Original Article

A Novel ^{1}H-MRS Quantification Approach Based on Spectral Fitting for Lateralization/Localization of Seizure Foci in Patients with Temporal Lobe Epilepsy

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ABSTRACT

Purpose- Proton magnetic resonance spectroscopy (^{1}H-MRS) is a non-invasive method with the capability to correctly lateralize the seizure foci in patients with Temporal Lobe Epilepsy (TLE), with the first evidence published in 1993. One major drawback of this modality is that the MRS data is naturally high dimensional. This, along with the time-consuming post-processing and quantification procedures such as spectral fitting, have made MRS impractical for clinical use. Dimension reduction techniques eliminate undesired properties of high-dimensional spaces, suggesting simple and feasible analysis techniques in comparison with quantification procedures.

Methods- In this study, we use two dimension reduction techniques so-called Isomap and Diffusion maps to quantify MRS data obtained from TLE patients for localization seizure foci. Then, we evaluate the results by comparison with obtained ratio of NAA/(Cr+Cho) from the quantification method.

Results- Our results show that the proposed methodology has the ability to localize and/or to lateralize the seizure foci in such patients, while it maintains minimal required amount of computations and time (Sensitivity= 60%, Specificity= 82.81%).

Conclusion- We are hoping that this method broadens new horizons to explore the informative yet complicated MRS modality into Epileptic diagnosis.

1. Introduction

Hippocampal sclerosis (HS) is the most common feature in patients with medically intractable Temporal Lobe Epilepsy (TLE) [1]. Patients with HS are the best candidates for surgery; and if the seizure foci is determined correctly, the probability for a successful surgery will be 70%- 90% [2]. The most common imaging technique to predict localization and lateralization of the epileptogenic zone in patients with seizure

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disorders is conventional magnetic resonance imaging (cMRI) [3] which can detect such disorders with sensitivity and specificity up to 90% and 85%, respectively [1]; meaning not only cMRI may miss to detect abnormalities related to seizure foci [1], but also seizures may remain in patients with MRI-visible lesions even after surgery.

Therefore, we need to investigate such patients at risk with other imaging modalities [4], like advanced MRI with qualitative and quantitative indications to help localize the epileptic lesions [5].

Proton magnetic resonance spectroscopy (^{1}H-MRS) is a non-invasive method that can add diagnostic sensitivity in lateralization of epileptic foci with demonstrating decreased N-acteyl-aspartate (NAA), elevation of glutamate and glutamine (Glx) and Myo-inositol [3]. ^{1}H-MRS can correctly lateralize epileptogenic zone (hippocampal and amygdal) with 50% specificity and 96% sensitivity [5], while it is useful for the identification of the underlying neoplastic pathology, as well as the prediction of seizure control in the long-term follow-up after surgery [6]. To evaluate the MRS data in lateralization and localization of the epileptogenic zone in patients with epilepsy, some studies investigated the correlation between ^{1}H-MRS findings with high-resolution MRI, positron emission tomography (PET) and single-photon emission computed tomography (SPECT) [7], showing that ^{1}H-MRS is more sensitive than other imaging techniques such as PET [8] while it has higher correlation with the EEG findings as the most important tool in the clinical diagnosis of TLE [5].

One major drawback of the data obtained from ^{1}H-MRS is its high dimensionality; to be considered as one of the main difficulties for the analysis of the MRS data [9]. On the other hand, MRS needs time-consuming post-processing and quantification procedures, such as spectral fitting [10]. Therefore, one technique for faster and easier analysis of the MRS data will be dimension reduction.

Dimension reduction techniques can transfer the high-dimensional data into a meaningful representation of reduced dimensionality that corresponds to the intrinsic dimensionality of the data. Dimension reduction eliminates undesired properties of high-dimensional spaces and are categorized into linear and nonlinear methods [11]. Principal components analysis (PCA) is the most common linear technique in MRS data analysis. Unfortunately, PCA has some limitations in this field such as its component is a linear combination of all the spectral frequencies which limits the interpretability of the results [9]. In contrast, nonlinear techniques such as Isomap, KernelPCA and Diffusion maps can deal with this complex nonlinear data, an essential characteristic for biological data including MRS, with highly nonlinear manifolds. In particular, Diffusion map (DM) algorithm calculates the proximity of the data-points, the so-called diffusion distance, by performing random walk for a number of time steps [11].

