Combining structural brain changes improves the prediction of Alzheimer's disease and mild cognitive impairment

Ningnannan Zhang[a,b], **Xiaowei Song**[a,c], and **Yunting Zhang**[b] **for the Alzheimer's disease Neuroimaging Initiative**[*]

[a]National Research Council Canada Institute for Biodiagnostics (Atlantic), Halifax, Canada

[b]Department of Radiology of the General Hospital, Tianjin Medical University, Tianjin, China

[c]Division of Geriatric Medicine, Department of Medicine, Dalhousie University, Halifax, Canada

Abstract

Background—Several structural brain changes have been associated with Alzheimer's disease (AD). This study investigated the prediction of AD by combining multiple brain changes with the hallmark medial temporal lobe atrophy (MTA).

Methods—High resolution MRI data of people with mild AD (n=39), mild cognitive impairment (MCI; n=82), and of healthy controls (HC; n=58) were obtained at baseline. Among these people, 26 AD, 53 MCI, and 46 HC subjects had 24-month follow-up MRI scans. Bilateral MTA was evaluated using a medial temporal lobe atrophy scale (MTAS). Common changes in the aging brain were summarized using a brain atrophy and lesion index (BALI). The performance of the MTAS, BALI, and a score combining both, using logistic regression model, were assessed.

Results—The MTAS and BALI scores were closely correlated ($r^2 > 0.56$), each differed between the diagnostic groups. Having an unfavorable MTAS was associated with an increased risk of MCI-AD conversion (OR=3.71, p=0.039), adjusted for age, sex, and education; having an unfavorable BALI score marginally contributed to such risks (OR=4.08, p=0.080). Combining MTS and BALI components resulted in a greater odds ratio (8.99, p=0.007) and an improved predictive accuracy (75.9%, p=0.002).

Conclusion—Multiple structural changes have an additive effect on AD. The data support potential future roles of combining multiple co-existing structural changes to benefit AD diagnose, progression monitoring, and/or treatment effect evaluation.

Correspondence: Xiaowei Song, PhD, MSCS, Neuroimaging Research Laboratory, National Research Council Canada, Institute for Biodiagnostics (Atlantic), Suite 3900, 1796 Summer Street, Halifax, NS B3H 3A7, Canada, Tel: (902) 4731876, Fax: (902) 4731851, Xiaowei.Song@nrc.ca & Yunting Zhang, MD, PhD, Department of Radiology, Tianjin General Hospital, Tianjin Medical University, 154 Anshan Road, Heping District, Tianjin, 300052, China, Tel: 86-22-60362811, Fax: 86-22-60362990, cjr.zhangyunting@vip.163.com.

Key works

aging; Alzheimer's disease; brain atrophy and lesion index; mild cognitive impairment; medial temporal lobe atrophy scale; structural MRI

INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by brain damage primarily in the medial temporal lobe (MTL; *i.e.*, the entorhinal cortex, hippocampus, and the adjacent peri/para-hippocampal cortices) - the key structure for declarative memory. Magnetic resonance imaging (MRI) evaluation of medial temporal lobe atrophy (MTA) has been sensitively related to AD expression and been proposed as a neuroimaging biomarker to aid in AD diagnosis and differentiation [1–3]. Characteristic MTA has also been proven valuable in predicting dementia and AD progression [4,5]. In recent years, a number of additional structural changes commonly present in the aging brain (e.g., global gray matter atrophy, subcortical infarcts, white matter lesions, and cerebrovascular diseases) have also been found to increase the risks of cognitive impairment and dementia [6–12]. Importantly, many such changes coexist; each can be associated with MTA worsening and affect cognition [13–20]. Consequently, the importance of evaluating the combined effect of multiple brain deficits on cognitive decline is increasingly recognized [16–18].

To facilitate the evaluation of the combined effect of global brain changes on cognition, a high-field MRI-based semi-quantitative brain atrophy and lesion index (BALI) has been developed [21,22]. The BALI adapts several standardized visual rating scales to capture a range of structural deficits in the supratentorial and infratentorial regions and summarizes these brain changes with a total score. BALI rating is feasible to perform and has been shown to be useful to describe the variability of the brain in people with AD, MCI and in healthy control (HC) older adults, as well as to correlate brain structural and functional changes [21,22]. However, it is yet to be understood whether multiple structural deficits other than MTA, as combined in BALI, can contribute to AD and MCI discrimination and prediction. The objectives of the present study were to investigate 1) the correlation between BALI and MTA and 2) the value of combining multiple brain changes in the prediction of AD and MCI. To accomplish these objectives, we carried out a secondary analysis using the high-field (i.e., 3 Tesla) high resolution MRI from the Alzheimer's Disease Neuroimaging Initiative (ADNI). A MTA rating scale (MTAS) and a BALI score were assigned for each subject. We assessed the performance of BALI, MTAS, and a combination of both (i.e., BALI-MTAS) in discriminating MCI and mild AD and in predicting MCI to AD conversion.

METHODS

Subjects and clinical assessments

Data used for the present analysis were obtained from the Alzheimer's Disease Neuroimaging Initiative with permission [23]. The ADNI was launched in 2003 by the National Institute on Aging (NIA), the National Institute of Biomedical Imaging and Bioengineering (NIBIB), the Food and Drug Administration (FDA), private pharmaceutical companies and non-profit organizations, as a $60 million, 5-year public-private partnership. The primary goal of ADNI has been to test the use of serial magnetic resonance imaging (MRI), positron emission tomography (PET), and other biological markers in the progression of mild cognitive impairment (MCI) and early Alzheimer's disease (AD). Determination of sensitive and specific markers of very early AD progression is intended to

aid researchers and clinicians to develop new treatments and monitor their effectiveness, as well as lessen the time and cost of clinical trials. Subjects have been recruited from over 50 sites across the U.S.A. and Canada, with the initial goal to recruit 800 adults, ages 55 to 90; (200 cognitively normal older individuals to be followed for 3 years, and 400 people with MCI to be followed for 3 years, and 200 people with early AD to be followed for 2 years) [23].

