ELSEVIER

Neurobiology of Aging 29 (2008) 514–523

NEUROBIOLOGY OF AGING

www.elsevier.com/locate/neuaging

Detection of prodromal Alzheimer's disease via pattern classification of magnetic resonance imaging

Christos Davatzikos [a,*], Yong Fan [a], Xiaoying Wu [a], Dinggang Shen [a], Susan M. Resnick [b]

[a] *Section of Biomedical Image Analysis, Department of Radiology, University of Pennsylvania, United States*
[b] *Laboratory of Personality and Cognition, National Institute on Aging, United States*

Received 12 July 2006; received in revised form 3 October 2006; accepted 14 November 2006
Available online 14 December 2006

Abstract

We report evidence that computer-based high-dimensional pattern classification of magnetic resonance imaging (MRI) detects patterns of brain structure characterizing mild cognitive impairment (MCI), often a prodromal phase of Alzheimer's disease (AD). Ninety percent diagnostic accuracy was achieved, using cross-validation, for 30 participants in the Baltimore Longitudinal Study of Aging. Retrospective evaluation of serial scans obtained during prior years revealed gradual increases in structural abnormality for the MCI group, often before clinical symptoms, but slower increase for individuals remaining cognitively normal. Detecting complex patterns of brain abnormality in very early stages of cognitive impairment has pivotal importance for the detection and management of AD.

Keywords: Prodromal Alzheimer's disease; MCI; Pattern recognition; MRI

1. Introduction

Prevalence of AD doubles every 5 years of life after age 60, with more than 4 million individuals affected in the US alone. AD is the most common dementing illness and a major public health issue of increasing importance as life expectancy increases. Although noninvasive approaches for antemortem diagnosis of AD are under development, definitive diagnosis of AD requires neuropathologic confirmation of the characteristic amyloid plaques and neurofibrillary tangles (Braak et al., 1998). New drugs under development will target different stages of disease pathophysiology, and efficacious AD treatments likely will require early initiation before irreversible brain tissue damage. Thus, a great deal of attention has been paid recently to the prodromal stage of AD, referred to as mild cognitive impairment (MCI), which includes individuals with memory problems who do not meet criteria for dementia. Although MCI definitions vary across studies (Petersen, 2003), MCI individuals convert to AD with rates of 6–15% annually (Petersen, 2003). Therefore, MCI individuals are a high risk group likely to benefit from effective treatments.

Structural magnetic resonance imaging (MRI) promises to aid diagnosis and treatment monitoring of MCI and AD, offering the potential for easily obtainable surrogate markers of diagnostic status and disease progression. Unlike relatively more advanced stages of MCI and AD, quantifying patterns of structural change during early stages of AD or during clinically normal stages is a major challenge. Brain atrophy in the early stages of AD may be relatively subtle and spatially distributed over many brain regions (Chetelat et al., 2002; Convit et al., 2000; Dickerson et al., 2001; Kaye et al., 1997; Killiany et al., 2000b), including the entorhinal cortex, the hippocampus, lateral and inferior temporal structures, anterior and posterior cingulate, and possibly other regions that have only recently been investigated (Medina et al., 2006). Furthermore, spatially heterogeneous patterns of atrophy have been found within the hippocampus, with regions known to correspond to the CA1 field presenting relatively more pro-

* Corresponding author at: Department of Radiology, University of Pennsylvania, 3600 Market Street, Suite 380, Philadelphia, PA 19104, USA. Tel.: +1 215 349 8587; fax: +1 215 614 0266.
E-mail addresses: christos@rad.upenn.edu, christos.davatzikos@uphs.upenn.edu (C. Davatzikos).

0197-4580/$ – see front matter © 2006 Elsevier Inc. All rights reserved.
doi:10.1016/j.neurobiolaging.2006.11.010

nounced atrophy (Frisoni et al., 2006; Wang et al., 2006). Patterns of atrophy associated with pathology are confounded by complex patterns of atrophy associated with normal aging (Resnick et al., 2000). Moreover, the error associated with structural measurements can vary throughout the brain, since some structures are more difficult to delineate, especially via computer algorithms, thereby rendering the measurement of certain brain regions more informative than others merely for methodological reasons (Bookstein, 2001). Therefore, powerful and sensitive statistical image analysis methods must be used to capture morphological characteristics that are different between normal aging and MCI, and to determine which are most informative, from a diagnostic perspective.

