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Original Article

New longitudinal Visual Rating Scale Identifies Structural Alterations in People with Mild Cognitive Impairment and Those who are Cognitively Normal

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SUMMARY

Background: The cross-sectional visual rating scale (c-VRS) is an easy and effective method of evaluating medial temporal atrophy (MTA). In evaluating longitudinal morphological change, c-VRS cannot express slight changes as precisely as volumetry.
Methods: We selected 87 people 65 years old from the Alzheimer's Disease Neuroimaging Initiative database. Their high resolution magnetic resonance images, brain structural volume data, and cognitive performances, were downloaded. We evaluated the temporal lobe atrophy in the baseline images, and the longitudinal alterations by judging the widening of the parahippocampal cerebrospinal fluid space one year and two years later. These results from c-VRS and longitudinal VRS (l-VRS) were also compared with the volume data derived from the FreeSurfer.
Results: The cross-sectional and longitudinal visual rating assessments showed significant differences between mild cognitive impairment (MCI) and cognitively normal subjects. In a receiver operating characteristic (ROC), the longitudinal assessment showed higher sensitivity/specificity and area-under curve than did the cross-sectional assessment.
Conclusions: Our findings demonstrated that longitudinal visual rating is a useful tool for detecting longitudinal morphological alterations caused by MCI, and would improve diagnostic accuracy.

1. Introduction

In radiological investigations, structural magnetic resonance imaging (MRI) and functional imaging using fluorine 18 fluorodeoxyglucose-positron emission tomography (FDG-PET) are the most studied radiological biomarkers, followed by carbon 11 Pittsburg Compound B (PiB) PET for amyloid imaging.[1–4] Functional alterations precede morphological changes in the early stages of cognitive impairment. There is a decrease in regional blood flow or glucose metabolism in the posterior cingulate cortex and the temporoparietal regions in early cognitive impairment, which can be assessed by cerebral blood flow using single-photon emission computed tomography and FDG-PET.[2,3]

Several studies have reported the usefulness of these biomarkers for mild cognitive impairment (MCI), and structural MRI analyses have shown medial temporal lobe atrophy in the hippocampus, parahippocampal gyrus, entorhinal cortex (ERC), and amygdala. Structural MRI has been carried out on people with MCI and Alzheimer's disease (AD), using visual rating, manual volumetric, and automatic volume measurement (VM) analyses.[5–7] VM method has been used as the most appropriate and feasible method for a decade by investigators who aim to assess more objective and accurate pathological regions in the whole brain when comparing people with dementia with healthy controls.[8] Cross-sectional visual rating scale (c-VRS) has advantages over VM method in that it provides an easy and simple estimation of medial temporal atrophy, and it has been used to diagnose patients who are cognitively-impaired.[9,10]

The aim of the present study is to test the hypothesis that longitudinal VRS (l-VRS) estimation exceeds cross-sectional estimation of the medial temporal atrophy. This is the first report of l-VRS.

2. Materials and methods

2.1. Subjects

The data used in this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). This study was approved by the ADNI. Our institutional review board did not require an approval because open access data downloaded from the ADNI was used in this study, and each data set contain no personally identifiable information. We obtained data for 87 people who were less than 65 years old from the ADNI database. Ten people who were cognitively normal (CN) and 77 people with MCI were

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included in the final analysis. Ten people with MCI were excluded from the study as they did not have a follow-up examination following their initial visit. Thirteen people with MCI at the one-year follow-up and 29 people (28 with MCI and 1 CN) at the two-year follow-up were also excluded owing to conversion to AD or as there were no MRI examinations performed. MCI participants have reported a subjective memory concern either autonomously or via an informant or clinician. However, there are no significant levels of impairment in other cognitive domains, essentially preserved activities of daily living and there are no signs of dementia (http://adni.loni.usc.edu/study-design/backgroundrationale/).

2.2. Image analysis

2.2.1. c-VRS at baseline and l-VRS examinations

We adopted the VRS that was reported by Kaneko et al. as our c-VRS.[9] To distinguish the hippocampus from other neighboring structures, c-VRS needs high-resolution coronal magnetic resonance images perpendicular to the long axis of the hippocampus. We used high-resolution sagittal T1-weighted images (magnetization prepared rapid acquisition with gradient echo: MP-RAGE). The full details of the ADNI protocol have been described previously, and are listed on the ADNI database (http://www.adni.loni.usc.edu/ADNI/).[11] We reconstructed coronal images perpendicular to the hippocampus on the image viewer (EV insite; PSP cooperation, Tokyo, Japan), and a single image in which the cerebral peduncles appeared widest was adopted for assessment. The images for the evaluation of c-VRS and l-VRS were reconstructed using the same procedure.

