NeuroImage 56 (2011) 212–219

Contents lists available at ScienceDirect

NeuroImage

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

Automated hippocampal shape analysis predicts the onset of dementia in mild cognitive impairment

Sergi G. Costafreda [a,*,1], Ivo D. Dinov [b,1], Zhuowen Tu [b,1], Yonggang Shi [b,1], Cheng-Yi Liu [b,1], Iwona Kloszewska [c,1], Patrizia Mecocci [d,1], Hilkka Soininen [e,1], Magda Tsolaki [f,1], Bruno Vellas [g,1], Lars-Olof Wahlund [h,1], Christian Spenger [h,1], Arthur W. Toga [b,1], Simon Lovestone [a,1], Andrew Simmons [a,1]

[a] NIHR Biomedical Research Centre for Mental Health at South London and Maudsley NHS Foundation Trust and King's College London, London, UK
[b] Laboratory of NeuroImaging, UCLA, Los Angeles, CA, USA
[c] Department of Old Age Psychiatry and Psychotic Disorders, Medical University of Lodz, Poland
[d] Institute of Gerontology and Geriatrics, University of Perugia, Perugia, Italy
[e] Department of Neurology, University of Eastern Finland and Kuopio University Hospital, Kuopio, Finland
[f] Department of Neurology, Aristotle University, Thessaloniki, Greece
[g] Toulouse Gérontopôle University Hospital, Université Paul Sabatier, INSERM U 558, France
[h] Department of Clinical Science, Intervention and Technology, Karolinska Institutet, Stockholm, Sweden

ARTICLE INFO

Article history:
Received 2 September 2010
Revised 14 January 2011
Accepted 17 January 2011
Available online 25 January 2011

Keywords:
Neuroimaging
Hippocampus
Prognosis
Automated methods
Alzheimer's disease
Mild cognitive impairment

ABSTRACT

The hippocampus is involved at the onset of the neuropathological pathways leading to Alzheimer's disease (AD). Individuals with mild cognitive impairment (MCI) are at increased risk of AD. Hippocampal volume has been shown to predict which MCI subjects will convert to AD. Our aim in the present study was to produce a fully automated prognostic procedure, scalable to high throughput clinical and research applications, for the prediction of MCI conversion to AD using 3D hippocampal morphology. We used an automated analysis for the extraction and mapping of the hippocampus from structural magnetic resonance scans to extract 3D hippocampal shape morphology, and we then applied machine learning classification to predict conversion from MCI to AD. We investigated the accuracy of prediction in 103 MCI subjects (mean age 74.1 years) from the longitudinal AddNeuroMed study. Our model correctly predicted MCI conversion to dementia within a year at an accuracy of 80% (sensitivity 77%, specificity 80%), a performance which is competitive with previous predictive models dependent on manual measurements. Categorization of MCI subjects based on hippocampal morphology revealed more rapid cognitive deterioration in MMSE scores ($p<0.01$) and CERAD verbal memory ($p<0.01$) in those subjects who were predicted to develop dementia relative to those predicted to remain stable. The pattern of atrophy associated with increased risk of conversion demonstrated initial degeneration in the anterior part of the cornus ammonis 1 (CA1) hippocampal subregion. We conclude that automated shape analysis generates sensitive measurements of early neurodegeneration which predates the onset of dementia and thus provides a prognostic biomarker for conversion of MCI to AD.

Introduction

Mild cognitive impairment (MCI) refers to a clinical syndrome characterized by significant cognitive impairments which are beyond normal for healthy adults but not sufficient to meet clinical criteria for Alzheimer's disease (AD). The rate of conversion from MCI to overt dementia is substantial, at 10%–15% per year, the majority of which is AD (Petersen et al., 2001). As the clinical features of AD are the outcome of at least a decade of progressive neuropathological changes (Nelson et al., 2009; Jack et al., 2010), structural neuroimaging has shown potential in predicting the onset of AD in MCI subjects (Jack et al., 1999; Killiany et al., 2002; Teipel et al., 2007; Misra et al., 2009; Frisoni et al., 2010).

