Neurobiology of Aging 34 (2013) 2815–2826

Contents lists available at SciVerse ScienceDirect

Neurobiology of Aging

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

How early can we predict Alzheimer's disease using computational anatomy?

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ARTICLE INFO

Article history:
Received 2 April 2013
Received in revised form 24 May 2013
Accepted 20 June 2013
Available online 26 July 2013

Keywords:
Structural magnetic resonance imaging
Alzheimer's disease
Mild cognitive impairment
Biomarker

ABSTRACT

Computational anatomy with magnetic resonance imaging (MRI) is well established as a noninvasive biomarker of Alzheimer's disease (AD); however, there is less certainty about its dependency on the staging of AD. We use classical group analyses and automated machine learning classification of standard structural MRI scans to investigate AD diagnostic accuracy from the preclinical phase to clinical dementia. Longitudinal data from the Alzheimer's Disease Neuroimaging Initiative were stratified into 4 groups according to the clinical status—(1) AD patients; (2) mild cognitive impairment (MCI) converters; (3) MCI nonconverters; and (4) healthy controls—and submitted to a support vector machine. The obtained classifier was significantly above the chance level (62%) for detecting AD already 4 years before conversion from MCI. Voxel-based univariate tests confirmed the plausibility of our findings detecting a distributed network of hippocampal-temporoparietal atrophy in AD patients. We also identified a subgroup of control subjects with brain structure and cognitive changes highly similar to those observed in AD. Our results indicate that computational anatomy can detect AD substantially earlier than suggested by current models. The demonstrated differential spatial pattern of atrophy between correctly and incorrectly classified AD patients challenges the assumption of a uniform pathophysiological process underlying clinically identified AD.

1. Introduction

Recent advances in computer-based diagnosis making use of structural magnetic resonance imaging (sMRI) and machine learning methods provide evidence of sufficient accuracy in discriminating Alzheimer's disease (AD) patients not only from healthy controls but also from other common types of dementia (Davatzikos et al., 2008b; Dukart et al., 2011a, 2012; Fan et al., 2008; Kloppel et al., 2008a, 2008b). For the clinically and neuroscientifically pertinent case of early AD detection, support vector machine (SVM) classification and other machine learning studies tapping into the preclinical phase of AD convincingly demonstrate the potential for reliable early diagnosis (Casanova and Hsu, 2012; Davatzikos et al., 2008a; Devanand et al., 2007; McEvoy et al., 2009; Misra et al., 2009; Modrego, 2006). Two limitations applying to most of the previous studies are the tuning of the classifiers to specific cohorts and with respect to cross-validation. Both restrict their generalizability to the general population. Tuning of a classifier to achieve a high accuracy for detection of mild cognitive impairment (MCI) patients might result in a substantial drop in accuracy when applying the same classifier to AD patients. Similarly, the tuning of a classifier to achieve high cross-validation accuracies might substantially increase the risk of overfitting the classification model to the particular dataset used in the study therewith providing an overoptimistic estimation for the accuracy of the method when applied to a general population.

Despite the progress in the field of computer-based AD detection, our knowledge about the capability of sMRI for early diagnosis even before the first manifestation of clinical signs is still very limited. The most recent model of brain anatomy–derived biomarker in AD (Jack et al., 2010) suggested a protracted progression of atrophy compared with functional changes as observed by [F18]fluorodeoxyglucose positron emission tomography. In contrast, other prospective studies provided evidence that sMRI measurements may contain information of ongoing disease-related process already before clinical

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[2] Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (http://adni.loni.ucla.edu/). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at http://adni.loni.ucla.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

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http://dx.doi.org/10.1016/j.neurobiolaging.2013.06.015

Table 1
Subject group characteristics

	Training set		Testing set				ANOVA
	AD	Control subjects	AD	Control subjects	ncMCI	cMCI	*F*, df, *p*
n	54	54	54	83	61	142	—
Age (y) (mean ± SD)	74.4 ± 8.3	74.6 ± 5.5	75.8 ± 6.9	75.3 ± 5.0	74.0 ± 7.6	74.0 ± 7.0	0.8, 5, 0.544
Gender (M/F)	31/23	29/25	25/29	40/43	45/16	93/49	—
MMSE (mean ± SD)	23.1 ± 1.9	29.0 ± 1.1	23.4 ± 2.1	29.3 ± 0.8	27.5 ± 1.9	26.7 ± 1.7	166.5, 5, <0.001
Follow-up time (y) (mean ± SD)	2.1 ± 0.2	3.3 ± 0.7	2.8 ± 0.4	3.8 ± 1.0	3.4 ± 0.9	3.5 ± 0.9	—

