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Third ventricle width on routine MRI is associated with processing speed in multiple sclerosis: a single-centre retrospective observational study

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Abstract

Background: Cognitive impairment is common in multiple sclerosis (MS), and slowed information processing is among its most frequent manifestations. Although brain volumetry can quantify atrophy, automated volumetric tools are not universally available in routine practice. We investigated whether third ventricle width (3VW), a simple linear measure obtainable on conventional MRI, is associated with standardised Symbol Digit Modalities Test performance.

Methods: This single-centre retrospective observational study included 100 adults with MS assessed in routine care between 2021 and 2023. Current MRI was acquired within one month of cognitive testing. A neuroradiologist blinded to cognitive results measured 3VW three times at the foramen of Monro, and the mean value was analysed. The primary analysis examined the association between current 3VW and age-standardised SDMT performance (SDMT-SD) using Spearman correlation with false-discovery-rate correction. Post hoc multivariable linear-regression sensitivity analyses adjusted for demographic and clinical covariates. MRI measurements approximately 3, 5 and 10 years earlier and analyses of SDMT impairment were exploratory.

Results: Twenty-five participants (25%) met the prespecified definition of SDMT impairment (SDMT-SD ≤ -1). Current 3VW was inversely associated with SDMT-SD (rho = -0.556, 95% CI -0.678 to -0.404; $q = 2.28 \times 10^{-8}$). The association persisted in a fully adjusted linear-regression sensitivity model including age, sex, education and EDSS (β = -0.232 SDMT-SD units per 1-mm greater 3VW, 95% CI -0.391 to -0.074; p = 0.0045). Excluding 14 records previously labelled as CIS produced similar results. Analyses of prior MRI showed associations in selected subgroups but were limited by non-random availability of earlier scans.

Conclusions: Greater third ventricle width on routine MRI is associated with worse processing-speed performance in MS. Because it is rapid to obtain and widely accessible, 3VW may serve as a simple imaging marker that prompts cognitive assessment when volumetric tools are unavailable. It should not replace cognitive testing or volumetric MRI, and predictive thresholds require prospective external validation.

Background

Cognitive impairment is frequent in multiple sclerosis (MS) and can have substantial consequences for everyday functioning. Information-processing speed and episodic memory are particularly often affected, while deficits in attention and executive functions are also recognised [1–3]. Cognitive problems may occur even when physical disability is limited and can influence employment, treatment adherence, daily activities and quality of life. Definitions of cognitive impairment and meaningful change differ across domains and studies [4, 5], but regular cognitive assessment is increasingly regarded as an important part of MS care [3, 6].

Among brief cognitive tests, the Symbol Digit Modalities Test (SDMT) is particularly well established in MS. It is sensitive to slowing of information processing, can be administered easily in the outpatient

setting and has been extensively validated as an outcome measure [7]. Current recommendations support cognitive screening at baseline with the SDMT, or another validated measure, and repeated testing during follow-up [6]. A simple MRI feature that is already visible on routine scans could be useful as an additional reason to pay closer attention to cognition in an individual patient.

Lesion burden on conventional MRI accounts for only part of the variability in cognitive performance in MS. More consistent relationships have been reported for grey-matter damage, thalamic involvement and global or regional brain atrophy [2, 3, 8–10]. Third ventricle width (3VW) is an indirect linear measure of central atrophy; enlargement of the ventricle may partly reflect tissue loss in the adjacent thalamic and perithalamic regions. Earlier studies have linked 3VW with cognitive dysfunction and have shown that simple ventricular measurements can reflect cerebral atrophy [11–14]. These measurements are less anatomically specific than volumetric methods, but they have the practical advantage of being obtainable directly from conventional MRI without dedicated post-processing [15, 16]. Whether such a simple measure can provide useful information about cognitive status in routine MS care remains uncertain.

We examined the relationship between 3VW measured on routine MRI and age-standardised SDMT performance in a clinical MS cohort. MRI obtained close to cognitive testing formed the primary analysis. Measurements from earlier scans were analysed separately as exploratory data because these scans were unavailable for some participants and their availability was unlikely to be random. The study was intended to assess association and within-cohort discrimination rather than to develop a prediction model or define a treatment threshold.

Methods

Study design and participants

This single-centre retrospective observational study used prospectively recorded routine-care clinical and cognitive data together with retrospective review of clinically acquired MRI. Consecutive patients assessed between 2021 and 2023 were considered. The analytical cohort comprised 100 adults managed within the institutional MS pathway who fulfilled the 2017 McDonald criteria for MS [17] and had complete contemporaneous clinical, cognitive and MRI data. No a priori sample-size calculation was performed; the sample size reflected the number of eligible patients with complete current data.

Eligibility required age > 18 years, confirmed MS and ability to complete cognitive and motor assessments. Walking aids were permitted, but participants had to be able to walk without another person’s physical support. Exclusion criteria were acute relapse or corticosteroid treatment at the time of testing, comorbid neurodegenerative disease, inability to complete the SDMT or motor tests, severe or decompensated depression, and a confirmed sleep disorder. Assessments were performed during clinical remission.

The source database retained a clinically isolated syndrome (CIS)-labelled category for 14 records. All 14 participants fulfilled the 2017 McDonald criteria for MS at the time of cognitive assessment; the CIS label reflected legacy source-database coding and was retained only for descriptive reporting. Reporting was guided by the STROBE recommendations for observational studies.

