Journal of Alzheimer's Disease 44 (2015) 1023–1034
DOI 10.3233/JAD-142088
IOS Press

A Comprehensive Visual Rating Scale of Brain Magnetic Resonance Imaging: Application in Elderly Subjects with Alzheimer's Disease, Mild Cognitive Impairment, and Normal Cognition

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Handling Associate Editor: YongSoo Shim

Accepted 12 October 2014

Abstract.
Background: Brain magnetic resonance imaging (MRI) shows cerebral structural changes. However, a unified comprehensive visual rating scale (CVRS) has seldom been studied. Thus, we combined brain atrophy and small vessel disease scales and used an MRI template as a CVRS.
Objective: The aims of this study were to design a simple and reliable CVRS, validate it by investigating cerebral structural changes in clinical groups, and made comparison to the volumetric measurements.
Methods: Elderly subjects ($n = 260$) with normal cognition (NC, $n = 65$), mild cognitive impairment (MCI, $n = 101$), or Alzheimer's disease (AD, $n = 94$) were evaluated with brain MRI according to the CVRS of brain atrophy and small vessel disease. Validation of the CVRS with structural changes, neuropsychological tests, and volumetric analyses was performed.
Results: The CVRS revealed a high intra-rater and inter-rater agreement and it reflected the structural changes of subjects with NC, MCI, and AD better than volumetric measures (CVRS-coronal: $F = 13.5$, $p < 0.001$; CVRS-axial: $F = 19.9$, $p < 0.001$). The area under the receiver operation curve (aROC) of the CVRS showed higher accuracy than volumetric analyses. (NC versus MCI aROC: CVRS-coronal, 0.777; CVRS-axial, 0.773; MCI versus AD aROC: CVRS-coronal, 0.680; CVRS-axial, 0.681).
Conclusion: The CVRS can be used clinically to conveniently measure structural changes of brain. It reflected cerebral structural changes of clinical groups and correlated with the age better than volumetric measures.

Keywords: Alzheimer's disease, mild cognitive impairment, visual rating scale

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INTRODUCTION

Brain magnetic resonance imaging (MRI) is commonly used to evaluate subjects with cognitive decline and detect structural changes. MRI shows anatomical changes, such as diffuse and focal cortical atrophy, ventricular enlargement, white matter changes, infarction, and microbleeds [1–4]. Structural changes have been shown to be related to cognitive decline in patients with Alzheimer's disease (AD) or the normal elderly, and they are commonly associated with each other [5–9]. Several MRI visual rating scales have been introduced to assess various brain lesions [10–12]. Some tools, such as the Scheltens' scale, are widely used in many studies. However, for cortical atrophy, ventricular enlargement, lacunes, and microbleeds, there are no widely used visual rating scales. Additionally, previously reported visual rating scales vary according to imaging modality, study groups, and sample size [13], and unified comprehensive visual rating scales (CVRS) are seldom evaluated. In addition, the current formal reading of brain MRI by neuroradiologists cannot provide enough information about the future risk of cognitive decline. However, brain MRIs might be used to support the clinical evaluation of subjects with cognitive decline as well as to exclude diagnoses, such as vascular lesion, hydrocephalus, or tumor [14].

The aim of the present study was to develop a fast, simple, and reliable CVRS that could be used by neurologists or neuroradiologists to screen patients with cognitive decline. Based on a comprehensive review of existing visual rating scales, the CVRS consisted of previously validated visual rating scales or modified versions of them. The MRI structural changes in patients with AD and mild cognitive impairment (MCI) and subjects with normal cognition (NC) were assessed with the newly designed CVRS and volumetric measures. We investigated whether the CVRS reflected the cerebral structural changes among the clinical groups better than the volumetric measures.

METHODS

Subjects

The subjects in this study included 94 patients with AD, 101 patients with MCI, and 65 patients with NC who were identified consecutively at the Neurocognitive Behavior Center at Seoul National University Bundang Hospital between March 2011 and May 2013. The subjects were consecutively enrolled and retrospectively analyzed. The patients with AD met the criteria for probable AD proposed by the National Institute of Neurological and Communicative Diseases and Stroke and Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) [15]. The MCI patients were diagnosed according to the following criteria proposed by Peterson et al. [16]: 1) subjective memory complaints by the patient and/or caregiver; 2) normal general cognitive function, as defined by scores on the Mini-Mental State Examination (MMSE) greater than or equal to −1.0 standard deviation (SD) of the norms for age-and education-matched normal subjects; 3) the ability to participate in normal activities of daily living, judged clinically and by an Activities of Daily Living scale; 4) objective memory decline below the −1.0 SD on neuropsychological tests (this cutoff value has been used in previous studies; Supplementary Method 1); and 5) nonconformance to clinical criteria for a diagnosis of dementia.

The NC were subjects with preserved daily living activities and normality in global cognitive function with memory decline less than 1.0 SD below the normative mean on neuropsychological tests.

All of the subjects underwent brain MRI and comprehensive neurological and neuropsychological evaluations. In addition, a detailed medical history, a neurological examination, and laboratory tests were performed to exclude secondary causes of cognitive impairment. Because all of the data were analyzed retrospectively, a waiver of informed consent was obtained from the institutional review board of Seoul National University Bundang Hospital, which approved this study.

Acquisition of MRI

The MRI studies were performed with a 1.5-Tesla (INTERA) and 3-Tesla (ACHIEVA) superconducting magnet (Philips Healthcare, Best, The Netherlands). The standardized MRI protocols consisted of an axial T2-weighted fast spin echo image, a fluid-attenuated inversion recovery image (FLAIR), a gradient-echo image, an axial T1-weighted spin echo image, a coronal T1-weighted spin echo image, and a T1-weighted three-dimensional volumetric spoiled gradient echo image (Supplementary Table 1).

Neuropsychological evaluation

All patients were evaluated by the MMSE and the Seoul Neuropsychological Screening Battery (SNSB), which is a comprehensive neuropsychological test that assesses the five cognitive domains: attention, memory,