Diagnostic categorization and classification of conversion between diagnostic groups were made by ADNI site physicians in accordance to the criteria of the National Institute of Neurologic and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) and were reviewed by ADNI clinical monitors Analyses involving diagnostic categorization at follow-up have taken into account information about disease conversion. Clinical testing scores on global cognition were downloaded from the ADNI clinical dataset. These scores included the mini-mental state examination (MMSE), the Alzheimer's disease assessment scale - cognitive subscale (ADAS-cog), and the clinical dementia rating scale (CDR).

For this analysis, all the accessible imaging data of the subjects who had 3T MRI were downloaded (AD=39; MCI=82; HC=58; from 30 ADNI sites). At the 24-month follow-up, 13 AD, 29 MCI, and 12 HC did not have a scan. High resolution (1.2mm thickness) 3D images (MP-RAGE) were evaluated [24]. Before they were made available in the ADNI database for public access, all MRI scans had been checked by ADNI researchers for quality control purposes so that any image with unsatisfactory quality had been excluded from the downloadable data. All images obtained from ADNI website satisfied the requirements of the present study; therefore no further selection criteria were imposed for further image selection after they were downloaded.

Evaluation of structural changes

Evaluation of the imaging data was performed independently by two neuroradiologists trained with the rating methods (as described in Appendix 1). Brain images were rated in a random order, while the raters were blind to the subjects' demographic, diagnosis, cognitive information, and to the time of scan. Examples for MTAS and BALI evaluations are shown in Figure 1.

MTAS Evaluation—A standardized MTA rating scale was used to assess each side of the bilateral MTA in the coronal plane, applying the approach described by Scheltens and colleagues [25]. Specifically, the left and the right sides of the medial temporal lobe were assessed independently according to a 0–4 grading schema that rates the width of choroidal fissure, width of temporal horn, and the height of hippocampus. A total MTAS was assigned to each subject as the sum of both-sides' scores, with a possible maximum value of 8, where a higher score meant greater MTAS (Appendix 1, Panel A).

BALI Evaluation—Seven categories of structural changes commonly present in the aging brain were evaluated by adapting existing rating scales for the construction of the BALI [21,22]. These changes included deficits in the infratentorial, deep white matter, periventricular, basal ganglia, gray matter, small vessels, global atrophy, and other aspects if applicable (e.g., neoplasm, trauma, and deformation). Specifically, ratings of each category were performed in the axial plane on the images applying the rating schema to generate category sub-scores. A total BALI rating score was assigned to each subject as the sum of the sub-scores, with a possible maximum value of 25, with a higher score representing a greater level of global brain structural deficits (Appendix 1, Panel B).

Combined BALI-MTAS—To combine MTAS and BALI, a logistic regression (LR) model that allows the discrimination between affected and unaffected individuals was employed. Here, being affected meant converting from MCI to AD during the two-year follow-up period. The MTAS and the BALI components were included in the LR as covariates, so that their relative risks for MCI conversion (vs. MCI stable), analogous to the regression coefficients, were estimated. The combined BALI-MTAS score was calculated as the sum of the input scores (i.e., the covariates) in accordance with their relative risk estimated using the LR model, as described by the following: $f(z)=1/(1+e^{-z};$ $z=\beta_0+\beta_1 x_1+\beta_2 x_2+\ldots+\beta_k x_k$; where $f(z)$ represents the combined BALI-MTAS score ranging between a possible minimum of 0 and maximum of 1, $x_1, x_2, \ldots x_k$ represent MTAS and BALI items, β_0 represents the intercept, and $\beta_1, \beta_2 \ldots \beta_k$ represent the respective regression coefficients associated with each item.

Statistical analyses

Analyses were performed using 179 subjects at baseline and using 125 subjects who had follow-up scans. Reliability of the ratings was examined using the intraclass correlation coefficient (ICC) and the inter-rater agreement rate (Cohen's kappa) on a sub-sample of 20% of randomly selected subjects. The mean value was used in the analyses in case of disagreement between the two raters. Group differences regarding demographics, clinical assessments, and the brain structural rating scores were examined using Kruskal-Wallis nonparametric tests for interval data and Chi-Square tests for categorical/ordinal data. Odds ratios (OR) and the 95% confidence intervals (CI) of the MTAS, BALI, and BALI-MTAS in discriminating AD and MCI versus HC and in predicting MCI subjects who converted to AD over two years versus those who remained MCI were assessed using uni-variable logistic regression (LR) and using multivariate LR, adjusted for age, sex, and education level. Correlations between MTAS and BALI and their relationships with global cognitive testing scores were examined using correlation and regression analyses. Receiver operating characteristic analysis (ROC) was used to examine the performance of MTAS, BALI, and BALI-MTAS in predicting the two-year conversion from MCI to AD, with performance assessed using the areas under the ROC curve (AUC). Sensitivity analysis was performed for which dichotomization of the scores was made using optimal cut-points at which a further increase of sensitivity resulted in a minimal decrease of specificity. The cut-points were MTAS 3 vs. >3 of 8 (the possible maximum value), BALI 11 vs. >11 of 25, and BALI-MTA 0.6 vs. >0.6 of 1.

All analyses were performed using SPSS© 17.0 software package and codes developed using Matlab© R2007. Significance level was set at $p<0.05$ with two tailed tests.

RESULTS

There was no baseline difference in the mean age, education level, or sex proportion between the AD and HC groups (Table 1). As expected, subjects with AD showed worse cognitive testing scores and greater levels of structural brain changes in terms of both MTAS and BALI (p 0.001). The MCI-AD converters did not statistically differ from the non-converters regarding age, sex, or education (Table 1), but they showed comparatively poorer cognitive performance (p<0.010). The converters also had worse MTAS and BALI scores, especially at the follow-up scans (p_s=0.006).