Clinical and cognitive assessment

Cognitive processing speed was assessed using the oral Czech-language SDMT according to the Western Psychological Services manual [18]; the SDMT is an established, previously published instrument and was not developed for the present study. The raw score was the number of correct responses within 90 seconds. To reduce the effect of age on cognitive performance, the primary cognitive outcome was an age-standardised SDMT score (SDMT-SD), calculated as (observed score – age-specific mean) / age-specific standard deviation using manual age-group norms. Lower SDMT-SD values indicate worse performance.

SDMT impairment was defined a priori as SDMT-SD ≤ -1, representing performance at least one standard deviation below the relevant age-group norm. This threshold was used as a marker of processing-speed impairment rather than as a definition of multidomain cognitive impairment. Global cognitive screening was additionally performed using the Addenbrooke's Cognitive Examination-III (ACE-III) [19]. Because validated Czech population norms were not available, ACE-III scores were treated as raw descriptive scores and no diagnostic cut-offs were applied. Patients unable to complete the SDMT because of relevant visual or motor limitations were excluded.

Recorded variables included age, sex, years of education, body mass index, smoking status, age at MS onset, disease duration, source-database disease category, Expanded Disability Status Scale (EDSS), scored according to the established scale described by Kurtzke [20], annual relapse rate and annualised EDSS change. Motor performance was assessed with the Nine-Hole Peg Test and Timed 25-Foot Walk. Disease-modifying therapy (DMT) variables included number of therapies, total treatment duration and high-efficacy therapy exposure within prespecified time windows. The EDSS was a previously published clinical scale and was not developed for the present study.

MRI acquisition and linear measurements

Brain MRI was performed on a 3-T Siemens MAGNETOM scanner using the institutional MS protocol, which included T2-weighted, fluid-attenuated inversion recovery, T1-weighted MPRAGE, diffusion-weighted, double-inversion recovery and susceptibility-weighted imaging. Current MRI was obtained within one month of cognitive testing. Prior MRI measurements corresponded approximately to 3, 5 and 10 years before cognitive assessment. Exact scan dates were unavailable; these measurements were therefore analysed as approximate time categories rather than exact longitudinal intervals.

Third ventricle width was measured on axial images at the level of the foramen of Monro as the maximal transverse width. A neuroradiologist blinded to SDMT results and impairment status performed three measurements, and their mean was used for analysis. Intra-rater reliability was good (intraclass correlation coefficient = 0.82); the confidence interval and ICC model were not available, and inter-rater reliability was not assessed. Additional linear measures were the bicaudate, bifrontal, frontal ventricular and posterior ventricular widths and the corpus callosum angle.

Statistical analysis

Continuous variables are summarised as mean and standard deviation or median and interquartile range (IQR), as appropriate, and categorical variables as counts and percentages. Non-parametric methods were used for the principal association analyses because several variables were non-normally distributed or ordinal.

The prespecified primary analysis assessed the association between current 3VW and SDMT-SD using Spearman rank correlation. The prior-MRI time categories were exploratory. To account for multiple testing across the six linear MRI measures and four MRI time categories, a family of 24 MRI–SDMT-SD correlations was controlled using the Benjamini–Hochberg false discovery rate (FDR) [21, 22]. Confidence intervals for Spearman correlations were estimated using the Fisher z approximation. To assess robustness of the primary contemporaneous association to potential confounding, post hoc ordinary least-squares linear-regression sensitivity analyses modelled SDMT-SD as a continuous outcome with HC3 heteroscedasticity-robust standard errors and t-based inference. A demographic model adjusted for age, sex and education; a clinical model adjusted for age and EDSS; and a full sensitivity model adjusted for age, sex, education and EDSS.

Because availability of prior MRI could introduce selection bias, participants with and without MRI available approximately 3 years before cognitive assessment were compared using Mann–Whitney U tests for continuous variables and chi-square or Fisher exact tests for categorical variables. Rank-biserial correlation, Cramer's V or odds ratios were reported as effect-size measures [23–25].

Associations with the binary SDMT-impairment outcome were evaluated using Firth penalised logistic regression to reduce finite-sample bias and separation [26, 27]. After inspection of the exploratory correlations from prior MRI, additional regression and receiver operating characteristic (ROC) analyses were performed for the approximately 3-year MRI subgroup; these analyses were therefore considered post hoc and exploratory. The demographic model included 3VW, age, sex and education, and a clinical sensitivity model included 3VW, age and EDSS. Model fragility was considered in relation to the number of outcome events per predictor parameter [28–30].

Exploratory ROC analysis assessed discrimination of 3VW for SDMT impairment and used the Youden index to derive a descriptive cut-off. Internal validation used 1,000 bootstrap resamples, re-estimating the ROC curve and cut-off to estimate optimism in area under the curve (AUC), sensitivity and specificity [31, 32]. This validation addressed threshold estimation within the approximately 3-year subgroup but did

not account for data-driven selection of that time category; therefore, all cut-offs were treated as descriptive and requiring external validation.

The original analyses were performed using MATLAB Online R2025a (MathWorks, Natick, MA, USA) and custom scripts. The additional post hoc multivariable sensitivity analyses were performed in Python 3.13.5 using statsmodels 0.14.6. All tests were two-sided. Interpretation prioritised effect sizes and confidence intervals in addition to FDR-adjusted q values. Because the multivariable models evaluated robustness of the same primary association rather than a new family of hypotheses, their p values were not multiplicity-adjusted.

