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Combining anatomical, diffusion, and resting state functional magnetic resonance imaging for individual classification of mild and moderate Alzheimer's disease

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ABSTRACT

Magnetic resonance imaging (MRI) is sensitive to structural and functional changes in the brain caused by Alzheimer's disease (AD), and can therefore be used to help in diagnosing the disease. Improving classification of AD patients based on MRI scans might help to identify AD earlier in the disease's progress, which may be key in developing treatments for AD. In this study we used an elastic net classifier based on several measures derived from the MRI scans of mild to moderate AD patients ($N = 77$) from the prospective registry on dementia study and controls ($N = 173$) from the Austrian Stroke Prevention Family Study. We based our classification on measures from anatomical MRI, diffusion weighted MRI and resting state functional MRI. Our unimodal classification performance ranged from an area under the curve (AUC) of 0.760 (full correlations between functional networks) to 0.909 (grey matter density). When combining measures from multiple modalities in a stepwise manner, the classification performance improved to an AUC of 0.952. This optimal combination consisted of grey matter density, white matter density, fractional anisotropy, mean diffusivity, and sparse partial correlations between functional networks. Classification performance for mild AD as well as moderate AD also improved when using this multimodal combination. We conclude that different MRI modalities provide complementary information for classifying AD. Moreover, combining multiple modalities can substantially improve classification performance over unimodal classification.

1. Introduction

Early diagnosis is key to the development of treatments for Alzheimer's disease (AD) (Prince et al., 2011). In this respect it is well recognised that magnetic resonance imaging (MRI) might be highly useful as an early AD biomarker (Jack et al., 2010). Several MRI techniques have been applied successfully to study average group differences between AD patients and controls in voxel based grey matter (Ferreira et al., 2011), white matter (Li et al., 2012), diffusion measures (Douaud et al., 2011), and functional connectivity (Gour et al., 2014; Binnewijzend et al., 2012).

In addition to average group difference in case control studies, similar MRI measures have also been used to predict or classify the disease class (i.e., patient or control) of individuals. This classification based on MRI scans could be helpful in making a reliable diagnosis of AD in the future. Machine learning classification is a suited candidate to make such individual predictions, because it is well equipped to handle high-dimensional data such as those from MRI. Reliable individual classification of AD and controls has already been achieved with MRI measures of grey matter atrophy (Klöppel et al., 2008; Plant et al., 2010; Cuingnet et al., 2011), white matter integrity (Nir et al., 2014), and brain activity (Lee et al., 2013; Koch et al., 2012).

Some studies suggest that classification of Alzheimer's disease may further improve when combining several MRI modalities (Mesrob et al., 2012; Sui et al., 2013), while another recent study found better classification by using a single MRI modality (Dyrba et al., 2015). It is not yet clear which MRI modality or combination of modalities provide the best classification performance of AD patients.

The goal of this study is to perform individual classification of mild to moderate AD from healthy controls, and to combine information from several modalities to improve this individual classification. We compare classification performance for typical measures of grey matter atrophy, white matter integrity, and functional connectivity. Then we investigate

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whether combining modalities improves classification performance. We test how this multimodal classification model is able to separate patients with mild AD and patients with moderate AD from healthy controls.

2. Materials and methods

2.1. Data sample

2.1.1. Participants

Our dataset was collected as a part of the prospective registry on dementia (PRODEM; see also Seiler et al., 2012). Our sample only contained subjects scanned at the Medical University of Graz. The inclusion criteria are: dementia diagnosis according to DSM-IV criteria (American Psychiatric Association, 2000), non-institutionalisation and no need for 24-h care, and availability of a caregiver who agrees to provide information on the patients' and his or her own condition. Patients were excluded from the study if they were unable to sign a written informed consent or if co-morbidities were likely to preclude termination of the study. We conducted our study with the baseline scans from the PRODEM study, and included only patients diagnosed with AD in according the NINCDS-ADRDA Criteria (McKhann et al., 1984), for which anatomical MRI, diffusion MRI, and resting state functional MRI scans were present. Amyloid imaging for additional confirmation of the diagnosis was unavailable in our sample.

The healthy controls were drawn from the Austrian Stroke Prevention Family Study, which is a prospective single-centre community-based follow-up study with the goal of examining the frequency of vascular risk factors and their effects on cerebral morphology and function in the healthy elderly. On the basis of structured clinical interview and a physical and a neurological examination, participants had to be free of overt neurologic or psychiatric findings and had to have no history of a neuropsychiatric disease, including cerebrovascular attacks and dementia. The study protocol was approved by the ethics committee of the Medical University of Graz, Austria, and written informed consent was obtained from all subjects.

This resulted in a dataset of 77 AD patients between ages 47 and 83, of which 39 had mild AD (MMSE > 20), and 38 had moderate AD (MMSE ≤ 20) (Perneczky et al., 2006), and 173 healthy controls between ages 47 and 83 (see Table 1).