Good ICC values and moderate kappa values were obtained for both MTAS (ICC=0.88, 95% CI=0.79–0.94; kappa=0.66, 95% CI=0.46–0.76) and BALI (ICC=0.91, 95% CI=0.84–0.96; kappa=0.50, 95% CI=0.35–0.66), demonstrating acceptable reliability of these measures. The MTAS and BALI scores were highly correlated (r^2>0.56, p_s<0.001; Figure 2); but they varied considerably in a few individuals, suggesting a certain level of

independency. MTAS and BALI each correlated significantly with the global cognition scores (r^2=0.13–0.30, p_s<0.001 for MTAS; r^2>0.04, p_s<0.050 for BALI).

An increase in the MTAS was associated with an increased risk of AD (OR=1.80 at baseline, OR=2.01 at follow-up, 95% CI=1.32–2.81) and of baseline MCI (OR=1.36, 95% CI=1.00–1.80). An increase in BALI was also associated with an increased risk of AD (OR=1.19 at baseline, OR=1.22 at follow-up, 95% CI=1.02–1.44), although not with MCI (p_s>0.05). Using the combined BALI-MTAS score, the OR for AD increased to 1.94 at baseline and 2.15 at follow-up (95% CI=1.41–2.87); the OR for MCI increased to 1.69 at baseline and 1.75 at follow-up (95% CI=1.30–2.63).

In a multivariable model adjusted for age, sex, and education, the two-year conversion from MCI to AD was significantly associated with MTAS (OR=3.71, p=0.039; Table 2), and somewhat with BALI (OR=4.08, p<0.080; Table 2). This was in contrast to the typical insignificant association when the predictive validity of each individual BALI component (but save global atrophy) was assessed (p_s>0.05; Appendix 2). Compared to either BALI or MTAS, the combined BALI-MTAS was associated with a greater risk for MCI-AD conversion (OR=8.99, p<0.007; Table 2). Improved performance for discriminating individuals who had AD (AUC=82.4%, p<0.001) and MCI (AUC=67.0%, p=0.004), and for predicting individuals who converted from MCI to AD (AUC=75.9%, p=0.002), was also observed (Figure 3; Table 3).

DISCUSSION

We investigated the effect of combining medial temporal lobe atrophy and several other common changes including global atrophy, white matter lesions, and cerebrovascular changes in the prediction of AD. We compared the performance of the combined score with that of either the MTA measure (i.e., MTAS) or the global measure of brain structure (i.e., BALI). While the data confirmed that MTA was the most dominating brain deficit for AD, they also strongly suggested that other brain changes had an additive effect. In addition, the result demonstrated that combining various co-existing structural changes helped improve the discrimination of AD and MCI, and the prediction of short-term (here, 24-monhs) MCI-AD conversion.

MRI-based MTAS is a recognized clinical neuroimaging biomarker for AD [1–5,26,27]. The featured MTA has been used to predict AD-dementia with performance ranging from 60% to 81%, depending on study settings, disease severity, follow-up durations, measurement methods, and statistical approaches [4,5,28–30]. AD prediction with a higher accuracy may be achieved, although typically in well established disease and when neuropsychological and clinical assessments are also taken into consideration, which can be over a decade behind the detectable structural MRI changes [31]. In general, volumetric measures and visual rating have each been used evaluating neuroimaging, particular MRI, although inter-study variations exist with either technique [32–35]. Consistent with previous studies, our data showed a medium-high predictive value with the use of MTAS [4,28,36].

An apparent difficulty with solely MTA-based clinical AD diagnosis is the comparatively unsatisfactory specificity that may not be superior to the level based on detailed clinical assessments, whereas people with AD may not just show MTA in the brain. In recent years, multiple other structural deficits, especially those affected by vascular risk factors, have been shown to present in AD with greater severity and prevalence. As a result, additional structural brain changes have been proven informative; some of them have been proposed as novel AD MRI biomarkers [6,8,10,15,37–39]. Importantly, more and more studies have shown that multiple structural deficits may not present in isolation, but often interactively

coexist in the aging brain [13–15,19]. Further, these changes can affect MTA interactively and can have an impact on cognition collectively [14,40–44].

Prediction of AD and cognitive decline using multiple structural MRI-defined deficits has emerged as a promising topic in AD research. Including additional structural changes to achieve more accurate discriminative and diagnostic performance of MTA has been demonstrated [6,45–47]. In these studies, improved predictive specificity, sensitivity, and/or accuracy have been achieved by combining MTA with regional or global white matter changes [6,45], with cerebral atrophy in parietal and prefrontal regions [46], or with cerebral atrophy and white matter lesions [47]. As a global measure of brain aging, the BALI facilities such multivariable approaches, by not just selecting a specific deficit of choice, but considering various common changes that coexist in the brain. As shown by the data, several seemingly subtle structural changes, when each showed only an inclination of contribution to AD and MCI, revealed a significant effect when considered collectively using a summarizing index (i.e., BALI); combining them with MTA greatly improved the predictive validity of MTA. Here, an additive effect of multiple brain changes on AD is seen. Thus the study supports the potential future role of combining multiple structural changes to help improve AD diagnosis, progression monitoring, and/or treatment evaluation, which should also shed light on controlling various risk factors, including modifiable vascular risk factors that affect these brain changes [48].

