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ORIGINAL ARTICLE

The Brief International Cognitive Assessment in Multiple Sclerosis (BICAMS): Regression-based norms for German-speaking countries

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Abstract

Background and purpose: Cognitive impairment in multiple sclerosis (MS) is common and is associated with problems in employment, driving ability, and quality of life. Since cognitive impairment at time of diagnosis is predictive of disability progression, early assessment and annual monitoring is recommended. The Brief International Cognitive Assessment in Multiple Sclerosis (BICAMS) was introduced as a time-efficient screening tool that can easily be applied in standard clinical care. However, besides application, tests need to be analysed and the raw values obtained must be interpreted accordingly. Since normative values have not been available for German-speaking countries, BICAMS has not been implemented in clinical routine. The aim of this study was to calculate German normative BICAMS data to improve the current diagnostic process for people with MS.

Methods: Healthy control subjects in different age categories were recruited to enable regression-based norm analysis. Raw scores for each BICAMS test were converted into scaled scores before they were regressed for age, age squared, gender, and education. The obtained scores were then normalised to a *z*-score by dividing the difference between the scaled score and the predicted score by the root mean squared error of the model.

Results: In all, 237 HCs were recruited (68.8% female, 31.2% male) and examined with BICAMS. Datasets entered the regression-based norms analysis and formed the basis for a final *z*-score calculation. To simplify handling in everyday clinical practice, nomograms and look-up tables were created which provide clinicians with age- and education-corrected norms.

Conclusion: Our work fills the gaps between BICAMS application, evaluation and interpretation and will make a significant contribution to more regular cognitive assessment of MS patients.

KEYWORDS
BICAMS, cognition, cognitive assessment, multiple sclerosis, neuropsychology

INTRODUCTION

Cognitive impairment is frequently observed in people with multiple sclerosis (pwMS) and has a major impact on employment, hours missed at work, driving ability and overall quality of life [1, 2]. Despite knowledge of this fact and the evidence that the Expanded Disability Status Scale (EDSS) is insufficient to capture cognitive performance in pwMS [1], cognitive assessment has not yet been implemented in routine neurological care. In Germany, as well as in Switzerland and Austria, the most relevant reasons not to conduct a neuropsychological evaluation are limited time during neurological consultation hours, little familiarity with neuropsychological testing procedures, and lack of reimbursement options in insurance schemes. In recent years, however, there has been a growing understanding that regular assessment is not only important to determine the status quo but also that cognition assessed at time of diagnosis can be a significant predictor of long-term patient outcome [3].

In 2012, the Brief International Cognitive Assessment in Multiple Sclerosis (BICAMS) was introduced by an expert panel as an international screening battery for cognitive impairment in MS [4]. It was intended to facilitate testing of cognitive domains typically affected in pwMS in standard clinical care. In order to advance the application of BICAMS in German-speaking countries, we first validated the battery in a cohort of 172 pwMS and 100 healthy controls [5] according to the official protocol for the international standards for validation [6]. Second, we applied BICAMS to a wide age range (18–90 years) of 237 healthy control subjects, in order to determine the normative values for German-speaking countries. Since data collection in healthy people of all age categories always represents a challenge, we decided to calculate the final normative values using regression-based norms analyses, as has been done in other countries [7–11]. Thus, the aim of this study was to calculate German normative BICAMS data in order to improve the current diagnostic process for pwMS and to provide these in a such a way that they can easily be applied in standard clinical care by healthcare professionals. For this overall aim we provide nomograms and look-up tables for use in clinical routine.

MATERIALS AND METHODS

Participants

A total of 237 healthy control subjects were recruited by advertisement at the University Hospital and the University of Düsseldorf. Subjects were eligible to participate if they were aged between 18 and 90 years and did not have a pre-diagnosed disease that might impact cognitive performance (any central nervous system disease, major depression, anxiety disorder, or chronic fatigue syndrome). This health-related information was the basic prerequisite for participating in the study as a healthy control subject. To confirm the information, screening instruments were applied to assess fatigue, depression, anxiety and self-perceived cognitive deficits (Table 1). All subjects gave written informed consent to participate. The study was approved by the Ethics Committee of the Heinrich Heine University Düsseldorf (study number: 6035) and conducted in accordance with the principles of the Declaration of Helsinki.

Neuropsychological test measures

All participants underwent neuropsychological examination by trained psychologists and medical postgraduates using the three BICAMS tests used in the German validation study [5]: the Symbol Digit Modalities Test (SDMT [12]), the Brief Visual Memory Test Revised (BVMT-R [13]) and the Verbaler Lern- und Merkfähigkeitstest (VLMT [14]). In addition, further data were collected on age, gender, education, depression (Hospital Anxiety and Depression Scale-Depression [HADS-D] [15]), anxiety (Hospital Anxiety and Depression Scale-Anxiety [HADS-A] [15]), fatigue (Fatigue Scale for Motor and Cognitive Functions [FSMC] [16]) and self-perceived cognitive impairment (Perceived Deficits Questionnaire [PDQ-20] [17]).

Statistical analyses

Statistical analyses were calculated using IBM SPSS Statistics for Windows, version 28.0.1.1 (IBM Corp., Armonk, NY, USA) and using Matlab, version R2021b (The MathWorks Inc., Natick, MA, USA).

Power of the sample

In all age categories, which cover actual and future prevalences in MS (18–29, 30–39, 40–49, 50–59, 60–69, 70–79, 80–89 years), there were sufficient subjects to carry out a regression-based norms analysis in order to provide reliable and clinically usable norm data for German-speaking countries.

Regression-based norms calculation

The regression-based norms were calculated according to the method used by Parmenter et al. [18] Raw scores for each BICAMS component were converted into scaled scores based on the cumulative frequency distribution of each measure. The distribution was non-linearly transformed to a Gaussian distribution ($M = 10$, $SD = 3$). The scaled scores were regressed for age, age squared (to control for a non-linear relation between age and the dependent

variable to be predicted), gender and education level. For a person with a given age, gender and education level, these regression models allow us to predict the average score of peers with the same age, gender and education level. These scores can then be normalised to a *z*-score by dividing the difference between the scaled score and the predicted score by the root mean squared error (RMSE) of the model. A *z*-score equal to or below −1.5 (meaning that performance is 1.5 SD below the mean) is taken to indicate impairment, meaning that 93.3% of the healthy controls would score higher than this score.