In particular, hippocampal atrophy has emerged as an independent risk factor of progress towards dementia (Jack et al., 1999; Kantarci et al., 2009; Risacher et al., 2009; Frisoni et al., 2010). The hippocampus and entorhinal cortex suffer the earliest neuropathological changes of AD (Braak and Braak, 1991), and the ensuing hippocampal neurodegeration may be more directly linked to cognitive and clinical decline than other features of the pathological process (Price et al., 2001; Savva et al., 2009; Jack et al., 2008). Longitudinal studies have indicated that MCI subjects destined to convert towards dementia have reduced hippocampal volume relative to non-converters (Kantarci et al., 2009; Risacher et al., 2009).

* Corresponding author at: Institute of Psychiatry, King's College London, De Crespigny Park, PO Box 89, London SE5 8AF, UK. Fax: +44 203 228 2016.
E-mail address: sergi.1.costafreda@kcl.ac.uk (S.G. Costafreda).
[1] The AddNeuroMed Consortium.

1053-8119/$ – see front matter © 2011 Elsevier Inc. All rights reserved.
doi:10.1016/j.neuroimage.2011.01.050

Three-dimensional shape analysis can pinpoint the precise localization of early hippocampal atrophy (Csernansky et al., 2005; Apostolova et al., 2006; Morra et al., 2009). Shape analysis may therefore provide more accurate prognostic predictions of cognitive decline than hippocampal volume, as already suggested using manual expert segmentation (Ferrarini et al., 2009; Frisoni et al., 2010). Manual segmentation, however, is highly resource intensive and is not scalable to routine clinical use. Developing a fully automated approach able to capitalize on the predictive potential of hippocampal shape abnormalities for prognostic prediction would be a key step towards clinical application. In the present study, we sought to investigate to what extent 3D hippocampal shape abnormalities predicted 1-year conversion to overt AD and cognitive decline in individuals with MCI. We employed an automated segmentation technique, which has been validated in AD (Morra et al., 2008), to ensure efficient and consistent hippocampal measurements in a large sample. We applied a novel mapping algorithm (Shi et al., 2009) to transform the segmented hippocampi into 3D shapes with one-to-one point correspondence across subjects to permit direct inter-subject statistical analysis. This algorithm models the intrinsic geometric properties of each hippocampus and thus achieves a correspondence robust to variations in orientation or position of the hippocampus across subjects.

From the AddNeuroMed multisite study (Lovestone et al., 2007; Simmons et al., 2009, 2011), 103 amnestic MCI subjects with baseline and 1-year neuroimaging and behavioral assessments were investigated. We hypothesized that those MCI subjects already expressing at baseline a hippocampal atrophic phenotype that is compatible with AD would suffer an accelerated cognitive decline and would be more likely to convert to dementia than those not presenting with this atrophic phenotype. To test this hypothesis, we used the baseline scans of 71 AD and 88 age-matched healthy controls (HC) from the same study to develop a classifier trained to separate AD from HC individuals based on hippocampal shape. The trained classifier can therefore be seen as an accurate detector of the atrophic phenotype characteristic of AD. We then inputed the baseline morphometric features for each MCI individual into the trained classifier and received for each subject a label as to whether the atrophic phenotype characteristic of AD was present or not at the beginning of the follow-up in a given MCI individual. To test whether this phenotypic labeling was valuable for prognostic prediction, we then compared the clinical and cognitive 1-year outcome of MCI individuals with and without the atrophic phenotype. In addition to this individual classification analysis, we employed a conventional group analysis to reveal the hippocampal subregions most associated with conversion to AD and cognitive decline.

The shape-based predictive model was developed using Support Vector Machine (SVM) (Vapnik, 2000) classification, which has been shown to be a powerful tool for statistical pattern recognition in neuroimaging-based clinical prediction (Davatzikos et al., 2005; Fu et al., 2008; Fan et al., 2008b; Kloppel et al., 2008; Vemuri et al., 2008; Costafreda et al., 2009; Nouretdinov et al., in press). For comparison purposes, we also trained a volume-based SVM model, with the expectation that shape-based models would result in superior prediction accuracy of conversion to AD.