2.2.2. c-VRS and baseline MRI

To evaluate medial temporal lobe atrophy, we compared the shape and size of the hippocampus with the cerebrospinal fluid (CSF) space around the hippocampus. To simplify the evaluation, we defined the hippocampus as the structure with equal intensity to that of the grey matter. Therefore, the cornu ammonis, dentate gyrus, and subiculum were contained within the hippocampus, in the anterior region of the body of the hippocampal formation. Perpendicular lines were drawn on both sides of the hippocampus to divide the CSF space around the hippocampus into three parts: an outer part (temporal horn), an upper part (choroidal fissure), and an inner part (ambient cistern) (Fig. 1A). Each part was compared with the hippocampus and classified into four ranks using the following criteria: score 0: outer and upper part is slit-like and as narrow as the diameter of the vessels in the inner part; score 1: CSF space is smaller than the hippocampus; score 2: CSF space is nearly the same as the hippocampus; score 3: CSF space is larger than the hippocampus (Fig. 1B). Raters were instructed not to measure the area but to put the hippocampus into each part of the CSF space while keeping its original shape and size, as with a jigsaw puzzle piece.

2.2.3. l-VRS and follow-up MRI

We compared follow-up MRI images with baseline images. To simplify the evaluation, we only compared the shape of the parahippocampal CSF space, which was divided into three parts in the same way as the baseline VRS (Fig. 2). Each part was compared with the baseline image and classified into four ranks using the following criteria: score 0: no change detected; score 1: CSF space slightly expanded; score 2: CSF space was obviously larger than that of the baseline image; score 3: CSF space was severely expanded. Fig. 3 showed the example of assessment. The sum of each score ranges from 0 to 9. We do not assign the total score an atrophy grade, because the mean of total score would varies according to the age, sex, and background disorders of subjects.

Two radiologists, blinded to the patients' age, sex, and diagnosis, evaluated the images. One of the original radiologists re-evaluated the same images.