As an example, we consider a 42-year-old woman with 15 years of education, with a raw score of 51 on the SDMT. For women, the gender variable is encoded as 0, and 15 years of education represents category 4 for education. Thus, the predicted score for this woman is 10.35. Her raw score of 51 can be transformed to a scaled score according to the conversion table, and in this case, the scaled score is 8.

Z-score calculation

The *z*-score can be calculated by taking the difference between the scaled score and the predicted score and dividing the result by the RMSE of the regression model: *z*-score = (8–10.3514)/1.9087 = −1.13. Since this score is higher than −1.5, the person in our example is not impaired based on the SDMT.

RESULTS

Participants

In total, 237 healthy control subjects were recruited, of whom 163 (68.8%) were female and 74 (31.2%) were male. Of these, 39.7% belonged to the age category 18 to 29 years, 9.3% to the age category 30 to 39 years, 7.2% to the age category 40 to

TABLE 1 Demographic characteristics of the normative sample ($n = 237$).

Demographic data	*n* (%)	Raw scores (SD)	Mean (SD)	Median (IQR)	*z*-value
Gender					
Female	163 (68.8)				
Male	74 (31.2)				
Age group					
18 to 29 years	94 (39.7)				
30 to 39 years	22 (9.3)				
40 to 49 years	17 (7.2)				
50 to 59 years	59 (24.9)				
60 to 69 years	25 (10.5)				
≥70 years	20 (8.4)				
School certificates (years of education)					
Without school certificate (≤8 years)	1 (0.4)				
Secondary school (9 years)	7 (3.0)				
Intermediate school (10–11 years)	26 (11.0)				
A-levels/University	203 (85.7)				
FSMC total score			34.16 (10.49)	32 (15)	
FSMC motor			17.06 (5.46)	16 (7)	
FSMC cognitive			17.10 (5.68)	16 (8)	
HADS-A			4.48 (2.83)	4 (4)	
HADS-D			2.19 (2.30)	1.5 (3)	
PDQ-20 total score		14.16 (7.80)	0.71 (0.39)	0.65 (1)	0.72
PDQ-20 attention and concentration		5.32 (2.85)	1.06 (0.57)	1.0 (0.8)	0.27
PDQ-20 retrospective memory		2.79 (2.35)	0.56 (0.47)	0.4 (0.6)	0.88
PDQ-20 prospective memory		3.03 (2.16)	0.61 (0.43)	0.6 (0.59)	0.73
PDQ-20 planning and organization		3.01 (2.31)	0.60 (0.46)	0.6 (0.6)	0.99

Note: Total $n = 237$; for PDQ-20: $n = 224$; for FSMC: $n = 223$; for HADS: $n = 224$.

Abbreviations: FSMC, Fatigue Scale for Motor and Cognitive Functions; HADS-A, Hospital Anxiety and Depression Scale-Anxiety Score; HADS-D, Hospital Anxiety and Depression Scale-Depression Score; IQR, interquartile range; *n*, number of subjects; PDQ-20, Perceived Deficits Questionnaire; SD, standard deviation.

49 years, 35.4% to the age category 50 to 69 years, and 8.4% to the age category older than 70 years.

Since the school systems and certificates in the three target countries Germany, Switzerland and Austria are not comparable, we categorised education according to number of years of school education. The lowest school certificate in Germany is '*Hauptschule*' (secondary school), which corresponds to 9 years of school education. The next level is '*Realschule*' (intermediate school) and corresponds to 10–11 years. The highest educational school level is '*Gymnasium*' (equivalent to A-levels), which is summarized as ≥12 years of education and which qualifies students to attend university. Most of the participants had the highest school education level (≥12 years of school in 85.7% [Table 1]).

To ensure the representativeness of our healthy control sample, all participants underwent screening examination with regard to fatigue, depression, anxiety and self-perceived cognitive problems. Of the 223 subjects screened for fatigue, 94.6% reported no to minimal fatigue. Similarly, of the 224 subjects screened for anxiety and depression, no one showed meaningful signs of depression and 96% did not show meaningful signs of anxiety (cut-off ≥11, respectively). This underlined that the subjects who served as our healthy control sample were representative of the general population. More detailed information is given in Table 1.

Model development

The development of regression-based models was based on a total of 235 subjects due to missing values in two participants. To create the appropriate models the following variables were selected: sex, age, education, SDMT raw score, VLMT total score, and BVMT-R total score. Figure 1 shows the demographics and performance distribution of the three BICAMS tests.

Next, we converted the control group's raw scores on each of the three neuropsychological measures to scaled scores, defined as a mean of 10 ($M = 10$) and a standard deviation of 3 (SD = 3) using the cumulative frequency distribution of each measure (Figure 2).

The conversion process enabled us to create a table allowing concrete conversion of test raw scores to corresponding normative scaled scores, as well as a rough classification system (Table 2).