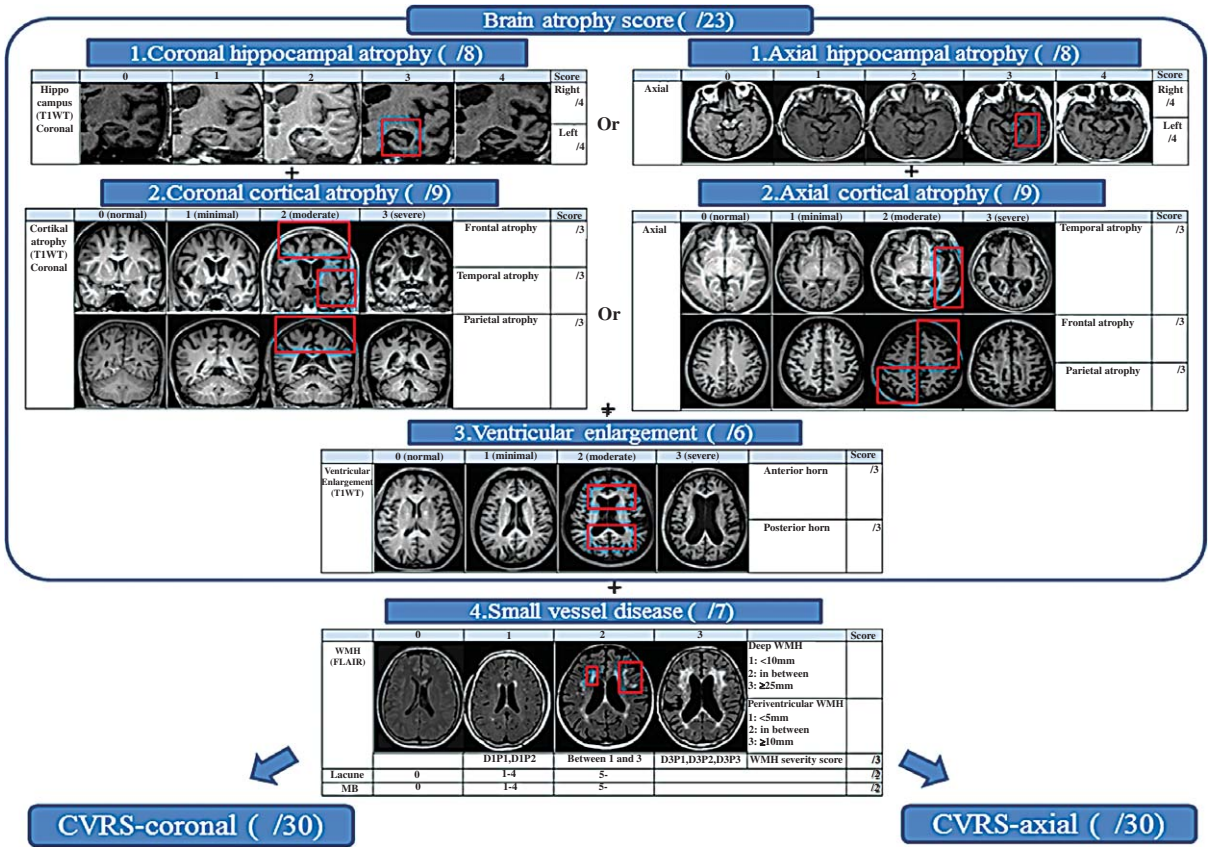


Fig. 1. The scoring table of the Comprehensive Visual Rating Scale (CVRS). T1WI, T1-weighted images; FLAIR, fluid-attenuated inversion recovery; WMH, white matter hyperintensity; D, deep; P, periventricular; MB, microbleeds; The red rectangles are the brain regions that need to be focused on.

language, visuospatial function, and frontal/executive function [17]. It is considered abnormal when scores on the relevant neuropsychological tests are below −1.0 SD of the norm, as described in a previous study [18]. The SNSB provides a dementia version of the SNSB (SNSB-D) that can be used as a global cognitive function score and that represents the sum of the five assessed cognitive domains [19]. The SNSB-D score significantly correlates with the MMSE and has been shown to be a valid and reliable tool for assessing overall cognitive function as a quantitative score [19] (Supplementary Table 2).

Comprehensive Visual Rating Scale

The structure of the CVRS is largely composed of four parts, which are the scales of hippocampal atrophy, cortical atrophy, ventricular enlargement (subcortical atrophy), and small vessel disease (Fig. 1). For hippocampal atrophy and cortical atrophy, we designed both coronal and axial rating scales because there were subjects without coronal brain images. The brain atrophy scales consist of hippocampal atrophy, cortical atrophy, and ventricular enlargement (subcortical atrophy). The small vessel disease scales include subcortical white matter hyperintensities (WMH), lacunes, and microbleeds. We combined the brain atrophy scales with those of small vessel disease because vascular damage is associated with increased brain atrophy in the context of AD pathology [20]. Instead of developing new scales, we adapted these from existing tools or modified versions of them that have been validated and combined them as a comprehensive tool. The raters used a template-based scoring program on a tablet computer that summed the total score automatically by matching the closest template image to the real MRI finding of the subject (Supplementary Figure 1).

Hippocampal atrophy

Hippocampal atrophy was measured on coronal T1-weighted images with Scheltens' scale [1] that is based on the surrounding cerebrospinal fluid (CSF) space and the hippocampal height in the left and right

hemispheres (Supplementary Table 3). A coronal template image is a slice that shows the cerebral peduncle most prominently. In addition, axial T1-weighted images were evaluated to rate the hippocampus and surrounding CSF, and they showed good agreement with Scheltens' T1-weighted coronal visual rating scale [21] (Supplementary Table 4). An axial template image is a slice that shows the lower midbrain prominently.

Cortical atrophy

Cortical atrophy was determined by rating the axial images and coronal images separately with 8 template images and a four-point scale (0, 1, 2, and 3) that was modified from Victoroff's visual rating scale [11]. The original Victoroff's method used 6 standard T1-weighted images and a four-point scale (0, 0.5, 1, and 2) that measures the anterior frontal lobe with axial images and anterior temporal and midparietal lobes with coronal images [11]. However, we modified this because of the complexity of the use of axial and coronal images at the same time. Our coronal template images included slices that showed both temporal stems connecting the temporal and frontal lobes to assess frontal and temporal atrophy and a slice posterior to the splenium of the corpus callosum to assess parietal atrophy. The axial template images included slices that showed the superior colliculus to assess temporal atrophy and the first slice above the lateral ventricle to assess frontal and parietal atrophy (Fig. 1). The parietal atrophy assessment was very similar to the posterior cortical atrophy scale by Koedam et al. [22], although the CVRS was simpler because it did not include a regional index (posterior cingulate sulcus and the parieto-occipital sulcus) or sagittal images. More severe atrophy was used to evaluate when there was asymmetry.

Ventricular enlargement as a representation of subcortical atrophy

We measured ventricular enlargement on the T1-weighted images with a template-based 4-point scale (0, 1, 2, and 3) by examining the enlargement of the anterior and posterior lateral ventricles separately, which was a modification of a previously published method [23]. The anterior and posterior horns of the lateral ventricle were rated separately, which was adequate because there were many cases with anterior and posterior discrepancies of ventricular size. The use of template-based ventricular enlargement as a representation of subcortical atrophy has also been used in a previous study by the LADIS group who showed good correlations with cognitive decline [12].

White matter hyperintensity

The severity of WMHs was evaluated according to the modified Fazekas and Scheltens scale on T2 axial FLAIR images [10]. WMHs were rated in the periventricular white matter (PWM, P rating) and deep white matter (DWM, D rating) areas separately, and the D and P ratings were combined to provide a final ischemia score. DWM lesions were divided into D1 (DWM < 10 mm), D2 ($10 \leq$ DWM<25 mm), and D3 (≥ 25 mm) based on the longest diameter of the lesions. PWM lesions were classified into P1 (cap and band <5 mm), P2 (between P1 and P3), and P3 (cap or band ≥ 10 mm) based on the size of the cap and band, which were perpendicular and horizontal to the ventricle, respectively. The results were combined to provide a representative rating of minimal (D1P1 or D1P2), moderate (between the minimal and severe group), or severe (D3P1, D3P2, or D3P3). Finally, the group with no WMHs was rated 0, the minimal group was 1, the moderate group was 2, and the severe group was 3 [24, 25].