2.2.4. Regional volume data from the MRI scans

The regional volumes were computed using FreeSurfer (the

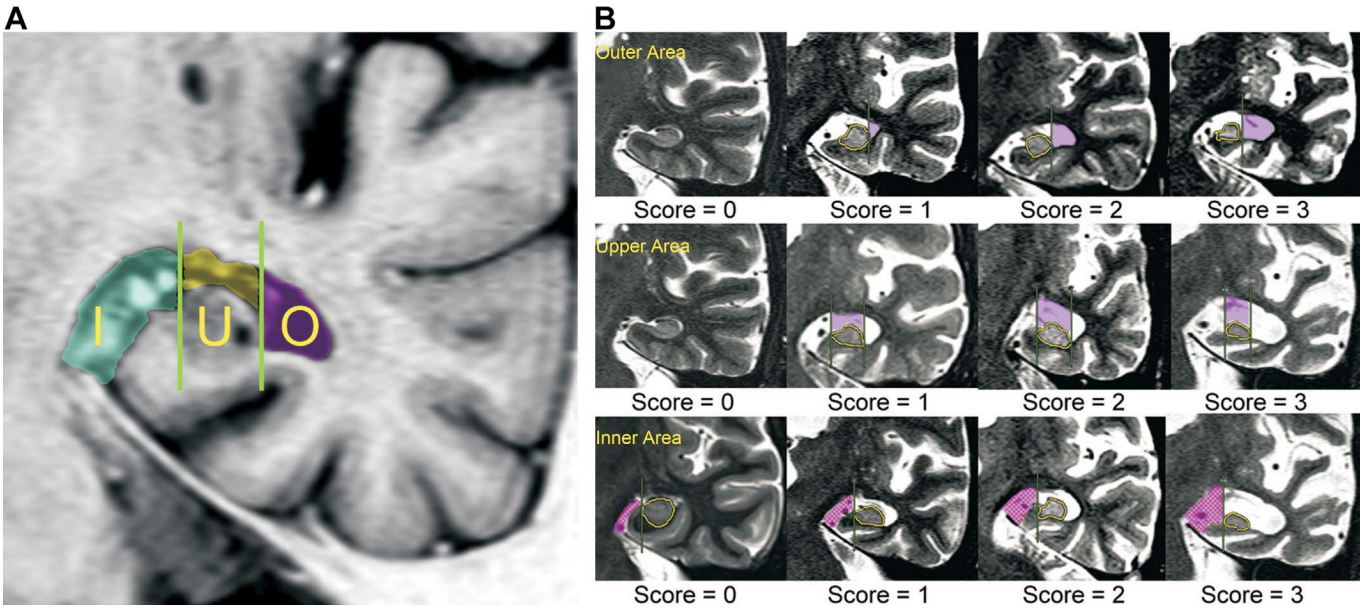

Fig. 1. VRS at baseline MR imaging. (A) shows the way to divide the CSF space around the hippocampus into three parts. We draw two perpendicular lines by the inner and outer edge of the left hippocampus, and then we can divide the CSF space into the outer (O), upper (U), and inner (I) areas. (B) shows a representative image of those used to evaluate widening of the CSF space. The outer, upper, and inner areas are arranged from top to bottom. Each row has four images arranged from left to right in accordance with the values of the VRS. Each area for evaluation is painted in pink. The following classifications were used; score 0: lateral (top row) and over (second row) part is slit-like and as narrow as the diameter of the vessels at the inner (bottom row) part; score 1: CSF space is smaller than the hippocampus; score 2: CSF space is nearly the same as the hippocampus; score 3: CSF space is larger than the hippocampus.