Use of generative artificial intelligence in manuscript preparation

ChatGPT (OpenAI) was used to assist with English-language editing, manuscript restructuring. ChatGPT was not used to generate or modify source data, select references, or independently formulate scientific interpretations or conclusions. AI-assisted adjustment was afterwards critically reviewed by the authors, who take full responsibility for the accuracy, integrity, interpretation and final content of the manuscript.

Results

Participant characteristics

The analytical cohort included 100 participants, of whom 74 (74%) were women. Median age was 45.0 years (IQR 39.0–54.5), median education was 13 years, median disease duration from diagnosis was 9.0 years (IQR 4.0–16.0), and median EDSS was 3.5 (IQR 1.5–5.0). Median raw SDMT score was 57 (IQR 47–67), and median SDMT-SD was − 0.30 (IQR − 0.90 to 0.35). Median ACE-III score was 97.0 (IQR 94.0–98.5), with a mean of 95.3 ± 4.8. Twenty-five participants (25.0%) met the prespecified definition of SDMT impairment (Table 1).

Contemporaneous MRI measurements were available for all participants. Prior 3VW measurements were available in 87 participants at approximately 3 years, 73 at approximately 5 years and 56 at approximately 10 years before cognitive assessment. In the approximately 3-year subgroup, 23 of 87 participants had SDMT impairment. Median current 3VW was 4.75 mm (IQR 4.00–6.30). Median total DMT duration was 9.0 years (IQR 4.0–14.0), and 22 participants had received high-efficacy therapy within 3 years of diagnosis.

Table 1
Selected characteristics of the analytical cohort

Characteristic	Value
Total cohort	100
Female sex	74 (74%)
Age, years	Median 45.0 (IQR 39.0-54.5); mean 46.2 ± 11.8
Education, years	Median 13.0; mean 13.5 ± 2.3
Disease duration from diagnosis, years	Median 9.0 (IQR 4.0–16.0); mean 10.7 ± 7.8
Source-database disease category	RRMS 62 (62%); CIS-labelled 14 (14%); PPMS 14 (14%); SPMS 10 (10%)
EDSS	Median 3.5 (IQR 1.5-5.0); mean 3.43 ± 1.94
SDMT raw score	Median 57.0 (IQR 47.0–67.0); mean 57.6 ± 12.9
SDMT-SD	Median − 0.30 (IQR − 0.90 to 0.35); mean − 0.19 ± 1.06
SDMT impairment	25 (25.0%)
ACE-III raw score	Median 97.0 (IQR 94.0-98.5); mean 95.3 ± 4.8
Current third ventricle width, mm	Median 4.75 (IQR 4.00-6.30); mean 5.24 ± 1.79
Prior 3VW availability	3-year: 87; 5-year: 73; 10-year: 56
DMT duration, years	Median 9.0 (IQR 4.0–14.0); mean 9.53 ± 6.15
High-efficacy therapy within 3 years of diagnosis	22 (22%)
High-efficacy therapy within 10 years of diagnosis	39 (39%)

Values are n (%) unless otherwise specified. The CIS-labelled category reflects prior source-database coding; all participants fulfilled the 2017 McDonald criteria for MS at cognitive assessment. SDMT impairment was defined as SDMT-SD ≤ -1. ACE-III values are raw scores; no diagnostic cut-off was applied. Abbreviations: ACE-III, Addenbrooke's Cognitive Examination-III; CIS, clinically isolated syndrome; DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; IQR, interquartile range; PPMS, primary progressive MS; RRMS, relapsing-remitting MS; SDMT, Symbol Digit Modalities Test; SPMS, secondary progressive MS; 3VW, third ventricle width.

Primary association between current 3VW and SDMT performance

In the primary analysis, greater current 3VW was associated with worse age-standardised SDMT performance (rho = -0.556, 95% CI -0.678 to -0.404; $q = 2.28 \times 10^{-8}$) (Table 2; Fig. 1). The association

remained present in post hoc linear-regression sensitivity analyses: β = -0.285 SDMT-SD units per 1-mm greater 3VW (95% CI -0.423 to -0.147; p < 0.001) after adjustment for age, sex and education; β = -0.246 (95% CI -0.399 to -0.092; p = 0.0020) after adjustment for age and EDSS; and β = -0.232 (95% CI -0.391 to -0.074; p = 0.0045) in the full model including age, sex, education and EDSS (Table 3). Excluding the 14 records previously labelled as CIS did not materially alter the primary association (rho = -0.542; n = 86); in the fully adjusted model restricted to these 86 participants, β was − 0.206 (95% CI -0.379 to -0.034; p = 0.0197). Other contemporaneous ventricular-enlargement measures also showed inverse associations with SDMT-SD, whereas the corpus callosum angle was not associated after FDR correction.

