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Usefulness of two-dimensional measurements for the evaluation of brain volume and disability in multiple sclerosis

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Abstract

Background: Two-dimensional (2D) measures have been proposed as potential proxies for whole-brain volume in multiple sclerosis (MS).

Objective: To verify whether 2D measurements by routine MRI are useful in predicting brain volume or disability in MS.

Methods: In this cross-sectional analysis, eighty-five consecutive Japanese MS patients—relapsing-remitting MS (81%) and progressive MS (19%)—underwent 1.5 Tesla T1-weighted 3D MRI examinations to measure whole-brain and grey matter volume. 2D measurements, namely, third ventricle width, lateral ventricle width (LVW), brain width, bicaudate ratio, and corpus callosum index (CCI), were obtained from each scan. Correlations between 2D measurements and 3D measurements, the Expanded Disability Status Scale (EDSS), or processing speed were analysed.

Results: The third and lateral ventricle widths were well-correlated with the whole-brain volume ($p < 0.0001$), grey matter volume ($p < 0.0001$), and EDSS scores ($p = 0.0001$, $p = .0004$, respectively).The least squares regression model revealed that 78% of the variation in whole-brain volume could be explained using five explanatory variables, namely, LVW, CCI, age, sex, and disease duration. By contrast, the partial correlation coefficient excluding the effect of age showed that the CCI was significantly correlated with the EDSS and processing speed ($p < 0.0001$).

Conclusion: Ventricle width correlated well with brain volumes, while the CCI correlated well with age-independent (i.e. disease-induced) disability.

Keywords: ventricle width, corpus callosum index, brain volume, grey matter, processing speed, EDSS

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Introduction

Multiple sclerosis (MS) is a chronic autoimmune disease of the central nervous system that is characterized by focal and diffuse inflammation and neurodegeneration leading to axonal loss.[1] The brain volume (a surrogate marker of brain atrophy) has been shown to be a robust magnetic resonance imaging (MRI) measure for assessing the neurodegenerative component of the disease.[2] The assessment of brain volume loss, particularly grey matter (GM) volume loss, is of high clinical relevance because it has substantial predictive value with respect to long-term physical disability, cognitive decline and disease progression.[3]

Several automated tools have been developed for calculating brain volume loss in an accurate and reliable way.[2,4] However, standardized automated quantification of the brain volume and its change over time is not always possible using routine clinical scans because the process is time-consuming and requires preliminary preprocessing steps, including manual or semiautomated segmentation of T2 hyperintense white matter lesions that could impact brain volume measurements. Thus, the identification of more broadly applicable markers of brain volume loss represents an important challenge to translate the assessment of brain atrophy into clinical practice.[5]

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Quantitative two-dimensional (2D) measures, such as third ventricle width, lateral ventricle width, brain width, the corpus callosum index (CCI), and the bicaudate ratio (BCR), have been proposed as potential proxies for whole-brain atrophy. Quantitative 2D measures of brain volume include linear measures, which can be quantified on a single-image section with a distance tool on a computer workstation or even by a ruler on hardcopy films.[6] These 2D measures of brain atrophy have shown longitudinal sensitivity to disease progression,[7] meaningful correlations with clinical findings,[7,8] and strong associations with 3D measures of whole-brain atrophy.[6,9] However, to date, little data are available regarding which 2D measure or their combination is the most accurate in assessing whole-brain volume and disability.

Therefore, in this study, we attempted to clarify (i) which of the 2D measures are accurate enough to assess whole-brain volume; (ii) whether the 2D measures can also predict grey matter volume, physical disability, and processing speed; and (iii) whether the combination of several 2D measures would improve accuracy in predicting whole-brain volume in MS.

Methods

Patients

Eighty-five consecutive Japanese MS patients were recruited cross-sectionally from the Department of Neurology at Tohoku Medical and Pharmaceutical University Hospital, Sendai, Japan between 2019 and 2020. The inclusion criteria were as follows: 1) MS diagnosed according to the 2017 revisions of the McDonald criteria[10] and 2) age between 20 and 70 years. The exclusion criteria were as follows: 1) neuromyelitis optica spectrum disorders (NMOSD) or myelin oligodendrocyte glycoprotein (MOG) antibody-associated disorders and 2) a history of psychiatric illness other than stable depressive symptoms. Aquaporin 4 (AQP4)-IgG and MOG-IgG were detected with an in-house live-cell-based assay using full-length human AQP4- or MOG-transfected HEK 293 cells with IgG gamma-specific secondary antibodies as performed in our previous reports.[11,12] We used the Expanded Disability Status Scale (EDSS)[13] and Multiple Sclerosis Severity Score (MSSS)[14] to measure patient disability. Among the 85 MS patients, 74 who agreed to be evaluated for their processing speed had undergone cognitive assessments with CogEval (Biogen Inc.) (https://apps.apple.com/us/app/cogeval/id1366437045).
CogEval is an iPad-based screening assessment designed to evaluate cognitive function in patients with MS and is based on and validated against the Symbol Digit Modalities Test (SDMT).[15,16] The local institutional ethics committee at Tohoku Medical and Pharmaceutical University approved the study protocol (2017-2-011). Written informed consent was obtained from all participants.