In this paper, we employed a dimension reduction technique for spectral fitting of the MRS data-set for localization and/or lateralization of seizure foci in TLE patients, and from the multi-voxel MRS data with TE= 30 msec. Then, we evaluated the results based on the opinion of a neurologist, to show the ability of this algorithm for localization and/or lateralization of the epileptogenic zone in TLE patients and results comprised with obtained ratio of NAA/(Cr+Cho) from quantification method. One should note that dimension reduction techniques have been successfully used in the interpretation of MRS data acquired from brain tumor or prostate cancer [9, 12, 13], but to the best of our knowledge there has been no study to report the role of such methods for the localization of seizure foci in patients with epilepsy especially TLE patients.

2. Materials and Methods

2.1. Measurements

All MR imaging and proton MR spectroscopic imaging were acquired with a 1.5 T (Magnetom Avanto; Siemens, Erlangen, Germany) by using a standard head coil. The procedure involved conventional MRI, (1) axial T_1- weighted gradient echo (MPRAGE) TR/TE/TI = 1630/2.82/1100 ms, 15° flip angle, slice thickness 1 mm, FOV= 256×192, (2) axial and coronal T_2-weighted 2D turbo spin echo TR/TE= 5200/92 ms, slice thickness 3 mm with gap= 3.3 mm, FOV= 180×180, T_2-weighted Fluid Attenuated Inversion Recovery (FLAIR) TR/TE/TI= 7800/82/2300.8 ms, slice thickness 3 mm, gap= 3.3 mm, FOV= 163×190. MRS data was obtained as chemical shift imaging (CSI) with this protocol: 3D Point Resolved Spectroscopy (PRESS) and added phase encoding TR/TE=

1200/30 ms, flip angel 90°, vector size= 512, number of phase encoding steps= 12, 5.62×8.125×8.75 mm resolution, and total acquisition time= 7 min. A single voxel was prescribed in white matter or gray matter (only one type of tissue) for correction of eddy current artifact with these parameters: TR/TE= 1000/30 ms, flip angle= 90°, vector size= 512, and acquisition time= 5 min.

2.2. Pre-processing of the MRS Signal

The MRS signals rarely decay as quite exponential due to experimental conditions such as physiological movements, shimming non-ideality and the residual water signal. Therefore, pre-processing of the data is an important step to minimize analysis errors. Some time-domain pre-processing steps are proposed as follows [14]:

Eddy current compensation (ECC):

Eddy currents induce time-varying magnetic fields that cause frequency-dependent phase shifts or de-phasing of the time-domain signal. Such eddy currents can be corrected by subtracting a reference signal such as water signal from the original signal [15].

Residual water suppression:

There are various algorithms to remove residual water [15]. The maximum-phase finite impulse response (MP-FIR) filter method is an accurate and efficient technique for the elimination of the residual water signal which is employed in this paper [14].

2.3. Data Quantification

An overview from quantification procedure is as follow (Figure 1):

- Neighborhood estimation
- Dimensionality reduction with Isometric feature mapping (ISOMAP)
- Spectral fitting of the MRS data using DM

2.3.1. Neighborhood Estimation

Isometric feature mapping (ISOMAP) which is based on the classical multi dimensional scaling (MDS) employs distances along a geodesic path between all pairs of data points to preserve the intrinsic geometry of the data. A sequence of "short hops" is added between neighboring points, then shortest paths in graph with connecting neighboring data points are computed to estimate the geodesic distance between faraway points. The overall neighborhood estimation is estimating the geodesic distance between faraway points based on the input-space distances [16].

2.3.2. Dimensionality Reduction with ISOMAP

ISOMAP assumes that the data lies on an unknown sub-manifold M which is embedded in a p-dimensional space. It seeks a mapping that preserves the intrinsic metric structure of the observations. It also assumes that the manifold M is globally isometric to a convex subset of a low-dimensional Euclidean space [16-18].

ISOMAP has three steps, 1) The first step is to construct neighborhood graph. It determines neighboring data-points from the MRS data-set using the Euclidean metric to create a graph as nodes. 2) The second step is to compute shortest paths. The geodesic distance between two faraway data-points on the graph is determined based on shortest distance between the nodes, which is computed using the Dijkstra's algorithm and used to create the *distance matrix* relating all MRS data-points. 3) The final step is to construct d-dimensional embedding [16-18].