Lacunes and microbleeds

Lacunes were defined as cavities with a size of 3 to 10 mm with signal intensities that were similar to CSF on FLAIR, T1, and T2 images to distinguish lacunes from microbleeds and Virchow Robin spaces [26]. The number of lacunes was recorded as grade 0 (no lacunes), grade 1 (1–4 lacunes), or grade 2 (5 or more lacunes), which was also used in a previous study [27]. Microbleeds were defined as focal areas with very low signal intensities on gradient-recalled echo images. Signal voids by sulcal vessels, symmetrical calcification in the basal ganglia, the choroid plexus, and pineal calcification were excluded [4]. The number of microbleeds was graded as grade 0 (no microbleeds), grade 1 (1–4 microbleeds), or grade 2 (5 or more microbleeds) based on the Rotterdam Scan Study of the association between cerebral microbleeds and performance in multiple cognitive domains [6]. The scales for the lacunes and microbleeds were newly made because there are no existing scoring tools as far as we know. Nevertheless, the incidences of lacunes and microbleeds are consistently reported to correlate with the decline of cognition, such as executive function, speed, and motor control [6, 27–29]. Although both the location and number of lacunes and microbleeds are important factors in cognitive decline, only their

total number was included in the rating with reference to large community-based studies [6, 27].

The subtotal scores of the brain atrophy scales were 23 points and those of small vessel disease were 7 points, which totaled 30 points for the CVRS (Fig. 1). The CVRS-coronal score consisted of the coronal scale of the hippocampal and cortical atrophy, while the CVRS-axial score included their axial scales. For all subjects, the effects of the four subscales, including the scales of hippocampal atrophy, cortical atrophy, ventricular enlargement, and small vessel disease, on the global cognitive scales (SNSB-D) were assessed with the standardized β coefficient of linear regression analyses (Supplementary Table 5). Comparing the four CVRS subscales, the standardized β coefficients of hippocampal atrophy, cortical atrophy, and ventricular enlargement were similar, while that of small vessel disease was smaller than the others. The actual allocation of the scores by the CVRS was 8 points for hippocampal atrophy, 9 points for cortical atrophy, 6 points for ventricular atrophy, and 7 points for small vessel disease. Thus, compared to the standardized β coefficients, there was some discrepancy with the actual CVRS scores. This might be partly solved by relative weights of the CVRS subscales according to their effects on cognitive decline, but we did not consider this in the current study because there were no significant differences between the current rating method compared to the weighted method for group discrimination and the correlation with cognitive function. In addition, this would ruin the simplicity of the CVRS by adding complex calculations. Therefore, we adapted the scores as described above without additional weights. The MRI scans were evaluated independently by three raters (JW Jang, SY Park, and YH Park) who were blinded to all of the clinical diagnoses of the patients because only the MRI scans and the CVRS template on the tablet computer were provided during the scoring. JW Jang was a developer of the CVRS modifications, while the others were naïve users. A reliability analysis was performed with inter-rater interclass correlation coefficients (ICC) in a random sample of 20% of all of the subjects with the three raters used as independent variables [30]. The intra-rater agreement was also evaluated with the same method.

Image processing and statistical parametric maps

We performed the volumetric analyses with the Individual Brain Atlases in the Statistical Parametric Mapping Toolbox (IBASPM; http://www.thomaskoenig.ch/Lester/ibaspm.htm) [31], which is an extension of Statistical Parametric Mapping 5 (SPM5, Welcome Department of Cognitive Neurology, London, UK) that works on MATLAB 7.5.0 (The MathWorks, Inc., Natick, MA, USA). To segment the individual MRIs into different anatomical structures, we used the atlasing processes in IBASPM. The MRIs were normalized with Montreal Neurological Institute (MNI) templates, and spatial transformation matrices were obtained. Additionally, individual MRIs were segmented, and each individual gray matter (GM) voxel was labeled based on the MNI anatomical atlas and transformation matrices. The volumes of different structures were computed based on the individual atlases that were previously obtained by the atlasing process. The total intracranial volume was measured by summing the GM, white matter, and CSF volumes, and it was used to normalize each brain region's volume. For the quantitative analysis of the whole brain, a standard voxel-based morphometry (VBM) protocol was performed involving spatial normalization, segmentation, and smoothing [32, 33]. Differences between the MRIs of each patient were corrected according to the International Consortium for Brain Mapping template for East Asian Brains during the normalization. All of the images were smoothed with a Gaussian filter set at 8 mm to minimize the between-subject variability in local anatomy. We performed a quality control protocol for the images that were used for automated segmentation. All of the scans with excessive motion artifact were excluded and visually inspected for misregistration errors. These smoothed GM segments were used for the voxel-based multiple regression analysis, and we examined the correlations between the GM space concentration and the CVRS subscales after controlling for age, gender, and years of education. The absolute threshold masking was 0.1. The results were considered statistically significant with p values less than 0.05 and were corrected for the false discovery rate. The x, y, and z coordinates of the areas with significant correlations that were obtained from the analyses were converted into MNI coordinates and then identified by MRIcron (http://www.mccauslandcenter.sc.edu/mricro/mricron/).

Statistical analysis

Comparisons of the means among the diagnostic groups were made by analysis of variance (ANOVA) with Scheffe's posthoc analyses and one-way analysis of covariance (ANCOVA) tests with age, education level, and gender as covariates. The chi-squared (χ^2)

test was used to assess differences in categorical variables. Sensitivity and specificity analyses were performed, and receiver operating characteristic (ROC) curves were obtained to assess whether the CVRS showed differences in the clinical groups compared to the volumetric measures. In addition, the relationships between the brain MRI variables and the psychological tests were evaluated with correlation and regression analyses. Subsequently, the associations between the CVRS and the neuropsychological tests were assessed with a general linear model with the SNSB-D, MMSE, and Clinical Dementia Rating scale sum of boxes (CDR-SOB) scores used as dependent variables. The basic associations between the visual rating scale and the cognitive measures were examined with unadjusted analyses (model 1). Age, gender, and years of education were used as covariates (model 2). To assess the independent contributions of the visual rating scales, the scores of hippocampal atrophy, cortical atrophy, ventricular enlargement, and small vessel disease were entered simultaneously into multivariable models that were adjusted for age, gender, and years of education (model 3). The data were analyzed with PASW 18.0 Statistics and MedCalc. The significance level was set at $p < 0.05$.

