Combining Structural Brain Changes Improves the Prediction of Alzheimer's Disease and Mild Cognitive Impairment

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Key Words

Aging · Alzheimer's disease · Brain atrophy and lesion index · Mild cognitive impairment · Medial temporal lobe atrophy scale · Structural magnetic resonance imaging

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 magnetic resonance imaging (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 a 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 score 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 MTAS and BALI components resulted in a greater OR (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 coexisting structural changes to benefit AD diagnosis, progression monitoring, and/or treatment effect evaluation.

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Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by brain damage pri-

Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (www.loni.ucla.edu/ADNI). 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. ADNI is the result of efforts of many coinvestigators from a broad range of academic institutions and private corporations. The Principal Investigator is Michael W. Weiner, MD, VA Medical Center and University of California – San Francisco. A complete listing of ADNI investigators is available at http://www.loni.ucla.edu/ADNI/Collaboration/ADNI_Manuscript_Citations.pdf.

marily in the medial temporal lobe (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, mild cognitive impairment (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 T) high-resolution MRI from the Alzheimer's Disease Neuroimaging Initiative (ADNI). An MTA rating scale (MTAS) and a BALI score were assigned to 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 ADNI with permission [23]. 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 non-profit organizations, as a USD 60-million, 5-year public-private partnership. The primary goal of ADNI has been to test the use of serial MRI, positron emission tomography, and other biological markers in 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 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 USA and Canada, with the initial goal to recruit 800 adults, ages 55–90 (200 cognitively normal older individuals to be followed for 3 years, 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 with 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, the Alzheimer's Disease Assessment Scale-cognitive subscale, and the Clinical Dementia Rating Scale.

For this analysis, all the accessible imaging data of the subjects who had 3-tesla 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 (1.2 mm 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 the 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 online suppl. Appendix 1; for all online suppl. material, see www.karger.com/doi/10.1159/000339364). Brain images were rated in a random order, while the raters were blinded to the subjects' demographic, diagnosis, cognitive information, and to the time of scan. Examples for MTAS and BALI evaluations are shown in figure 1.

	a (a HC subject)	b (an AD subject)
Medial temporal lobe atrophy
Lesions in gray 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)

Fig. 1. Example images showing the rating of the MTAS and the BALI. **a** A HC (76 years old, male). **b** A subject diagnosed with AD (83 years old, female). Locations of specific deficits under evaluation are indicated by white arrows.

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 et al. [25]. Specifically, the left and the right sides of the medial temporal lobe were assessed independently according to a grading schema of 0–4 that rates the width of the choroidal fissure, the width of the temporal horn, and the height of the hippocampus. A total MTAS score 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 MTA (online suppl. 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 subscores. A total BALI rating score was assigned to each subject as the sum of the subscores, with a possible maximum value of 25, with a higher score representing a greater level of global brain structural deficits (online suppl. 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 2-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: $f(z) = 1 / (1 + e^{-z})$; $z = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \dots + \beta_k x_k$; where $f(z)$ represents the combined BALI-MTAS score ranging between a possible minimum of 0 and maximum of 1, $x_1, x_2, \dots, x_k$ represent MTAS and BALI items, β_0 represents the intercept, and $\beta_1, \beta_2 \dots \beta_k$ 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 interrater agreement rate (Cohen's kappa) on a subsample 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 χ^2 tests for categorical/ordinal data. Odds ratios (ORs) and the 95% confidence intervals (CIs) of the MTAS, BALI, and BALI-MTAS in discriminating AD and MCI versus HC and in predicting MCI subjects who converted to AD over 2 years versus those who remained MCI were assessed using univariate 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 2-year conversion from MCI to AD, assessed using the areas under the ROC curve (AUC). Sensitivity analysis was performed; dichotomization of the scores was made using optimal cut-off points at which a further increase of sensitivity resulted in a minimal decrease of specificity. The cut-off points were: MTAS ≤ 3 vs. > 3 (of 8, the possible maximum value), BALI ≤ 11 vs. > 11 (of 25), and BALI-MTAS ≤ 0.6 vs. > 0.6 (of 1).

Table 1. Demographics of the study sample

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	46	–	31	22	–
Age, years	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, years	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) ¹	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

Data are presented as means ± standard deviations, otherwise as indicated. ADAS-cog = Alzheimer's Disease Assessment Scale-cognitive subscale; CDR = clinical dementia rating. p value = Significance for the comparisons between AD, MCI, HC and between MCI subjects who converted to AD and those who maintained with MCI.

¹ Median values are presented in brackets.

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 ratio 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 ($p \leq 0.001$). The MCI-AD converters did not statistically differ from the nonconverters 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 ($p = 0.006$).

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 ($r^2 > 0.56$, $p < 0.001$; fig. 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 , $p < 0.001$ for MTAS; $r^2 > 0.04$, $p < 0.050$ for BALI).

Fig. 2. Relationships between the BALI and the MTAS. Symbols represent the observational data (circles: AD; diamond: MCI; squares: HC) and lines describe the linear fitting (MTAS = $a + b \cdot \text{BALI}$). 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.

An increase in the MTAS score 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

Table 2. Prediction of the risk for 2-year AD conversion from MCI (n = 53) using the MTAS, BALI, and the combined BALI-MTAS scores in a multivariate logistic regression model adjusted for age (years), sex, and education

Model	Covariate	Odds ratio	95% Confidence interval		Wald's	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

= 1.36, 95% CI = 1.00–1.80). An increase in the 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 ($p > 0.05$). 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 2-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 ($p > 0.05$; online suppl. 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 (fig. 3; table 3).

Discussion

We investigated the effect of combining MTA and several other common changes including global atro-

Fig. 3. ROC analysis for the 2-year prediction of individuals with MCI (n = 53) who converted to AD versus those who remained with MCI. Dashed line: BALI; dot-dashed line: MTAS; solid line: combined BALI-MTAS. Diagonal lines indicate accuracy = 0.50.

Table 3. Sensitivity (Sen), specificity (Spe), and AUC for the MTAS, BALI, and the combined BALI-MTAS scores in discriminating AD and 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

phy, 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 struc-

ture (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 coexisting structural changes helped improve the discrimination of AD and MCI, and the prediction of short-term (here, 24 months) 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 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 can occur using 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 studies have shown that multiple structural brain deficits may not present in isolation. They often coexist [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 facilitates such multivariable approaches, by not just considering 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. 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 AD risk factors, including modifiable vascular risk factors that are associated with 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 of MTA for a subset of the sample from the 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., 3 T that has become the mainstream of clinical MRI); we only included subjects with 3-tesla scans in the analysis; the greater tissue contrasts have allowed reliable rating [21, 22]. Whether this finding can be generalized using low-moderate MRI systems (e.g. 1.5 T 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 an approach is widely available and commonly applied. Certainly, other processing methods may also be applicable to carry out the task, although it has been shown that differences in the predictive performance are chiefly determined by the nature of data [51]. How to better coordinate 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 a long follow-up time would be particularly beneficial.

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