Regional Analysis of FDG-PET for the Classification of Alzheimer's Disease

Katherine R. Gray[1]
katherine.gray03@imperial.ac.uk

Robin Wolz[1]
r.wolz@imperial.ac.uk

Shiva Keihaninejad[24]
keihaninejad@drc.ion.ucl.ac.uk

Rolf A. Heckemann[34]
soundray@fondation-neurodis.org

Paul Aljabar[1]
paul.aljabar@imperial.ac.uk

Alexander Hammers[34]
alexander.hammers@fondation-neurodis.org

Daniel Rueckert[1]
d.rueckert@imperial.ac.uk

[1] Department of Computing
Imperial College London
London, UK

[2] Dementia Research Centre
UCL Institute of Neurology
London, UK

[3] Fondation Neurodis
Lyon, France

[4] Centre for Neuroscience
Division of Experimental Medicine
Department of Medicine
Imperial College London
London, UK

Abstract

We present a multi-region analysis of FDG-PET data for classification of subjects from the Alzheimer's Disease Neuroimaging Initiative. Image data were obtained from 69 healthy controls, 71 Alzheimer's disease patients, and 147 patients with mild cognitive impairment. Anatomical segmentations were automatically generated in the native MRI space of each subject, and regional signal intensities extracted from the FDG-PET images. Using a support vector machine classifier, we achieve excellent discrimination between healthy controls and patients with both Alzheimer's disease and mild cognitive impairment. Using FDG-PET, a technique which is often used clinically in the workup of dementia patients, we achieve results comparable with those obtained using data from research-quality MRI, or biomarkers obtained invasively from the cerebrospinal fluid.

1 Introduction

Alzheimer's disease (AD) is the most common cause of dementia in the elderly. There is no cure at present, and patients with mild cognitive impairment (MCI), who are at increased risk of developing AD, are of particular interest for treatment trials. Numerous FDG-PET studies (e.g. [6]) have shown that MCI and AD are associated with significant reductions in the cerebral metabolic rate of glucose in brain regions preferentially affected by AD. FDG-PET, in conjunction with other neuroimaging methods and clinical biomarker measurements, may therefore be a useful tool for the early diagnosis of AD, and for monitoring its progression.

We investigate the use of a support vector machine (SVM) to classify subjects, based on their baseline FDG-PET scans, as healthy controls (HC); AD patients; or as having a baseline diagnosis of MCI, which may either convert to AD (progressive MCI; p-MCI), or remain stable (s-MCI). Machine learning techniques based on FDG-PET data have been successful in discriminating AD patients from HC (e.g. [5]). Various MRI-based methods, including SVM classifiers, have been applied for the discrimination of AD patients from HC, with reported accuracies generally ranging between 80% and 95% (e.g. [2, 5]).

We present a multi-region analysis of FDG-PET for classification of subjects from the Alzheimer's Disease Neuroimaging Initiative (ADNI). Segmentations into 83 anatomical regions were generated in native MRI space, and the FDG-PET signal intensity in each region sampled. FDG-PET image normalisation was performed using an independently derived cluster of regions that are relatively preserved during the course of AD [8].

2   Methods

2.1   Imaging Data

Data were obtained from the ADNI database (www.loni.ucla.edu/ADNI), in which subjects undergo regular cognitive assessments, as well as neuroimaging with MRI and FDG-PET. We used baseline FDG-PET scans from 287 ADNI subjects, whose groupwise characteristics are provided in Table 1. The MCI subjects were divided into p-MCI and s-MCI based on changes in status occurring over 24 ± 11 (range $0 - 36$) months. Full details of the image acquisition protocols may be found in the ADNI technical procedures manuals.

Table 1: Group characteristics for the subjects whose images are used in this study. Mini-mental state examination (MMSE) scores provide a measure of cognitive impairment.