RESULTS

Reliability of CVRS

The analysis revealed a high intra-rater agreement for both the CVRS-coronal [ICC = 0.94, 95% confidence interval (CI), 0.89–0.97] and CVRS-axial (ICC = 0.95, 95% CI, 0.91–0.97) scores. The inter-rater agreement was 0.93 for the CVRS-coronal (95% CI, 0.90–0.96) and 0.94 for the CVRS-axial (95% CI, 0.91–0.97) scores (Table 1). The inter-rater agreement for sub-scales also showed high reliability.

Differences in clinical groups

The demographic and neuropsychological characteristics and MRI visual rating scales of each group are described in Table 2. There was a significant female predominance and age difference among the three groups. All of the neuropsychological tests, including the MMSE, CDR-SOB, and SNSB-D, revealed a significant difference among the three groups (AD, MCI, and NC subjects; $p < 0.001$) after adjusting for age, gender, and years of education. Regarding the cognitive domain scores, which constitute the SNSB-D, the three groups differed in each of the domains evaluated: attention, language and related function, visuospatial, memory, and frontal/executive function ($p < 0.001$ for all), except for attention, which showed a difference only between the AD and MCI groups. The same analyses were done to examine the validity of each of the brain MRI visual rating scales in the three groups. Significant group differences among the AD, MCI, and NC groups were present in both the CVRS-coronal ($F = 13.5$, $p < 0.001$) and CVRS-axial ($F = 19.9$, $p < 0.001$) scores.

For the CVRS subscales, a significant difference was observed among the AD, MCI, and NC groups on the axial hippocampal atrophy scale ($F = 12.5$, $p < 0.001$), while the coronal hippocampal scale showed a difference between the MCI and NC group ($F = 4.5$, $p < 0.012$). Only the volumetric hippocampal measures differentiated the AD and NC groups ($F = 2.4$, $p < 0.092$) (Table 2). The coronal and axial cortical atrophy scales showed a difference between the AD and non-AD groups ($F = 7.3$, $p = 0.001$; $F = 6.6$, $p = 0.002$), while the volumetric cortical measures revealed no significant differences among the three groups ($F = 0.2$, $p = 0.860$). The ventricular enlargement scale also showed a significant difference among the three groups ($F = 9.6$, $p < 0.001$), while the volumetric CSF space (without the subarachnoid CSF) assessment was not significantly different among the

Table 1
Values for inter-rater and intra-rater agreement of CVRS and subscales

	Inter-rater (95% CI)	Intra-rater (95% CI)
CVRS (coronal/axial)	0.939 (0.903–0.964)/ 0.943 (0.909–0.966)	0.938 (0.890–0.965)/ 0.947 (0.906–0.970)
Hippocampal atrophy (coronal/axial)	0.865 (0.784–0.919)/ 0.901 (0.842–0.941)	0.889 (0.804–0.937)/ 0.901 (0.826–0.944)
Cortical atrophy (coronal/axial)	0.905 (0.848–0.943)/ 0.895 (0.833–0.937)	0.943 (0.900–0.968)/ 0.891 (0.807–0.938)
Ventricular enlargement	0.895 (0.832–0.937)	0.877 (0.783–0.930)
Small vessel disease	0.904 (0.847–0.943)	0.902 (0.827–0.944)

Table 2
The demographic, neuropsychological characteristics and MRI profile with group difference for AD, MCI, and NC

	AD	MCI	NC	*p* value	F	$p<0.05^*$
Demographics						
Sample Size	94	101	65			
Gender, n (% female)	57 (67.9)	54 (53.5)	47 (72.3)	0.019		
Age (y)±SD	75.5 ± 6.9	71.4 ± 8.4	64.1 ± 9.5	<0.001†	37.6	a, b, c
Education (y)±SD	9.5 ± 5.6	11.3 ± 5.2	11.5 ± 4.9	0.024†	3.8	
Neuropsychological Tests						
MMSE (/30)	20.0 ± 3.6	25.8 ± 2.7	28.2 ± 2.1	<0.001§	116.7	a, b, c
CDR-SOB	4.4 ± 2.2	1.3 ± 0.8	0.7 ± 0.5	<0.001§	135.8	a, b, c
SNSB-D (/300)	104.8 ± 31.2	155.6 ± 34.4	209.2 ± 33.8	<0.001§	127.5	a, b, c
-Attention (/17)	7.8 ± 2.2	9.5 ± 2.1	10.4 ± 2.7	<0.001§	11.3	a, c
-Language and related function (/27)	14.5 ± 5.6	20.1 ± 5.3	24.0 ± 3.8	<0.001§	29.4	a, b, c
-Visuospatial function (/36)	22.6 ± 8.4	29.8 ± 6.2	33.4 ± 3.6	<0.001§	29.9	a, b, c
-Memory (/150)	30.0 ± 11.8	53.9 ± 15.0	88.7 ± 19.4	<0.001§	183.7	a, b, c
-Frontal/Executive function (/70)	31.4 ± 7.0	41.0 ± 8.3	49.8 ± 7.5	<0.001§	42	a, b, c
MRI profile						
3-tesla MRI (%)	61.7	61.4	56.9	0.92		
Coronal hippocampal atrophy (/8)	3.0 ± 1.8	2.4 ± 1.6	1.1 ± 1.3	0.012§	4.5	a, b
Axial hippocampal atrophy (/8)	3.5 ± 1.9	2.5 ± 1.9	1.0 ± 1.3	<0.001§	12.5	a, b, c
Volumetric hippocampal measures	0.46 ± 0.14	0.50 ± 0.12	0.55 ± 0.13	0.092§	2.4	a
Coronal cortical atrophy (/9)	6.0 ± 1.8	4.9 ± 1.8	3.6 ± 1.6	0.001§	7.3	a, c
Axial cortical atrophy (/9)	5.5 ± 2.1	4.6 ± 2.1	3.1 ± 2.1	0.002§	6.6	a, c
Volumetric cortical measures	45.9 ± 4.1	46.6 ± 3.7	47.6 ± 4.4	0.860§	0.2	
Ventricular enlargement (/6)	3.1 ± 1.2	2.4 ± 1.3	1.4 ± 1.2	<0.001§	9.6	a, b, c
Volumetric subcortical measures	37.5 ± 5.1	36.4 ± 5.7	33.4 ± 6.7	0.596§	0.5	
Small vessel disease (/7)	2.1 ± 1.4	1.6 ± 1.1	1.3 ± 1.1	0.114§	2.1	
CVRS-coronal (/30)	14.0 ± 4.1	11.1 ± 3.8	7.2 ± 3.6	<0.001§	13.5	a, b, c
CVRS-axial (/30)	14.1 ± 4.3	11.1 ± 4.5	6.7 ± 4.1	<0.001§	19.9	a, b, c

AD, Alzheimer's disease; MCI, mild cognitive impairment; NC, normal cognition; ANCOVA, analysis of covariance (age, gender and years of education); SD, standard deviation; MMSE, mini-mental status examination; CDR-SOB, Clinical Dementia Rating scale sum of boxes; SNSB-D, Seoul Neuropsychological Screening Battery Dementia version; WMH, white matter hyperintensity; CVRS, Comprehensive Visual Rating Scale In volumetric measures, the regional volume was normalized by dividing individual tissue volume by total intracranial volume then multiplying by 100. *Test of overall association. a, AD versus NC; b, MCI versus NC; c, AD versus MCI. †*p* value from analysis of variance followed by Scheffe's *post hoc* analyses. §*p* value from analysis of covariance using age, education level and gender as covariate.

