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Different multivariate techniques for automated classification of MRI data in Alzheimer's disease and mild cognitive impairment

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ABSTRACT

Automated structural magnetic resonance imaging (MRI) processing pipelines and different multivariate techniques are gaining popularity for Alzheimer's disease (AD) research. We used four supervised learning methods to classify AD patients and controls (CTL) and to prospectively predict the conversion of mild cognitive impairment (MCI) to AD from baseline MRI data. A total of 345 participants from the AddNeuroMed cohort were included in this study; 116 AD patients, 119 MCI patients and 110 CTL individuals. High resolution sagittal 3D MP-RAGE datasets were acquired and MRI data were processed using FreeSurfer. We explored the classification ability of orthogonal projections to latent structures (OPLS), decision trees (Trees), artificial neural networks (ANN) and support vector machines (SVM). Applying 10-fold cross-validation demonstrated that SVM and OPLS were slightly superior to Trees and ANN, although not statistically significant for distinguishing between AD and CTL. The classification experiments resulted in up to 83% sensitivity and 87% specificity for the best techniques. For the prediction of conversion of MCI patients at baseline to AD at 1-year follow-up, we obtained an accuracy of up to 86%. The value of the multivariate models derived from the classification of AD vs. CTL was shown to be robust and efficient in the identification of MCI converters.

1. Introduction

Alzheimer's disease (AD) is one of the most common forms of neurodegenerative disorders. The disease is related to pathological amyloid depositions and hyper-phosphorylation of structural proteins which leads to progressive loss of cognitive function, synaptic dysfunction and structural changes in the brain. Magnetic resonance imaging (MRI) has been extensively investigated in AD and, consistent with pathology, very early changes have been demonstrated in the hippocampus and entorhinal cortex. However, no imaging measure currently provides a reliable prediction of which patients with mild cognitive impairment (MCI) will rapidly progress to develop AD (O'Brien, 2007; Ries et al., 2008). With MRI it is possible to measure both regional (hippocampus/entorhinal cortex) and global (whole brain) atrophy, which are considered sensitive surrogate markers, capable of quantifying the extent of brain degeneration in dementia (Apostolova et al., 2006). It is possible to obtain multiple volumetric and cortical thickness measures from high resolution MRI by automated segmentation techniques. It has previously been shown that a combination of global and prediction of conversion of MCI to AD as compared with using manual volumetric measures of the hippocampus (still considered to be the gold standard) (Westman et al., 2011c). Further, multivariate analysis using multiple regions in the brain as input gives better accuracy for AD classification and MCI prediction than visual assessment (Scheltens scale for medial temporal lobe atrophy) performed by an experienced radiologist (Westman et al., 2011a). Positive results have also been reported using a whole-brain grey-

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matter-based support vector machine (SVM) approach (Kloppel et al., 2008a). A large number of multivariate methods have been introduced in recent years for classifying individual patients with AD using structural MRI (Vemuri et al., 2008; Plant et al., 2010; Kloppel et al., 2008b; Teipel et al., 2007; Davatzikos et al., 2008; Magnin et al., 2009: Fan et al., 2008). However, the lack of studies using multiple methods on the same data has made it difficult to directly compare the results of the different techniques.

In this study we combine multiple morphometric measures derived from an automated pipeline to directly compare different multivariate classifiers. The specific aims were (1) to compare linear and non-linear multivariate methods for the classification of AD vs. cognitively normal controls (CTL) using an automated pipeline; (2) to test the resulting classifiers in predicting AD conversion from the prodromal stage of the disease, MCI; (3) to assess the effect of age, education and APOE genotype in the prediction of AD vs. CTL; and (4) to identify the optimal classifier(s).

2. Materials and methods

2.1. Subjects and inclusion criteria

All participants originated from the AddNeuroMed project, part of InnoMed (Innovative Medicines in Europe), a European Union program designed to make drug discovery more efficient. The project is designed to develop and validate novel surrogate markers in Alzheimer's disease and includes a human neuroimaging component (Simmons et al., 2009, 2011), which includes the collection of MRI data, other biomarkers, clinical and cognitive measures. Data were collected from six different sites across Europe: University of Kuopio, Finland, University of Perugia, Italy, Aristotle University of Thessaloniki, Greece, King's College London, United Kingdom, University of Lodz, Poland, and University of Toulouse, France. MR images from a total of 345 participants were included in this study; 116 AD patients, 119 MCI patients and 110 CTL individuals. Table 1 gives the demographics of the study cohort. All AD and MCI patients were recruited from local memory clinics of the six participating sites while the control individuals (cognitively normal/CTL) were recruited from non-related members of the patient's families, caregiver's relatives or social centres for the elderly. Written consent was obtained where the research participant had capacity, and in those cases where dementia compromised capacity, then assent was obtained from the patient and written consent from a relative, according to local law and process. This study was approved by ethical review boards in each participating country. The inclusion and exclusion criteria were as follows. *Alzheimer's disease*: *Inclusion criteria*: (1) ADRDA/NINCDS and DSM- IV criteria for probable Alzheimer's disease. (2) Mini Mental State Examination score range between 12 and 28. (3) Age 65 years or above. *Exclusion criteria*: (1) Significant neurological or psychiatric illness other than Alzheimer's disease. This would exclude patients with vascular dementia or large infarcts, for example. (2) Significant unstable systematic illness or organ failure. All AD patientss had a Clinical Dementia Rating (CDR) scale score of 0.5 or above.