Most MRI studies in MCI and AD have relied on measurement of volumes of specific brain regions (Chetelat, 2003; Nestor et al., 2004), especially the hippocampus and the entorhinal cortex, which show histopathogical changes at early stages of AD (Braak et al., 1998). Computational neuroanatomy has also been used to evaluate voxel-by-voxel brain changes in healthy aging, MCI and AD (Ashburner et al., 2003). These studies have confirmed patterns of atrophy involving medial temporal lobe structures in MCI and AD. They have reinforced the value of MRI as a potential surrogate marker of disease at the *group-analysis* level, i.e. for examining overall differences between individuals with and without pathology. However, their *diagnostic* value is limited, especially at early stages of brain pathology, since their sensitivity and specificity are not sufficient for prediction of the status of a given individual.

Herein we report results from a longitudinal study that provide strong evidence that there is a subtle and spatially distributed pattern of brain structure that is characteristic of MCI, and which often begins developing prior to the recognition of cognitive deficits. Moreover, this pattern can be detected with high sensitivity and specificity using a high-dimensional image analysis and pattern classification method that examines spatial patterns of brain atrophy in their entirety, instead of applying separate region-by-region evaluations. Therefore, detection of this structural pattern can lead to very early diagnosis of prodromal AD. This study adds to mounting evidence in the literature for the importance of pattern classification methods in detecting subtle and complex structural and functional patterns (Davatzikos et al., 2005a,b; Golland et al., 2002; Liu et al., 2004).

2. Materials and methods

2.1. Subjects

MRI scans from 30 elderly individuals were obtained annually as part of the Baltimore Longitudinal Study of Aging neuroimaging substudy (Resnick et al., 2000). At initial enrollment, all individuals were free of dementia and other central nervous system disorders, severe cardiovascular disease, and metastatic cancer (detailed in (Resnick et al., 2000)). Screening of mental status by the blessed-information-memory-concentration (BIMC) test was performed at each annual visit in conjunction with a comprehensive neuropsychological assessment. Subject and informant based assessments with the clinical dementia rating (CDR) (Morris et al., 1989) scale were administered by certified examiners to participants in the BLSA autopsy study annually (about 50% of participants) and to remaining participants scoring 3 or more BIMC errors. After as many as 9 annual neuroimaging and cognitive assessments, 20 participants with MCI were identified from a sample of 155 neuroimaging study participants who completed MRI studies. These 20 participants were characterized as MCI, based on CDR scores of 0.5 and/or consensus diagnosis indicating memory impairment that does not meet criteria for dementia. Of these individuals, 15 were eligible for inclusion in the current study. Five participants who developed cognitive impairment over the course of the study were excluded from these analyses due to documentation of other pathological processes (e.g., clinical stroke (1), brain trauma (1), heavy alcohol use (1), post-surgical confusion (1), absence of Alzheimer's pathology at autopsy (1)). A control sample of 15 individuals who remained unimpaired (CDR = 0), matched for age, sex, and follow-up interval, was identified from the remaining 135 participants. Subject characteristics are shown in Table 1. It is important to emphasize that the MCI participants in this study are identified within the context of prospective longitudinal follow-ups and typically represent relatively mild cases of cognitive impairment in contrast to those followed in other studies who typically present with memory complaints (e.g. Grundman et al., 2004). None had CDR total scores greater than 0.5 for any of the visits used in these analyses, and the mean (S.D.) of the sum of the individual CDR box scores was 1.2 (0.9) for the most recent visit included in the analyses. Therefore, in this group AD pathology is likely to be at a relatively early stage. To date, 10 of the 15 MCI individuals have been assigned diagnoses of Alzheimer disease at subsequent follow-up visits, verifying that we are including individuals who are progressing as well as those who may be more stable.

2.2. Imaging protocol

MR acquisition procedures are detailed in (Resnick et al., 2000). MR scanning was performed on a GE

Table 1
Characteristics of the participants in this MCI study

Group	MCI	Normal
No. of subjects	15	15
Sex no. of males	10	10
No. of left-handed	0	1
Years of education, mean (S.D.)	15.80 (3.73)	16.73 (3.22)
Baseline age, mean (S.D.)	76.92 (7.28)	75.21 (6.85)
Age at last visit, mean (S.D.)	82.40 (6.59)	81.76 (6.57)
Follow-up interval, mean (S.D.)	5.49 (2.42)	6.55 (2.51)
MMSE at last visit, mean (S.D.)	25.80 (2.96)	29.00 (1.41)