Machine learning classification of mesial temporal sclerosis in epilepsy patients

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ABSTRACT

Background and purpose: Novel approaches applying machine-learning methods to neuroimaging data seek to develop individualized measures that will aid in the diagnosis and treatment of brain-based disorders such as temporal lobe epilepsy (TLE). Using a large cohort of epilepsy patients with and without mesial temporal sclerosis (MTS), we sought to automatically classify MTS using measures of cortical morphology, and to further relate classification probabilities to measures of disease burden.

Materials and methods: Our sample consisted of high-resolution T1 structural scans of 169 adults with epilepsy collected across five different 1.5 T and four different 3 T scanners at UCLA. We applied a multiple support vector machine recursive feature elimination algorithm to morphological measures generated from FreeSurfer's automated segmentation and parcellation in order to classify Epilepsy patients with MTS ($n = 85$) from those without MTS ($N = 84$).

Results: In addition to hippocampal volume, we found that alterations in cortical thickness, surface area, volume and curvature in inferior frontal and anterior and inferior temporal regions contributed to a classification accuracy of up to 81% ($p = 1.3 \times 10^{-17}$) in identifying MTS. We also found that MTS classification probabilities were associated with a longer duration of disease for epilepsy patients both with and without MTS.

Conclusions: In addition to implicating extra-hippocampal involvement of MTS, these findings shed further light on the pathogenesis of TLE and may ultimately assist in the development of automated tools that incorporate multiple neuroimaging measures to assist clinicians in detecting more subtle cases of TLE and MTS.

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1. Introduction

During the diagnostic workup of epilepsy, the identification of major structural abnormalities, including mesial temporal sclerosis (MTS), is critical for guiding clinical decision-making. In the past two decades, more advanced imaging acquisition and analysis methods have been used to detect more subtle morphological abnormalities in epilepsy patients. However, a majority of these studies identify a group-level difference, which has little clinical utility. Therefore, diagnosis of MTS and other structural abnormalities continues to be based on visual inspection by trained

neuroradiologists. More advanced machine-based learning methods can be applied to individual subjects and have significant potential for assisting with diagnosis and predicting treatment response in individuals with epilepsy and other neurological illnesses.

The majority of neuroimaging research has focused on temporal lobe epilepsy (TLE), which is the most prevalent form of medically intractable epilepsy (Engel, 1996). The pathologic finding of MTS exists in up to 65% of cases of TLE (Babb et al., 1984). MTS is characterized histologically by cellular loss and hippocampal reorganization and is often identified on MRI by hippocampal atrophy and signal abnormalities (Berkovic et al., 1991).

A multitude of prior neuroimaging studies have examined whole-brain differences in cortical morphology between patients with TLE and controls using both voxel based morphometry (VBM) and cortical thickness methods. As reviewed by Keller and Roberts (2008), VBM studies have found the largest effects in nearby ipsilateral medial temporal cortex, as well as more widespread effects in regions including the thalamus and frontal and parietal lobes. The

findings of more widespread alterations in cortical morphology that extend beyond the hippocampus are consistent with TLE's comorbid deficits in executive, intellectual and language functioning (Oyegbile et al., 2004). More recently, using methods that reconstruct the cortical surface to more precisely measure gray matter structure, researchers found up to 30% reductions in cortical thickness bilaterally in multiple frontal, temporal and occipital regions in TLE patients with MTS compared to controls (Lin et al., 2007; Bernhardt et al., 2010; Kemmotsu et al., 2011). These findings are present in TLE patients with and without MTS but have been shown to be stronger in patients with MTS (Labate et al., 2011). Additionally, these methods allow for measurements of cortical folding and complexity, which have also been reported to be abnormal in individuals with TLE and MTS, particularly in ipsilateral temporal and frontal cortices (Voets et al., 2011; Alhusaini et al., 2012).

These computer-based methods have improved our understanding of the neurobiology of TLE. However, relative to the classic findings of hippocampal atrophy and T2 signal abnormalities, the alterations are more subtle, distributed and variable across patients, which makes visual assessment by neuroradiologists a more challenging task. Additionally, in order for the methods to have clinical utility they need to be able to be applied to individual subjects, yet these approaches generally report differences at the group level. Thus, an automated tool that incorporates all of these findings into a single metric that predicts MTS or TLE has more promise in supplementing the visual analysis of neuroradiologists. Machine learning approaches seek to incorporate multiple data points in order to build a model that can make predictions in future data sets. Support vector machines (SVM) are a class of machine learning algorithms that are well suited for neuroimaging data as they are fast, flexible and can be readily automated. They have been studied extensively in computer science and have been applied to neuroimaging data from a variety of neurological diseases including Alzheimer's disease (Klöppel et al., 2008), autism spectrum disorder (Ecker et al., 2010) and ADHD (Colby et al., 2012).