Mild Cognitive Impairment and Controls: *Inclusion criteria*: (1) Mini Mental State Examination score range between 24 and 30. (2) Geriatric Depression Scale score less than or equal to 5. (3) Age 65 years or above. (4) Medication stable. (5) Good general health. *Exclusion criteria*: (1) Meet the DSM-IV criteria for dementia. (2) Significant neurological or psychiatric illness other than Alzheimer's disease. (3) Significant unstable systematic illness or organ failure. The distinction between MCI and controls was based on two criteria: (1) Subject scores 0 on the Clinical Dementia Rating Scale=control. (2) Subject scores 0.5 on the Clinical Dementia Rating Scale=MCI. For the MCI patients it was preferable that the subject and informant reported occurrence of memory problems.

MCI conversion to AD: MCI conversion was defined when patients met the criteria for MCI at baseline and subsequently the criteria for AD (ADRDA/NINCDS and DSM-IV) at 1-year follow-up as described above.

At baseline, a health interview was administered to all participants following a standardized protocol available at http://www.innomed-addneuromed.com, and data on demographics, medical history, current health status, medication use and family history were collected. For AD and MCI cases, information on the duration and severity of cognitive decline was obtained from the patients or informants through a detailed questionnaire: the presence of memory problems, time of their onset, subsequent course, and investigations performed. All diagnoses, including follow-up diagnoses were made by the local center clinician based on the criteria above.

For all participants, cognition, behaviour, functional status and global severity were assessed and the Mini-Mental State Examination (MMSE) (Folstein et al., 1975) and the Clinical Dementia Rating Scale (CDR) (Hughes et al., 1982) were administered. Evaluation of AD included the Hachinski ischemic scale (Hachinski et al., 1975), the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) (Rosen et al., 1984), the Neuropsychiatric Inventory (Cummings et al., 1994) and the Alzheimer's Disease Cooperative Study (ADCS)-Activities of Daily Living Scale (Galasko etal.,1997). Evaluation of MCI and CTL individuals comprised the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) Cognitive Battery (Morris et al., 1989) and the Geriatric Depression Scale (GDS) (Yesavage and Sheik, 1986). MRI findings were not known to clinicians, so as not to influence the clinical diagnosis.

2.2. MRI acquisition

Data acquisition for the AddNeuroMed study was designed to be compatible with the Alzheimer Disease Neuroimaging Initiative (ADNI) (Jack et al., 2008). The imaging protocol for both studies included high resolution sagittal 3D T1-weighted magnetization-prepared rapid acquisition with gradient echo (MPRAGE) volume (voxel size $1.1 \times 1.1 \times 1.2$ mm^3) and axial proton density/T2-weighted fast spin echo images. The MPRAGE volume was acquired using a custom pulse sequence specifically designed for the ADNI study to ensure compatibility across scanners. Full brain and skull coverage was required for both of the latter datasets and detailed quality control procedures were carried out on all MR images from both studies according to the AddNeuroMed quality control procedure (Simmons et al., 2009, 2011).

2.3. Regional volume segmentation and cortical thickness parcellation

FreeSurfer (version 4.5.0) was used for image processing and analysis. The pipeline produces regional cortical thickness and volumetric measures. Cortical reconstruction and volumetric segmentation procedures include removal of non-

Table 1
Demographic variables and cognitive scores.

	AddNeuroMed				
	CTL	MCI	AD	MCI-nc	MCI-c
Women/men[a]	51/59	61/58	40/76	53/45	8/13
Age in years[b]	73.0 [53–88]	74.4 [57–89]	75.5 [58–88]	74.7 [64–89]	72.9 [57–81]
Education in years[c]	10.8 [2–25]	8.9 [0–20]	8.0 [0–22]	8.8 [0–18]	9.4 [4–20]
MMSE	29.1 [25–30]	27.1 [24–30]	20.8 [12–28]	27.2 [24–30]	26.6 [24–30]
ADAS1	4.5 [1–9]	6.3 [3–9]	6.7 [2–10]	6.3 [3–9]	6.2 [4–9]
CDR	0	0.5	1.2 [0.5–2]	0.5	0.5

Data are presented as mean [minimum–maximum]. AD=Alzheimer's disease, MCI=mild cognitive impairment, MCI-c=MCI converter, MCI-nc=MCI non-converter, MMSE=Mini Mental State Examination, Alzheimer s Disease Assessment Scale (ADAS)=word list non-learning, CDR=Clinical Dementia Rating.

[a] No differences between groups, Kruskal–Wallis ANOVA $P=0.0503$, df=2 and chi-sq=6.0.

[b] Significantly different between groups, Kruskal–Wallis ANOVA $P=0.0097$, df=2 and chi-sq=9.3; significant difference two-tailed t-test AD vs. CTL: $P=0.004$, df=220 and t-test=2.9; and CTL vs. MCI-nc: $P=0.0483$, df=205 and t-test=2.0.

[c] Significantly different between groups, Kruskal–Wallis ANOVA $P=0.0001$, df=2 and chi-sq=20.6; significant difference two-tailed t-test at $P<0.0017$ for AD vs. CTL (df=213 and t-test=4.8), MCI vs. CTL (df=220 and t-test=3.2) and CTL vs. MCI-nc (df=206 and t-test=3.2).