Table 2
FDR-corrected Spearman correlations between linear MRI markers and SDMT-SD

Time point	N	BCM rho (q)	BFM rho (q)	3VW rho (q)	FVW rho (q)	PVW rho (q)	CA rho (q)
Current	100	-0.410 (5.46×10^{-5})	-0.430 (2.37×10^{-5})	-0.556 (2.28×10^{-8})	-0.444 (1.24×10^{-5})	-0.402 (7.23×10^{-5})	-0.117 (0.255)
~ 3 years earlier	87	-0.492 (6.16×10^{-6})	-0.360 (9.89×10^{-4})	-0.637 (7.75×10^{-10})	-0.415 (1.31×10^{-4})	-0.527 (1.27×10^{-6})	0.137 (0.223)
~ 5 years earlier	73	-0.439 (1.88×10^{-4})	-0.296 (1.46×10^{-2})	-0.522 (8.58×10^{-6})	-0.384 (1.19×10^{-3})	-0.563 (1.32×10^{-6})	0.173 (0.164)
~ 10 years earlier	56	-0.433 (1.22×10^{-3})	-0.333 (1.53×10^{-2})	-0.469 (4.56×10^{-4})	-0.215 (0.134)	-0.554 (2.46×10^{-5})	0.067 (0.622)

q values are Benjamini-Hochberg FDR-adjusted within the 24-correlation MRI-SDMT-SD family. Abbreviations: 3VW, third ventricle width; BCM, bicaudate measure; BFM, bifrontal measure; CA, corpus callosum angle; FDR, false discovery rate; FVW, frontal ventricular width; PVW, posterior ventricular width.

Table 3
Post hoc multivariable linear-regression sensitivity analyses for the association between current 3VW and SDMT-SD

Model	N	Adjustment	3VW β (95% CI)	p value	R^2	Adjusted R^2
Unadjusted	100	None	-0.309 (-0.409 to -0.209)	< 0.001	0.273	0.266
Demographic	100	Age, sex, education	-0.285 (-0.423 to -0.147)	< 0.001	0.372	0.346
Clinical	100	Age, EDSS	-0.246 (-0.399 to -0.092)	0.0020	0.384	0.364
Full sensitivity	100	Age, sex, education, EDSS	-0.232 (-0.391 to -0.074)	0.0045	0.456	0.427

Ordinary least-squares regression with HC3 heteroscedasticity-robust standard errors and t-based inference. β represents the change in SDMT-SD per 1-mm greater current 3VW. The demographic model adjusted for age, sex and education; the clinical model adjusted for age and EDSS; and the full model adjusted for age, sex, education and EDSS. Abbreviations: CI, confidence interval; EDSS, Expanded Disability Status Scale; SDMT-SD, age-standardised Symbol Digit Modalities Test score; 3VW, third ventricle width.

Prior MRI availability and exploratory associations

Availability of MRI approximately 3 years before cognitive assessment was clearly non-random. Compared with participants without such imaging, those with an available scan from this period had longer disease duration (median 10 vs 1 year; rank-biserial r = 1.00; $p = 6.68 \times 10^{-9}$), longer DMT exposure (10 vs 1 year; r = 1.00; $p = 6.54 \times 10^{-9}$), older age (47 vs 38 years; r = 0.56; p = 0.00119), higher EDSS (4 vs 2; r = 0.53; p = 0.00208), greater current 3VW (5.0 vs 4.2 mm; r = 0.38; p = 0.0271), and a different source-database disease-category distribution (Cramer's V = 0.48; $p = 4.09 \times 10^{-5}$) (Fig. 2).

Among participants with prior MRI, 3VW was inversely associated with SDMT-SD at approximately 3 years (rho = -0.637, 95% CI -0.748 to -0.493; $q = 7.75 \times 10^{-10}$), 5 years (rho = -0.522; $q = 8.58 \times 10^{-6}$) and 10 years (rho = -0.469; $q = 4.56 \times 10^{-4}$) before cognitive assessment (Table 2; Fig. 1). Because participants with prior MRI differed systematically from those without it, these estimates should be interpreted as subgroup associations rather than evidence for an optimal biological time interval.

Exploratory SDMT-impairment models and discrimination

In the approximately 3-year MRI subgroup, exploratory univariable Firth regression showed that each 1-mm increase in 3VW was associated with higher odds of SDMT impairment (OR 1.71, 95% CI 1.31–2.25; p = 0.00010; n = 87; 23 events). The association remained present in the demographic model adjusted for age, sex and education (OR 1.50, 95% CI 1.11–2.04; p = 0.0086) and in the clinical sensitivity model

adjusted for age and EDSS (OR 1.44, 95% CI 1.04–1.99; p = 0.0287) (Table 4). Given the limited number of events and post hoc selection of this time category, these adjusted estimates are exploratory.

Table 4
Exploratory Firth penalised logistic regression for SDMT impairment in the approximately 3-year MRI subgroup

Model	N	Events	Predictor parameters	EPV	3VW OR (95% CI)	p value
3VW only	87	23	1	23.00	1.71 (1.31–2.25)	0.00010
3VW + age + sex + education	87	23	4	5.75	1.50 (1.11–2.04)	0.0086
3VW + age + EDSS	87	23	3	7.67	1.44 (1.04–1.99)	0.0287

The outcome was SDMT impairment, defined as SDMT-SD ≤ -1. Third ventricle width was measured approximately 3 years before cognitive assessment and is reported per 1-mm increase. Abbreviations: 3VW, third ventricle width; CI, confidence interval; EDSS, Expanded Disability Status Scale; EPV, events per predictor parameter; OR, odds ratio.

The approximately 3-year 3VW measure yielded an apparent AUC of 0.836 (95% CI 0.743–0.913); the optimism-corrected AUC was also 0.836 after rounding. The Youden-derived cut-off was 5.9 mm, with sensitivity of 91.3% and specificity of 70.3%. However, the bootstrap distribution of optimal cut-offs was broad (median 5.9 mm; 95% bootstrap interval 4.9–7.1 mm), and the bootstrap procedure did not reproduce selection of the approximately 3-year category from multiple time points. The threshold is therefore descriptive and not clinically validated (Table 5; Fig. 3).