Table 3
Comparison of area under the curve (AUC) of the CVRS and volumetric measurement between clinical subgroups

NC versus MCI	AUC	SE	95% CI
CVRS-coronal/-axial	0.777/0.773	0.033/0.036	0.692–0.862/0.682–0.858
Hippocampus-coronal/-axial	0.730/0.730	0.046/0.045	0.640–0.821/0.642–0.818
Hippocampus-volumetric measures	0.611	0.059	0.494–0.727
Cortical atrophy-coronal/-axial	0.694/0.707	0.049/0.049	0.598–0.789/0.611–0.802
Cortical atrophy-volumetric measures	0.564	0.062	0.442–0.687
Ventricular enlargement	0.706	0.041	0.626–0.785
Ventricular enlargement-volumetric measures	0.617	0.062	0.496–0.738
Small vessels disease	0.586	0.046	0.496–676
MCI versus AD	**AUC**	**SE**	**95% CI**
CVRS-coronal/-axial	0.680/0.681	0.042/0.041	0.598–0.762/0.600–0.763
Hippocampus-coronal/-axial	0.593/0.639	0.044/0.043	0.506–0.681/0.554–0.723
Hippocampus-volumetric measures	0.608	0.048	0.514–0.701
Cortical atrophy-coronal/-axial	0.662/0.637	0.043/0.043	0.578–0.746/0.552–0.721
Cortical atrophy-volumetric measures	0.554	0.048	0.459–0.649
Ventricular enlargement	0.637	0.039	0.560–0.714
Ventricular enlargement-volumetric measures	0.564	0.048	0.470–0.659
Small vessels disease	0.599	0.041	0.519–0.678

AUC, area under the curve; SE, standard error; CI, confidence interval; CVRS, Comprehensive Visual Rating Scale; MCI, mild cognitive impairment; NC, subjects with normal cognition; AD, Alzheimer's disease.

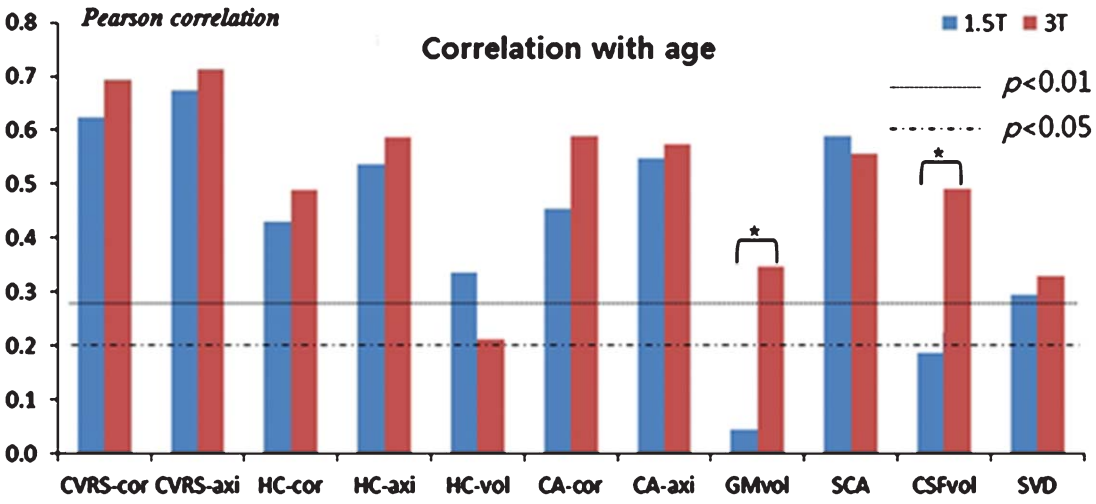


Fig. 2. Visual rating scales correlated with age according to MRI tesla used. Data presented are Pearson correlation between visual rating scale (or volumetric measures) and score for neuropsychological tests and that of age. Dotted lines: correlation reached the level of significance at $p < 0.01$. Dashed lines: correlation reached the level of significance at $p < 0.05$.1.5T, 1.5 Tesla, 3.0T, 3.0 Tesla; -cor, coronal visual rating; -axi, axial visual rating; vol; volumetric measurement; CVRS, Comprehensive Visual Rating Scale; HC, hippocampus; CA, cortical atrophy; GM, grey matter; SCA, subcortical atrophy (ventricular enlargement); CSF, cerebrospinal fluid space; SVD, small vessel disease score CVRS = hippocampal atrophy score + cortical atrophy score + small vessel disease score Small vessel disease score = white matter hyperintensity score + lacune score + microbeeds score. *Comparison of correlation coefficients reached the level of significance at $p < 0.05$ between 1.5T and 3T measures.

three groups ($F = 0.5$, $p = 0.596$). The score for small vessel disease, which was the sum of the scores of WMHs, microbleeds, and lacunes, showed no difference among the three groups ($F = 2.1$, $p = 0.114$).

We performed a ROC analysis and estimated the area under the curve (AUC) to assess the diagnostic utility of the CVRS between the groups compared to the subscales. As described in Table 3, the AUC-ROC of the CVRS was greater than that of any other single subscale and volumetric measurement. The AUC of the CVRS-coronal and CVRS-axial scores were 0.777 and 0.773 between the NC and MCI groups, respectively, and 0.680 and 0.681 between the MCI and AD groups, respectively.

Correlations among the age, the volumetric measures, and the visual rating scales

Most of the brain MRI measures significantly increased with age (Fig. 2). Both the coronal and axial cortical atrophy scales and the ventricular enlargement scale had greater correlations with age than the volumetric analysis did. When we divided the groups according to the tesla (T) into either 1.5 T or 3.0 T, they still showed similar correlation patterns between the CVRS and age. However, the volumetric measurements of the cerebral cortex (the GM volume) and the CSF space showed significantly different correlations with the cognitive tests or age according to the MRI tesla.

Validation with the volumetric assessments

The subscales of the brain atrophy scale were compared to the volumetric measurements with the VBM multiple regression analysis presented in Fig. 3. The regression analyses that were adjusted for age, gender, and years of education revealed that higher scores on the CVRS subscales were correlated with volume reductions in the specific brain regions that the visual scales intended to rate. The correlation maps showed a similar distribution between the coronal and axial scales, while some differences were noted. All of the above subscales were rated regardless of the right and left hemispheric differences, which showed a relatively symmetric topographic distribution on the VBM.