MRI acquisition

All study subjects were scanned on the same whole-body 1.5 Tesla MRI system (MAGNETOM Aera, Siemens, Germany) using a standardized acquisition protocol, including a high-resolution sagittal 3-dimensional (3D) T1-weighted magnetization-prepared rapid gradient-echo (MPRAGE) sequence (repetition time (TR): 2730 ms; echo time (TE): 3.3 ms; inversion time (TI): 1000 ms; 176 slices; field of view (FoV): 256 mm; measured isotropic voxel size: $1 \times 1 \times 1$ mm) and a sagittal 3D fluid-attenuated inversion recovery (FLAIR) sequence (TR: 5000 ms; TE: 335 ms; TI: 1800 ms; 176 slices; FoV: 256 mm; measured isotropic voxel size: $1 \times 1 \times 1$ mm).

Measurements of whole-brain and grey matter volume and lesion volumes by icometrix

The 3D FLAIR and 3D T1 MPRAGE datasets obtained from each patient were analysed using the program "icobrain ms" by uploading the DICOM data to the Icometrix website (http://icometrix.com) as previously described.[17] The IcoBrain MS quantifies cross-sectional volumes with software based on Nifty Seg.[4]

MRI postprocessing to measure 2d measures of brain volume

Measurement of third ventricle width was performed by measuring the width along the anteroposterior midpoint of the third ventricle[6] (Figure 1A). Lateral ventricle width was determined along a plane corresponding to the anteroposterior midpoint of the ventricle on an anatomical level from an axial slice at which the septum pellucidum remained thin[6] (Figure 1B). Brain width was determined as the distance between two points on the cortical surface, measured at the same level and along the same line as the lateral ventricle width[6] (Figure 1C). The BCR was defined as the minimum intercaudate distance divided by brain width along the same line. The BCR was measured in the FLAIR axial slice, where the heads of the caudate nuclei were most visible and closest to one another[8] (Figure 1D). The CCI was calculated according to the method proposed by Figueira et al.[18]: on a mid-sagittal T1-weighted

