, ipsilaterally pronounced hippocampal and mesial temporal gray matter volume loss that extends into posterior temporo-parietal and frontal lobe regions while TLE with normal MRI (TLE-no) shows less well lateralized temporo-lateral volume losses extending into the insula and frontal lobes (Mueller et al., 2009a). Both are associated with temporal and frontal white matter abnormalities (Concha et al., 2009). The seizure semiology of frontal lobe epilepsy (FLE) is clinically more variable than that of TLE. Furthermore, frontal lobe regions are densely interconnected between themselves and with extrafrontal regions that allows a variety of pathways for seizure spread. Therefore, gray matter abnormalities in FLE are more heterogeneous and in group comparisons less pronounced in the frontal lobe but more prominent in subcortical relay structures, e.g. thalamus (Salmenpera et al., 2007; Widjaja et al., 2011).

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Given the characteristic differences at the group level, the question arises to what degree these type-specific patterns exist in individual patients and if they could be exploited for diagnostic purposes. A precondition to answer these two questions though, is the availability of a method that reliably identifies these abnormalities in individual subjects. Currently, the most common strategies to characterize brain structural abnormalities in individual subjects are either to use an imbalanced (single patient vs. control group) version of the general linear model or to employ a thresholding approach, e.g., by generating z-score maps. Both approaches are highly dependent on subjectively chosen thresholds and the former method also violates the basic assumptions of parametric statistical mapping. The diagnostic decision finally is typically made by comparing the extent and distribution of the abnormalities found in the group comparison with those in the single subject analysis either by visual inspection or by calculating a measure of overlap. Unfortunately, the between-subject variation of brain structural abnormalities even within well defined and seemingly uniform patient populations complicates the interpretation interpretation of these comparisons. If information from two or more imaging modalities has to be integrated, this process gets even more complex.

The objective of this study was therefore to develop a robust and unbiased multi-modality (volumetric MR and DTI), whole brain, single subject analysis approach that assesses to what degree the characteristic brain gray and white matter abnormalities found in group comparisons in non-lesional TLE with and without MTS and FLE are present in individual patients and if that information can be used to distinguish between the three epilepsy types. To that purpose a two-level Bayesian network approach was chosen. At the first level, Graphical-Model-based Morphometric Analysis (GAMMA; Chen and Herskovits, 2012) was used to determine the characteristic brain structural abnormalities for each of the three epilepsy types. GAMMA uses a Bayesian network approach to detect linear and non-linear associations between voxel clusters and a function variable, e.g. group, in each of the modalities. The second level Bayesian network used the combined information from the first level to calculate the probability of an individual patient belonging to each of the three epilepsy types. It was expected that a network using two modalities would have a higher classification accuracy than a single modality network.

Methods

Study population

The committees of human research at the University of California, San Francisco (UCSF), California Pacific Medical Center, San Francisco (CPMC) and VA Medical Center, San Francisco approved the study, and written informed consent was obtained from each subject according to the Declaration of Helsinki. The study population consisted of 80 subjects: 25 controls (34.2 ± 15.6, female/male: 18/7), 19 patients suffering from TLE with unilateral mesial temporal seizure origin and ipsilateral mesial-temporal sclerosis (TLE-MTS) (mean age: 40.8 ± 10.9, female/male: 11/8, left/right focus: 12/7, mean age at onset: 10.8 ± 9.1, mean epilepsy duration: 31.2 ± 12.7 years), 22 patients suffering from TLE with unilateral mesial-temporal seizure origin and normal MRI (TLE-no) (39.2 ± 10.4, female/male: 16/6, left/right focus: 14/8, mean age at onset: 24.6 ± 11.7, mean epilepsy duration: 15.4 ± 12.7 years) and 14 patients suffering from non-lesional frontal lobe epilepsy (FLE) (mean age: 27.3 ± 9.8; female/male: 7/7, left/right/bilateral: 6/4/4, mean age at onset: 15.4 ± 8.4, mean epilepsy duration: 13.0 ± 8.7 years). The identification of the epileptogenic focus was based on seizure semiology and prolonged ictal and interictal Video/EEG/Telemetry (VET) in all patients; the presence/absence of MTS in TLE was based on hippocampal subfield volumetry (Mueller et al., 2009b). All patients reported having been seizure free for at least 24 h before the 4 T study. FLE were significantly younger than TLE-MTS and TLE-no. TLE-no were significantly older at the onset of their epilepsy than TLE-MTS who had a longer duration of epilepsy than TLE-no and FLE.

