NeuroImage: Clinical 17 (2018) 628–641

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

Selecting the most relevant brain regions to discriminate Alzheimer's disease patients from healthy controls using multiple kernel learning: A comparison across functional and structural imaging modalities and atlases

Jane Maryam Rondina[a,b,*], Luiz Kobuti Ferreira[a,f], Fabio Luis de Souza Duran[a], Rodrigo Kubo[c], Carla Rachel Ono[c], Claudia Costa Leite[c,d], Jerusa Smid[e], Ricardo Nitrini[e], Carlos Alberto Buchpiguel[c], Geraldo F. Busatto[a,f,g]

[a] Laboratory of Psychiatric Neuroimaging (LIM 21), Department of Psychiatry, Faculty of Medicine, University of São Paulo, São Paulo, Brazil
[b] Sobell Department of Motor Neuroscience and Movement Disorders, Institute of Neurology, University College London, London, UK
[c] Department of Radiology and Oncology, University of São Paulo Medical School, São Paulo, Brazil
[d] Department of Radiology, University of North Carolina at Chapel Hill, NC, USA
[e] Department of Neurology and Cognitive Disorders Reference Center (CEREDIC), University of São Paulo, São Paulo, Brazil
[f] Núcleo de Apoio à Pesquisa em Neurociência Aplicada (NAPNA), University of São Paulo, São Paulo, Brazil
[g] Department and Institute of Psychiatry, University of São Paulo, São Paulo, Brazil

ARTICLE INFO

Keywords:
Alzheimer's Disease
MRI
PET
SPECT
Multiple kernel learning
Brain atlas

ABSTRACT

Background: Machine learning techniques such as support vector machine (SVM) have been applied recently in order to accurately classify individuals with neuropsychiatric disorders such as Alzheimer's disease (AD) based on neuroimaging data. However, the multivariate nature of the SVM approach often precludes the identification of the brain regions that contribute most to classification accuracy. Multiple kernel learning (MKL) is a sparse machine learning method that allows the identification of the most relevant sources for the classification. By parcelating the brain into regions of interest (ROI) it is possible to use each ROI as a source to MKL (ROI-MKL).

Methods: We applied MKL to multimodal neuroimaging data in order to: 1) compare the diagnostic performance of ROI-MKL and whole-brain SVM in discriminating patients with AD from demographically matched healthy controls and 2) identify the most relevant brain regions to the classification. We used two atlases (AAL and Brodmann's) to parcelate the brain into ROIs and applied ROI-MKL to structural (T1) MRI, ^{18}F-FDG-PET and regional cerebral blood flow SPECT (rCBF-SPECT) data acquired from the same subjects (20 patients with early AD and 18 controls). In ROI-MKL, each ROI received a weight (ROI-weight) that indicated the region's relevance to the classification. For each ROI, we also calculated whether there was a predominance of voxels indicating decreased or increased regional activity (for ^{18}F-FDG-PET and rCBF-SPECT) or volume (for T1-MRI) in AD patients.

Results: Compared to whole-brain SVM, the ROI-MKL approach resulted in better accuracies (with either atlas) for classification using ^{18}F-FDG-PET (92.5% accuracy for ROI-MKL versus 84% for whole-brain), but not when using rCBF-SPECT or T1-MRI. Although several cortical and subcortical regions contributed to discrimination, high ROI-weights and predominance of hypometabolism and atrophy were identified specially in medial parietal and temporo-limbic cortical regions. Also, the weight of discrimination due to a pattern of increased voxel-weight values in AD individuals was surprisingly high (ranging from approximately 20% to 40% depending on the imaging modality), located mainly in primary sensorimotor and visual cortices and subcortical nuclei.