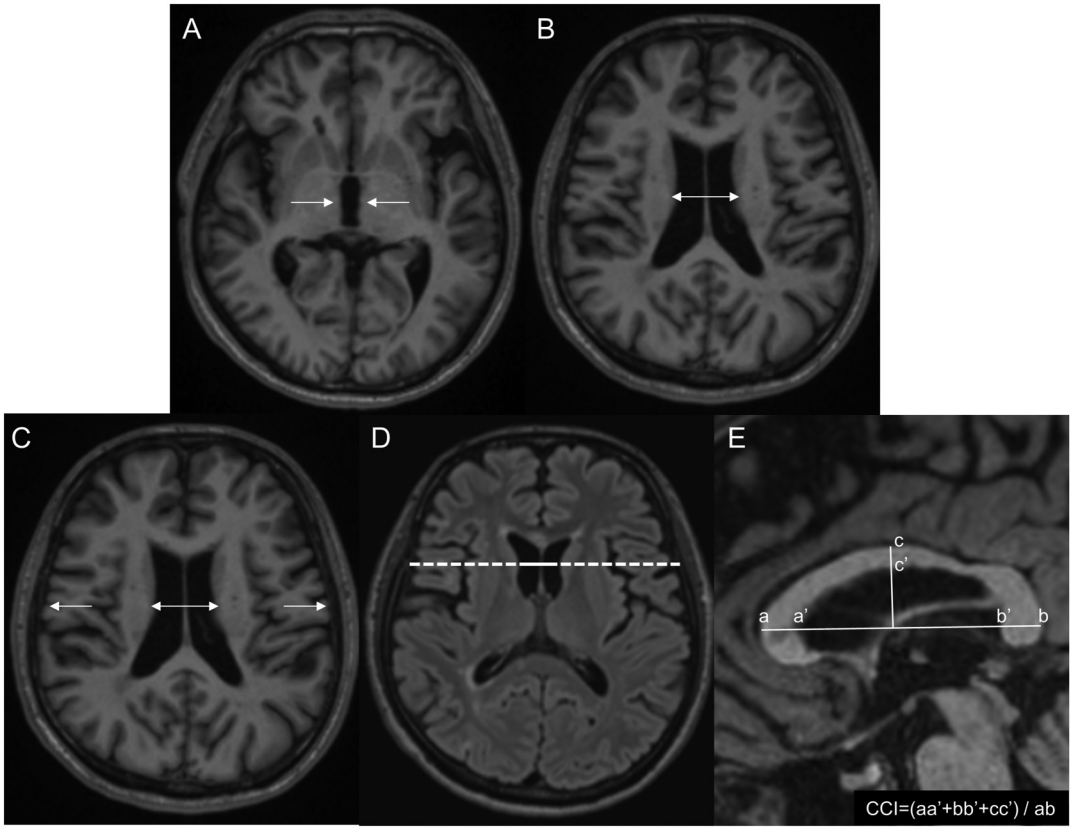

Figure 1. Two-dimensional measures of brain atrophy.
Third ventricle width (A), lateral ventricle width (B; arrows), brain width (C; arrows), bicaudate ratio (BCR) (D), and corpus callosum index (CCI) (E). (A) Measurement of third ventricle width was performed by measuring the width along the anteroposterior midpoint of the third ventricle. (B) Lateral ventricle width was determined along a plane corresponding to the anteroposterior midpoint of the ventricle on an anatomical level from an axial slice at which the septum pellucidum remained thin. (C) Brain width was determined as the distance between two points on the cortical surface, measured at the same level and along the same line as the lateral ventricle width. (D) The BCR was defined as the minimum intercaudate distance [solid line] divided by brain width along the same line [dashed line]. The BCR was measured in the FLAIR axial slice, where the heads of the caudate nuclei were most visible and closest to one another. (E) The CCI was calculated according to the method proposed by Figueira et al.[18]: On a mid-sagittal T1-weighted magnetic resonance image, a straight line was drawn across the greatest anteroposterior axis of the CC, and another straight line was drawn across its craniocaudal axis at its midpoint, leading to points a, a', b, b', and c, c'. The anterior, middle, and posterior segments of the CC were then measured and normalized to the greatest anteroposterior diameter of the CC, according to the formula (CCI = (aa' + bb' + cc')/ab).

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Longitudinal analysis

The whole-brain volumes, as obtained using the prediction formula in conjunction with several 2D measurements and clinical variables and as evaluated by 3D measurements, were evaluated chronologically in patients for whom data were available at more than three time points.

Statistical analysis

Statistical analyses were performed using JMP version 16.0 software. For the assessment of normal distributions, the Shapiro–Wilk test for normality was used. Distributions of normally distributed quantitative variables are described as the mean (standard

deviation), whereas those of nonnormally distributed quantitative variables are described as the median (interquartile range). Interrater agreement analysis was performed using the intraclass correlation coefficient (ICC). ICC values of <0.40 were considered poor, 0.40–.75 fair to good, and >.75 excellent based on statistical convention.[21] Comparisons of numerical variables between two disease groups were performed by the Mann–Whitney U test, and comparisons of categorical variables were performed by the chi-square test Nonparametric correlations between two quantitative variables were evaluated using Spearman's rank correlation coefficient (rho). In the multivariate correlation analysis, we computed the partial correlation coefficient. Statistical significance was defined using an α level of 0.05, which, after Bonferroni correction with a factor of 50 for multiple comparisons, was equivalent to 0.001 for this hypothetical exploratory study. A least squares regression model was used for multiple regression analysis. 2D measurements (of the third ventricle width, lateral ventricle width, brain width, BCR, and CCI), age, sex, and disease duration were considered as variables. To construct the final model, a stepwise method was followed to select the best set of predictors.

Results

Patient clinical profiles and MRI measurements

MS patients in the study (female/male = 64/21) included those with relapsing-remitting MS (RRMS) ($n = 69$, 81%) and progressive MS (PMS) ($n = 16$, 19%) (Table 1). The mean age of the patients was 40.7 ± 8.99 years, and the median disease duration was 9 (IQR, 5.17–14.9) years. The median EDSS score was 2.0 (IQR, 1.0–3.0), and the median MSSS score was 1.76 (IQR, 0.57–3.94). In total, 78 of the MS patients (92%) were being treated with disease-modifying therapy (DMT): 2 patients were receiving interferon beta (2%), 36 received fingolimod (43%), 33 received dimethyl fumarate (39%), and 7 received natalizumab (8%). None of the patients had longitudinal spinal cord lesions or sequelae of severe visual impairment.

The mean whole-brain volume and grey matter volume were 1482 (75.9) ml and 876 (43.9) ml, respectively. The median FLAIR hyperintensity volume was 4.25 (IQR, 2.02–10.2) ml. The median lateral ventricle width, third ventricle width, CCI, BCR, and brain width were 27.78 (IQR, 25.6–30), 4.44 (IQR, 3.33–6.12), 0.37 (IQR, 0.32–0.43), 0.14 (IQR, 0.12–0.16), and 133 (IQR, 130–138), respectively. The interrater ICCs for the 2 raters were 0.95, 0.95, 0.98, 0.97, and 0.95 for lateral ventricle width, third ventricle width, CCI, BCR, and brain width, respectively.

Patients with PMS had significantly longer disease duration, higher EDSS and MSSS scores, and lesion loads. They also showed more severe whole-brain and grey matter volume loss when evaluated with 3D and 2D measurements.