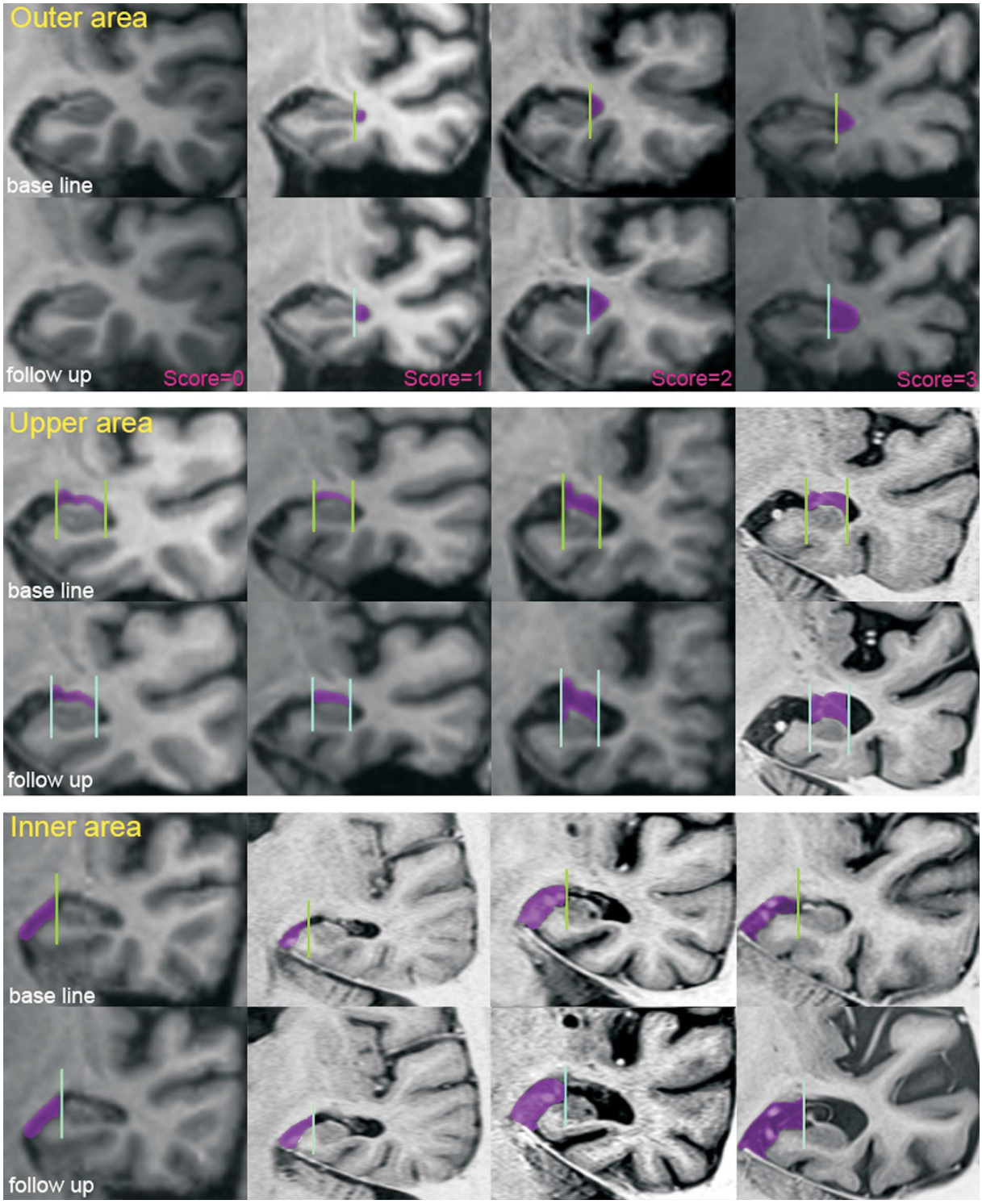

Fig. 2. l-VRS at follow up MR imaging. This figure shows a representative image of those used to evaluate longitudinal VRS (l-VRS). The CSF space around the hippocampus was divided into three parts, in the same way as Figure 1A. The outer, upper, and inner areas are arranged from top to bottom. Each row has the upper base line image and the follow up image below, and four sets of the images arranged from left to right in accordance with the values of the VRS. Each area for evaluation is painted in pink. The extent of the CSF widening between the baseline and follow-up image was ranked as follows: score = 0: no difference; score = 1: slight widening; score = 2: remarkable enlargement; score = 3: severe enlargement from baseline to follow-up.

University of California at San Francisco, USA), and the results were downloaded into a 2013 Microsoft Excel. The regions used in this study were the ERC: sum of ST83CV [Volume (Cortical Parcellation (CP)) of Right ERC] and ST24CV [Left ERC(CP)], the hippocampus: sum of ST29SV [Volume (WM Parcellation (WMP)) of Left Hippocampus] and ST88SV [Right Hippocampus (WMP)], the inferior lateral ventricle: sum of ST30SV [Left Inferior Lateral Ventricle (WMP)] and ST89SV [Right Inferior Lateral Ventricle (WMP)], the lateral ventricle: sum of ST37SV [Left Lateral Ventricle (WMP)] and ST96SV [Right Lateral Ventricle (WMP)], the temporal lobe: sum of ST117CV [Right Superior Temporal Lobe (CP)], ST32CV [Left Inferior Temporal Lobe (CP)], ST40CV [Left Middle Temporal Lobe (CP)], ST58CV [Left

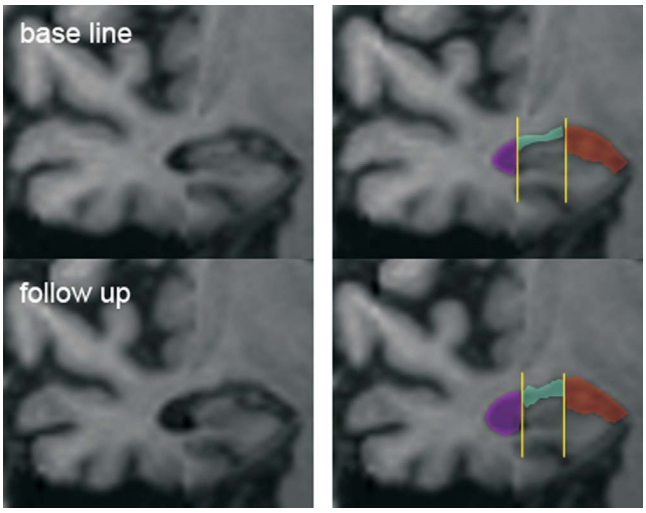

Fig. 3. Example case of assessment. The right column shows the raw images (the upper baseline, and the follow up below). Additional lines drawn on the left column divide the CSF space into three parts and each area is painted in different color. The image shows severe enlargement of the lateral part with the conversion of the VRS score from baseline (score = 1) to follow-up (score = 2). The image shows slight widening of the over part, and no change in the medial part. The total value is five (lateral = 3, over = 1, and medial = 0).

Superior Temporal Lobe (CP)], CT91CV [Right Inferior Temporal Lobe (CP)] and ST99CV [Right Middle Temporal Lobe (CP)]. We also calculated the volume of each region at one-year and two-year follow-up. Finally, the decrease in volume of each region was calculated by subtracting the volumes at one-year and two-year follow-up from those at baseline.