Conclusion: The MKL-ROI approach highlights the high discriminative weight of a subset of brain regions of

Abbreviations: ^{18}F-FDG-PET, ^{18}F-Fluorodeoxyglucose-Positron Emission Tomography; AAL, Automated Anatomical Labeling (atlas); AD, Alzheimer's Disease; BA, Brodmann's Area; GM, Gray Matter; MKL, Multiple Kernel Learning; MKL-ROI, MKL based on regions of interest; ML, Machine Learning; NF, number of features; NSR, Number of Selected Regions; PVE, Partial Volume Effects; rAUC, Ratio between negative and positive Area Under Curve; rCBF-SPECT, Regional Cerebral Blood Flow; ROI, Region of Interest; SVM, Support Vector Machine; T1-MRI, T1-weighted Magnetic Resonance Imaging; TN, True Negative (specificity - proportion of healthy controls correctly classified); TP, True Positive (sensitivity - proportion of patients correctly classified)

* Corresponding author at: Sobell Department of Motor Neuroscience and Movement Disorders, Institute of Neurology, University College London, London, UK.
E-mail address: j.rondina@ucl.ac.uk (J.M. Rondina).

https://doi.org/10.1016/j.nicl.2017.10.026
Received 31 December 2016; Received in revised form 12 October 2017; Accepted 24 October 2017
Available online 09 November 2017

known relevance to AD, the selection of which contributes to increased classification accuracy when applied to ^{18}F-FDG-PET data. Moreover, the MKL-ROI approach demonstrates that brain regions typically spared in mild stages of AD also contribute substantially in the individual discrimination of AD patients from controls.

1. Introduction

Many neuroimaging studies to date have investigated brain abnormalities associated with the diagnosis of Alzheimer's disease (AD), most often using magnetic resonance imaging (MRI), ^{18}F-fluorodeoxyglucose-positron emission tomography (^{18}F-FDG-PET) to measure regional brain metabolism, and single photon emission computed tomography (SPECT) to measure regional cerebral blood flow (rCBF SPECT) (Johnson et al., 2012; Matsuda, 2007; Nordberg et al., 2010; Vemuri et al., 2010). These studies have typically carried out comparisons of mean imaging indices between samples of AD patients and healthy elderly controls across separate brain regions using either regions of interest (ROIs) (Kinkingnéhun et al., 2008; Lehmann et al., 2011; Nadkarni et al., 2012; Ortiz et al., 2014) or voxel-based techniques, applying mass univariate approaches for statistical inference (Kinkingnéhun et al., 2008; Lehmann et al., 2011; Matsuda, 2013). These imaging studies have identified abnormalities in several brain regions in association with the diagnosis of AD from early stages of the disease onwards (Mosconi et al., 2009; Ruan et al., 2016; Thompson et al., 2004). When such traditional mass-univariate approach is used, the detection of the relevance of different brain regions to characterize AD is straightforward; since each ROI or voxel is treated independently, thresholds based on statistical significance and spatial extent can be applied to the statistical parametric results in order to select clusters of voxels with greatest relevance to distinguish AD patients from controls (Ashburner and Friston, 2000; Busatto et al., 2008; Guo et al., 2010; Hirata et al., 2005; Karas et al., 2003).

More recently, a number of neuroimaging investigations of AD have applied machine learning (ML) techniques that allow detection of spatially complex and often subtle neuroimaging patterns of brain abnormalities in individual subjects, building high-dimensional classifiers based on multivariate methods that simultaneously assess multiple voxels within the brain space (Davatzikos et al., 2008; Duara et al., 2013; Klöppel et al., 2008; Ritter et al., 2015; Zhang et al., 2011). Rather than determining statistical group differences, this approach allows classification of images of each subject, providing individual predictions which might ultimately be used in the clinical context (Ferreira and Busatto, 2011; Mcevoy et al., 2009; Petersen et al., 2010; Ruan et al., 2016; Zhang et al., 2011). In contrast with the above mass-univariate strategies, the determination of the most relevant voxels that characterize the difference between groups is not as easily achieved in ML-based approaches, as the weight of each voxel to classify groups depends on all the other voxels, in a multivariate model. In order to address this problem, strategies aiming to select the most relevant voxels to be used as input to the models may be sought to facilitate the interpretation of the weight maps.