MS patients evaluated for processing speed included those with RRMS ($n = 60$, 81%) and PMS ($n = 14$, 19%) (Table 1). The mean age of the patients was 41.4 (8.8) years, and the median education level was 14 (IQR, 12–15) years. The median raw score of processing speed was 55.5 (IQR, 47–62). Clinical and imaging profiles did not significantly differ between the 74 MS patients evaluated for processing speed and the 85 MS patients.

Correlation between MRI measurements and physical disability or cognitive function

Age was significantly correlated with the whole-brain volume (rho = −0.38, $p = 0.0003$) and grey matter volume (rho = −0.63, $p < 0.0001$) (Table 2, eFigure 1). Age was also significantly correlated with the EDSS scores (rho = 0.4237, $p = 0.0002$). The disease duration was found to be significantly correlated with the whole-brain volume (rho = −0.42, $p < 0.0001$), grey matter volume (rho = −0.38, $p = 0.0004$), and EDSS (rho = 0.39, $p = 0.0002$) (eTable 1).

EDSS scores were significantly correlated with whole-brain volume (rho = −0.52, $p < 0.0001$) and grey matter volume (rho = −0.57, $p < 0.0001$), third ventricle width (rho = 0.40, $p = 0.0001$), lateral ventricle width (rho = 0.38, $p = 0.0004$), and BCR (rho = 0.35, $p = 0.0009$) (Table 2, eFigure 2). In contrast, the partial correlation coefficient excluding the effect of age showed that the EDSS score significantly correlated with whole-brain volume (rho = −0.48, $p < 0.0001$), grey matter volume (rho = −0.36, $p = 0.0008$), third ventricle width ($r = 0.37$, $p = 0.0005$), and CCI (rho = −0.42, $p < 0.0001$).

The raw processing speed score was significantly correlated with whole-brain volume (rho = 0.45, $p < 0.0001$) and grey matter volume (rho = 0.45, $p < 0.0001$) (Table 3, eFigure 3). The correlation between processing speed and age was not statistically significant ($r = -0.3163$, $p = 0.006$). The partial correlation coefficient excluding the effect of

Table 1. Clinical profiles.

Clinical profiles	MS ($n = 85$)	RRMS ($n = 69$)	PMS ($n = 16$)	Comparisons between RRMS and PMS (p value)	MS patients evaluated for processing speed ($n = 74$)
Sex (F/M)	64/21	54/15	9/7	0.07 [a]	55/19
Age *	40.7 (8.99)	39.2 (8.31)	46.9 (9.42)	0.0049 [b]	41.4 (8.8)
Duration (years) **	9 (5.17–14.9)	8 (4.21–13.3)	17.7 (9.37–25)	0.0009 [b]	9.13 (5.25–15.4)
EDSS score **	2 (1–3)	1 (0–2)	6 (3.75–6.5)	< 0.0001 [b]	2 (1–3)
MSSS score **	1.76 (0.57–3.94)	1.13 (0.42–2.88)	5.1 (3.71–8.69)	< 0.0001 [b]	1.73 (0.48–3.94)
Interferon beta	$n = 2$ (2%)	$n = 2$	$n = 0$		$n = 2$ (3%)
Fingolimod	$n = 36$ (43%)	$n = 24$	$n = 12$		$n = 33$ (45%)
Dimethyl fumarate	$n = 33$ (39%)	$n = 32$	$n = 1$		$n = 28$ (38%)
Natalizumab	$n = 7$ (8%)	$n = 6$	$n = 1$		$n = 7$ (9%)
None	$n = 7$ (8%)	$n = 5$	$n = 2$		$n = 4$ (5%)
Whole-brain vol (ml) *	1482 (75.9)	1506 (56.4)	1380 (62.8)	< 0.0001 [b]	1480 (74.8)
Grey matter vol (ml) *	876 (43.9)	888 (36.8)	831 (43.4)	< 0.0001 [b]	875 (40.9)
FLAIR hyper intensity vol (ml) **	4.25 (2.02–10.2)	3.73 (1.43–7.45)	15.9 (6.59–20.9)	0.0001 [b]	5.03 (2.17–11.0)
Lateral ventricle width (mm) **	27.8 (25.6–30)	26.7 (25–27.8)	31.7 (28.3–37.8)	< 0.0001 [b]	27.8 (25.6–30)
Third ventricle width (mm) **	4.44 (3.33–6.12)	4.44 (2.22–5)	7.78 (5.56–8.89)	< 0.0001 [b]	4.44 (3.33–6.67)
Corpus callosum index **	0.37 (0.32–0.43)	0.39 (0.35–0.43)	0.26 (0.2–0.32)	< 0.0001 [b]	0.37 (0.31–0.43)
Bicaudate ratio **	0.14 (0.12–0.16)	0.13 (0.11–0.15)	0.2 (0.16–0.21)	0.0002 [b]	0.14 (0.12–0.16)
Brain width (mm) **	133 (130–138)	133 (130–138)	132 (128–134)	0.23 [b]	133 (130–138)

Abbreviations: RRMS, relapsing-remitting MS; PMS, progressive MS; EDSS, Expanded Disability Status Scale; MSSS, MS Severity Score; vol, volume.
*Mean (standard deviation). ** Median (interquartile range). p value [a], p value evaluated by Pearson's chi-squared test p value [b], p value evaluated by the Mann–Whitney U test.