2.3.3. Spectral Fitting of the MRS Data Using DM

Spectral fitting is a method to group samples into lower dimensional by the results of spectral methods that reveal the manifold, such as the diffusion map. The main idea is that the dimensionality reduction has already simplified the fitting problem so that the fitting in the low-dimensional space is an easy problem.

Implemented DM algorithm is outlined in three steps as below:

- Constructing the Similarity Matrix:

The initial step of the DM algorithm is to calculate the similarity matrix W. The entries of W are the weights along the edges connecting corresponding nodes, where for any given nodes i and j, the weight is determined by the heat kernel [19, 20]:

$$W_{ij} = \exp\left(-\frac{\| t_i - t_j \|^2}{\varepsilon}\right) \quad (1)$$

- Calculate Markov random matrix:

P, *Markov* matrix, defines the forward transition probability matrix of a dynamical process. This matrix represents the transition probabilities between the data points [19, 20]:

$$D_{ii} = \sum W_{ij},\ i \in 1...n\ . \quad (2)$$

$$P = D^{-1}W \quad (3)$$

Then eigen-values of *p*; the conjugate matrix of *p* is calculated as below:

$$\tilde{P} = D^{-\frac{1}{2}}\ W\ D^{\frac{1}{2}}$$

This so-called normalized graph Laplacian preserves the eigenvalues.

For asmuch as this note that, eigen-vectors calculate as matrix $U = [u_1, u_2, ..., u_n]$ and eigen values of *P* and $\tilde{P}$ stay the same $V = D^{-\frac{1}{2}}U$ low-dimensional coordinates in the embedded space ψ using Λ and V create as $\Psi = V\,\Lambda$.

- Calculating the Eigen-value and Eigen-vector of Markov Random Matrix:

In this step singular value decomposition (SVD) of matrix P yields eigen-value and eigen-vector. The low-dimensional coordinate in spectral space are created using eigen-values and eigen-vectors [19, 20].

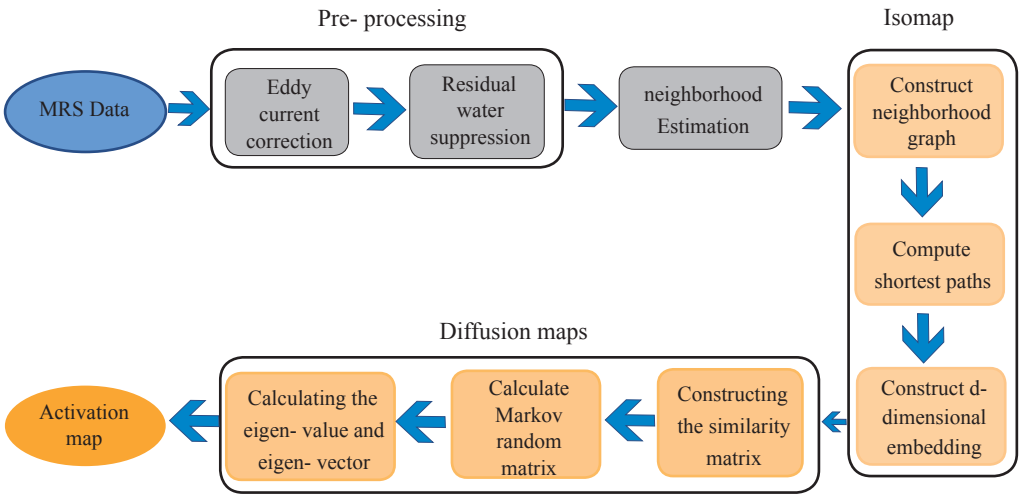

Figure 1. Overview of the method.

3. Results

The obtained results from ^{1}H-MRS data after pre-processing, dimensionality reduction and spectral clustering, are presented; then in order to evaluate the obtained results, they are compared with quantitation based on semi-parametric quantum estimation (QUEST) method and diagnosis of neurologist.

3.1. Comparison with Diagnosis by the Neurologist:

The proposed method could correctly lateralize the seizure foci. The result of the proposed algorithm is shown in Figure 2, and its sensitivity and specificity are presented in Table 1.