2.3. Statistical analysis

All analyses were performed using R commander (version 2.3–2) equipped on R (version 3.3.0, R Foundation for Statistical Computing, Vienna, Austria). A Mann-Whitney Wilcoxon test was used to examine differences between the MCI and CN groups with respect to age, scores on the Mini-Mental State Examination (MMSE), Alzheimer's Disease Assessment Scale (ADAS), VRS, and l-VRS, and volumes of the ERC, inferior lateral ventricle, temporal lobe, hippocampus, and lateral ventricle. The effect of sex was examined using a Fisher's exact test. A polyserial correlation test was used to analyze the association between the VRS and volumetric data, and between the VRS and cognitive examinations. The rho values were interpreted using the following criteria: $|\rho| = 1$; perfect, $|\rho| \geq 0.70$; very strong, $0.69 > |\rho| \geq 0.40$; strong, $0.39 > |\rho| \geq 0.30$; moderate, $0.29 > |\rho| \geq 0.20$; weak, and no negligible relationship, $0.19 > |\rho| \geq 0.01$.[12]

The area under receiver operating characteristic (ROC) curve was used to compare c-VRS and l-VRS assessments. P-value was calculated by Bootstrap test for two correlated ROC curves corrected partial area under curve (pAUC) ranged 100-80 specificity.[13]

Inter-rater agreement was evaluated with weighted κ scores. The κ agreement scores were interpreted using the following criteria: a κ score of 0.0–0.2 indicated slight agreement; a κ score of 0.21–0.40 indicated fair agreement; a κ score of 0.41–0.60 indicated moderate agreement; a κ score of 0.61–0.80 indicated substantial agreement; and a κ score of 0.81–1.0 indicated almost perfect agreement.[14]

3. Results

Table 1 shows the demographics of the participants. There was no significant difference between the CN and MCI groups with respect to age. The CN participants were predominantly men, as shown by the Fisher's exact test. Participants with MCI had worse scores on the ADAS and MMSE than those in the CN group.

Table 2 demonstrates the differences in the visual rating system and volume measurements between the groups. With regard to the visual rating methods, significant differences were observed between the groups when l-VRS and c-VRS data were analyzed. In contrast to c-VRS results, the ERC and temporal lobe volumes at baseline did not show significant differences between the groups. The volume of the hippocampus and the inferior lateral ventricle at the one-year follow-up showed no significant differences between the groups.

Table 3 shows the correlations between the visual rating scale and volume analysis data. With regard to the data from the baseline examination, c-VRS scores very strongly correlated with the inferior lateral ventricle volume. At one-year follow-up, l-VRS scores strongly correlated with the decrease in volume of the ERC and the expansion of the inferior lateral ventricle volume significantly. At two-year follow-up, the ERC and hippocampal volumes were strongly correlated with l-VRS scores. Although both of the inferior lateral ventricle and the lateral ventricle volumes very strongly correlated with l-VRS, it showed no significant differences each other.

Table 4 shows the correlation between VRS and ADAS and between VRS and MMSE. l-VRS in the one-year and two-year follow-ups were strongly correlated with ADAS and MMSE, respectively.

ROC analysis (Table 5, Fig. 4) showed that the score on c-VRS at baseline provided the optimal sensitivity, using a cut-off score of 4. The sensitivity and specificity were 90% and 58%, respectively, and it had an area under the curve (AUC) of 0.75. c-VRS in the one-year and two-year follow-ups showed sensitivity/specificity ratios (cutoff point) of 90%/51% (5) and 56%/84% (3), respectively, and AUCs of 0.74 and 0.74, respectively. l-VRS at one-year and two-year follow-up showed a sensitivity/specificity (cut off) of 100%/76% (0) and 100%/68% (2), respectively, and AUCs of 0.88 and 0.83, respectively.

Table 1
Demographics.

	MCI subjects	CN subjects	W	*P*-value
Female: Male[a]	31: 36	1: 9	–	0.039*
Age (median [min, max])[b]	62.8 [55.2,65.9]	63.2 [60.0,65.5]	289	0.49
ADAS (median [min, max])[b]	11.67 [2,42.67]	4.33 [2.67,10.33]	583.5	<0.001**
MMSE (median [min, max])[b]	26 [21,30]	29 [24,30]	128.5	0.002**

*Significantly different at $P < 0.05$ according to the Fisher's exact test. **Significantly different at $P < 0.01$ according to the Mann-Whitney Wilcoxon test. ADAS, Alzheimer's Disease Assessment Scale; MMSE, Mini-Mental State Examination; CN, Cognitive Normal; MCI, Mild Cognitive Impairment.
[a] Fisher's Exact test.
[b] Mann-Whitney Utest.