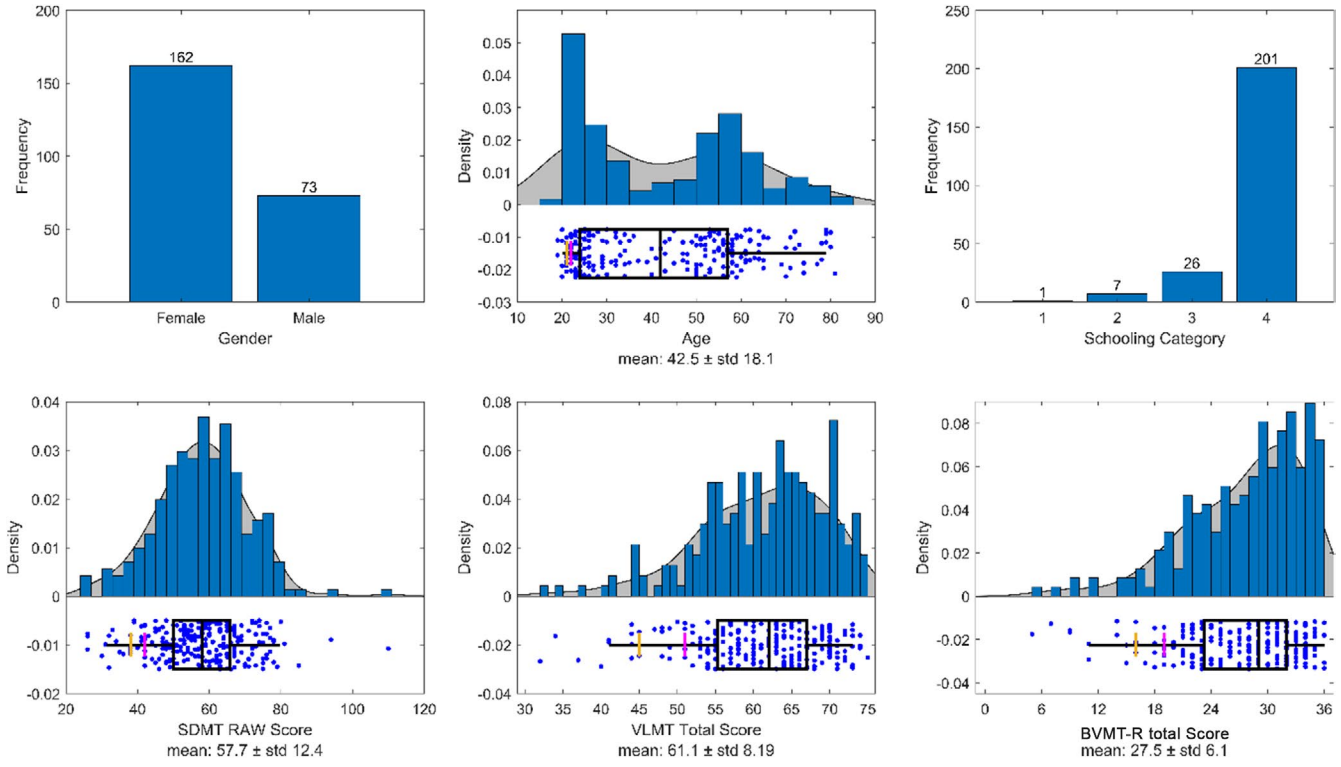


FIGURE 1 Visualisation of the demographics of the dataset. The bar charts indicate the group distributions for categorical variables. For longitudinal variables, histograms are plotted on top of raincloud plots. The boxplot shows the 5th and 10th percentile in orange and magenta, respectively. BVMT-R, Brief Visual Memory Test-Revised; SDMT, Symbol Digit Modalities Test; std, standard deviation; VLMT, Verbaler Lern- und Merkfähigkeitstest.