Table 5
Exploratory ROC analysis of third ventricle width for SDMT impairment

Time point	N	Events	Apparent AUC (95% CI)	Optimism-corrected AUC	Cut-off, mm	Sensitivity	Specificity
~ 3 years earlier	87	23	0.836 (0.743–0.913)	0.836	5.9	91.3%	70.3%
~ 5 years earlier	73	20	0.730 (0.598–0.845)	0.733	5.6	75.0%	66.0%
~ 10 years earlier	56	17	0.701 (0.554–0.861)	0.691	5.3	70.6%	74.4%

Cut-offs were derived using the Youden index and are exploratory. For the approximately 3-year category, the bootstrap median optimal cut-off was 5.9 mm and the 95% bootstrap interval was 4.9–7.1 mm. Internal validation did not account for selection of the approximately 3-year category from multiple time points. Abbreviations: AUC, area under the ROC curve; CI, confidence interval; ROC, receiver operating characteristic.

Discussion

Principal findings

In our cohort, a wider third ventricle on routine MRI obtained close to cognitive testing was associated with poorer age-standardised SDMT performance. This relationship remained after FDR correction and after adjustment for demographic and clinical covariates, and its magnitude was similar when records previously labelled as CIS were excluded. Associations of comparable or greater size were seen for 3VW measured on earlier scans, although those analyses involved selected subgroups because prior imaging was not available at random. The results therefore support a relationship between 3VW and processing speed, but they do not establish 3VW as a predictive biomarker or a validated clinical threshold.

Interpretation in relation to previous research

A relationship between 3VW and SDMT performance is biologically plausible. Information-processing speed depends on distributed networks that include the thalamus and other deep grey-matter structures, and atrophy in these regions has been linked to poorer SDMT performance in MS [8, 10]. Third ventricular enlargement does not measure thalamic volume directly, but it may reflect tissue loss in the surrounding central structures. Previous studies have reported associations between 3VW and cognitive dysfunction and have related simple ventricular measurements to volumetric or clinical markers of atrophy [11–14]. In the current cohort, this question was examined using age-standardised SDMT scores, repeated blinded 3VW measurements, correction for multiple MRI comparisons and an explicit analysis of the bias introduced by availability of earlier scans.

Of the earlier MRI time points, the strongest association was seen for scans obtained approximately 3 years before cognitive assessment. This finding needs cautious interpretation. Participants with scans available from that period had longer disease and treatment duration, were older, had greater disability and also had a larger current 3VW. The availability of an earlier scan was therefore probably related to length of follow-up, monitoring intensity, treatment history or disease severity. The corresponding subgroup estimates cannot be assumed to apply to patients without comparable longitudinal imaging.

The ROC analysis deserves similar caution. In the approximately 3-year subgroup, the AUC was 0.836, but the 5.9-mm cut-off was both derived and evaluated in the same selected sample and its bootstrap interval was wide. Bootstrap validation within that subgroup cannot account for the earlier data-driven choice of the 3-year time point, and a threshold obtained from a single centre, scanner and protocol may

not transfer to other settings [32]. For these reasons, 3VW is more appropriately interpreted as a continuous measure associated with cognitive performance than as a binary clinical rule.

A recent study by Jardine et al. examined routinely collected structural MRI in 120 patients with MS using automated MorphoBox-derived normalised brain, grey-matter and white-matter volumes together with the corpus callosum index [33]. Some MRI measures were associated with cognitive impairment, but discrimination based on MRI alone was modest and improved after demographic variables were added. Their approach and ours address the same clinical problem from different directions. Automated volumetry provides more detailed anatomical information, whereas 3VW can be measured directly on routine images without additional software. In both cases, MRI appears more useful as complementary information that can prompt cognitive assessment than as a stand-alone screening test.

Clinical implications

In routine practice, automated volumetric MRI is not available in every centre, despite its growing role in MS research and clinical assessment. Third ventricle width can be obtained quickly from standard images and requires no dedicated software. In a patient with a visibly enlarged third ventricle, our findings suggest that it is reasonable to ensure that cognitive screening has not been overlooked, particularly where volumetric analysis is unavailable. This should remain an adjunct to established assessment: 3VW cannot replace the SDMT, formal neuropsychological testing, volumetric MRI or clinical judgement, and the exploratory 5.9-mm value should not be used to guide treatment.

Strengths and limitations

Several features strengthen the study. The cohort was clinically characterised, SDMT results were age-standardised, and 3VW was measured repeatedly by a reader blinded to cognitive results. The analyses also accounted for multiple MRI comparisons and tested the primary contemporaneous association in multivariable sensitivity models. We separately examined the effect of excluding records previously labelled as CIS, used penalised regression for the exploratory binary outcome, assessed the instability of the ROC threshold by bootstrap, and directly evaluated the non-random availability of earlier MRI. Throughout, the results were interpreted as associations rather than as evidence of causality or prediction.

The limitations are equally important. This was a single-centre observational study with a partly retrospective design, and earlier MRI was available for a selected rather than random subset of participants. Exact dates of those scans were unavailable, which prevented precise longitudinal modelling. Only 25 participants met the definition of SDMT impairment, limiting the complexity of multivariable analyses for the binary outcome. SDMT-SD relied on age-group Western Psychological Services norms rather than contemporary Czech normative data. ACE-III was reported only as a raw descriptive measure because validated Czech population norms were not available. Third ventricle width is an indirect and anatomically non-specific measure, and its value may vary with image acquisition and scan plane. Intra-rater reliability was not fully documented and inter-rater reliability was not assessed. Finally, the study addressed processing speed rather than multidomain cognition and did not include

lesion volume, cortical lesions, cognitive reserve, practice effects, fatigue, mild-to-moderate depressive symptoms or several other factors that can influence SDMT performance. The consistency of the adjusted and sensitivity analyses is reassuring, but residual confounding remains possible.