Table 2
VRS and VM differences between MCI and CN subjects.

		MCI subjects median [min, max]	CN subjects median [min, max]	*P*-value
Baseline	n	66	10	
	c-VRS	5 [0,13]	2.5 [1,7]	0.009**
	Entorhinal Cortex	3640 [2412,4987]	4138.5 [2164,4597]	0.446
	Hippocampus	6424 [4238,9076]	7492 [6010,8133]	0.0072**
	Temporal lobe	57967 [36016,80596]	63654 [47519,75356]	0.118
	Inf. Lat. Ventricle	1091 [80,5713]	508 [23,1165]	0.008**
	Lat. Ventricle	27734 [8398,133995]	16727 [5337,43331]	0.009**
1Y follow-up	n	54	10	
	l-VRS (1Y)	2 [0,14]	0 [0,0]	<0.001***
	c-VRS (1Y)	5 [0,14]	2.5 [1,7]	0.025*
	Decrease in Volume [(basline)-(follow-up)]			
	ΔEntorhinal Cortex-1Y	160 [-304,778]	10.5 [-202,159]	0.008**
	ΔHippocampus-1Y	146.5 [-131,701]	68 [-101,232]	0.11
	ΔTemporal lobe-1Y	1092 [-1604,6347]	−151.5 [-2246,1640]	0.024*
	Increase in Volume [(follow-up)-(baseline)]			
	ΔInf. Ventricle-1Y	157.0 [-806,1267]	60.5 [-11,584]	0.835
	ΔLat. Ventricle-1Y	2748 [-1419,9146]	494 [-397,1933]	<0.001***
2Y follow-up	n	39	9	
	l-VRS (2Y)	4 [0,16]	1 [0,2]	0.003**
	c-VRS (2Y)	4.5 [2,14]	2 [1,7]	0.026*
	Decrease in Volume [(basline)-(follow-up)]			
	ΔEntorhinal Cortex-2Y	220 [-190,676]	38 [-246,142]	0.017*
	ΔHippocampus-2Y	282.25 [-225,818]	165 [-35,188]	0.027*
	ΔTemporal lobe-2Y	3071.5 [-2435,7409]	1364 [-1959,2257]	0.02*
	Increase in Volume [(follow-up)-(baseline)]			
	ΔInf. Ventricle-2Y	380.5 [-144,1993]	58 [-32,203]	0.005**
	ΔLat. Ventricle-2Y	4976 [-1784,19106]	822 [-169,3801]	0.003**

A unit of measurement used for volumetric data is mm^3. *Significantly different at $P < 0.05$ according to the Mann-Whitney Wilcoxon test. **Significantly different at $P < 0.01$ according to the Mann-Whitney Wilcoxon test. *** Significantly different at $P < 0.001$ according to the Mann-Whitney Wilcoxon test. VM, Volume Measurement; c-VRS, conventional-Visual Rating Scale at base line; l-VRS (1Y, 2Y), longitudinal-Visual Rating Scale at 1-year and 2-year follow-ups; Inf. Ventricle, Inferior lateral Ventricle; Lat. Ventricle, Lateral Ventricle, MCI, Mild-Cognitive Impairment; CN, Cognitive Normal.

The pAUC of l-VRS was significantly higher than that of c-VRS in the one-year and two-year follow-ups.

The inter-rater κ value for c-VRS scores was 0.71, which indicates good agreement.

4. Discussion

c-VRS is a method of evaluating hippocampal atrophy in comparison with CSF space around the hippocampus. We previously reported usefulness of c-VRS in differentiating between AD and CN subjects.[9] On the other hand, c-VRS scores may overlap between MCI and CN in younger subjects who are thought to have minimal atrophy in the medial temporal region. We have designed l-VRS to evaluate only the widening of the CSF space around the hippocampus in comparison with the images from the baseline study, independent of the components of the medial temporal lobe such as the ERC and hippocampus. We obtained three major findings in this study. First, VRS aids comprehensive evaluation of MTA more than VM. Second, l-VRS is correlated with volume changes in the ERC and hippocampus, and with clinical examinations of cognitive functions. Third, l-VRS showed higher pAUC than c-VRS.