	Age (mean $\pm$ std. dev.)	Gender (%) Male	Gender (%) Female	MMSE Score (mean $\pm$ std. dev.)
HC (n = 69)	75.6 ± 5.0	61	39	29.0 ± 1.1
s-MCI (n = 85)	76.0 ± 6.9	73	27	27.5 ± 1.7
p-MCI (n = 62)	75.2 ± 6.9	65	35	26.8 ± 1.7
AD (n = 71)	76.2 ± 7.0	59	41	23.3 ± 2.2

2.2   Image Processing

The anatomical segmentations required for regional sampling were generated in native MRI space. The FDG-PET images were co-registered with the corresponding native space MRI, and sampled in this higher resolution space. The independently derived cluster required for FDG-PET image normalisation was provided in the space of the Montreal Neurological Institute template (MNI space). This cluster was then transformed into the native MRI space of each subject. An overview of the image processing pipeline is provided in Fig. 1.

2.2.1   MRI Anatomical Segmentation

Automatic segmentations of the 1.5 T MRI were generated in native MRI space using multi-atlas propagation with enhanced registration (MAPER), which has been previously described
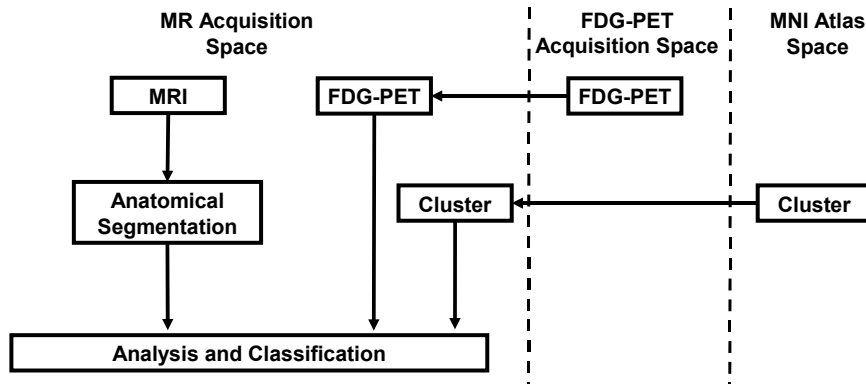
Figure 1: Image processing pipeline. Horizontal arrows indicate image registration and re-slicing steps.

and validated for use in AD [4]. The segmentations are available through the ADNI website [3]. Individual tissue probability maps for cerebrospinal fluid, grey matter and white matter were obtained using FSL FAST (www.fmrib.ox.ac.uk/fsl). For FDG-PET image analysis, the grey matter portion within each cortical label is of relevance. Masked segmentations were therefore employed, in which all regions except ventricles, central structures, cerebellum and brainstem have been masked with a grey matter label, and the lateral ventricles have been masked with a cerebrospinal fluid label.

2.2.2 FDG-PET Image Processing

FDG-PET acquisition was performed according to one of three protocols, so standardisation was necessary before the images could be compared. Dynamic scans acquired over 30-60 minutes were motion corrected using rigid registration with the Image Registration Toolkit (IRTK; www.doc.ic.ac.uk/~dr/software). Co-registered frames were averaged to produce static images, which were affinely aligned with the corresponding MRI. Although the intra-subject registration of brain MRI and PET images is a rigid-body problem, an affine transformation was preferred, because it can account for scaling or voxel size errors which may remain after phantom correction of the MRI [1]. For FDG-PET normalisation, we obtained a MNI-space image of the reference cluster used in [8] from the author. Using the "Segment" module of SPM5 (www.fil.ion.ucl.ac.uk/spm), each MRI was linearly and non-linearly deformed to the MNI template. The inverse transformation parameters were then used to transform the MNI-space cluster into the native MRI space of each subject.

2.3 Image Analysis and Classification

Each of the native MRI-space FDG-PET images was overlaid with its corresponding masked anatomical segmentation, and the signal intensity per mm^3 was determined for all 83 regions. Global variations in the cerebral metabolic rate of glucose between subjects were accounted for by normalisation to the signal intensity per mm^3 in the reference cluster. The effects of gender and age at scan were regressed out using a linear regression model..