Further work should therefore focus on prospective multicentre validation. In particular, inter-rater reproducibility, scanner and protocol effects, direct comparison with automated volumetric measures and the relationship between change in 3VW and later cognitive decline all require study. A numerical threshold should not be considered for clinical use until it has been tested in an independent population.

Conclusions

In adults with MS, greater third ventricle width on routine MRI was associated with poorer age-standardised SDMT performance. The measure is simple and does not depend on dedicated volumetric software, which may make it useful as an additional prompt for cognitive assessment when more advanced imaging tools are unavailable. Findings from earlier MRI and the exploratory 5.9-mm cut-off were derived from selected subgroups and should not be treated as validated predictive results. Independent prospective validation is needed before 3VW is used in clinical decision rules.

Abbreviations

3VW
third ventricle width
ACE-III
Addenbrooke's Cognitive Examination-III
AUC
area under the curve
BCM
bicaudate measure
BFM
bifrontal measure
CA
corpus callosum angle
CIS
clinically isolated syndrome
DMT
disease-modifying therapy
EDSS
Expanded Disability Status Scale
EPV
events per predictor parameter
FDR

false discovery rate
FVW
frontal ventricular width
IQR
interquartile range
MRI
magnetic resonance imaging
MS
multiple sclerosis
PVW
posterior ventricular width
ROC
receiver operating characteristic
SDMT
Symbol Digit Modalities Test
SDMT-SD
age-standardised Symbol Digit Modalities Test score.

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee of University Hospital Olomouc and the Faculty of Medicine and Dentistry, Palacký University Olomouc (approval no. 37/26). The requirement for individual informed consent to participate was waived by the Ethics Committee for this anonymised retrospective analysis of routinely collected clinical and imaging data. The study was conducted in accordance with applicable institutional requirements and the principles of the Declaration of Helsinki.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Authors' information

Not applicable.

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Author Contribution

Dalibor Zimek and Matous Rous conceived the study, contributed to investigation and project administration, and drafted and revised the manuscript. Martina Miklusova contributed to investigation, methodology and manuscript revision. Katerina Hrabinska contributed to investigation. Jan Mares supervised the study and revised the manuscript. Eva Cechakova contributed to investigation and performed radiological measurment. Ladislav Stanke and Jana Zapletalova performed the formal statistical analysis, contributed to methodology and revised the manuscript; Ladislav Stanke additionally independently verified the post hoc multivariable sensitivity analyses. All authors read and approved the final manuscript.

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Not applicable.

Data Availability

The patient-level datasets analysed during the current study are not publicly available because of privacy and institutional restrictions. Anonymised derived data and analysis scripts supporting the reported analyses may be available from the corresponding author on reasonable request, subject to institutional and ethics approval.