First, in volumetry, the volume of the ERC and hippocampus and the difference in volume between the baseline and follow-up did not always show a significant difference between MCI and CN. On the other hand, c-VRS and l-VRS consistently showed a significant difference between MCI and CN. Jauhiainen et al. reported that the volume of the ERC, but not of the hippocampus, was shown to differ significantly between people with MCI and those who were cognitively normal.[15] On the other hand, Yushkevich et al. reported that CA1 subfield and the left Brodmann's area 35, but not the ERC, showed the most significant differences between people with MCI

Table 3
Collelation analysis between VRS and VM.

	l-VRS (1Y)	l-VRS (2Y)
ΔEntorhinal Cortex	0.34*	0.51**
ΔHippocampus	0.47	0.54*
ΔTemporal lobe	0.31	0.65
ΔInf. Lat. Ventricle	0.30*	0.89
ΔLat. Ventricle	0.67	0.78

Correlation ratio (rho) according to the Polyserial correlation alaysis. VM, Volume Measurement; c-VRS, conventional-Visual Rating Scale at base line; l-VRS (1Y,2Y), longitudinal-Visual Rating Scale at 1-year and 2-year follow up; Inf. Ventricle, Inferior latelral Ventricle; Lat. Ventricle, Lateral Ventricle.

*Significantly different at $P < 0.05$ according to the Polyserial correlation analysis.

**Significantly different at $P < 0.01$ according to the Polyserial correlation analysis.

Table 4
Collelation analysis between VRS and ADAS MMSE.

	l-VRS (1Y)	l-VRS (2Y)
ADAS	0.51*	0.58***
MMSE	−0.48**	−0.66***

Correlation ratio (rho) according to the Polyserial correlation alaysis. ADAS, Volume Measurement; l-VRS (1Y,2Y), longitudinal-Visual Rating Scale at 1-year and 2-year follow up; Inf. Ventricle, Inferior latelral Ventricle; Lat. Ventricle, Lateral Ventricle.

Table 5
ROC analysis of c-VRS and l-VRS.

	AUC [95% CI]	Sensitivity/Specificity [cut off]	*P*-value
Baseline			
c-VRS	0.75 [0.58e0.93]	90%/58% [4]	
1 year follow-up			
l-VRS (2Y)	0.88 [0.82e0.94]	100%/76% [0]	0.01*
c-VRS (1Y)	0.74 [0.56e0.92]	90%/51% [5]	
2 year follow-up			
l-VRS (2Y)	0.83 [0.71e0.94]	100%/66% [2]	0.03*
c-VRS (2Y)	0.74 [0.54e0.94]	56%/84% [3]	

P-value was calculated by Bootstrap test for two correlated ROC curves corrected partial AUC ranged 100-80 specificity. c-VRS, conventional-Visual Rating Scale at base line; l-VRS (1Y, 2Y), longitudinal-Visual Rating Scale at 1-year and 2-year follow-ups.