Table 2. Correlation coefficients between EDSS scores and MRI measurements.

	Age	EDSS	
Whole-brain volume	$r=-0.3801$, $p=0.0003$	$r=-0.5153$, $p<0.0001$	($r=-0.4796$, $p<0.0001$)
Grey matter volume	$r=-0.6258$, $p<0.0001$	$r=-0.5712$, $p<0.0001$	($r=-0.3600$, $p=0.0008$)
Third ventricle width	$r=0.2492$, $p=0.0214$	$r=0.4013$, $p=0.0001$	($r=0.3703$, $p=0.0005$)
Lateral ventricle width	$r=0.1367$, $p=0.2122$	$r=0.3750$, $p=0.0004$	($r=0.2736$, $p=0.0118$)
Bicaudate ratio	$r=0.1358$, $p=0.2153$	$r=0.3545$, $p=0.0009$	($r=0.3411$, $p=0.0015$)
Corpus callosum index	$r=-0.0334$, $p=0.7613$	$r=-0.3332$, $p=0.0018$	($r=-0.4234$, $p<0.0001$)
Brain width	$r=-0.033$, $p=0.7644$	$r=-0.0816$, $p=0.4580$	($r=-0.1102$, $p=0.3183$)

Values in parentheses indicate partial correlation coefficients and p values excluding the effect of age.

Table 3. Correlation coefficients between processing speed and MRI measurements.

	Processing speed	
Whole brain volume	$r=0.4547$, $p<0.0001$	($r=0.5284$, $p<0.0001$)
Grey matter volume	$r=0.4470$, $p<0.0001$	($r=0.3585$, $p=0.0018$)
Third ventricle width	$r=-0.3641$, $p=0.0014$	($r=-0.4322$, $p=0.0001$)
Lateral ventricle width	$r=-0.2468$, $p=0.034$	($r=-0.3970$, $p=0.0005$)
Bicaudate ratio	$r=-0.3386$, $p=0.0032$	($r=-0.4042$, $p=0.0004$)
Corpus callosum index	$r=0.2946$, $p=0.0108$	($r=0.5005$, $p<0.0001$)
Brain width	$r=0.0746$, $p=0.5278$	($r=0.1183$, $p=0.3187$)

Values in parentheses indicate partial correlation coefficients and p values excluding the effect of age.

age showed that the raw processing speed score was significantly correlated with whole-brain volume (rho = 0.53, $p<0.0001$), third ventricle width (rho = −0.43, $p=0.0001$), lateral ventricle width ($r=-0.40$, $p=0.0005$), BCR ($r=-0.40$, $p=0.0004$), and CCI ($r=0.50$, $p<0.0001$).

Correlation between 3d and 2d measurements

Among the five 2D measurements, lateral ventricle width (rho = −0.67, $p<0.0001$), third ventricle width (rho = −0.62, $p<0.0001$), CCI (rho = 0.60, $p<0.0001$), and BCR (rho = −0.57, $p<0.0001$) significantly correlated with whole-brain volume (eFigure 4). Among the five 2D measurements, third ventricle width (rho = −0.55, $p<0.0001$), lateral ventricle width (rho = −0.52, $p<0.0001$), and BCR (rho = −0.44, $p<0.0001$) significantly correlated with grey matter volume (eFigure 5, Table 4).

Multiple regression analysis to predict whole-brain volume

The least squares regression model revealed that approximately 78% of the variation in the whole-brain volume could be explained by the regression equation using five explanatory variables, namely, the lateral ventricle width, CCI, age, sex, and disease duration (Figure 2). This combination was found to be the best among several combinations of explanatory variables to predict whole-brain volume. The prediction formula was as follows:

$$\begin{aligned} \textit{Whole brain volume} = {} & 1605.7559289 - 5.596965994 \\ & * \textit{lateral ventricle width} \\ & + 368.87008708 * \textit{CCI} - 2.473944217 * \textit{age} \\ & - 0.818994327 * \textit{disease duration} \\ & + \textit{Match}\ (\textit{sex})\ (\text{``}F\text{''} \Rightarrow 20.751685342,\ \text{``M}\} \\ & \Rightarrow -20.75168534) \end{aligned}.$$

Table 4. Correlation coefficients between 3D and 2D measurements.