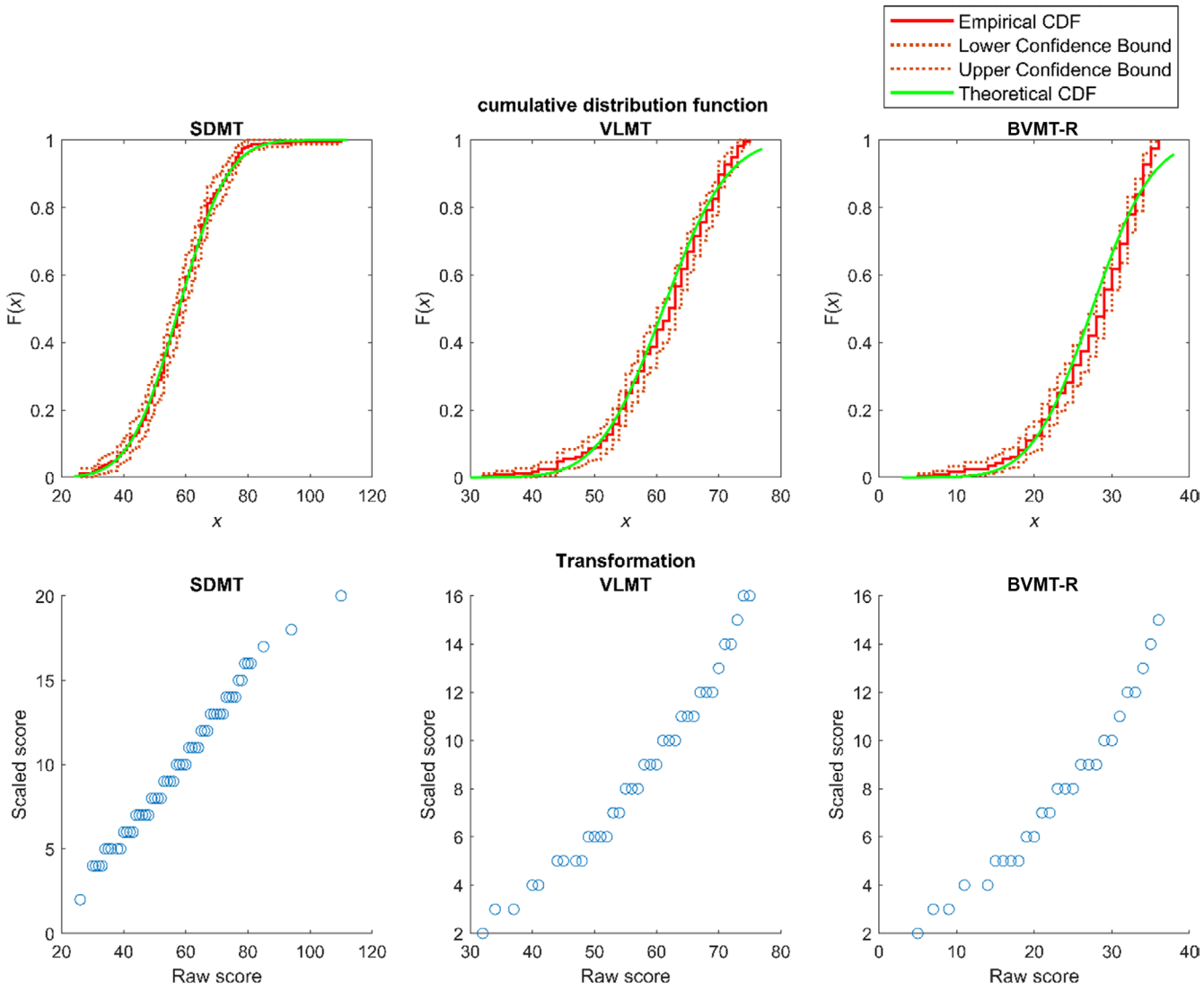


FIGURE 2 Top row: cumulative distribution function of empirical data compared to theoretical Gaussian distribution with same mean and standard deviation. Bottom row: transformation from raw scores to scaled scores. BVMT-R, Brief Visual Memory Test Revised; CDF, cumulative distribution function; SDMT, Symbol Digit Modalities Test; std, standard deviation; VLMT, Verbaler Lern- und Merkfähigkeitstest.

Further, we set up a regression model with the obtained scores, scaled with regard to age, age-squared, sex, and education.

The formula for the regression models of the three BICAMS measures was as follows, with gender (male = 1 and female = 0) and education classified as levels 1 to 4 according to the German education system: 1 = no school certificate and/or ≤8 years of school; 2 = secondary school and/or 9 years of school; 3 = intermediate school and/or 10–11years of school; 4 = A-levels/university and/or ≥12 years of school:

$$\text{score} = \text{intercept} + \text{age} \times \beta_{\text{age}} + \text{age}^2 \times \beta_{\text{age}^2} + \text{gender} \times \beta_{\text{gender}} + \text{education} \times \beta_{\text{education}}$$

Table 3 shows the concrete regression parameters for the different BICAMS sub-tests, while Table 4 provides information on the statistical measures used.

Application in clinical practice

Since the simple raw score or scaled score does not give information on whether an individual patient has impairment or not with regard to information processing speed, verbal- and visuo-spatial short-term memory and learning, a *z*-score must be calculated using the following formula:

$$z = \frac{(\text{scaled score} - \text{score})}{\text{RMSE}}$$

A *z*-score ≤−1.5 is considered to indicate impairment in the specific cognitive domain.

Nomograms and look-up tables

As neurologists in German-speaking countries see a large number of MS patients during their consultation hours each day, and given that

TABLE 2 Conversion table from raw scores to scaled scores.

Scaled score	SDMT		VLMT		BVMT-R		Classification
2		<26		<33		<6	Extremely low
3	27	29	34	39	7	9	
4	30	33	40	43	10	14	
5	34	39	44	48	15	18	Borderline
6	40	43	49	52	19	20	
7	44	48	53	54	21	22	Low average
8	49	52	55	57	23	25	
9	53	56	58	60	26	28	Average
10	57	60	61	63	29	30	
11	61	64	64	66	31	31	
12	65	67	67	69	32	33	High average
13	68	72	70	70	34	34	
14	73	76	71	72	35	35	Superior
15	77	78	73	73	36	36	
16	79	81	74	75			Very superior
17	82	90					
18	91	102					
19	103	108					
20	>109						

Abbreviations: BVMT-R, Brief Visual Memory Test-Revised; SDMT, Symbol Digit Modalities Test; VLMT, Verbaler Lern- und Merkfähigkeitstest.

TABLE 3 Parameters of the regression models for the different BICAMS sub-tests.

Predictors β	Intercept	Age	Age^2	Gender	Education
SDMT	10.1914	0.0076	−0.0012	0.1080	0.4894
VLMT	9.8837	−0.1340	0.0009	−1.0659	1.0948
BVMT-R	9.8030	−0.0777	0.0002	−0.4818	0.7755

Abbreviations: BVMT-R, Brief Visual Memory Test-Revised; SDMT, Symbol Digit Modalities Test; VLMT, Verbaler Lern- und Merkfähigkeitstest.

TABLE 4 Statistical measures of the regression models for the different BICAMS sub-tests.

	R^2 statistic	*F*-statistic	*p* value	MSE	RMSE
SDMT	0.4060	39.3023	4.6067e-25	5.4458	1.9087
VLMT	0.2545	19.6244	6.5414e-14	6.0670	1.4236
BVMT-R	0.2318	17.3551	1.8545e-12	5.8906	1.3191

Abbreviations: BVMT-R, Brief Visual Memory Test-Revised; MSE, mean squared error RMSE, root mean squared error; SDMT, Symbol Digit Modalities Test; VLMT, Verbaler Lern- und Merkfähigkeitstest.

the calculation of a *z*-score for three separate tests is not only time consuming but also very error-prone and cumbersome, we decided as a final step to compile nomograms and norm tables that were age- and education-corrected and that are easy to use in clinical routine.

Operating instructions

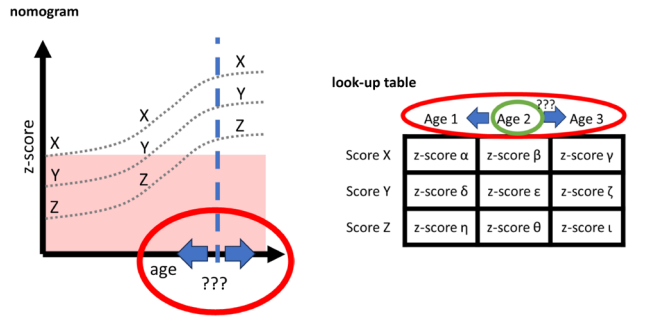
Nomograms and look-up tables should be used according to the following steps:

Step 1: select the right test for the nomogram or look-up table:
SDMT [p 4–p 12] && [p 29–p 45] in Appendix S1.
VLMT [p 13–p20] && [p 46–p 53] in Appendix S1.
BVMT-R [p 21–p28] && [p 54–p 58] in Appendix S1.