2.1.2. MR acquisition

Each participant was scanned on a Siemens Magnetom TrioTim 3 T MRI scanner. Anatomical T1-weighted images were acquired with TR = 1900 ms, TE = 2.19 ms, flip angle = 9, isotropic voxel size of 1 mm. Diffusion images were acquired along 12 non-collinear directions, scanning each direction 4 times with TR = 6700 ms, TE = 95 ms, 50 axial slices, voxel size = 2.0 × 2.0 × 2.5 mm. Resting-state fMRI series of 150 volumes were obtained with TR = 3000 ms, TE = 30 ms, flip angle = 90°, 40 axial slices, with an isotropic voxel size of 3 mm. We instructed participants to lie still with their eyes closed, and to stay awake.

Table 1
Demographics for the study population.

Demographics	Controls	Mild AD	Moderate AD
Age	66.1 ± 8.71	70.3 ± 7.85	66.9 ± 9.06
Gender, ♂/♀	74/99 (57%♀)	17/22 (56%♀)	14/ 24 (63%♀)
Education (years)	11.5 ± 2.76	11.6 ± 3.45	10.0 ± 2.79
Disease duration (months)	0.00 ± 0.00	22.6 ± 15.5	30.9 ± 30.7
MMSE	26.7 ± 5.80	24.2 ± 2.07	16.6 ± 2.73
CDR	–	0.72 ± 0.25	0.92 ± 0.39
GDS	2.11 ± 2.15	2.54 ± 2.09	2.74 ± 3.02

Data is represented as mean ± standard deviation. MMSE = mini mental state exam, CDR = clinical dementia rating, GDS = geriatric depression scale.

2.2. Software

The MRI data were preprocessed using FMRIB Software Library (FSL, version 5.0) (Smith et al., 2004; Jenkinson et al., 2012). For all further data analyses we used MATLAB and Statistics Toolbox Release 2015b.

2.3. MRI preprocessing

The preprocessing of the anatomical MRI included brain extraction, bias field correction, and non-linear registration to standard MNI152 (Grabner et al., 2006). The preprocessing of the diffusion MRI included brain extraction and correction of eddy currents. For the fMRI data the preprocessing included brain extraction, motion correction (Jenkinson et al., 2002), a temporal high pass filter with a cutoff point of 100 s, and 3 mm FWHM spatial smoothing. Additionally, we used the FMRIB's ICA-based Xnoiseifier (FIX, version 1.06), with the included standard training data to automatically identify and remove noise components from the fMRI time course (Salimi-Khorshidi et al., 2014).

2.4. Anatomical atlases

In order to compare properties across subjects we used two anatomical atlases (Fig. 1) included in FSL. For grey matter regions we used the

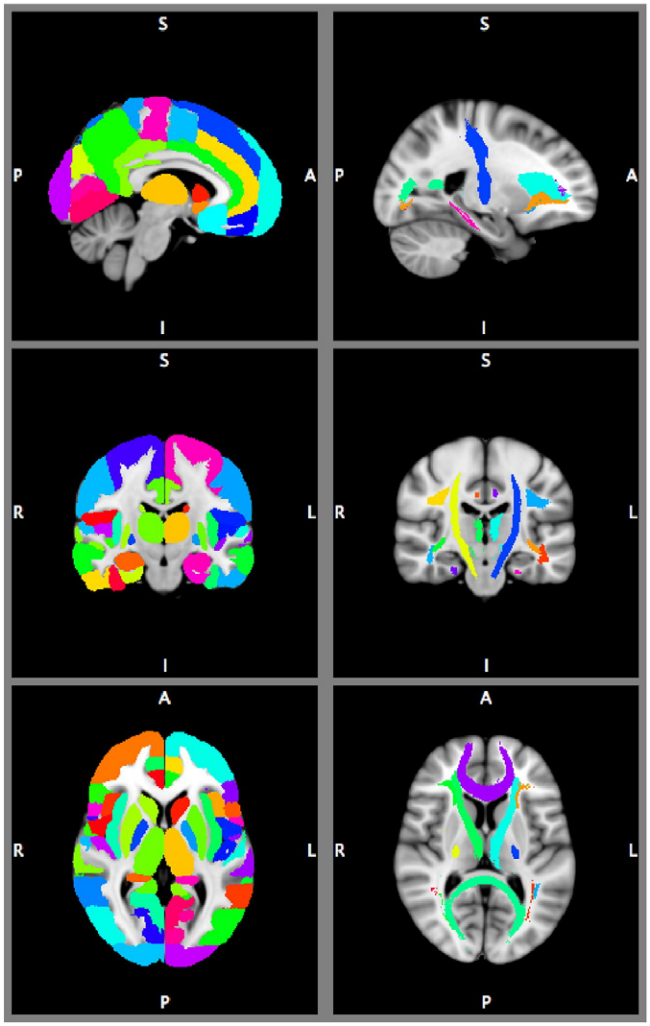

Fig. 1. Anatomical atlases overlaid on MNI brain template. Left part shows the Harvard–Oxford cortical and subcortical areas. Right part shows the JHU white-matter tractography atlas. The images are thresholded at 25%, and showing the area with the maximum probability for displaying purposes, but the atlases were treated as probabilistic in our analyses.