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Classification of mild cognitive impairment and Alzheimer's Disease with machine-learning techniques using ^{1}H Magnetic Resonance Spectroscopy data

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ABSTRACT

Several magnetic resonance techniques have been proposed as non-invasive imaging biomarkers for the evaluation of disease progression and early diagnosis of Alzheimer's Disease (AD). This work is the first application of the Proton Magnetic Resonance Spectroscopy ^{1}H-MRS data and machine-learning techniques to the classification of AD. A gender-matched cohort of 260 subjects aged between 57 and 99 years from the Alzheimer's Disease Research Unit, of the Fundación CIEN-Fundación Reina Sofía has been used. A single-layer perceptron was found for AD prediction with only two spectroscopic voxel volumes (Tvol and CSFvol) in the left hippocampus, with an AUROC value of 0.866 (with TPR 0.812 and FPR 0.204) in a filter feature selection approach. These results suggest that knowing the composition of white and grey matter and cerebrospinal fluid of the spectroscopic voxel is essential in a ^{1}H-MRS study to improve the accuracy of the quantifications and classifications, particularly in those studies involving elder patients and neurodegenerative diseases.

1. Introduction

Over the past decades, researchers have tried to define this grey area of cognitive decline that probably represents a transitional state between usual brain ageing and dementia (Metastasio et al., 2006). Mild cognitive impairment (MCI) was proposed as a transitional state between healthy ageing and Alzheimer's Disease (AD) (Grundman et al., 2004). Although MCI is a category at high risk of developing dementia, namely 10–15% per year compared to 1–2% in the healthy elderly population (Ackl et al., 2005), some MCI patients never develop dementia and not all AD patients pass through MCI stage. Many studies were performed in order to detect clinical, neuropsychological and biological predictive markers of progression of MCI to AD (Metastasio et al., 2006). Brain damage in AD and MCI begins in the medial temporal lobe, including the hippocampus, the parahippocampal gyrus and entorhinal cortex extending to the limbic system (Devanand et al., 2007; Hampel et al., 2008; Holland, Brewer, Hagler, Fennema-Notestine, & Dale, 2009; Raji, Lopez, Kuller, Carmichael, & Becker, 2009). Medial temporal lobe and hippocampal atrophy was considered as a significant marker of dementia in subjects with mild cognitive impairment (de Leon et al., 1993; Korf, Wahlund, Visser, & Scheltens, 2004; Visser, Verhey, Hofman, Scheltens, & Jolles, 2002).

Several structural and functional magnetic resonance (MR) techniques have been proposed as non-invasive imaging biomarkers for the evaluation of disease progression and early diagnosis of AD. The analysis of these biomarkers allows the study of differences between groups (e.g. disease vs. healthy groups). However, these methods are not applicable on a single-subject level and therefore do not improve the clinical diagnosis potential. In order to overcome this issue, machine-learning techniques have recently been identified as promising tools in neuroimaging data analysis for individual class prediction. Advances in medical imaging and medical image analysis have provided a means to generate and

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extract valuable neuroimaging information. Automatic classification techniques provide tools to analyse this information and observe inherent disease-related patterns in the data. In particular, these classifiers have been used to discriminate AD patients from healthy control subjects and to predict conversion from MCI to AD.

MR modalities produce extremely high-dimensional raw data that can contain inherent patterns related to AD. Machine-learning methods are helpful tools for analysing many variables simultaneously and finding inherent patterns in the neuroimaging data. A wide range of different supervised classifiers has been used in the field of AD classification and MCI prediction (Falahati, Westman, & Simmons, 2014).

Support vector machines (SVM) are commonly used in AD research for multivariate classification (Adaszewski, Dukart, Kherif, Frackowiak, & Draganski, 2013; Aguilar et al., 2013; Andrade de Oliveira, Carthery-Goulart, Oliveira Junior, Carrettiero, & Sato, 2015; Kloppel et al., 2008; Liu, Tosun, Weiner, Schuff, & Alzheimer's Disease Neuroimaging Initiative, 2013; Magnin et al., 2009; Plant et al., 2010; Tong et al., 2014; Varol, Gaonkar, Erus, Schultz, & Davatzikos, 2012; Vemuri et al., 2008; Young et al., 2013). Principal Components Analysis (PCA) (Eskildsen et al., 2013; Koikkalainen et al., 2011; Teipel et al., 2007; Westman et al., 2011) and linear discriminant analysis (LDA) (Cho, Seong, Jeong, Shin, & Alzheimer's Disease Neuroimaging Initiative, 2012; Coupe, Eskildsen, Manjon, Fonov, Collins, & Alzheimer's Disease Neuroimaging Initiative, 2012; Eskildsen et al., 2013; Liu, Tosun, Weiner, Schuff, & Alzheimer's Disease Neuroimaging Initiative, 2013; McEvoy et al., 2011) are well-known statistical classifiers which have been used for AD classification. Among other methods, there are artificial neural networks (ANNs) (Aguilar et al., 2013; Escudero, Zajicek, Ifeachor, & Initiative, 2011) or decision trees (DT) (Aguilar et al., 2013; Hamou et al., 2011; Querbes et al., 2009). All these works are based on anatomical MR imaging (MRI) biomarkers, such as volumetric or cortical thickness measures, to help discriminate AD subjects from elderly control or MCI subjects. However, other MR techniques, such as Diffusion Tensor Imaging (DTI), have been explored in the automatic classification of MCI patients (Dyrba et al., 2013; Haller et al., 2010; O'Dwyer et al., 2012). The collection of Weka machine-learning algorithms (Hall et al., 2009) was also used for the learning and classification processes in the detection of microstructural white matter degeneration in AD with DTI (Dyrba et al., 2013) and for the detection of brain atrophy patterns based on MRI for the prediction and early detection of AD (Farhan, Fahiem, & Tauseef, 2014; Plant et al., 2010). Weka is a full toolkit for classification and regression used for several other purposes such as the detection of autism (Kosmicki, Sochat, Duda, & Wall, 2015), annotation of diverse human tissues (Ernst & Kellis, 2015) or for the classification of cell death-related proteins (Fernandez-Lozano, Gestal, et al., 2014).