Our data must be interrelated with caution. First, we used visual scales, which in general are relatively crude compared to some more precise quantifications that usually involve a great deal of expert input and tiresome processing. On the other hand, the good ICC and the moderate kappa are in favor of them as reliable measures that are useful in both clinical and research settings [49,50]. To test the agreement of visual scale and volumetric estimation, we also obtained the voxel-based morphometry (VBM) of MTA for a subset of the sample from ADNI clinical dataset; the correlation coefficient between the two was significant (r^2=0.43, p<0.001). In addition, the BALI rating has been validated using high-resolution, high-field MRI (i.e., 3T that has become the main stream of clinical MRI), we thus only included subjects with 3T scans in the analysis, where the greater tissue contrasts have allowed reliable rating [21,22]]. Whether this finding can be generalized using low-moderate MRI systems (e.g., 1.5T or lower) is not yet evident. Another limitation concerns the way of component weighting. We chose to use the LR model to obtain the relative risks of the input categories to combine MTAS and BALI. This was chiefly because such approach is widely available and commonly applied. Certainly, other processing methods may also be applicable to carry out the task, although differences in the predictive performance are chiefly determined by the nature of data [51]. How to better cooperate the relative contributions of MTA and multiple other relevant brain deficits to improve AD diagnosis deserves further investigation. In the future, larger scale MRI studies with long follow-up time would be particularly beneficial.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

References

1. Duara R, Loewenstein DA, Potter E, Appel J, Greig MT, Urs R, Shen Q, Raj A, Small B, Barker W, Schofield E, Wu Y, Potter H. Medial temporal lobe atrophy on MRI scans and the diagnosis of Alzheimer disease. Neurology. 2008; 71:1986–1992. [PubMed: 19064880]

2. Dubois B, Feldman HH, Jacova C, Dekosky ST, Barberger-Gateau P, Cummings J, Delacourte A, Galasko D, Gauthier S, Jicha G, Meguro K, O'brien J, Pasquier F, Robert P, Rossor M, Salloway S, Stern Y, Visser PJ, Scheltens P. Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria. Lancet Neurol. 2007; 6:734–746. [PubMed: 17616482]

3. Galluzzi S, Talassi E, Belussi M, Scheltens P, van de Pol L, Nobili F, Rodriguez G, Froelich L, Damian M, Martinez-Lage P, Gomez-Isla T, Reynish E, Ousset PJ, Vellas B, Frisoni GB. Multi-center comparison of medial temporal atrophy in patients with Alzheimer's disease--data from the ICTUS study. Dement Geriatr Cogn Disord. 2008; 26:314–322. [PubMed: 18841016]

4. Korf ES, Wahlund LO, Visser PJ, Scheltens P. Medial temporal lobe atrophy on MRI predicts dementia in patients with mild cognitive impairment. Neurology. 2004; 63:94–100. [PubMed: 15249617]

5. Geroldi C, Rossi R, Calvagna C, Testa C, Bresciani L, Binetti G, Zanetti O, Frosoni GB. Medial temporal atrophy but not memory deficit predicts progression to dementia in patients with mild cognitive impairment. J Neurol Neurosurg Psychiatry. 2006; 77:1219–1222. [PubMed: 16891386]

6. Prasad K, Wiryasaputra L, Ng A, Kandiah N. White matter disease independently predicts progression from mild cognitive impairment to Alzheimer's disease in a clinic cohort. Dement Geriatr Cogn Disord. 2011; 31:431–4. [PubMed: 21757908]

7. Vernooij MW, Ikram MA, Tanghe HL, Vincent AJ, Hofman A, Krestin GP, Niessen WJ, Breteler MM, van der Lugt A. Incidental findings on brain MRI in the general population. N Engl J Med. 2007; 357:1821–1828. [PubMed: 17978290]

8. Schneider JA, Boyle PA, Arvanitakis Z, Bienias JL, Bennett DA. Subcortical infarcts, Alzheimer's disease pathology, and memory function in older persons. Ann Neurol. 2007; 62:59–66. [PubMed: 17503514]

9. Prins ND, van Dijk EJ, den Heijer T, Vermeer SE, Koudstaal PJ, Oudkerk M, Hofman A, Breteler MM. Cerebral white matter lesions and the risk of dementia. Arch Neurol. 2004; 61:1531–1534. [PubMed: 15477506]

10. Sinka L, Kövari E, Gold G, Hof PR, Herrmann FR, Bouras C, Giannakopoulos P. Small vascular and Alzheimer disease-related pathologic determinants of dementia in the oldest-old. J Neuropathol Exp Neurol. 2010; 69:1247–1255. [PubMed: 21107137]

11. Silbert LC, Howieson DB, Dodge H, Kaye JA. Cognitive impairment risk: white matter hyperintensity progression matters. Neurology. 2009; 73:120–125. [PubMed: 19597134]

12. Stenset V, Hofoss D, Berstad AE, Negaard A, Gjerstad L, Fladby T. White matter lesion subtypes and cognitive deficits in patients with memory impairment. Dement Geriatr Cogn Disord. 2008; 26:424–431. [PubMed: 18946220]

13. Agosta F, Pievani M, Sala S, Geroldi C, Galluzzi S, Frisoni GB, Filippi M. White matter damage in Alzheimer disease and its relationship to gray matter atrophy. Radiology. 2011; 258:853–863. [PubMed: 21177393]

14. Eckerström C, Olsson E, Klasson N, Bjerke M, Göthlin M, Jonsson M, Rolstad S, Malmgren H, Wallin A, Edman A. High white matter lesion load is associated with hippocampal atrophy in mild cognitive impairment. Dement Geriatr Cogn Disord. 2011; 31:132–138. [PubMed: 21293123]

15. de Leeuw FE, Korf E, Barkhof F, Scheltens P. White matter lesions are associated with progression of medial temporal lobe atrophy in Alzheimer disease. Stroke. 2006; 37:2248–2252. [PubMed: 16902173]

16. Raji CA, Lopez OL, Kuller LH, Carmichael OT, Longstreth WT Jr, Gach HM, Boardman J, Bernick CB, Thompson PM, Becker JT. White matter lesions and brain gray matter volume in cognitively normal elders. Neurobiol Aging. 2012; 33:834.e7–834.e16. [PubMed: 21943959]

17. Savva GM, Wharton SB, Ince PG, Forster G, Matthews FE, Brayne C. Medical Research Council Cognitive Function and Ageing Study: Age, neuropathology, and dementia. N Engl J Med. 2009; 360:2302–2309. [PubMed: 19474427]

18. Launer LJ, Hughes TM, White LR. Microinfarcts, brain atrophy, and cognitive function: the Honolulu Asia Aging Study Autopsy Study. Ann Neurol. 2011; 70:774–780. [PubMed: 22162060]