Step 2: select the correct gender and education score.

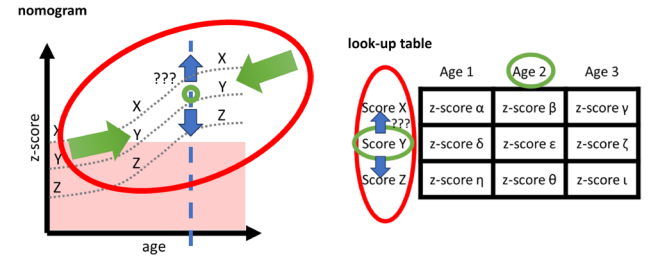
Step 3: select the age.

Nomogram	Look-up table



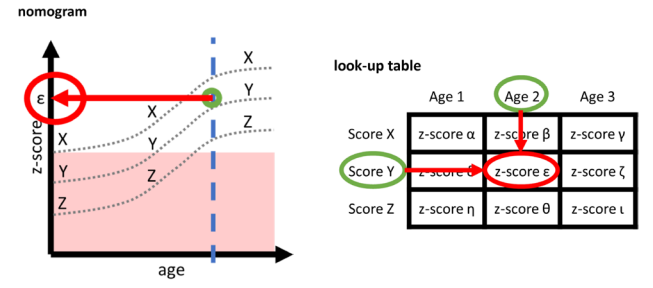
Step 4: select the score.

Nomogram	Look-up table



Step 5: read the *z*-score.

Nomogram	Look-up table



We provide an example of a nomogram (Figure 3) and a look-up table (Table 5) for the SDMT and a female subject with level 4 education. In the example of the female patient described above, aged 42 years, with education level 4, and reaching a raw score of 51 in the 90 s oral version of the SDMT, the patient would receive a z-score of −1.13 and would, by definition, not be impaired with regard to information processing speed.

TABLE 5 The *z*-score look-up table for SDMT, female gender and education score 4 (years of school ≥12, A-levels/university).