Methods

Participants and behavioral assessment

AddNeuroMed is a longitudinal, multisite study of biomarkers for AD (Lovestone et al., 2007), recruiting subjects from six European sites. Ethical approval was obtained at each data acquisition site, and informed consent was obtained for all subjects (Table 1). Control subjects were aged 65 years or above, in good general health and had a baseline Mini Mental State Examination (MMSE, (Tombaugh and McIntyre, 1992)) score higher than 24. Subjects with MCI had subjective memory impairment and a score below 1.5 SD of population age-adjusted norms on the Consortium to Establish a Registry for Alzheimer's Disease cognitive battery (CERAD, (Welsh et al., 1994)), a score of 0.5 on the Clinical Dementia Rating scale (CDR, (Hughes et al., 1982)), an MMSE score above 24 and did not have any functional impairments. Subjects with AD were recruited as defined by both NINCDS–ADRDA criteria for mild to moderate AD (McKhann et al., 1984) and DSM-IV criteria for probable AD. AD subjects also had an MMSE score range between 12 and 28, Hachinski Modified Ischemic (HMI, (Hachinski et al., 1975)) score of at most 4 and a Global Deterioration Scale (GDS, (Reisberg et al., 1982)) score between 2 and 5. Clinical assessments included a detailed case and family history, the CDR, HMI, MMSE, GDS and CERAD cognitive battery, the latter only for MCI and HC subjects. General exclusion criteria were neurological or psychiatric disease other than AD, significant unstable systemic illness or organ failure, and alcohol or substance misuse. Recruited subjects underwent MRI scanning, with follow-up assessments at 3 and 12 months.

Table 1
Demographic and clinical characteristic of the participants.

	MCI ($N=103$)		HC ($N=88$)		AD ($N=71$)	
	Mean	SD	Mean	SD	Mean	SD
Demographics						
Age	74.1	5.8	73.6	6.7	74.9	5.8
Female sex (No. %)	51	51	46	52	50	70
Years of education	9	4.3	10.6	4.8	7.6	4
Clinical measures						
Baseline						
CDR score	0.5	0	0	0	1.3	0.6
GDS score	2.3	0.5	1	0	3.7	0.8
MMSE score	27.1	1.7	29.1	1.2	21.1	4.6
CERAD delayed recall*	3.9	2	6.5	2.1		
Change at 12 months						
Diagnostic changes (No.%)	22	21%	0	0	0	0
MMSE score	−1.2	4	−0.2	1.3	−1.7	6.2
CERAD delayed recall*	−0.4	1.9	0.5	1.8		
Volume (cm^3)						
Right hippocampus	4.1	0.6	4.3	0.5	3.8	0.6
Left hippocampus	3.9	0.5	4.1	0.4	2.5	0.6

MCI: mild cognitive impairment, HC: healthy controls, AD: Alzheimer's disease. *: AD subjects were not assessed using the CERAD battery. All diagnostics changes were conversions from MCI to AD.

In the present report, we included those MCI and control subjects who had satisfactorily completed their baseline and 12-month behavioral assessment, resulting in a final sample of 103 MCI, 71 ADC and 88 HC1. At follow-up, the clinical diagnosis of 22 of the MCI subjects was changed to AD, according to NINCDS–ADRDA criteria (McKhann et al., 1984). This binary measure of clinical deterioration was complemented by two continuous measures: change in MMSE score between baseline and 12 months as an estimate of general cognitive decline and the change in delayed recall test score of the CERAD battery as a specific measure of memory function (Welsh et al., 1991) dependent on hippocampal integrity (Kramer et al., 2004).

MR data acquisition and pre-processing

The neuroimaging protocol was designed for compatibility with the Alzheimer's disease Neuroimaging Initiative (ADNI) magnetic resonance (MR) protocol and has been presented in detail previously (Jack et al., 2008; Simmons et al., 2009, 2011). Briefly, MR data were obtained from six 1.5 T MR systems with a standardized protocol, including quality assurance and control. The present report is based on high resolution sagittal 3D MP-RAGE scans acquired at baseline with full brain and skull coverage, optimized for morphometric analyses. After reconstruction, in-plane resolution was 256×256 with in-plane voxel size of 0.9375×0.9375 mm and slice thickness of