19. Chowdhury MH, Nagai A, Bokura H, Nakamura E, Kobayashi S, Yamaguchi S. Age-related changes in white matter lesions, hippocampal atrophy, and cerebral microbleeds in healthy subjects without major cerebrovascular risk factors. J Stroke Cerebrovasc Dis. 2011; 20:302–309. [PubMed: 20634092]

20. Shim YS, Youn YC, Na DL, Kim SY, Cheong HK, Moon SY, Park KW, Ku BD, Lee JY, Jeong JH, Kang H, Kim EJ, Lee JS, Go SM, Kim SH, Cha KR, Seo SW. Effects of medial temporal atrophy and white matter hyperintensities on the cognitive functions in patients with Alzheimer's disease. Eur Neurol. 2011; 66:75–82. [PubMed: 21778730]

21. Chen W, Song X, Zhang Y, Darvesh S, Zhang N, D'Arcy RC, Black S, Rockwood K. An MRI-Based semiquantitative index for the evaluation of brain atrophy and lesions in Alzheimer's disease, mild cognitive impairment and normal aging. Dement Geriatr Cogn Disord. 2010; 30:121–130. [PubMed: 20733305]

22. Zhang N, Song X, Zhang Y, Chen W, D'Arcy RC, Darvesh S, Fisk JD, Rockwood K. Alzheimer's disease Neuroimaging Initiative: An MRI brain atrophy and lesion index to assess the progression of structural changes in Alzheimer's disease, mild cognitive impairment, and normal aging: A follow-up study. J Alzheimers Dis. 2011; 26(Suppl 3):359–367. [PubMed: 21971475]

23. Weiner MW, Aisen PS, Jack CR Jr, Jagust WJ, Trojanowski JQ, Shaw L, Saykin AJ, Morris JC, Cairns N, Beckett LA, Toga A, Green R, Walter S, Soares H, Snyder P, Siemers E, Potter W, Cole PE, Schmidt M. Alzheimer's Disease Neuroimaging Initiative: The Alzheimer's disease neuroimaging initiative: progress report and future plans. Alzheimers Dement. 2010; 6:201–211.e7.

24. Jack CR Jr, Bernstein MA, Fox NC, Thompson P, Alexander G, Harvey D, Borowski B, Britson PJ, Whitwell LJ, Ward C, Dale AM, Felmlee JP, Gunter JL, Hill DL, Killiany R, Schuff N, Fox-Bosetti S, Lin C, Studholme C, DeCarli CS, Krueger G, Ward HA, Metzger GJ, Scott KT, Mallozzi R, Blezek D, Levy J, Debbins JP, Fleisher AS, Albert M, Green R, Bartzokis G, Glover G, Mugler J, Weiner MW. The Alzheimer's Disease Neuroimaging Initiative (ADNI): MRI methods. J Magn Reson Imaging. 2008; 27:685–691. [PubMed: 18302232]

25. Scheltens P, Leys D, Barkhof F, Huglo D, Weinstein HC, Vermersch P, Kuiper M, Steinling M, Wolters EC, Valk J. Atrophy of medial temporal lobes on MRI in "probable" Alzheimer's disease and normal ageing: diagnostic value and neuropsychological correlates. J Neurol Neurosurg Psychiatry. 1992; 55:967–972. [PubMed: 1431963]

26. Barber R, Ballard C, McKeith IG, Gholkar A, O'Brien JT. MRI volumetric study of dementia with Lewy bodies: a comparison with AD and vascular dementia. Neurology. 2008; 54:1304–1309. [PubMed: 10746602]

27. Burton EJ, Barber R, Mukaetova-Ladinska EB, Robson J, Perry RH, Jaros E, Kalaria RN, O'Brien JT. Medial temporal lobe atrophy on MRI differentiates Alzheimer's disease from dementia with Lewy bodies and vascular cognitive impairment: a prospective study with pathological verification of diagnosis. Brain. 2009; 132:195–203. [PubMed: 19022858]

28. Visser PJ, Verhey FR, Hofman PA, Scheltens P, Jolles J. Medial temporal lobe atrophy predicts Alzheimer's disease in patients with minor cognitive impairment. J Neurol Neurosurg Psychiatry. 2002; 72:491–497. [PubMed: 11909909]

29. Convit A, de Asis J, de Leon MJ, Tarshish CY, De Santi S, Rusinek H. Atrophy of the medial occipitotemporal, inferior, and middle temporal gyri in non-demented elderly predict decline to Alzheimer's disease. Neurobiol Aging. 2000; 21:19–26. [PubMed: 10794844]

30. Killiany RJ, Hyman BT, Gomez-Isla T, Moss MB, Kikinis R, Jolesz F, Tanzi R, Jones K, Albert MS. MRI measures of entorhinal cortex vs hippocampus in preclinical AD. Neurology. 2002; 58:1188–1196. [PubMed: 11971085]

31. Tondelli M, Wilcock GK, Nichelli P, De Jager CA, Jenkinson M, Zamboni G. Structural MRI changes detectable up to ten years before clinical Alzheimer's disease. Neurobiol Aging. 2012; 33:e25–36. [PubMed: 21782287]

32. Westman E, Cavallin L, Muehlboeck JS, Zhang Y, Mecocci P, Vellas B, Tsolaki M, Koszewska I, Soininen H, Spenger C, Lovestone S, Simmons A, Wahlund LO. AddNeuroMed consortium. Sensitivity and specificity of medial temporal lobe visual ratings and multivariate regional MRI classification in Alzheimer's disease. PLoS One. 2011; 6:e22506. [PubMed: 21811624]

33. Fox NC, Freeborough PA, Rossor MN. Visualisation and quantification of rates of atrophy in Alzheimer's disease. Lancet. 1996; 348:94–97. [PubMed: 8676724]

34. Shen Q, Loewenstein DA, Potter E, Zhao W, Appel J, Greig MT, Raj A, Acevedo A, Schofield E, Barker W, Wu Y, Potter H, Duara R. Volumetric and visual rating of magnetic resonance imaging scans in the diagnosis of amnestic mild cognitive impairment and Alzheimer's disease. Alzheimers Dement. 2011; 7:e101–108. [PubMed: 21784342]