DISCUSSION

The purpose of this study was to design and validate a simple and reliable CVRS that was based on

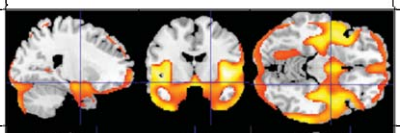
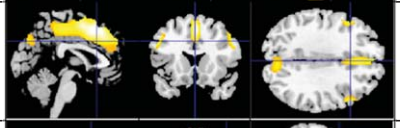
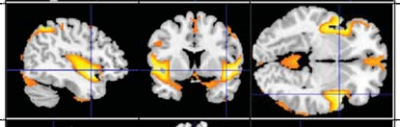
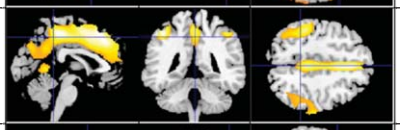
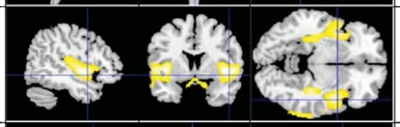
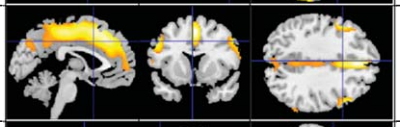
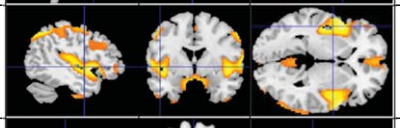
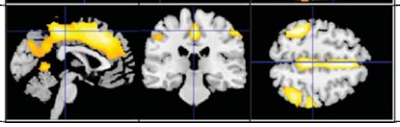
Visual rating		multiple regression correlation maps (min – max)	Coordinates x, y, z	Anatomical location	Z-score
Coronal Scales	Hippocampal		36 -16 -14	Rt. hippocampus	6.93
			52 2 -2	Rt. superior temporal gyrus	6.59
			-34 – 16 -16	Lt. Hippocampus	6.03
			-52 0 0	Lt. superior temporal gyrus	5.85
	Frontal		0 22 50	Lt. SMA	5.52
			2 0 54	Rt. SMA	5.12
			-42 -54 54	Lt. inferior parietal lobule	5.47
			0 -26 50	Lt. middle cingulate gyrus	4.24
	Temporal		46 10 -8	Rt. insula	6.23
			-48 10 -2	Lt. superior temporal pole	5.52
			58 8 0	Rt. superior temporal pole	5.40
			-42 14 -2	Lt. insula	5.07
	Parietal		0 -34 52	Rt. middle cingulate gyrus	5.68
			0 22 52	Lt. SMA	5.63
			-42 -50 54	Lt. inferior parietal lobule	5.54
			42 -52 54	Rt. inferior parietal lobule	5.21
Axial Scales	Hippocampal		34 -14 -16	Rt. hippocampus	7.07
			42 4 -2	Rt. insula	7.03
			-34 -16 -16	Lt. hippocampus	6.84
			-40 6 0	Lt. insula	6.77
	Frontal		2 16 50	Lt. SMA	6.09
			0 30 42	Lt. superior frontal gyrus	5.98
			2 -2 54	Rt. SMA	5.58
			50 20 36	Rt. inferior frontal opeculum	4.76
	Temporal		46 10 -8	Rt. insula	5.67
			66 -22 18	Lt. superior temporal gyrus	5.59
			-44 -2 -6	Lt. insula	5.29
			-46 8 -8	Rt. superior temporal gyrus	5.03
	Parietal		44 -48 54	Rt. inferior parietal lobule	5.23
			-42 -52 54	Lt. inferior parietal lobule	5.04
			0 -30 50	Lt. middle cingulate gyrus	4.86
			56 -28 52	Rt. Supra marginal gyrus	5.04

Fig. 3. The correlation maps of grey matter reduction according to the CVRS of the whole patient. Rt., right; Lt., left; SMA, supplementary motor area. VBM multiple regression adjusted for age, gender, and educational level indicates that the maximum value of the atrophy scale corresponds to each part of the brain region. ($p < 0.05$ corrected with false discovery rate).

a MRI template that can be used widely in clinical practice. It took less than 5 min to rate one subject with the tablet computer-based automated rating system. In this study, we showed that the CVRS reflected the structural changes better than the volumetric measures in each clinical group (Tables 2 and 3). This result was in agreement with previous studies that have compared visual ratings with volumetric analyses in normal subjects and patients with AD [14, 34, 35]. However, it did not mean that the CVRS was better than volumetric measurements because the brain atrophy scale of the CVRS was not adjusted for total intracranial volume as the volumetric measures were. We suggest that the CVRS better reflected what we saw in the brain images as a simple score. In addition, we have to consider that the positive results of the group differences of the CVRS might be derived from the significant age differences among the three groups even though we adjusted for it. And we have to consider that there might be a significant overlap between the diagnostic groups on any measure and any scale, including our CVRS. When the subscales were used alone, the overall AUC, sensitivity, and specificity decreased compared to the CVRS (Table 3), and the individual subscales did not reflect the overall aspects of the structural changes. It was another virtue of the CVRS that the difference in correlation according to the MRI tesla was relatively low compared to the volumetric measures (Fig. 2), which means that the CVRS was less influenced by the MRI tesla.

Although many studies that have used individual visual rating scales have been published in the past, few studies have created a CVRS that comprises the overall characteristics of brain lesions. Chen et al. have revealed that their T1-weighted-based brain lesion score correlates with age and MMSE [13]. However, their scale did not include hippocampal atrophy, which might be used to discriminate normal subjects from those with AD dementia [36], and the subscales have not been validated before. The reason why we accepted preexisting scales was to overcome these limitations as the CVRS was intended to comprise validated individual scales as well as a summed scale.

The strengths and benefits of the CVRS can be summarized as follows. First, we developed a very quick assessment tool for cerebral structural changes with a tablet computer-based user-friendly method (Supplementary Fig. 1) and demonstrated its high reliability for the inter-rater and intra-rater agreements for the total score and subscores (Table 1). The findings of the current study suggested that visual ratings were possible either by CVRS-coronal or CVRS-axial scores, which showed good interrelations with each other, and that these could be used more widely, especially when coronal views are unavailable. Moreover, if both the coronal and axial images are available together, they can complement each other during the rating as a reciprocal reference in case there is some ambiguity in the grading Although we combined the preexisting tools, the novelty of our study was their integration as a unified comprehensive scale without losing the value of the information of different regions because the CVRS scoring system with a tablet computer presented each detailed subscore of the different scales, such as hippocampal atrophy, cortical atrophy, ventricular enlargement, and small vessel disease, as well as the total score (Supplementary Figure 1). Thus, it can be compared to the MMSE, which provides a total score for general cognitive function and each of the subscores such as orientation, memory, calculation, language, and visuospatial function. Another strength was that, compared to already existing automated analyses, the CVRS was easier, quicker, and less influenced by the MRI tesla that was used (Fig. 2) and more suitable for individual longitudinal follow ups in a clinical setting. The goal of the CVRS was not to compete with or to replace automated imaging analysis tools that are appropriate for detailed research regarding group analyses but to suggest a quantitative and standardized comprehensive scale that can be used for individual assessments in a primary clinical setting. Although the current formal readings on brain MRIs by neuroradiologists provide good information to exclude diagnoses, such as hydrocephalus, vascular lesions, and tumors, they cannot provide enough information on structural changes, such as focal atrophy, that might be influenced by age or neurodegenerative processes. Thus, we tried to quantify the detailed structural changes of brain atrophy and small vessel disease with a template-based, quick, and reliable tool. In addition, the newly designed cortical atrophy scale and the hippocampal atrophy scale showed significant correlations with volume reductions in the brain regions that the visual rating scales intended to rate (Fig. 3). If a patient with an uncertain diagnosis shows a lower score on a follow-up CVRS, it is possible that some neurodegenerative or aging processes are progressing whether they are associated with cognitive function or not. Thus, the CVRS provides additional information without much burden with commonly used brain MRI.