	Whole-brain volume		Grey matter volume	
Third ventricle width	$r=-0.6263$, $p<0.0001$	($r=-0.6687$, $p<0.0001$)	$r=-0.5537$, $p<0.0001$	($r=-0.5784$, $p<0.0001$)
Lateral ventricle width	$r=-0.6669$, $p<0.0001$	($r=-0.7383$, $p<0.0001$)	$r=-0.5174$, $p<0.0001$	($r=-0.5566$, $p<0.0001$)
Bicaudate ratio	$r=-0.5709$, $p<0.0001$	($r=-0.6519$, $p<0.0001$)	$r=-0.437$, $p<0.0001$	($r=-0.5104$, $p<0.0001$)
Corpus callosum index	$r=0.5995$, $p<0.0001$	($r=0.7256$, $p<0.0001$)	$r=0.2653$, $p=0.0141$	($r=0.408$, $p=0.0001$)
Brain width	$r=-0.0170$, $p=0.8776$	($r=-0.0076$, $p=0.9456$)	$r=-0.25$, $p=0.021$	($r=-0.3198$, $p=0.003$)

Values in parentheses indicate partial correlation coefficients and p values excluding the effect of age.

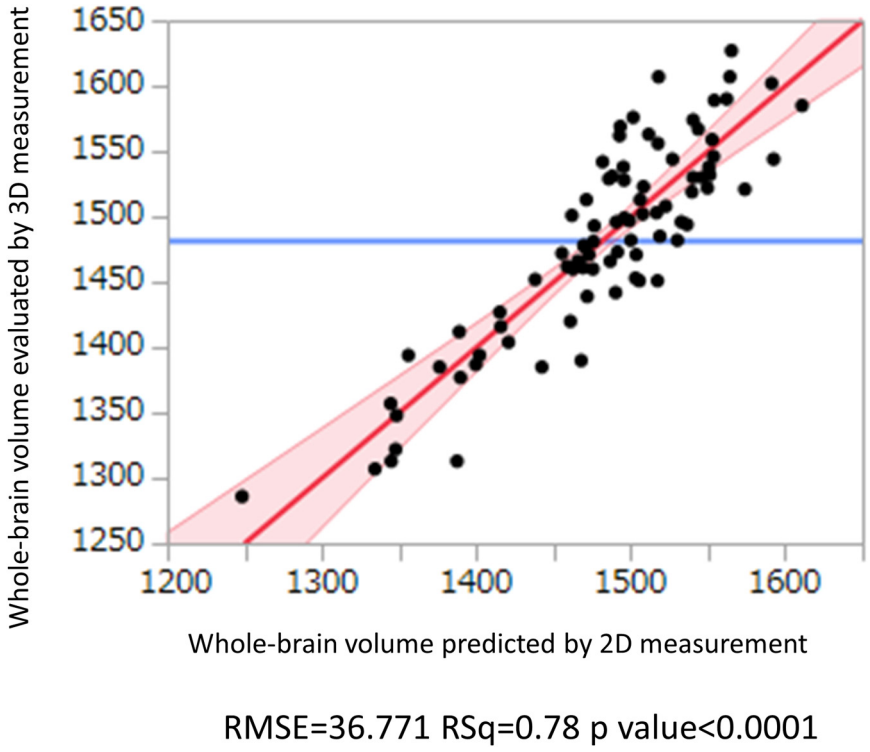

Figure 2. Multiple regression analysis.
The least squares regression model revealed that approximately 78% of the variation in the whole-brain volume could be explained by the regression equation using five explanatory variables, namely, the lateral ventricle width, CCI, age, sex, and disease duration. The prediction formula was as follows:
Whole brain volume $= 1605.7559289 - 5.596965994 * \textit{lateral ventricle width}$
$+368.87008708 * \textit{CCI} - 2.473944217 * \textit{age} - 0.818994327 * \textit{disease duration}$
$+\textit{Match}\ (\textit{sex})$ (``*F*" $\Rightarrow 20.751685342$, ``M$\} \Rightarrow -20.75168534$).
R squared (R^2) estimates the proportion of variation in the response that can be attributed to the model rather than to random error. An R^2 closer to 1 indicates a better fit to the data than an R^2 closer to 0. The root-mean-square error (RMSE) estimates the standard deviation of the random error.