35. Waldemar G. Visual rating and ROI-based parametric analysis of rCBF SPECT in patients with mild or questionable dementia: a comparative study. Dement Geriatr Cogn Disord. 2007; 24:429–433. [PubMed: 17952007]

36. DeCarli C, Frisoni GB, Clark CM, Harvey D, Grundman M, Petersen RC, Thal LJ, Jin S, Jack CR Jr, Scheltens P. Alzheimer's Disease Cooperative Study Group: Qualitative estimates of medial temporal atrophy as a predictor of progression from mild cognitive impairment to dementia. Arch Neurol. 2007; 64:108–115. [PubMed: 17210817]

37. Dickerson BC, Stoub TR, Shah RC, Sperling RA, Killiany RJ, Albert MS, Hyman BT, Blacker D, Detoledo-Morrell L. Alzheimer-signature MRI biomarker predicts AD dementia in cognitively normal adults. Neurology. 2011; 76:1395–1402. [PubMed: 21490323]

38. van Straaten EC, Harvey D, Scheltens P, Barkhof F, Petersen RC, Thal LJ, Jack CR Jr, DeCarli C. Alzheimer's Disease Cooperative Study Group: Periventricular white matter hyperintensities increase the likelihood of progression from amnestic mild cognitive impairment to dementia. J Neurol. 2008; 255:1302–1308. [PubMed: 18825439]

39. Chen W, Song X, Zhang Y. for the Alzheimer's Disease Neuroimaging Initiative. Assessment of the Virchow-Robin spaces in Alzheimer's disease, mild cognitive impairment, and normal aging, using high-field MRI. AJNR Am J Neuroradiol. 2011; 32:1490–1495. [PubMed: 21757525]

40. Gold G, Kövari E, Herrmann FR, Canuto A, Hof PR, Michel JP, Bouras C, Giannakopoulos P. Cognitive consequences of thalamic, basal ganglia, and deep white matter lacunes in brain aging and dementia. Stroke. 2005; 36:1184–1188. [PubMed: 15891000]

41. Carmichael O, Schwarz C, Drucker D, Fletcher E, Harvey D, Beckett L, Jack CR Jr, Weiner M, DeCarli C. Alzheimer's Disease Neuroimaging Initiative: Longitudinal changes in white matter disease and cognition in the first year of the Alzheimer disease neuroimaging initiative. Arch Neurol. 2010; 67:1370–1378. [PubMed: 21060014]

42. Schmidt R, Ropele S, Enzinger C, Petrovic K, Smith S, Schmidt H, Matthews PM, Fazekas F. White matter lesion progression, brain atrophy, and cognitive decline: the Austrian stroke prevention study. Ann Neurol. 2005; 58:610–616. [PubMed: 16178017]

43. Blum S, Luchsinger JA, Manly JJ, Schupf N, Stern Y, Brown TR, DeCarli C, Small SA, Mayeux R, Brickman AM. Memory after silent stroke: hippocampus and infarcts both matter. Neurology. 2012; 78:38–46. [PubMed: 22201111]

44. Rossi R, Geroldi C, Bresciani L, Testa C, Binetti G, Zanetti O, Frisoni GB. Clinical and neuropsychological features associated with structural imaging patterns in patients with mild cognitive impairment. Dement Geriatr Cogn Disord. 2007; 23:175–183. [PubMed: 17220628]

45. Appel J, Potter E, Bhatia N, Shen Q, Zhao W, Greig MT, Raj A, Barker WW, Potter H, Schofield E, Wu Y, Loewenstein DA, Duara R. Association of white matter hyperintensity measurements on brain MR imaging with cognitive status, medial temporal atrophy, and cardiovascular risk factors. AJNR Am J Neuroradiol. 2009; 30:1870–1876. [PubMed: 19643919]

46. Jacobs HI, Van Boxtel MP, van der Elst W, Burgmans S, Smeets F, Gronenschild EH, Verhey FR, Uylings HB, Jolles J. Increasing the diagnostic accuracy of medial temporal lobe atrophy in Alzheimer's disease. J Alzheimers Dis. 2011; 25:477–490. [PubMed: 21471642]

47. Brickman AM, Honig LS, Scarmeas N, Tatarina O, Sanders L, Albert MS, Brandt J, Blacker D, Stern Y. Measuring cerebral atrophy and white matter hyperintensity burden to predict the rate of cognitive decline in Alzheimer disease. Arch Neurol. 2008; 65:1202–1208. [PubMed: 18779424]

48. de la Torre JC. Vascular risk factor detection and control may prevent Alzheimer's disease. Ageing Res Rev. 2010; 9:218–225. [PubMed: 20385255]

49. Gouw AA, van der Flier WM, van Straaten EC, et al. Reliability and sensitivity of visual scales versus volumetry for evaluating white matter hyperintensity progression. Cerebrovasc Dis. 2008; 25:247–253. [PubMed: 18216467]

50. Gao FQ, Swartz RH, Scheltens P, et al. Complexity of MRI white matter hyperintensity assessments in relation to cognition in aging and dementia from the Sunnybrook Dementia Study. J Alzheimers Dis. 2011; 26:379–388. [PubMed: 21971477]