	Age, years																			
Score	18–21	22–25	26–29	30–33	34–37	38–41	42–45	46–49	50–53	54–57	58–61	62–65	66–69	70–73	74–77	78–81	82–85	86–89	90–93	94–97	98–101
26	−5.15	−5.05	−4.94	−4.80	−4.65	−4.47	−4.28	−4.06	−3.82	−3.57	−3.29	−3.00	−2.68	−2.34	−1.99	−1.61	−1.22	−0.80	−0.36	0.09	0.57
27	−4.62	−4.53	−4.41	−4.28	−4.12	−3.95	−3.75	−3.54	−3.30	−3.04	−2.77	−2.47	−2.16	−1.82	−1.46	−1.09	−0.69	−0.28	0.16	0.62	1.10
28	−4.62	−4.53	−4.41	−4.28	−4.12	−3.95	−3.75	−3.54	−3.30	−3.04	−2.77	−2.47	−2.16	−1.82	−1.46	−1.09	−0.69	−0.28	0.16	0.62	1.10
29	−4.62	−4.53	−4.41	−4.28	−4.12	−3.95	−3.75	−3.54	−3.30	−3.04	−2.77	−2.47	−2.16	−1.82	−1.46	−1.09	−0.69	−0.28	0.16	0.62	1.10
30	−4.10	−4.00	−3.89	−3.75	−3.60	−3.42	−3.23	−3.01	−2.78	−2.52	−2.24	−1.95	−1.63	−1.30	−0.94	−0.56	−0.17	0.25	0.69	1.14	1.62
31	−4.10	−4.00	−3.89	−3.75	−3.60	−3.42	−3.23	−3.01	−2.78	−2.52	−2.24	−1.95	−1.63	−1.30	−0.94	−0.56	−0.17	0.25	0.69	1.14	1.62
32	−4.10	−4.00	−3.89	−3.75	−3.60	−3.42	−3.23	−3.01	−2.78	−2.52	−2.24	−1.95	−1.63	−1.30	−0.94	−0.56	−0.17	0.25	0.69	1.14	1.62
33	−4.10	−4.00	−3.89	−3.75	−3.60	−3.42	−3.23	−3.01	−2.78	−2.52	−2.24	−1.95	−1.63	−1.30	−0.94	−0.56	−0.17	0.25	0.69	1.14	1.62
34	−3.57	−3.48	−3.36	−3.23	−3.07	−2.90	−2.70	−2.49	−2.25	−2.00	−1.72	−1.43	−1.11	−0.77	−0.42	−0.04	0.36	0.77	1.21	1.67	2.14
35	−3.57	−3.48	−3.36	−3.23	−3.07	−2.90	−2.70	−2.49	−2.25	−2.00	−1.72	−1.43	−1.11	−0.77	−0.42	−0.04	0.36	0.77	1.21	1.67	2.14
36	−3.57	−3.48	−3.36	−3.23	−3.07	−2.90	−2.70	−2.49	−2.25	−2.00	−1.72	−1.43	−1.11	−0.77	−0.42	−0.04	0.36	0.77	1.21	1.67	2.14
37	−3.57	−3.48	−3.36	−3.23	−3.07	−2.90	−2.70	−2.49	−2.25	−2.00	−1.72	−1.43	−1.11	−0.77	−0.42	−0.04	0.36	0.77	1.21	1.67	2.14
38	−3.57	−3.48	−3.36	−3.23	−3.07	−2.90	−2.70	−2.49	−2.25	−2.00	−1.72	−1.43	−1.11	−0.77	−0.42	−0.04	0.36	0.77	1.21	1.67	2.14
39	−3.57	−3.48	−3.36	−3.23	−3.07	−2.90	−2.70	−2.49	−2.25	−2.00	−1.72	−1.43	−1.11	−0.77	−0.42	−0.04	0.36	0.77	1.21	1.67	2.14
40	−3.05	−2.95	−2.84	−2.71	−2.55	−2.37	−2.18	−1.96	−1.73	−1.47	−1.20	−0.90	−0.59	−0.25	0.11	0.48	0.88	1.30	1.73	2.19	2.67
41	−3.05	−2.95	−2.84	−2.71	−2.55	−2.37	−2.18	−1.96	−1.73	−1.47	−1.20	−0.90	−0.59	−0.25	0.11	0.48	0.88	1.30	1.73	2.19	2.67
42	−3.05	−2.95	−2.84	−2.71	−2.55	−2.37	−2.18	−1.96	−1.73	−1.47	−1.20	−0.90	−0.59	−0.25	0.11	0.48	0.88	1.30	1.73	2.19	2.67
43	−3.05	−2.95	−2.84	−2.71	−2.55	−2.37	−2.18	−1.96	−1.73	−1.47	−1.20	−0.90	−0.59	−0.25	0.11	0.48	0.88	1.30	1.73	2.19	2.67
44	−2.53	−2.43	−2.32	−2.18	−2.03	−1.85	−1.66	−1.44	−1.20	−0.95	−0.67	−0.38	−0.06	0.27	0.63	1.01	1.40	1.82	2.26	2.71	3.19
45	−2.53	−2.43	−2.32	−2.18	−2.03	−1.85	−1.66	−1.44	−1.20	−0.95	−0.67	−0.38	−0.06	0.27	0.63	1.01	1.40	1.82	2.26	2.71	3.19
46	−2.53	−2.43	−2.32	−2.18	−2.03	−1.85	−1.66	−1.44	−1.20	−0.95	−0.67	−0.38	−0.06	0.27	0.63	1.01	1.40	1.82	2.26	2.71	3.19
47	−2.53	−2.43	−2.32	−2.18	−2.03	−1.85	−1.66	−1.44	−1.20	−0.95	−0.67	−0.38	−0.06	0.27	0.63	1.01	1.40	1.82	2.26	2.71	3.19
48	−2.53	−2.43	−2.32	−2.18	−2.03	−1.85	−1.66	−1.44	−1.20	−0.95	−0.67	−0.38	−0.06	0.27	0.63	1.01	1.40	1.82	2.26	2.71	3.19
49	−2.00	−1.91	−1.79	−1.66	−1.50	−1.33	−1.13	−0.92	−0.68	−0.43	−0.15	0.15	0.46	0.80	1.16	1.53	1.93	2.34	2.78	3.24	3.72
50	−2.00	−1.91	−1.79	−1.66	−1.50	−1.33	−1.13	−0.92	−0.68	−0.43	−0.15	0.15	0.46	0.80	1.16	1.53	1.93	2.34	2.78	3.24	3.72
51	−2.00	−1.91	−1.79	−1.66	−1.50	−1.33	−1.13	−0.92	−0.68	−0.43	−0.15	0.15	0.46	0.80	1.16	1.53	1.93	2.34	2.78	3.24	3.72
52	−2.00	−1.91	−1.79	−1.66	−1.50	−1.33	−1.13	−0.92	−0.68	−0.43	−0.15	0.15	0.46	0.80	1.16	1.53	1.93	2.34	2.78	3.24	3.72
53	−1.48	−1.38	−1.27	−1.13	−0.98	−0.80	−0.61	−0.39	−0.16	0.10	0.37	0.67	0.99	1.32	1.68	2.06	2.45	2.87	3.31	3.76	4.24
54	−1.48	−1.38	−1.27	−1.13	−0.98	−0.80	−0.61	−0.39	−0.16	0.10	0.37	0.67	0.99	1.32	1.68	2.06	2.45	2.87	3.31	3.76	4.24
55	−1.48	−1.38	−1.27	−1.13	−0.98	−0.80	−0.61	−0.39	−0.16	0.10	0.37	0.67	0.99	1.32	1.68	2.06	2.45	2.87	3.31	3.76	4.24
56	−1.48	−1.38	−1.27	−1.13	−0.98	−0.80	−0.61	−0.39	−0.16	0.10	0.37	0.67	0.99	1.32	1.68	2.06	2.45	2.87	3.31	3.76	4.24

(Continues)

TABLE 5 (Continued)