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Figures

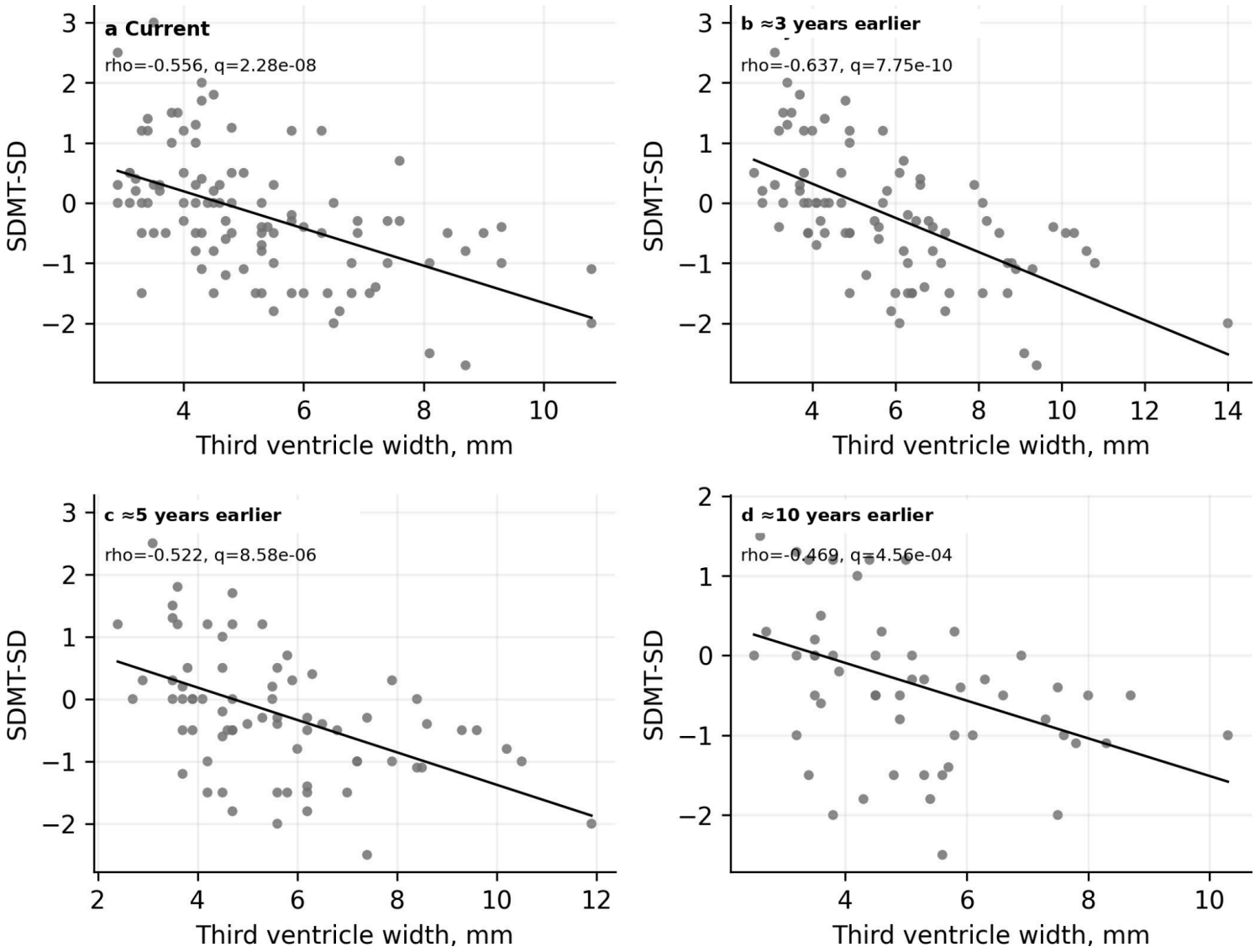


Figure 1

Association between third ventricle width and age-standardised Symbol Digit Modalities Test performance. Scatterplots show current 3VW (a) and 3VW measured approximately 3 years (b), 5 years (c), and 10 years (d) before cognitive assessment. Solid lines indicate linear trends for visualisation; reported coefficients are Spearman rank correlations with Benjamini-Hochberg false-discovery-rate-adjusted q values. Earlier MRI categories represent selected subgroups with available prior imaging and approximate, rather than exact, time intervals. Abbreviations: 3VW, third ventricle width; SDMT-SD, age-standardised Symbol Digit Modalities Test score.