51. Song X, Mitnitski A, Cox J, Rockwood K. Comparison of machine learning techniques with classical statistical models in predicting health outcomes. Stud Health Technol Inform. 2004; 107:736–740. [PubMed: 15360910]
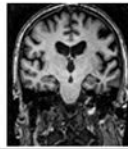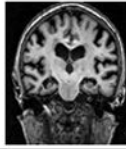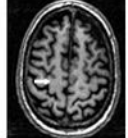
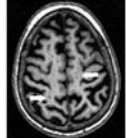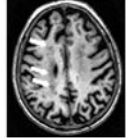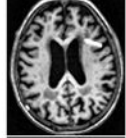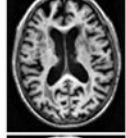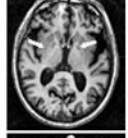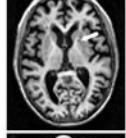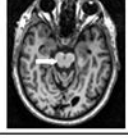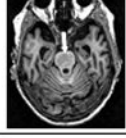|	**A** (a HC subject)	**B** (an AD subject)
medial temporal lobe atrophy		
lesions in grey matter and small vessels		
lesions in deep white matter		
lesions in periventricular regions		
global atrophy		
lesions in basal ganglia and surrounding areas		
lesions in infratentorial regions		
MTA rating score	Total =3 (1+2)	Total =8 (4+4)
BALI rating score	Total = 9 (1+2+1+2+2+1)	Total =16 (2+4+3+2+2+3)

Figure 1.
Example images showing the rating of the medial temporal lobe atrophy scale (MTAS) and the brain atrophy and lesion index (BALI). Left panel (A) shows a healthy control subject (HC; 76 years old, male); right panel (B) shows a subject diagnosed with Alzheimer's disease (AD; 83 years old, female). Locations of specific deficits under evaluation are indicated by white arrows.
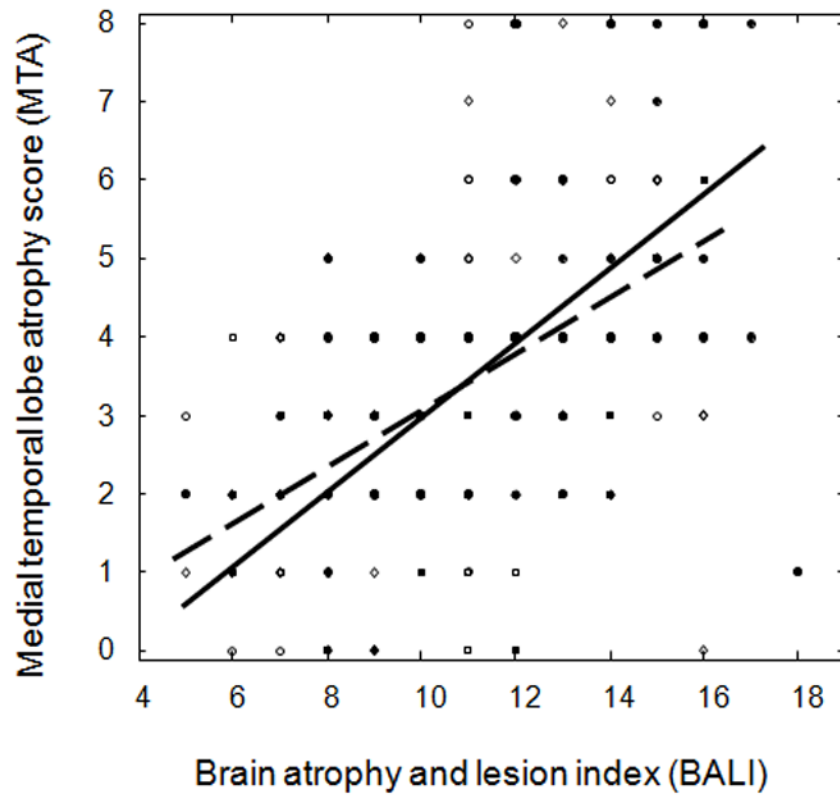
Figure 2.
Relationships between the brain atrophy and lesions index (BALI) and the medial temporal lobe atrophy scales (MTAS). Symbols represent the observational data (circles: Alzheimer's disease; diamond: mild cognitive impairment; squares: healthy control) and lines describe the linear fitting (MTAS=a+b·BALI). At baseline: a=−0.542, b=0.361, n=179, r^2=0.555, p<0.001; open symbols; dashed line. At follow-up: a=−1.865, b=0.480, n=125, r^2=0.565, p<0.001; filled symbols; solid line.

Figure 3.
Receiver operating characteristic analysis (ROC) for the two-year prediction of individuals with mild cognitive impairment (MCI; n=53) who converted to AD versus those who remained MC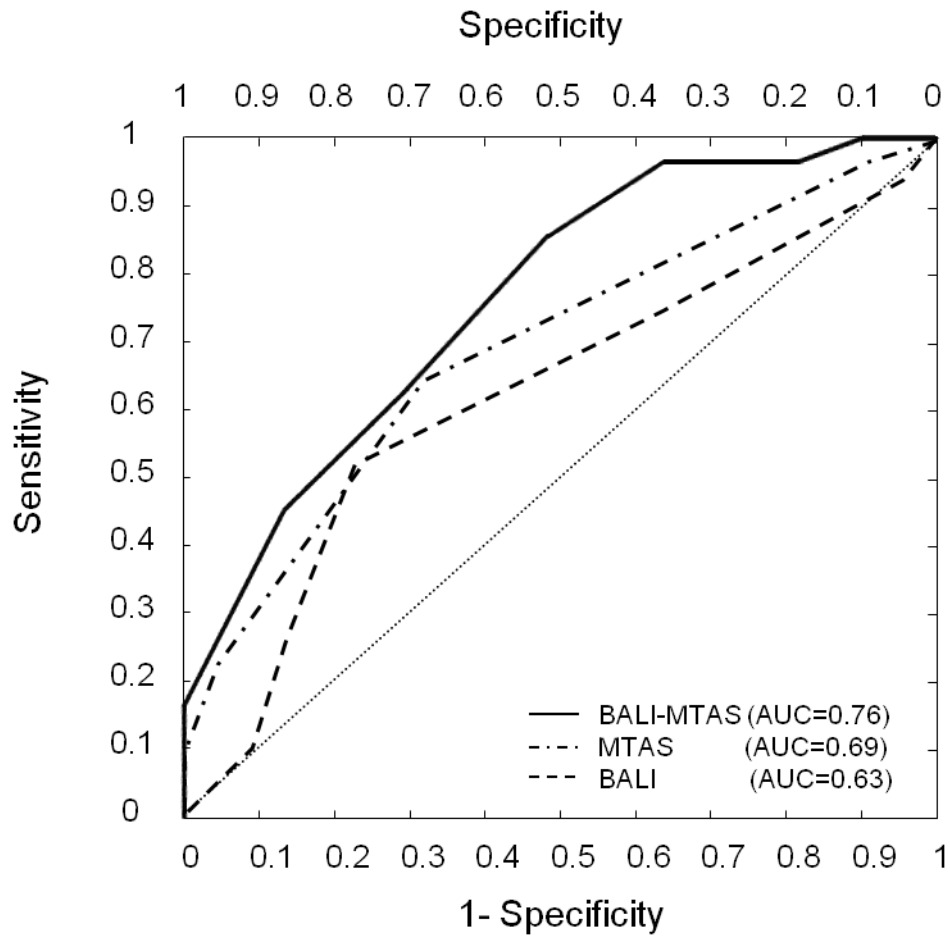I. Dashed line: brain atrophy and lesion index (BALI); dot-dashed line: medial temporal lobe atrophy scale (MTAS); solid line: combined BALI-MTAS. Diagonal lines indicate accuracy=0.50.