Key: AD, Alzheimer's disease; ANOVA, analysis of variance; cMCI, mild cognitive impairment (converters); df, degree of freedom; F, female; M, male; MMSE, mini-mental state examination; ncMCI, mild cognitive impairment (nonconverters); SD, standard deviation.

manifestation of cognitive decline (Dickerson and Wolk, 2012; Quiroz et al., 2012; Smith et al., 2008). However, these studies did not test the predictive power of sMRI information to detect AD in untested subjects or cross-validation. Therefore, there is a pressing need to investigate the timescale of disease-related structural brain changes in AD not only to advance our understanding of the disorder but also to provide better tools for early diagnosis when neuroprotection is possible. Another related aspect is that the application of multivariate pattern classification techniques for early AD detection produces a high proportion of erroneous predictions for conversion from MCI to AD (Ewers et al., 2010; Misra et al., 2009). Thus, the secondary aim of our study is to investigate if false predictions are because of random noise or deterministic atrophy pattern.

We systematically address the questions of timescale of disease detection and potential causes of erroneous prediction while aiming to overcome the aforementioned limitations. We first adopt a pragmatic strategy testing whether AD-related atrophy is already detectable several years before conversion followed by in-depth investigation of atrophy patterns comparing incorrectly and correctly diagnosed AD, MCI converting to AD during the follow-up (MCI converters [cMCI]), MCI nonconverters (ncMCI), and healthy control subjects. To this end, we apply classical mass-univariate voxel-based analysis paralleled by machine learning classification using SVMs.

2. Methods

2.1. Subjects

To evaluate temporal sensitivity of sMRI data for early detection of AD, we used 1.5-T T1-weighted images from the Alzheimer's Disease Neuroimaging Initiative (ADNI, http://www.adni-info.org/) of all available AD, cMCI, and ncMCI patients and healthy controls who had baseline and at least 2 years of follow-up MRI scans.

The AD patient and control subject data were split into a dataset used for SVM classifier training and another for diagnosis (Tables 1 and 2). Critically, the cMCI (Table 3) and ncMCI (Table 2) data were used for diagnosis only. Baseline and follow-up scans after 6, 12, 24, 36, 48, and 60 months, if available, were downloaded from the ADNI database along with the corresponding clinical information. All the data available in ADNI1 and ADNI-GO studies were used for subsequent evaluation. The diagnosis of AD was based on NINCDS/ADRDA (National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association) criteria (McKhann et al., 1984). Exclusion criteria were the presence of any significant neurologic disease other than AD, history of head trauma followed by persistent neurologic deficits or structural brain abnormalities, psychotic features, agitation or behavioral problems within the previous 3 months, or history of alcohol or substance abuse. The study was conducted according to the Declaration of Helsinki. Written informed consent was obtained from all participants before protocol-specific procedures were performed.

The ADNI was launched in 2003 by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, the Food and Drug Administration, private pharmaceutical companies, and nonprofit organizations, as a $60 million, 5-year public-private partnership. The primary goal of ADNI has been to test whether sMRI, positron emission tomography, other biological markers, and clinical and neuropsychological assessments can be combined to measure the progression of MCI and early AD. Determination of sensitive and specific markers of very early AD progression is intended to aid researchers and clinicians to develop new treatments, monitor their effectiveness, and lessen the time and cost of clinical trials. The Principal Investigator of this initiative

Table 2
Follow-up testing group characteristics

	Baseline	1 y	2 y	3 y	4 y
Control subjects					
n	42	42	37	38	14
Age (mean ± SD)	76.5 ± 4.7	77.1 ± 4.7	77.7 ± 5.1	79.2 ± 4.4	81.8 ± 4.4
Gender (M/F)	18/24	18/24	16/21	17/21	8/6
MMSE (mean ± SD)	29.2 ± 0.8	29.3 ± 1.0	29.4 ± 0.9	29.1 ± 1.3	29.5 ± 1.1
AD					
n	54	53	54	—	—
Age (mean ± SD)	76.7 ± 7.0	77.1 ± 6.7	78.8 ± 7.0	—	—
Gender (M/F)	25/29	25/28	25/29	—	—
MMSE (mean ± SD)	23.4 ± 2.1	22.4 ± 3.7	19.2 ± 5.8	—	—
ncMCI					
n	61	61	61	44	—
Age (mean ± SD)	75.1 ± 7.7	75.7 ± 7.7	76.8 ± 7.6	79.0 ± 7.4	—
Gender (M/F)	45/16	45/16	45/16	34/10	—
MMSE (mean ± SD)	27.5 ± 1.9	27.4 ± 2.3	27.0 ± 3.1	27.3 ± 2.1	—

Key: AD, Alzheimer's disease; cMCI, mild cognitive impairment (converters); F, female; M, male; MMSE, mini-mental state examination; ncMCI, mild cognitive impairment (nonconverters); SD, standard deviation.