3.2. Comparison with Subtract_QUEST Algorithm:

Processing of the MR spectroscopic imaging data was performed by software developed in MATLAB based on subtract_QUEST algorithm [21]. The mean NAA/(Cr+Cho) ratio shows a reduction in the seizure foci in TLE patients (0.59 ± 0.12) versus control group (0.81 ± 0.06) or contralateral (0.72 ± 0.16) [22, 23]. In Figure 2, the ratio of NAA/(Cr+Cho) is depicted, followed by the sensitivity and specificity results appeared in Table 1.

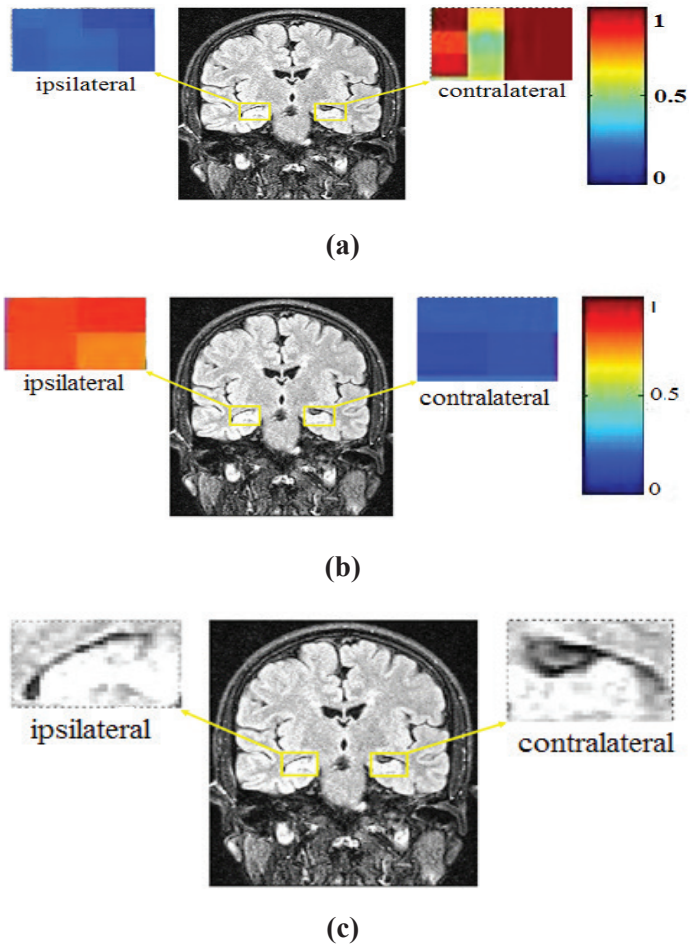

Figure 2. a) The ratio of NAA/(Cr+Cho); b) Activation map using the proposed method; and c) Opinion of a neurologist.

Table 1. Sensitivity and specificity.

Method	MRS Quantification	The Proposed Method
Sensitivity	60%	60%
Specificity	57.37%	82.81%

4. Discussion

In this paper, we proposed a method for spectral fitting of the MRS data acquired in patients with Temporal Lobe Epilepsy, for the first time. Most of the studies that had been done in this area, used long echo times (TEs) which is easier to analyze because these are less affected by artifacts from macromolecules and have a flatter baseline [24]. Investigation with shorter TE also produce data on concentrations of the combined glutamate plus glutamine signal (Glx) and myoinositol (Ins) that increased Ins may be a feature of gliosis [24]. But, short TEs needs time-consuming pre-processing and post-processing procedure that is not user friendly with existing applications. This has reduced the use of MRS as a diagnostic tool for clinical applications.

However, our results show that the proposed methodology has the ability to localize and/or to lateralize the seizure foci in such patients, while it maintains minimal required amount of computations and time. This method eliminates undesired properties of high-dimensional spaces by dealing with this nonlinear data, which is an essential characteristic for the biological data.

The method could be expanded to analyze other forms of Epilepsy with bigger/multi-modal datasets. Due to its fast and successful quantification on the high dimensional MRS data, we are hoping that this method broadens new horizons to explore the informative yet complicated MRS modality into Epileptic diagnosis.

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