Table 1

Demographics and characteristics of the subjects in different diagnostic groups.

Group	Alzheimer's Disease	MCI All	Healthy Control	p	MCI Converter	MCI Stable	p
Sample size baseline	39	82	58	-	-	-	-
Sample size follow-up	26	53	-	-	31	22	-
Age (year)	75.7±9.4	73.3±7.7	76.0±5.1	0.369	74.2±8.2	72.9±7.0	0.417
Female (%)	59.0	34.1	62.1	0.002	29.0	40.9	0.368
Education (year)	14.7±2.4	15.4±2.9	15.4±2.7	0.844	15.7±2.7	14.9±2.8	0.344
MMSE (/30)	23.0±2.1	26.6±2.9	29.3±0.9	<0.001	26.4±1.8	27.6±2.0	0.014
ADAS-cog (/70)	18.6±6.8	12.5±4.6	5.3±2.5	<0.001	13.8±3.4	9.1±4.0	<0.001
CDR (0–3) *	0.7±0.2 (0.5)	0.5±0.1 (0.5)	0 (0)	<0.001	0.5±0 (0.5)	0.5±0 (0.5)	-
MTAS (/8) baseline	3.9±2.0 (3)	3.4±1.8 (4)	2.4±1.2 (2)	<0.001	3.5±1.9 (3)	2.3±1.6 (2)	0.015
MTAS (/8) follow-up	4.9±2.3 (4)	3.7±2.0 (4)	2.6±1.2 (2)	<0.001	4.3±2.1 (4)	2.7±1.5 (3)	0.006
BALI (/25) baseline	11.2±3.1	10.4±2.7	9.9±2.4	0.072	10.7±2.8	9.5±2.6	0.118
BALI (/25) follow-up	12.4±2.7	11.0±2.3	11.0±2.4	0.001	12.0±2.7	9.9±2.1	0.006

Note: Data are presented as mean±standard deviation, unless otherwise as indicated. MCI: Mild Cognitive Impairment. MMSE: Mini-Mental Status Examination; ADAS-cog: Alzheimer's Disease Assessment Scale-cognitive subscale; CDR: Clinical Dementia Rating. MTAS: Medial temporal lobe atrophy scale. BALI: Brain atrophy and lesion index.

*
Median value. p: Significance for the comparisons between AD, MCI, HC and between MCI subjects who converted to AD and those who maintained MCI.

#
Median value is presented in brackets.

Table 2

Prediction of the risk for two-year Alzheimer's disease (AD) conversion from mild cognitive impairment (MCI; n=53) using the medial temporal lobe atrophy scale (MTAS), brain atrophy and lesion index (BALI), and the combined BALI-MTAS scores in a multivariate logistic regression model adjusted for age (year), sex, and education.

Model	Covariate	Odds Ratio	95% Confidence Interval		Walds	p
1	age	0.99	0.91	1.08	0.06	0.807
	sex	1.21	0.31	4.64	0.07	0.785
	education	1.10	0.88	1.38	0.75	0.385
	MTAS	3.71	1.07	12.91	4.24	0.039
2	age	0.97	0.89	1.06	0.48	0.491
	sex	0.76	0.20	2.87	0.17	0.683
	education	1.03	0.81	1.30	0.05	0.833
	BALI	4.08	0.85	19.68	3.07	0.080
3	age	0.94	0.85	1.04	1.65	0.200
	sex	1.21	0.29	4.92	0.07	0.791
	education	1.04	0.82	1.32	0.10	0.748
	BALI-MTAS	8.99	1.81	44.65	7.21	0.007

Table 3

Sensitivity (Sen), specificity (Spe), and areas under the curve (AUC) for the medial temporal lobe atrophy scale (MTAS), brain atrophy and lesion index (BALI), and the combined BALI-MTAS scores in discriminating Alzheimer's disease (AD) and mild cognitive impairment (MCI) and in predicting MCI-AD conversion.

Group	Score	Sen	Spe	AUC	p
AD vs HC n=97	**MTAS**	0.73	0.72	0.737	0.001
	BALI	0.65	0.70	0.702	0.003
	BALI-MTAS	0.73	0.74	0.824	<0.001
MCI vs HC n=140	**MTAS**	0.51	0.72	0.604	0.076
	BALI	0.53	0.41	0.485	0.803
	BALI-MTAS	0.51	0.76	0.670	0.004
AD vs MCI n=121	**MTAS**	0.50	0.60	0.605	0.130
	BALI	0.69	0.60	0.627	0.068
	BALI-MTAS	0.62	0.60	0.640	0.045
MCI-AD conversion vs stable n=53	**MTAS**	0.65	0.68	0.692	0.018
	BALI	0.61	0.59	0.625	0.125
	BALI-MTAS	0.74	0.68	0.759	0.002