	Age, years																			
Score	18–21	22–25	26–29	30–33	34–37	38–41	42–45	46–49	50–53	54–57	58–61	62–65	66–69	70–73	74–77	78–81	82–85	86–89	90–93	94–97	98–101
57	−0.95	−0.86	−0.74	−0.61	−0.45	−0.28	−0.08	0.13	0.37	0.62	0.90	1.19	1.51	1.85	2.20	2.58	2.98	3.39	3.83	4.29	4.76
58	−0.95	−0.86	−0.74	−0.61	−0.45	−0.28	−0.08	0.13	0.37	0.62	0.90	1.19	1.51	1.85	2.20	2.58	2.98	3.39	3.83	4.29	4.76
59	−0.95	−0.86	−0.74	−0.61	−0.45	−0.28	−0.08	0.13	0.37	0.62	0.90	1.19	1.51	1.85	2.20	2.58	2.98	3.39	3.83	4.29	4.76
60	−0.95	−0.86	−0.74	−0.61	−0.45	−0.28	−0.08	0.13	0.37	0.62	0.90	1.19	1.51	1.85	2.20	2.58	2.98	3.39	3.83	4.29	4.76
61	−0.43	−0.34	−0.22	−0.09	0.07	0.24	0.44	0.66	0.89	1.15	1.42	1.72	2.03	2.37	2.73	3.10	3.50	3.92	4.35	4.81	5.29
62	−0.43	−0.34	−0.22	−0.09	0.07	0.24	0.44	0.66	0.89	1.15	1.42	1.72	2.03	2.37	2.73	3.10	3.50	3.92	4.35	4.81	5.29
63	−0.43	−0.34	−0.22	−0.09	0.07	0.24	0.44	0.66	0.89	1.15	1.42	1.72	2.03	2.37	2.73	3.10	3.50	3.92	4.35	4.81	5.29
64	−0.43	−0.34	−0.22	−0.09	0.07	0.24	0.44	0.66	0.89	1.15	1.42	1.72	2.03	2.37	2.73	3.10	3.50	3.92	4.35	4.81	5.29
65	0.09	0.19	0.30	0.44	0.59	0.77	0.96	1.18	1.41	1.67	1.95	2.24	2.56	2.89	3.25	3.63	4.02	4.44	4.88	5.33	5.81
66	0.09	0.19	0.30	0.44	0.59	0.77	0.96	1.18	1.41	1.67	1.95	2.24	2.56	2.89	3.25	3.63	4.02	4.44	4.88	5.33	5.81
67	0.09	0.19	0.30	0.44	0.59	0.77	0.96	1.18	1.41	1.67	1.95	2.24	2.56	2.89	3.25	3.63	4.02	4.44	4.88	5.33	5.81
68	0.62	0.71	0.83	0.96	1.12	1.29	1.49	1.70	1.94	2.19	2.47	2.77	3.08	3.42	3.77	4.15	4.55	4.96	5.40	5.86	6.33
69	0.62	0.71	0.83	0.96	1.12	1.29	1.49	1.70	1.94	2.19	2.47	2.77	3.08	3.42	3.77	4.15	4.55	4.96	5.40	5.86	6.33
70	0.62	0.71	0.83	0.96	1.12	1.29	1.49	1.70	1.94	2.19	2.47	2.77	3.08	3.42	3.77	4.15	4.55	4.96	5.40	5.86	6.33
71	0.62	0.71	0.83	0.96	1.12	1.29	1.49	1.70	1.94	2.19	2.47	2.77	3.08	3.42	3.77	4.15	4.55	4.96	5.40	5.86	6.33
72	0.62	0.71	0.83	0.96	1.12	1.29	1.49	1.70	1.94	2.19	2.47	2.77	3.08	3.42	3.77	4.15	4.55	4.96	5.40	5.86	6.33
73	1.14	1.24	1.35	1.49	1.64	1.82	2.01	2.23	2.46	2.72	2.99	3.29	3.61	3.94	4.30	4.67	5.07	5.49	5.92	6.38	6.86
74	1.14	1.24	1.35	1.49	1.64	1.82	2.01	2.23	2.46	2.72	2.99	3.29	3.61	3.94	4.30	4.67	5.07	5.49	5.92	6.38	6.86
75	1.14	1.24	1.35	1.49	1.64	1.82	2.01	2.23	2.46	2.72	2.99	3.29	3.61	3.94	4.30	4.67	5.07	5.49	5.92	6.38	6.86
76	1.14	1.24	1.35	1.49	1.64	1.82	2.01	2.23	2.46	2.72	2.99	3.29	3.61	3.94	4.30	4.67	5.07	5.49	5.92	6.38	6.86
77	1.67	1.76	1.88	2.01	2.17	2.34	2.54	2.75	2.99	3.24	3.52	3.81	4.13	4.47	4.82	5.20	5.60	6.01	6.45	6.91	7.38
78	1.67	1.76	1.88	2.01	2.17	2.34	2.54	2.75	2.99	3.24	3.52	3.81	4.13	4.47	4.82	5.20	5.60	6.01	6.45	6.91	7.38
79	2.19	2.28	2.40	2.53	2.69	2.86	3.06	3.28	3.51	3.77	4.04	4.34	4.65	4.99	5.35	5.72	6.12	6.54	6.97	7.43	7.91
80	2.19	2.28	2.40	2.53	2.69	2.86	3.06	3.28	3.51	3.77	4.04	4.34	4.65	4.99	5.35	5.72	6.12	6.54	6.97	7.43	7.91
81	2.19	2.28	2.40	2.53	2.69	2.86	3.06	3.28	3.51	3.77	4.04	4.34	4.65	4.99	5.35	5.72	6.12	6.54	6.97	7.43	7.91
82	2.71	2.81	2.92	3.06	3.21	3.39	3.58	3.80	4.03	4.29	4.57	4.86	5.18	5.51	5.87	6.25	6.64	7.06	7.50	7.95	8.43
83	2.71	2.81	2.92	3.06	3.21	3.39	3.58	3.80	4.03	4.29	4.57	4.86	5.18	5.51	5.87	6.25	6.64	7.06	7.50	7.95	8.43
84	2.71	2.81	2.92	3.06	3.21	3.39	3.58	3.80	4.03	4.29	4.57	4.86	5.18	5.51	5.87	6.25	6.64	7.06	7.50	7.95	8.43
85	2.71	2.81	2.92	3.06	3.21	3.39	3.58	3.80	4.03	4.29	4.57	4.86	5.18	5.51	5.87	6.25	6.64	7.06	7.50	7.95	8.43
86	2.71	2.81	2.92	3.06	3.21	3.39	3.58	3.80	4.03	4.29	4.57	4.86	5.18	5.51	5.87	6.25	6.64	7.06	7.50	7.95	8.43
87	2.71	2.81	2.92	3.06	3.21	3.39	3.58	3.80	4.03	4.29	4.57	4.86	5.18	5.51	5.87	6.25	6.64	7.06	7.50	7.95	8.43
88	2.71	2.81	2.92	3.06	3.21	3.39	3.58	3.80	4.03	4.29	4.57	4.86	5.18	5.51	5.87	6.25	6.64	7.06	7.50	7.95	8.43

TABLE 5 (Continued)