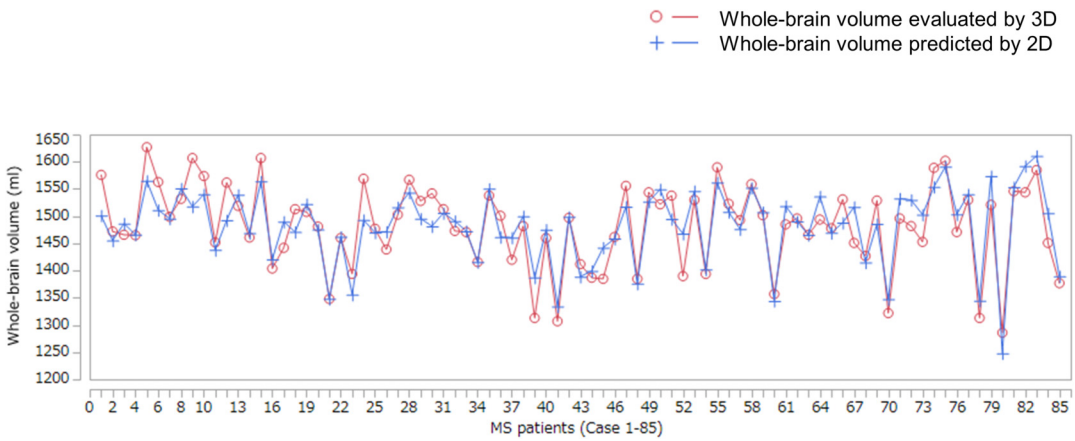

Figure 3. Whole-brain volume predicted by 2D measurements and that evaluated by 3D measurements.
The horizontal axis represents the 85 MS patients included in this study. The y-axis represents the whole-brain volume. Whole-brain volume predicted by the prediction formula using 2D measurements and that evaluated by 3D measurements mostly matched in each MS patient.

Whole-brain volume predicted by the abovementioned prediction formula and that evaluated by 3D measurement mostly matched in each MS patient (Figure 3).

Chronological changes in whole-brain volume predicted by 2d measurements and evaluated by 3d measurements

The whole-brain volumes, as obtained by the abovementioned prediction formula and as evaluated by 3D measurements, were also evaluated chronologically for two clinically stable patients for whom data were available at more than three time points. Patient 1 was a 38-year-old female RRMS patient with a disease duration of 12 years and an EDSS score of 3.5, and patient 2 was a 38-year-old female RRMS patient with a disease duration of 14 years and an EDSS score of 2. The changes in the whole-brain volumes, as obtained using the abovementioned prediction formula and as evaluated by 3D measurements, with time were similar for patient 1 but slightly different for patient 2 (Figure 4).

Discussion

In this study, we evaluated five 2D measures (third ventricle width, lateral ventricle width, brain width, CCI, and BCR) for the assessment of EDSS, processing speed, whole-brain volume, and grey matter volume in MS. We found that whole-brain volume was significantly correlated with lateral ventricle width, third ventricle width, CCI, and BCR, while the lateral and third ventricle widths showed stronger correlations than others. In contrast, grey matter volume and EDSS were significantly correlated with third ventricle width, lateral ventricle width, and BCR, while the third and lateral ventricle width showed stronger correlations than others. These results indicated that the third and lateral ventricle widths could be considered the most useful measurements for the assessments of EDSS, whole-brain volume, and grey matter volume in our MS cohort. In contrast, when we excluded the effect of age, both EDSS and processing speed were significantly correlated with third ventricle width and CCI, while both were most significantly correlated with CCI. Furthermore, a prediction formula using five explanatory variables, namely, the lateral ventricle width, CCI, age, sex, and disease duration, most effectively explained the whole-brain volume when assessed cross-sectionally and possibly over time.

Regarding the third ventricle width, a recent study reported a positive moderate correlation between the third ventricle width and EDSS scores ($r_s = 0.42$, $p < 0.01$), whereas the correlation between CCI and EDSS scores was statistically significant but weak ($r_s = -0.36$, $p < 0.01$).[2] In contrast, the study also reported that the correlations of third ventricle width and CCI with normalized brain volume were similar (approximately $r = -0.55$ and $r = 0.55$, respectively).[2] These results were basically in accordance with our results. In contrast, our study also found that third ventricle width was significantly correlated with grey matter volume.

A recent analysis of 2D linear measures of ventricular enlargement, such as frontal horn width, intercaudate distance, third ventricle width, and 4th ventricle width, in relapsing-remitting MS patients also

Figure 4. Chronological changes in whole-brain volume predicted by 2D measurements and evaluated by 3D measurements.
The whole-brain volume predicted by 2D measurements and that evaluated by 3D measurements were evaluated over time in patient 1 (a 38-year-old female RRMS patient with a disease duration of 12 years and an EDSS score of 3.5) and patient 2 (a 38-year-old female RRMS patient with a disease duration of 14 years and an EDSS score of 2). The changes in the whole-brain volumes, as obtained using the abovementioned prediction formula and as evaluated by 3D measurements, with time were similar for patient 1 but slightly different for patient 2.

reported that normalized intercaudate distance and third ventricle width showed moderate negative correlations with normalized brain volume (rho $= -0.484$, $p < 0.001$; rho $= -0.439$, $p < 0.001$, respectively).[5] Moreover, after accounting for age, sex, and disease duration, EDSS scores were moderately associated with normalized intercaudate distance (adjusted $R2 = 0.203$, $p < 0.001$) and third ventricle width (adjusted $R2 = 0.276$, $p < 0.001$).[5] Since whole-brain volume loss mainly reflects the degree of diffuse supratentorial brain volume loss in MS,[17] we assumed that lateral ventricular enlargement would represent whole-brain volume loss in MS.