Proton Magnetic Resonance Spectroscopy (^{1}H-MRS) is a useful technique for studying brain metabolites in both health and illness (Frederick et al., 2004; Lin, Ross, Harris, & Wong, 2005; Ross & Sachdev, 2004). The main difference between standard MRI and ^{1}H-MRS is that the frequency of the MR signal is used to encode different types of information. MRI uses high spatial resolution to generate anatomical images, whereas ^{1}H-MRS provides chemical information about the tissues. Rather than images, ^{1}H-MRS data are presented as line spectra where the peaks on the spectra obtained correspond to various metabolites, both normal and abnormal, which may be identified accurately. The area under each peak represents the relative concentration of nuclei detected for a given chemical species.

^{1}H-MRS studies provide insight into the *in vivo* metabolism of dementia and in particular Alzheimer's Disease, identifying an evolutionary pattern of regional metabolite abnormalities (Ackl et al., 2005). Among various substances assessed using ^{1}H-MRS, functional significances in 3 metabolites are of interest to the current study and have been discussed at length in the literature reporting on cognitive disorders (Watanabe, Shiino, & Akiguchi, 2010): N-acetylaspartate (NAA), myo-inositol (mI) and choline compounds (Cho). In AD, the main finding using ^{1}H-MRS is the decreased levels of NAA and the increased levels of mI in the occipital, temporal, parietal, and frontal regions of patients with AD, even at the early stages of the disease (Miller et al., 1993; Moats, Ernst, Shonk, & Ross, 1994; Valenzuela & Sachdev, 2001; Waldman & Rai, 2003). NAA is a marker of healthy neuronal density. Consistent with this and with the pathological changes known to occur in neurodegenerative dementing illnesses (Pearson, Esiri, Hiorns, Wilcock, & Powell, 1985), localised ^{1}H-MRS has shown reduced NAA in different brain regions of AD and MCI patients (Ackl et al., 2005; Chantal, Braun, Bouchard, Labelle, & Boulanger, 2004; Chantal, Labelle, Bouchard, Braun, & Boulanger, 2002; Falini et al., 2005; Kantarci et al., 2007; Modrego & Fayed, 2012; Schuff, Capizzano, Du, Amend, O'Neill, Norman, et al., 2002; Valenzuela & Sachdev, 2001). mI is primarily located in glial cells and has been interpreted as a marker for glial activation (Tumati, Martens, & Aleman, 2013). There have been reports of increased mI, which is suggestive of an increase in glial content or membrane abnormality in subjects with AD (Ernst, Chang, Melchor, & Mehringer, 1997; Huang et al., 2001; Kantarci, Jack, Xu, Campeau, O'Brien, Smith, et al., 2000; Parnetti et al., 1997; Shonk et al., 1995; Siger, Schuff, Zhu, Miller, & Weiner, 2009).

Despite the fact that machine-learning techniques have been widely used for MRI images in the study of AD, there are no studies on their application to ^{1}H-MRS data. However, there are several studies that use classification methods such as LDA and PCA, for brain tumour classifications with spectroscopic data (Davies et al., 2008; Opstad, Ladroue, Bell, Griffiths, & Howe, 2007; Raschke, Davies, Wilson, Peet, & Howe, 2013; Raschke, Fuster-Garcia, Opstad, & Howe, 2012). In the study of AD, the work carried out by Di Deco et al. (2013) uses combinations of different MR neuroimaging biomarkers, including ^{1}H-MRS metabolites, in order to find the most accurate biomarkers in diagnosing or predicting this pathology in its different phases.

Among the reasons why there are no machine-learning studies for single-subject level classification with ^{1}H-MRS in AD may be the increase of ^{1}H-MRS variability due to normal ageing and also as a result of atrophy in grey and white matter caused by neurodegeneration. ^{1}H-MRS techniques use rectangular or cubic voxels, which do not usually correspond to the curved shapes of the brain regions. In this regard, the spectroscopy voxel often includes a combination of cerebrospinal fluid (CSF), grey matter (GM) and white matter (WM). Because CSF has no measurable ^{1}H-MRS metabolites, the presence of a large portion of CSF within the voxel, as could happen by tissue atrophy in these diseases, could affect the metabolite concentrations.

The aim of this study was to test and evaluate the effectiveness of machine-learning schemes for single-subject level classification of individuals affected by different stages of dementia (healthy elderly subjects, MCI and AD subjects) based on ^{1}H-MRS data. The collection of Weka machine-learning algorithms was used for this purpose. To overcome the problem of variations in tissue composition in the voxel, the volumes of GM, WM and CSF within the spectroscopic voxel were also used for the analysis.

2. Materials

2.1. Subjects

A gender-matched cohort of 260 subjects aged between 57 and 99 years was used. They were submitted to the study in the