A few prior investigations have applied machine-learning methods to TLE. Using a linear discriminant analysis McDonald et al. (2008) showed that lateral temporal cortical thickness could significantly discriminate TLE patients from controls with 74% accuracy. By focusing solely on quantification of hippocampal volume and T2 signal changes, computer-aided methods were shown to improve detection of MTS by 28% compared to visual analysis alone (Coan et al., 2014). Using a voxel-based approach for white and gray matter segmentation as well as voxel based DTI measures, Focke et al. (2012) were able to distinguish TLE with MTS from controls with greater than 88% accuracy. Cantor-Rivera et al. (2015) used multiple measures, including quantitative regional T1/T2 and DTI values to classify TLE patients from controls with similarly high classification accuracies. Another recent study (Bernhardt et al., 2015) used a more advanced classification approach that identified multiple TLE subtypes showing distinct patterns of structural abnormalities that were further related to surgical outcomes.

In this study, we applied an SVM algorithm to measures of brain morphology, including cortical thickness, volume, and curvature, generated from FreeSurfer's automated segmentation and parcellation to a large sample of epilepsy patients at UCLA in order to identify MTS. Additionally, we related MTS classification scores with clinical measures, including age of onset, disease duration and seizure frequency in order to glean further insights into the pathogenesis and natural course of TLE and MTS.

2. Materials and methods

2.1. Subjects

Our sample consisted of high-resolution T1 structural scans of 169 adults scanned under UCLA's epilepsy protocol (IRB # 11-001678). There were a total of 848 individuals scanned across five different 1.5 T scanners (Avanto, Signa Genesis, Signa HD, two Sonata) and four different 3 T scanners (Verio, Skyra and two Trio-Tim) under UCLA's epilepsy protocol between April 2003 and May 2013. In order to be included in our study, individuals had to have a clinical diagnosis of epilepsy, either with or without MTS, and without evidence of other major structural abnormalities including isolated cortical dysplasia, tuberous sclerosis, leukomalacia, glioma, gray matter heterotopia or encephalomalacia as verified by a board certified neuroradiologist (N.S.). There were a total of 84 patients that had a clinical diagnosis of epilepsy without evidence of any structural abnormalities and which served as the control group. There were a total of 85 patients that had a diagnosis of epilepsy with left, right or bilateral MTS without any other structural abnormalities. Of the patients with MTS, 42 had left MTS, 35 had right MTS and 8 had bilateral MTS (Three of which were described to have left greater than right MTS). There were no significant differences (p > 0.05) between the control and MTS groups when comparing age, scanner strength (1.5 T vs. 3 T) and data resolution as measured by voxel volume (See Table 1 for group characteristics).

A retrospective chart review was done on all 169 patients in order to determine age of seizure onset, duration of disease and seizure frequency. In estimating seizure frequency, the average numbers of seizures were taken from chart reviews and/or a standardized clinical assessment written for each patient being evaluated by UCLA Adult Epilepsy Program. In cases where patients had multiple types of seizures, the total seizure frequency was summed across different seizure types. There were differences between groups for demographics including age of seizure onset, duration of disease, and seizure frequency, such that patients with MTS had an earlier onset of disease (p = 0.001) and disease duration (p = 0.0001) but lower seizure frequency (p = 0.01) than patients without MTS (Table 1).

2.2. MRI preprocessing

The basic T1-weighted anatomical MPRAGE sequence used across different scanners was as follows: TR/TE/TI = 1900/2.89/900 ms, 9° flip angle, 0.98 mm 0.98 mm 1.0–1.8 mm slice thickness. The exact parameters varied slightly across scanners. For additional details regarding acquisition parameters please see Lin et al. (2007), which used an overlapping dataset. The T1-weighted anatomical MRI scans were processed with FreeSurfer's *recon-all* processing pipeline for cortical reconstruction and volumetric segmentation (Fischl and Dale, 2000; Fischl, 2004) (software freely available at http://surfer.nmr.mgh.harvard.edu/). This method automatically generates reliable volume and thickness segmentations of white matter, gray matter, and subcortical volumes. The streamlined pipeline included removal of non-brain tissue, Tailarach transformations, segmentation of subcortical white and deep gray matter regions, intensity normalization and atlas registration. After these steps, a mesh model of the cortical surface was generated and the cortical surface was parcellated into 34 cortical regions based on gyral and sulcal landmarks for each hemisphere according to the Desikan–Killiany atlas (Desikan et al., 2006). Importantly, it has been shown that the normalization process performed by FreeSurfer has good test–retest reliability across field strengths and scanner manufacturers (Han et al., 2006; Pfefferbaum et al., 2012).

Nine measures for each of the 34 cortical regions were calculated per hemisphere. These measures consisted of surface area, gray matter volume, average cortical thickness, cortical thickness standard deviation, cortical mean curvature, Gaussian curvature, cortical folding index, cortical curvature index and number of vertices. Additionally, three morphological measures (regional volume in mm^3, regional voxel intensity mean, and regional voxel intensity standard deviation) were calculated for 45 non-cortical regions.