MR imaging

All studies were performed on a Bruker MedSpec 4 T system controlled by a Siemens Trio™ console and equipped with a USA instruments eight channel array coil. The following sequences, which were part of a larger research imaging and spectroscopy protocol, were acquired: 1) T1-weighted whole brain gradient echo MRI TR/TE/TI = 2300/3/950 ms, 1.0 × 1.0 × 1.0 mm^3 resolution (for tissue segmentation); 2) 3D T2-weighted turbo spin–echo sequence, TR/TE = 3500/356 ms, 1.0 × 1.0 × 1.0 mm^3 resolution (for calculation of intracranial volume); 3) high resolution T2 weighted fast spin–echo sequence for hippocampal subfield volumetry (TR/TE: 3500/19 ms, 0.4 × 0.4 mm in plane resolution, 2 mm slice thickness, 24 interleaved slices, angulated perpendicular to the long axis of the hippocampal formation); and 4) EPI-based DTI (TR/TE = 6000/77, 2 × 2 × 3 mm^3 resolution, 6 diffusion encoding directions with b = 800 s/mm^2, repeated 4 times to boost SNR). Total acquisition time for structural MRIs: ~30 min.

Post-processing and image analysis

Post-processing

The T1 weighted image was segmented into tissue categories (gray matter (GM), white matter and CSF) using the Expectation Maximization Segmentation algorithm (van Leemput et al., 2003) as implemented in SPM2. The DTI data was motion and eddy current corrected using the FLIRT and FUGUE algorithms from FSL (http://www.fmrib.ox.ac.uk/fsl) and an additional geometric distortion correction performed (Tao et al., 2009). The DTI images were then co-registered to the T1 image and up-sampled to the T1 resolution. Fractional anisotropy (FA) maps were calculated using the teem algorithms (teem.sourceforge.net). Unbiased project specific, symmetrical atlases (GM, FA) were generated from the original and side flipped control images using the fast, high degree diffeomorphic image registration algorithm (DARTEL) implemented in SPM8 (http://www.fil.ion.ucl.ac.uk/spm). Images from patients with right sided-focus were side-flipped to ensure that the seizure onset was on the same side in all patients with lateralized seizure onset. The original and side-flipped images from all subjects were warped onto the corresponding atlas using DARTEL. The spatially normalized GM maps were multiplied with the Jacobian determinants of the warping step to preserve the original volume and the intensity of the resulting maps were corrected for differences in intracranial volume (ICV). The spatially normalized subject images (GM, FA) were smoothed with an 8 mm FWMH kernel.

First level Bayesian network: graphical-model-based morphometric analysis

The smoothed spatially normalized original and side flipped control images were used to calculate a voxel-wise mean and standard deviation (SD) map for each image modality. Each subject's smoothed GM map and FA map was compared against the corresponding mean map and binary maps indicating voxels with intensities at least one SD below the mean generated. The threshold was intentionally chosen well within the control range to enhance the possibility to identify regions showing mild but consistent abnormalities in the patient groups. The binary maps were used as input for Graphical-Model-based Morphometric Analysis (GAMMA) (Chen and Herskovits, 2005, 2007, 2012). GAMMA uses a Bayesian network to represent associations among voxels and a function variable, e.g., group, and applies a Markov random field based contextual clustering method to identify clusters of voxels based on their spatial relationship and similar association with the function variable. The stability of the association between these voxels and the function variable is determined using ensemble learning with bootstrap aggregation. The result is a label map (binary image of the voxel subset associated with the function variable) and a belief map (label map weighted by the confidence in the voxel/function variable association). GAMMA also determines each subject's group membership using a