There are several limitations to consider in this study. First, the current study was based on MRI images from one center; therefore, further studies are essential to determine the generalizability of the utility of the CVRS to other centers with different MRI settings. Second, a separate evaluation of the right and left hemisphere was not considered, except for hippocampal atrophy, for fear of making the CVRS too complex for clinical use. Third, because this was a cross-sectional study, a longitudinal study correlating the CVRS with other biomarkers is necessary to predict progression in the future with the CVRS. Fourth, the prevalence of lacunes and microbleeds in our subjects was low (lacune, 15.7%; microbleeds, 12.8%) compared to the findings of previous studies [28, 37, 38]; thus, the effects of small vessel disease might be underevaluated in this study. Recent knowledge on the pathophysiology of AD emphasizes biologic markers of brain amyloidosis and neuronal injury [39, 46]. Besides these markers for AD, there are also many methods for measuring brain imaging data (visual ratings, manual methods, or semi- or fully-automated computations) [40]. Considering its easy accessibility, visual ratings of brain MRIs among various biomarkers could be one of the most practical measuring tools in a clinical setting where individual evaluations of a patient are the main interest. In addition to focusing on earlier diagnostic markers of AD, such as amyloid positron emission tomography or CSF protein, well-organized studies to optimize easily accessible and reliable tools that use MRI are important. A subsequent longitudinal study using a combination of CVRS and other biomarkers would enhance the value of routine brain MRIs.

ACKNOWLEDGMENTS

The authors thank the Medical Research Collaborating Center at Seoul National University Bundang Hospital for performing the statistical analyses and the Department of Biomedical Engineering at Seoul National University Hospital for developing the CVRS software based on a tablet computer.

Authors' disclosures available online (http://www.j-alz.com/disclosures/view.php?id=2591).

SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: http://dx.doi.org/10.3233/JAD-142088.

REFERENCES

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

[2] Coffey CE, Wilkinson WE, Parashos IA, Soady SA, Sullivan RJ, Patterson LJ, Figiel GS, Webb MC, Spritzer CE, Djang WT (1992) Quantitative cerebral anatomy of the aging human brain: A cross-sectional study using magnetic resonance imaging. *Neurology* **42**, 527-536.

[3] Chen X, Wen W, Anstey KJ, Sachdev PS (2009) Prevalence, incidence, and risk factors of lacunar infarcts in a community sample. *Neurology* **73**, 266-272.

[4] Greenberg SM, Vernooij MW, Cordonnier C, Viswanathan A, Al-Shahi Salman R, Warach S, Launer LJ, Van Buchem MA, Breteler MM (2009) Cerebral microbleeds: A guide to detection and interpretation. *Lancet Neurol* **8**, 165-174.

[5] Group LS (2011) 2001-2011: A decade of the LADIS (Leukoaraiosis And DISability) Study: What have we learned about white matter changes and small-vessel disease? *Cerebrovasc Dis* **32**, 577-588.

[6] Poels MM, Ikram MA, van der Lugt A, Hofman A, Niessen WJ, Krestin GP, Breteler MM, Vernooij MW (2012) Cerebral microbleeds are associated with worse cognitive function: The Rotterdam Scan Study. *Neurology* **78**, 326-333.

[7] Jang JW, Kim S, Na HY, Ahn S, Lee SJ, Kwak KH, Lee MA, Hsiung GY, Choi BS, Youn YC (2013) Effect of white matter hyperintensity on medial temporal lobe atrophy in Alzheimer's disease. *Eur Neurol* **69**, 229-235.

[8] Jack CR Jr, Shiung MM, Gunter JL, O'Brien PC, Weigand SD, Knopman DS, Boeve BF, Ivnik RJ, Smith GE, Cha RH, Tangalos EG, Petersen RC (2004) Comparison of different MRI brain atrophy rate measures with clinical disease progression in AD. *Neurology* **62**, 591-600.

[9] den Heijer T, van der Lijn F, Koudstaal PJ, Hofman A, van der Lugt A, Krestin GP, Niessen WJ, Breteler MM (2010) A 10-year follow-up of hippocampal volume on magnetic resonance imaging in early dementia and cognitive decline. *Brain* **133**, 1163-1172.

[10] Scheltens P, Erkinjunti T, Leys D, Wahlund LO, Inzitari D, del Ser T, Pasquier F, Barkhof F, Mantyla R, Bowler J, Wallin A, Ghika J, Fazekas F, Pantoni L (1998) White matter changes on CT and MRI: An overview of visual rating scales. European Task Force on Age-Related White Matter Changes. *Eur Neurol* **39**, 80-89.

[11] Victoroff J, Mack WJ, Grafton ST, Schreiber SS, Chui HC (1994) A method to improve interrater reliability of visual inspection of brain MRI scans in dementia. *Neurology* **44**, 2267-2276.

[12] Jokinen H, Lipsanen J, Schmidt R, Fazekas F, Gouw AA, van der Flier WM, Barkhof F, Madureira S, Verdelho A, Ferro JM, Wallin A, Pantoni L, Inzitari D, Erkinjuntti T (2012) Brain atrophy accelerates cognitive decline in cerebral small vessel disease: The LADIS study. *Neurology* **78**, 1785-1792.

[13] Chen W, Song X, Zhang Y, Darvesh S, Zhang N, D'Arcy RC, Black S, Rockwood K (2010) 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* **30**, 121-130.

[14] 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 (2011) Volumetric and visual rating of magnetic resonance imaging scans in the diagnosis of amnestic mild cognitive impairment and Alzheimer's disease. *Alzheimers Dement* **7**, e101-e108.

[15] McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM (1984) Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* **34**, 939-944.

[16] Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E (1999) Mild cognitive impairment: Clinical characterization and outcome. *Arch Neurol* **56**, 303-308.

[17] Kang YW, Na DL (2003) *Seoul Neuropsychological Screening Battery (SNSB)*. Human Brain Research & Consulting Co.

[18] Seo SW, Im K, Lee JM, Kim YH, Kim ST, Kim SY, Yang DW, Kim SI, Cho YS, Na DL (2007) Cortical thickness in single- versus multiple-domain amnestic mild cognitive impairment. *Neuroimage* **36**, 289-297.