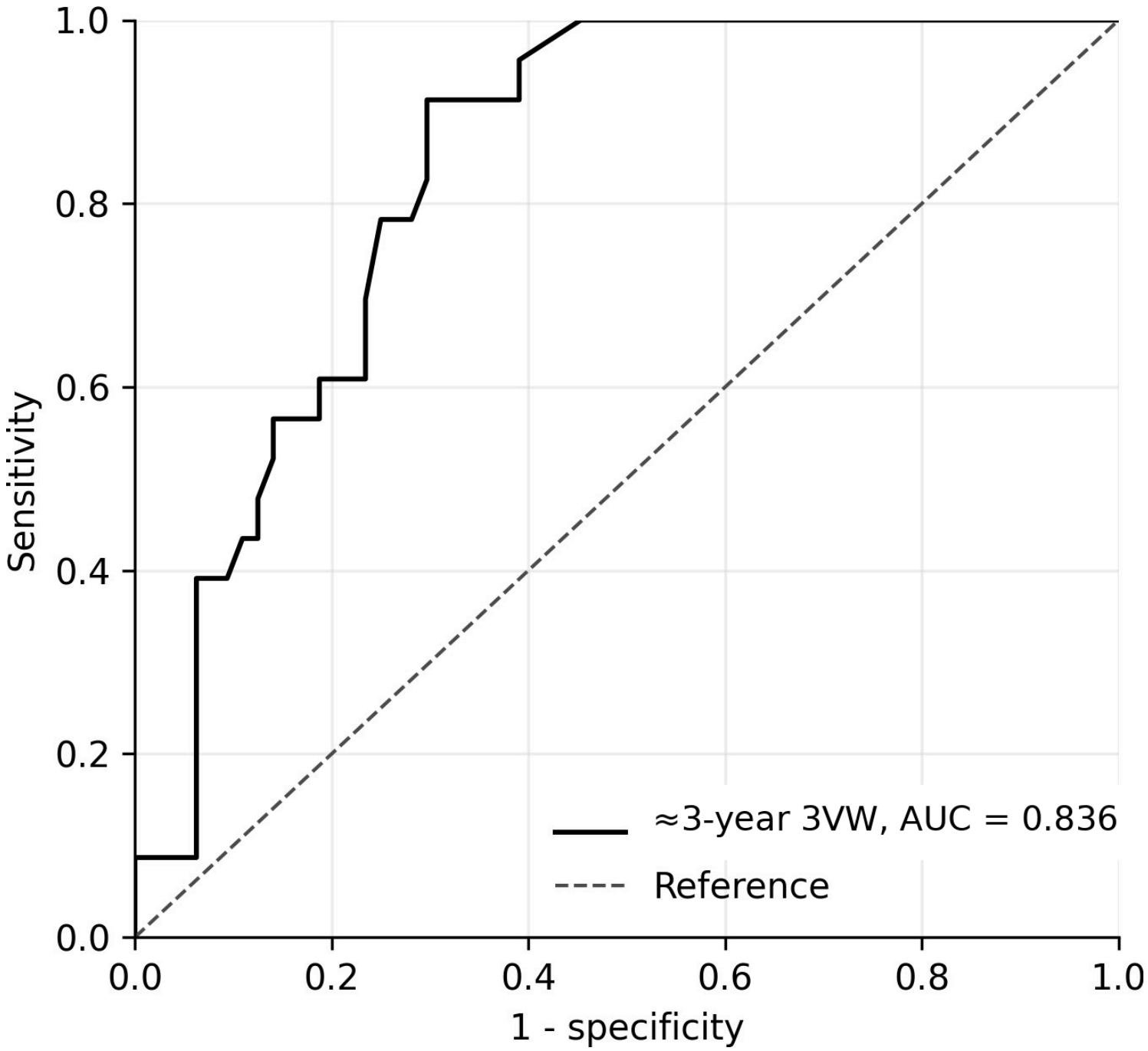


Figure 2

Non-random availability of MRI approximately 3 years before cognitive assessment. Bars show the absolute effect sizes for differences between participants with and without an available MRI from this period. Rank-biserial correlations are shown for continuous or ordinal variables, and Cramer's V for categorical variables; values therefore represent magnitude rather than direction. Abbreviations: CIS, clinically isolated syndrome; DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; 3VW, third ventricle width.

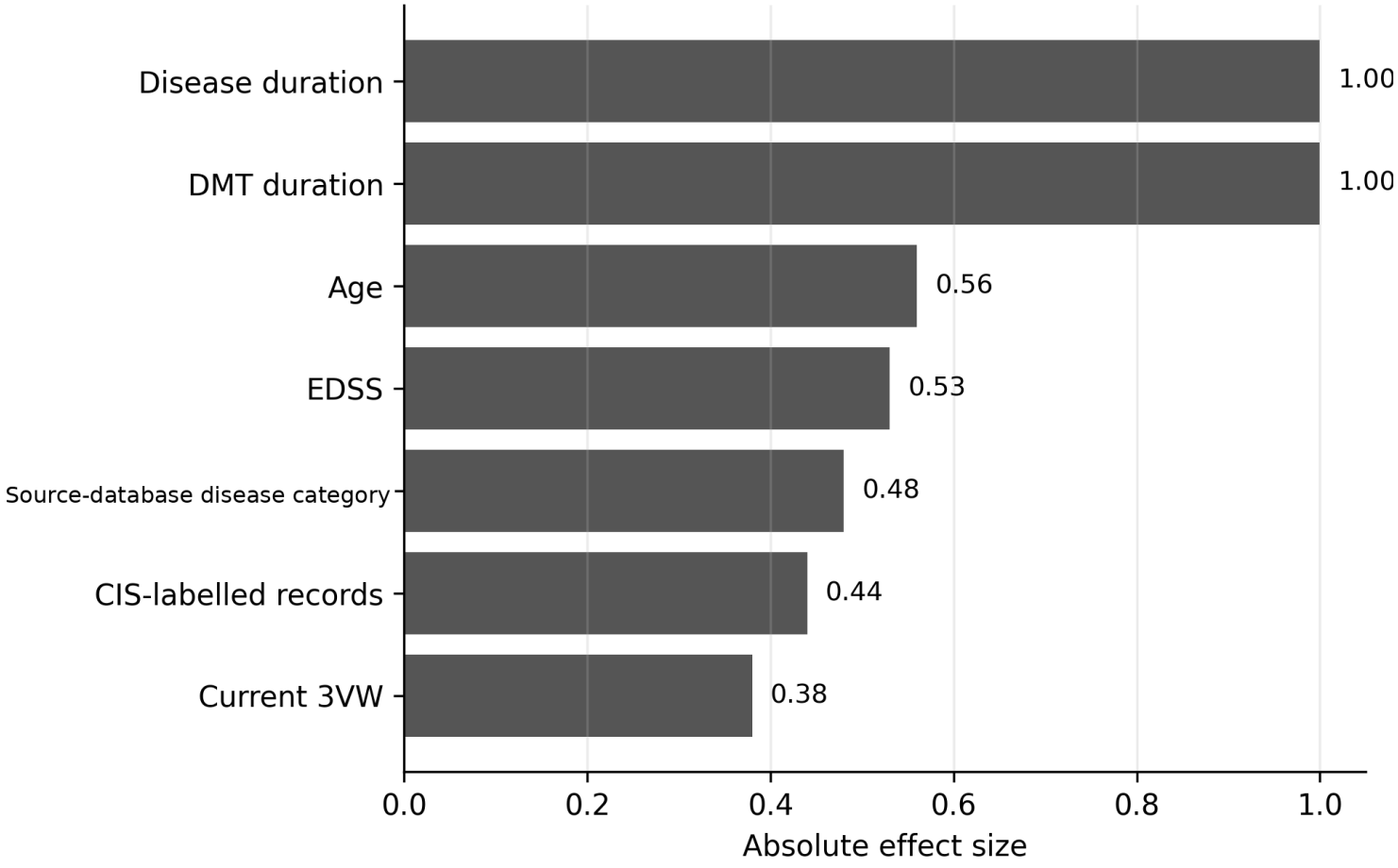


Figure 3

Exploratory discrimination of approximately 3-year third ventricle width for SDMT impairment. Receiver operating characteristic curve for 3VW measured approximately 3 years before cognitive assessment and SDMT impairment, defined as SDMT-SD ≤ -1 (n = 87; 23 events). The apparent area under the curve was 0.836 (95% CI 0.743-0.913); the dashed diagonal indicates chance-level discrimination. The Youden-derived 5.9-mm cut-off was obtained in the same selected subgroup and was not externally validated. Abbreviations: AUC, area under the curve; CI, confidence interval; ROC, receiver operating characteristic; SDMT-SD, age-standardised Symbol Digit Modalities Test score; 3VW, third ventricle width.