We applied a SVM classifier using LIBSVM (www.csie.ntu.edu.tw/~cjlin/libsvm). We used a soft-margin formulation ("C-SVC"), and selected a radial basis function kernel. Robust estimates of classifier performance were obtained via a bootstrapping approach, assessing the classification rates between pairs of clinical groups. The classifier performance was

evaluated over 1000 runs, where 75% of the subjects were randomly selected for training, and the remaining 25% for testing. Receiver operating characteristic (ROC) curves were plotted, and the area under the curve (AUC) evaluated, as this provides an overall measure of the discriminative ability of a classifier.

3   Results

Classification results are presented as ROC curves in Fig. 2. Regional t-values for comparisons between AD patients and HC, as well as MCI patients and HC were additionally calculated. In the comparison between AD patients and HC, the ten highest t-values were observed bilaterally in the posterior cingulate gyrus, hippocampus, posterior temporal lobe and parietal lobe, and in the left parahippocampal gyrus and middle and inferior temporal gyri. In the comparison between MCI patients and HC, the ten highest t-values were observed bilaterally in the hippocampus and parietal lobe, and in the left parahippocampal gyrus, amygdala, posterior temporal lobe, posterior cingulate gyrus, insula, and pre-subgenual frontal cortex.
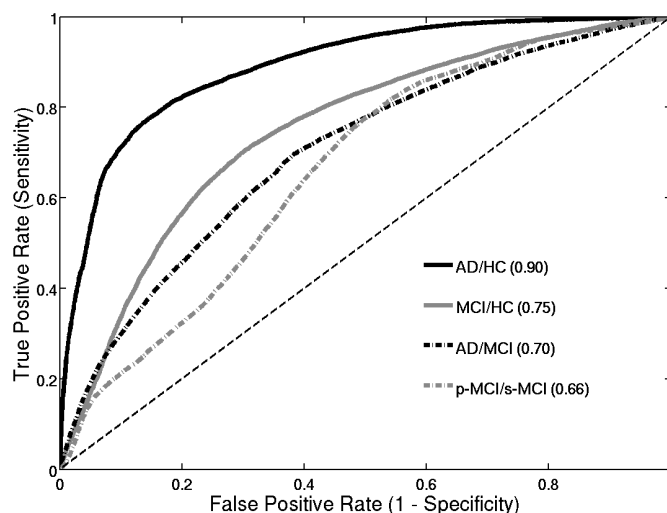

Figure 2: ROC curves for pairs of clinical groups, with the AUC for each given in brackets.

4   Discussion

We investigate the classification of AD and MCI subjects using a SVM classifier based on data obtained from a regional analysis of baseline FDG-PET scans. We achieve excellent discrimination of AD patients from HC (AUC 90%). This result is comparable with other published studies, and approaches the limit achievable in the best clinical centres, since commonly used diagnostic criteria themselves have an accuracy of around 90%. Reports that some of the ADNI AD patients may have a pattern of glucose metabolism that is more consistent with frontotemporal dementia than with AD [7] indicate a potential confounding factor which could also be limiting the classification accuracy.

     The majority of research surrounding the classification of AD and MCI focuses on the discrimination of AD patients from HC and, in fewer cases, MCI patients from HC. We propose the use of multi-region FDG-PET data for classification on the ADNI cohort, and further aim to discriminate between p-MCI and s-MCI patients. Good group discrimination

is achieved between MCI patients and HC (AUC 75%), as well as between AD and MCI patients (AUC 70%), with the results again comparable with other published studies (for example [2]). The discrimination between p-MCI and s-MCI patients is promising (AUC 66%), and it is important to consider that clinical follow-up data are still being acquired for the ADNI subjects, and therefore those currently in the s-MCI group may yet convert to AD.

In comparisons between both AD patients and HC, and MCI patients and HC, regional t-values indicate significant group differences across most of the brain. The most significant regions include those known to be affected in AD, consistent with previous voxel-wise t-tests performed on ADNI data [6]. Using FDG-PET, a technique which is often used clinically in the workup of dementia patients, we achieve classification results which are comparable with those obtained using data from research-quality MRI, or biomarkers obtained invasively from the cerebrospinal fluid. In particular, we obtain a promising classification result for the most challenging, but clinically significant, comparison between p-MCI and s-MCI.

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