In contrast, when we excluded the effect of age, the CCI was most significantly correlated with EDSS and processing speed. The corpus callosum is the primary commissural region of the brain consisting of white matter tracts that connect the left and right cerebral hemispheres. In MS, the corpus callosum is significantly affected by both focal lesions and Wallerian degeneration. Meanwhile, the corpus callosum is normally relatively resistant to age-related changes in healthy individuals.[21] Indeed, in our study, the correlation with age was lower in CCI than in third and lateral ventricle width and BCR. A recent study also suggested that the influence of normal ageing on volume loss might not be equivalent in various anatomical sites.[22] Therefore, we considered that CCI might be less affected by age among 2D measurements.

Structural disconnection of the corpus callosum due to axonal damage is thought to contribute to the development of cognitive dysfunction in MS. Corpus callosum has been widely appreciated in MS and correlates with the level of cognitive impairment.[23] A recent investigation of white matter microstructure in MS showed that processing speed function is associated preferentially with the level of integrity of commissural and frontal associative white matter tracts: the body of the corpus callosum, the anterior thalamic radiations and the inferior fronto-occipital fasciculus.[24] Since the corpus callosum must be involved in processing speed and is less affected by age, CCI can be one of the most useful 2D measurements to evaluate disease-induced and age-independent declines in processing speed, while processing speed can be decreased by normal ageing.

We also showed that a prediction formula using five explanatory variables, namely, the lateral ventricle width, CCI, age, sex, and disease duration, could effectively explain the whole-brain volume.

Although the whole-brain volume evaluated by 3D measurements transiently increased mildly, that predicted by 2D measurements did not. Brain volume measurements might have been affected by biological factors, such as lifestyle habits (e.g. alcohol, smoking, dehydration), and concomitant pathologic conditions that need to be taken into account when interpreting brain atrophy, particularly in the assessment of individual patients.[1,25,26] However, since we demonstrated longitudinal observation in only a few patients, we need to conduct further study in a large number of patients to confirm the discrepancy.

Our study has several limitations. First, this investigation was a single-centre study performed with a limited sample of Japanese MS patients; therefore, the results might have been influenced by selection bias. Furthermore, this categorization scheme may not be appropriate for other cohorts, since Japanese MS patients may have a slightly milder clinical course[27] and a slower rate of atrophy than Caucasian patients.[28] However, there is general agreement that the Western-type MS observed in Asia is not fundamentally different from that observed in typical MS of the Caucasian population once NMO and NMOSDs have been excluded.[29] Furthermore, this study is primarily cross sectional - a significant limitation for a study of brain atrophy. In the future, a multicentred longitudinal dataset is needed to perform a complete assessment of these measures and to obtain generalizability of the results. Moreover, a healthy control group should be included to validate the stability of those surrogate measures of brain tissue volumes.

In conclusion, in the treatment of MS patients, routine brain volume measures are valuable for the early evaluation of treatment responses and the prediction of disease evolution.[4] In an ideal setting, or in best practice, 3D scans should be acquired, even if 2D atrophy measurements are applied, as has been performed in most large MS centres. However, the acquisition of 3D scans is not always possible, especially in facilities other than large MS centres. Our study suggests that in these facilities 2D measurements obtained by routine MRI can be used to conveniently predict brain volume or disability in routine clinical practice. Although 3D measurements, such as those obtained using Icometrix, provide a more precise and detailed evaluation of the brain volume than 2D measurements, approximately 4–10 min is typically required to obtain additional 3D MRI images with additional costs. By contrast, 2D measurements do not involve 3D MRI images or additional costs and only take a few minutes when performed manually. Among several 2D measurements, the third and lateral ventricle widths were the most useful measurements to evaluate whole-brain and grey matter volume and physical disability. Furthermore, a prediction formula using 2D measurements could more effectively explain the whole-brain volume cross-sectionally and possibly over time. In contrast, when we excluded the effect of age, the CCI was most significantly correlated with physical disability and processing speed. Therefore, the CCI might best reflect age-independent (i.e. disease-induced) changes in physical disability and processing speed.

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Declaration of conflicting interests

IN is serving on scientific advisory boards for Biogen Japan and Novartis Pharma and is receiving honouraria for speaking engagements with Biogen Japan, Mitsubishi Tanabe Pharma, Novartis Pharma, Takeda Pharmaceutical, and Eisai. JF and SA report no disclosure.

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Ethics approval

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2013.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Xxxxxxx. IN is serving on scientific advisory boards for Biogen Japan and Novartis Pharma and is receiving honouraria for speaking engagements with Biogen Japan, Mitsubishi Tanabe Pharma, Novartis Pharma, Takeda Pharmaceutical, and Eisai. JF and SA report no disclosure.

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Supplemental material

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