[19] Ahn HJ, Chin J, Park A, Lee BH, Suh MK, Seo SW, Na DL (2010) Seoul Neuropsychological Screening Battery-dementia version (SNSB-D): A useful tool for assessing and monitoring cognitive impairments in dementia patients. *J Korean Med Sci* **25**, 1071-1076.

[20] Barnes J, Carmichael OT, Leung KK, Schwarz C, Ridgway GR, Bartlett JW, Malone IB, Schott JM, Rossor MN, Biessels GJ, DeCarli C, Fox NC (2013) Vascular and Alzheimer's disease markers independently predict brain atrophy rate in Alzheimer's Disease Neuroimaging Initiative controls. *Neurobiol Aging* **34**, 1996-2002.

[21] Kim GH, Kim JE, Choi KG, Lim SM, Lee JM, Na DL, Jeong JH (2014) T1-weighted axial visual rating scale for an assessment of medial temporal atrophy in Alzheimer's disease. *J Alzheimers Dis.*

[22] Koedam EL, Lehmann M, van der Flier WM, Scheltens P, Pijnenburg YA, Fox N, Barkhof F, Wattjes MP (2011) Visual assessment of posterior atrophy development of a MRI rating scale. *Eur Radiol* **21**, 2618-2625.

[23] O'Donovan J, Watson R, Colloby SJ, Firbank MJ, Burton EJ, Barber R, Blamire AM, O'Brien JT (2013) Does posterior cortical atrophy on MRI discriminate between Alzheimer's disease, dementia with Lewy bodies, and normal aging? *Int Psychogeriatr* **25**, 111-119.

[24] Park HK, Na DL, Han SH, Kim JY, Cheong HK, Kim SY, Kim SY, Hong CH, Kim DK, Ku BD, Moon SY, Lee JY, Shim YS, Youn YC, Kim EJ, Kim BC, Park KH, Cha KR, Seo SW, Lee JH (2011) Clinical characteristics of a nationwide hospital-based registry of mild-to-moderate Alzheimer's disease patients in Korea: A CREDOS (Clinical Research Center for Dementia of South Korea) study. *J Korean Med Sci* **26**, 1219-1226.

[25] Noh Y, Lee Y, Seo SW, Jeong JH, Choi SH, Back JH, Woo SY, Kim GH, Shin JS, Kim CH, Cho H, Park JS, Lee JM, Hong CH, Kim SY, Lee JH, Kim SY, Park KH, Han SH, Cheong HK, Na DL (2014) A new classification system for ischemia using a combination of deep and periventricular white matter hyperintensities. *J Stroke Cerebrovasc Dis* **23**, 636-642.

[26] Gouw AA, van der Flier WM, Fazekas F, van Straaten EC, Pantoni L, Poggesi A, Inzitari D, Erkinjuntti T, Wahlund LO, Waldemar G, Schmidt R, Scheltens P, Barkhof F (2008) Progression of white matter hyperintensities and incidence of new lacunes over a 3-year period: The Leukoaraiosis and Disability study. *Stroke* **39**, 1414-1420.

[27] Benisty S, Gouw AA, Porcher R, Madureira S, Hernandez K, Poggesi A, van der Flier WM, Van Straaten EC, Verdelho A, Ferro J, Pantoni L, Inzitari D, Barkhof F, Fazekas F, Chabriat H (2009) Location of lacunar infarcts correlates with cognition in a sample of non-disabled subjects with age-related white-matter changes: The LADIS study. *J Neurol Neurosurg Psychiatry* **80**, 478-483.

[28] Jokinen H, Gouw AA, Madureira S, Ylikoski R, van Straaten EC, van der Flier WM, Barkhof F, Scheltens P, Fazekas F, Schmidt R, Verdelho A, Ferro JM, Pantoni L, Inzitari D, Erkinjuntti T (2011) Incident lacunes influence cognitive decline: The LADIS study. *Neurology* **76**, 1872-1878.

[29] van Dijk EJ, Prins ND, Vrooman HA, Hofman A, Koudstaal PJ, Breteler MM (2008) Progression of cerebral small vessel disease in relation to risk factors and cognitive consequences: Rotterdam Scan study. *Stroke* **39**, 2712-2719.

[30] Shrout PE, Fleiss JL (1979) Intraclass correlations: Uses in assessing rater reliability. *Psychol Bull* **86**, 420-428.

[31] Alemán-Gómez Y. M-GL, Valdés-Hernandez. P. IBASPM: Toolbox for automatic parcellation of brain structures. *12th Annual Meeting of the Organization for Human Brain Mapping,* June 11-15, 2006, Florence, Italy. Available on CD-Rom in Neuroimage, Vol. 27, No.1.

[32] Villemagne VL, Rowe CC, Macfarlane S, Novakovic KE, Masters CL (2005) Imaginem oblivionis: The prospects of neuroimaging for early detection of Alzheimer's disease. *J Clin Neurosci* **12**, 221-230.

[33] Ashburner J, Friston KJ (2000) Voxel-based morphometry–the methods. *Neuroimage* **11**, 805-821.

[34] Bresciani L, Rossi R, Testa C, Geroldi C, Galluzzi S, Laakso MP, Beltramello A, Soininen H, Frisoni GB (2005) Visual assessment of medial temporal atrophy on MR films in Alzheimer's disease: Comparison with volumetry. *Aging Clin Exp Res* **17**, 8-13.

[35] Frisoni GB (2000) Visual rating and volumetry of the medial temporal lobe on magnetic resonance imaging in dementia. *J Neurol Neurosurg Psychiatr* **69**, 572.

[36] 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 (2008) Medial temporal lobe atrophy on MRI scans and the diagnosis of Alzheimer disease. *Neurology* **71**, 1986-1992.

[37] Patel B, Lawrence AJ, Chung AW, Rich P, Mackinnon AD, Morris RG, Barrick TR, Markus HS (2013) Cerebral microbleeds and cognition in patients with symptomatic small vessel disease. *Stroke* **44**, 356-361.

[38] Poels MM, Vernooij MW, Ikram MA, Hofman A, Krestin GP, van der Lugt A, Breteler MM (2010) Prevalence and risk factors of cerebral microbleeds: An update of the Rotterdam scan study. *Stroke* **41**, S103-S106.

[39] McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR Jr, Kawas CH, Klunk WE, Koroshetz WJ, Manly JJ, Mayeux R, Mohs RC, Morris JC, Rossor MN, Scheltens P, Carrillo MC, Thies B, Weintraub S, Phelps CH (2011) The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* **7**, 263-269.

[40] Frisoni GB, Bocchetta M, Chetelat G, Rabinovici GD, de Leon MJ, Kaye J, Reiman EM, Scheltens P, Barkhof F, Black SE, Brooks DJ, Carrillo MC, Fox NC, Herholz K, Nordberg A, Jack CR Jr, Jagust WJ, Johnson KA, Rowe CC, Sperling RA, Thies W, Wahlund LO, Weiner MW, Pasqualetti P, Decarli C (2013) Imaging markers for Alzheimer disease: Which vs how. *Neurology* **81**, 487-500.