In recent years, Multiple Kernel Learning (MKL) approaches have been proposed to combine multiple sources of data in ML algorithms. Up to the present date, the MKL approach has been applied to neuroimaging data predominantly to combine different representations (usually two or more imaging modalities) (Hinrichs et al., 2009; Liu et al., 2014). However, some recent pilot investigations have proposed models in which subsets of features are used as sources of data (Castro et al., 2014; Xia et al., 2014). If these subsets of features are extracted according to some neuroanatomical criterion, it is possible to obtain predictions based on anatomical localization (Mourão-Miranda et al., 2012) and to help to determine which are the most relevant brain regions that contribute to group classification.

In the present study, we aimed to investigate the predictive power of MKL models using ROIs (MKL-ROI) to classify patients with mild AD versus age- and gender-matched healthy controls, using a multimodal neuroimaging approach comprising morphological MRI, ^{18}F-FDG-PET and rCBF-SPECT data. In contrast with the vast majority of ML-based studies of AD using multimodal imaging designs, we examined exactly the same subjects using the three neuroimaging modalities, with short time intervals between the scanning sessions. We aimed to rank the brain regions affording the greatest degree of discrimination between AD patients and controls according to their contributing weights in each imaging modality, and to establish whether the contribution of each brain region was due to predominantly increased or decreased voxel values in AD patients compared to controls. In addition, diagnostic accuracy indices obtained with the MKL-ROI approach were compared to the indices obtained with Support Vector Machine (SVM) based on the whole-brain. Finally, since recent investigations have suggested that the choice of brain atlas for feature extraction may exert a significant influence on the accuracy of MRI or PET-FDG data in SVM studies of elderly populations (Ota et al., 2014), we compared MKL-ROI results obtained with two different atlases to delineate ROIs, in order to verify the robustness of the accuracies and ranking of weights for each selected brain region.

2. Material and Methods

2.1. Subjects

Thirty-eight individuals were enrolled in this study (20 patients with mild AD and 18 healthy elderly volunteers). The investigation was approved by the ethical committee of the involved institutions and all participants provided informed consent. For both groups, the exclusion criteria were as follows: less than four years of education, age below 60 or above 90 years, use of psychotropic drugs, diabetes mellitus, presence of systemic disorders associated with cognitive decline, contraindications for MRI and brain lesions incidentally detected on MRI.

All patients fulfilled the DSM-III-R (American Psychiatric Association, 1987) and NINCDS/ADRDA (McKhann et al., 1984) criteria for mild dementia and probable AD. Their Clinical Dementia Rating (CDR) scale was lower or equal to 1 (Morris, 1993). As the data were collected before the publication of the new 2011 NINCDS/ADRDA criteria for Alzheimer's disease (McKhann et al., 2011), the criteria for probable Alzheimer's disease from 1984 were used (McKhann et al., 1984).

Healthy controls did not present memory deficits or cognitive impairments (CDR = 0). Table 1 presents age, gender, education and results from Mini Mental State Examination (MMSE) of AD patients and healthy volunteers. Further details regarding the demographic and clinical characteristics of AD subjects and controls can be found in (Buchpiguel et al., 2014).

Table 1
Demographic characteristics of the participants.

	Healthy participants	Patients with AD	*p*-value
Age: mean (SD)	72.7 (4.2)	75.5 (4.0)	0.06
Sex: male (female)	7 (11)	9 (11)	0.70
Education in years: mean (SD)	10.4 (4.8)	7.3 (3.9)	0.05
MMSE: mean (SD)	28.1 (1.3)	21.3 (2.8)	< 0.01

AD – Alzheimer's disease; SD – standard deviation. The *p*-value was obtained using chi-square (for gender) and Mann-Whitney tests (for the continuous variables).