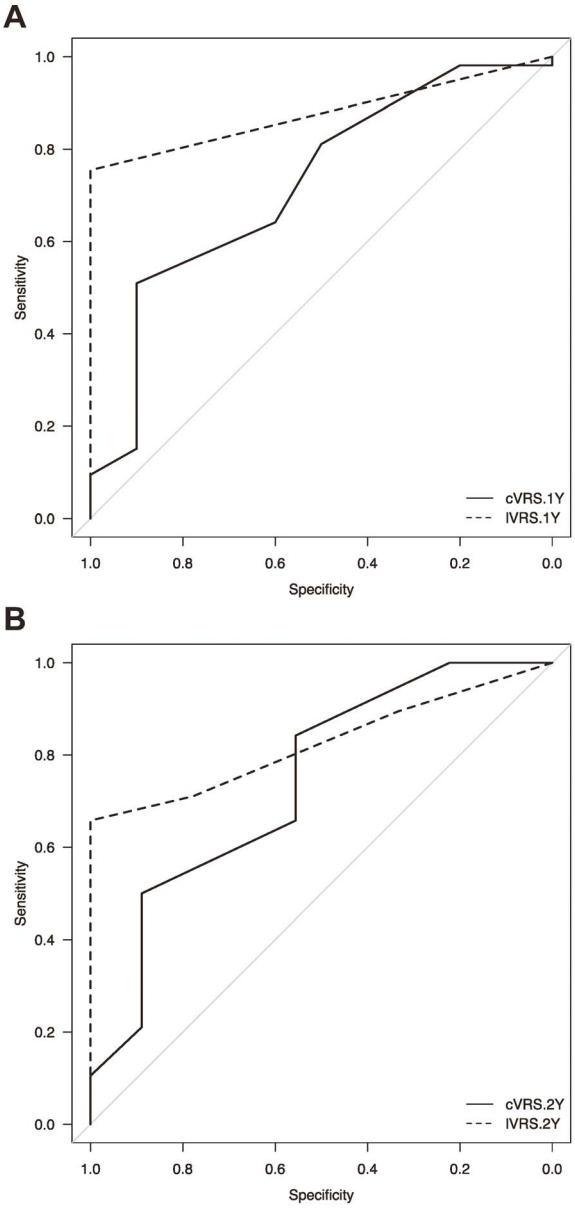

Fig. 4. ROC analysis of VRS. **A** shows c-VRS and l-VRS at one-year follow-up, and **B** shows at two-year follow-up.

and those who were aging healthily.[16] In addition, ADNI already demonstrated that there was no significant difference in ERC volume between MCI and CN subjects. Barbeau et al. have revealed different patterns of atrophy depending on the stage and subtype of MCI using VM.[17] In addition, various MCI patterns, such as amnestic/non-amnestic, single or multi-domain, have shown different atrophic patterns.[18] Accordingly, VRS is a comprehensive evaluating tool for distinguishing MCI from CN without taking the stage and subtype of MCI into consideration, and without evaluating various regions of medial temporal lobe using VM.

Second, l-VRS correlated with the ΔERC and Δhippocampus. However ventricular expansion is caused by various cerebral disorders or by aging, taking the AD pathology into account, it is reasonable that expansion of the CSF space around hippocampus closely correlates with medial temporal atrophy in MCI subjects.[19] Evans et al. showed that annualized brain atrophy and ventricular enlargement differed between CN, MCI, and AD subjects.[20] In addition, Leung et al. reported that the rate of acceleration of hippocampal atrophy and ventricular expansion in MCI and AD subjects were significantly higher than in CN subjects.[21] Thus, the widening of the CSF space around the hippocampus represents the MTA as well as the interactive atrophy of the whole brain. On the other hand, paying attention to the correlation between VRS and cognitive function, Duara et al. reported that VRS was significantly more strongly correlated to impairment on a range of memory tests than hippocampal volume was.[22] In addition, Varon et al. showed that subjects with minimal atrophy in the ERC showed in a faster rate of progression than those with no atrophy.[23] They also reported that VRS ratings of the ERC were superior to other MRI measures.[24] Our l-VRS consistently correlated with ΔERC; thus, we thought it acceptable that the ADAS and MMSE correlated with l-VRS.

Third, l-VRS showed significantly higher pAUC than c-VRS. That is to say, longitudinal evaluation showed higher accuracy than cross-sectional evaluation. Rhodius et al. studied MTA using c-VRS of in 2934 participants. In their study, c-VRS scores of MCI and CN subjects under 60 years of age overlapped each other, but the scores of MCI subjects changed more rapidly than that of CN subjects.[25] Our l-VRS was more sensitive to the progressive atrophy of MTA than c-VRS was because it focused only on Δvolume. Duara et al. compared the volumetric and VRS-MTA measures, and showed c-VRS accuracy (0.723: area under curve (AUC)) to discriminate amnestic MCI from CN in younger age group (63–75 years).[22] The AUC of our c-VRS estimation (0.75) showed the same accuracy as Duara's analyses. In addition, adopting the estimation using the l-VRS improved the AUC of 0.88 at one-year follow up. The pAUC of l-VRS was significantly higher than that of c-VRS in the one-year and two-year follow-ups. In this study, AUC in the 2Y follow-up was lower than in the 1Y follow-up. We thought this was because some of the MCI patients who converted to AD were excluded from the 2Y follow-up.

5. Conclusions

Our findings demonstrated that the l-VRS is a useful tool for detecting longitudinal morphological alterations caused by MCI, and would improve the diagnostic accuracy.

6. Limitations

Our study is limited by the fact that we had very few participants who were cognitively normal under the age of 65 years. It might affect the range of %CI in ROC analyses. In addition, gender difference was significant between CN and MCI subjects. It might affect

the volume measurement of CN subjects according to the previous study. Thus, more participants are needed to compare the CN and MCI groups fully. In addition, the subjects who converted to MCI or Alzheimer disease from CN or MCI were excluded in our study. Accordingly, comparison between the subdivided MCI groups is needed to confirm our findings.

Disclosure statement

The authors have no conflict of interest to report.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ijge.2018.06.002.

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