	Age, years																			
Score	18–21	22–25	26–29	30–33	34–37	38–41	42–45	46–49	50–53	54–57	58–61	62–65	66–69	70–73	74–77	78–81	82–85	86–89	90–93	94–97	98–101
89	2.71	2.81	2.92	3.06	3.21	3.39	3.58	3.80	4.03	4.29	4.57	4.86	5.18	5.51	5.87	6.25	6.64	7.06	7.50	7.95	8.43
90	2.71	2.81	2.92	3.06	3.21	3.39	3.58	3.80	4.03	4.29	4.57	4.86	5.18	5.51	5.87	6.25	6.64	7.06	7.50	7.95	8.43
91	3.24	3.33	3.45	3.58	3.74	3.91	4.11	4.32	4.56	4.81	5.09	5.39	5.70	6.04	6.39	6.77	7.17	7.58	8.02	8.48	8.95
92	3.24	3.33	3.45	3.58	3.74	3.91	4.11	4.32	4.56	4.81	5.09	5.39	5.70	6.04	6.39	6.77	7.17	7.58	8.02	8.48	8.95
93	3.24	3.33	3.45	3.58	3.74	3.91	4.11	4.32	4.56	4.81	5.09	5.39	5.70	6.04	6.39	6.77	7.17	7.58	8.02	8.48	8.95
94	3.24	3.33	3.45	3.58	3.74	3.91	4.11	4.32	4.56	4.81	5.09	5.39	5.70	6.04	6.39	6.77	7.17	7.58	8.02	8.48	8.95
95	3.24	3.33	3.45	3.58	3.74	3.91	4.11	4.32	4.56	4.81	5.09	5.39	5.70	6.04	6.39	6.77	7.17	7.58	8.02	8.48	8.95
96	3.24	3.33	3.45	3.58	3.74	3.91	4.11	4.32	4.56	4.81	5.09	5.39	5.70	6.04	6.39	6.77	7.17	7.58	8.02	8.48	8.95
97	3.24	3.33	3.45	3.58	3.74	3.91	4.11	4.32	4.56	4.81	5.09	5.39	5.70	6.04	6.39	6.77	7.17	7.58	8.02	8.48	8.95
98	3.24	3.33	3.45	3.58	3.74	3.91	4.11	4.32	4.56	4.81	5.09	5.39	5.70	6.04	6.39	6.77	7.17	7.58	8.02	8.48	8.95
99	3.24	3.33	3.45	3.58	3.74	3.91	4.11	4.32	4.56	4.81	5.09	5.39	5.70	6.04	6.39	6.77	7.17	7.58	8.02	8.48	8.95
100	3.24	3.33	3.45	3.58	3.74	3.91	4.11	4.32	4.56	4.81	5.09	5.39	5.70	6.04	6.39	6.77	7.17	7.58	8.02	8.48	8.95
101	3.24	3.33	3.45	3.58	3.74	3.91	4.11	4.32	4.56	4.81	5.09	5.39	5.70	6.04	6.39	6.77	7.17	7.58	8.02	8.48	8.95
102	3.24	3.33	3.45	3.58	3.74	3.91	4.11	4.32	4.56	4.81	5.09	5.39	5.70	6.04	6.39	6.77	7.17	7.58	8.02	8.48	8.95
103	3.76	3.86	3.97	4.11	4.26	4.44	4.63	4.85	5.08	5.34	5.61	5.91	6.23	6.56	6.92	7.29	7.69	8.11	8.54	9.00	9.48
104	3.76	3.86	3.97	4.11	4.26	4.44	4.63	4.85	5.08	5.34	5.61	5.91	6.23	6.56	6.92	7.29	7.69	8.11	8.54	9.00	9.48
105	3.76	3.86	3.97	4.11	4.26	4.44	4.63	4.85	5.08	5.34	5.61	5.91	6.23	6.56	6.92	7.29	7.69	8.11	8.54	9.00	9.48
106	3.76	3.86	3.97	4.11	4.26	4.44	4.63	4.85	5.08	5.34	5.61	5.91	6.23	6.56	6.92	7.29	7.69	8.11	8.54	9.00	9.48
107	3.76	3.86	3.97	4.11	4.26	4.44	4.63	4.85	5.08	5.34	5.61	5.91	6.23	6.56	6.92	7.29	7.69	8.11	8.54	9.00	9.48
108	3.76	3.86	3.97	4.11	4.26	4.44	4.63	4.85	5.08	5.34	5.61	5.91	6.23	6.56	6.92	7.29	7.69	8.11	8.54	9.00	9.48
109	4.29	4.38	4.49	4.63	4.78	4.96	5.16	5.37	5.61	5.86	6.14	6.43	6.75	7.09	7.44	7.82	8.21	8.63	9.07	9.53	10.00

Abbreviation: SDMT, Symbol Digit Modalities Test.

Limitations of nomograms and look-up tables

Concerning the mathematical precision of the nomograms and look-up tables, we need to be aware of a certain vagueness of the method in the sense that, for the nomograms, the index line or isopleth were chosen as a function of the raw score to scaled score conversion (Table 2). As the *z*-score formula relies on the scaled score, a small range of raw score values can lead to the same scaled value (e.g., SDMT scores of 57 or 59 will both result in a scaled score of 10). As this is a stepwise and not a continuous transformation, the nomograms should also be seen as a stepwise ladder; if the raw score is not one of the index lines or isopleths, the line with the highest score below the obtained raw score should be used (in our example you would not find 59, but would need to look at the score of 57; see Figure 3 for an illustration).

In the look-up tables, age was contracted by using age bins of 4 years to create a usable look-up table (Table 6). The value for these age bins is calculated using the middle of the age bin as reference, which may result in some error when looking at ages closer to the edges of the age bins. The maximal introduced error is calculated using the formula:

$$\widehat{\Delta\text{score}} = (\text{age} \pm 2) \times \beta_{\text{age}} + (\text{age} \pm 2)^2 \times \beta_{\text{age}^2}$$

Look-up tables and nomograms for all education levels and both genders are accessible and ready to use in routine clinical work Appendix S1. Look-up tables and nomograms provide the same information but illustrated differently, so that clinicians can decide which to use according to their own preference.

DISCUSSION

The present work was conducted to improve the current diagnostic process for pwMS who have cognitive impairment by providing age- and education-corrected norms so that the BICAMS battery can be applied in German-speaking countries.

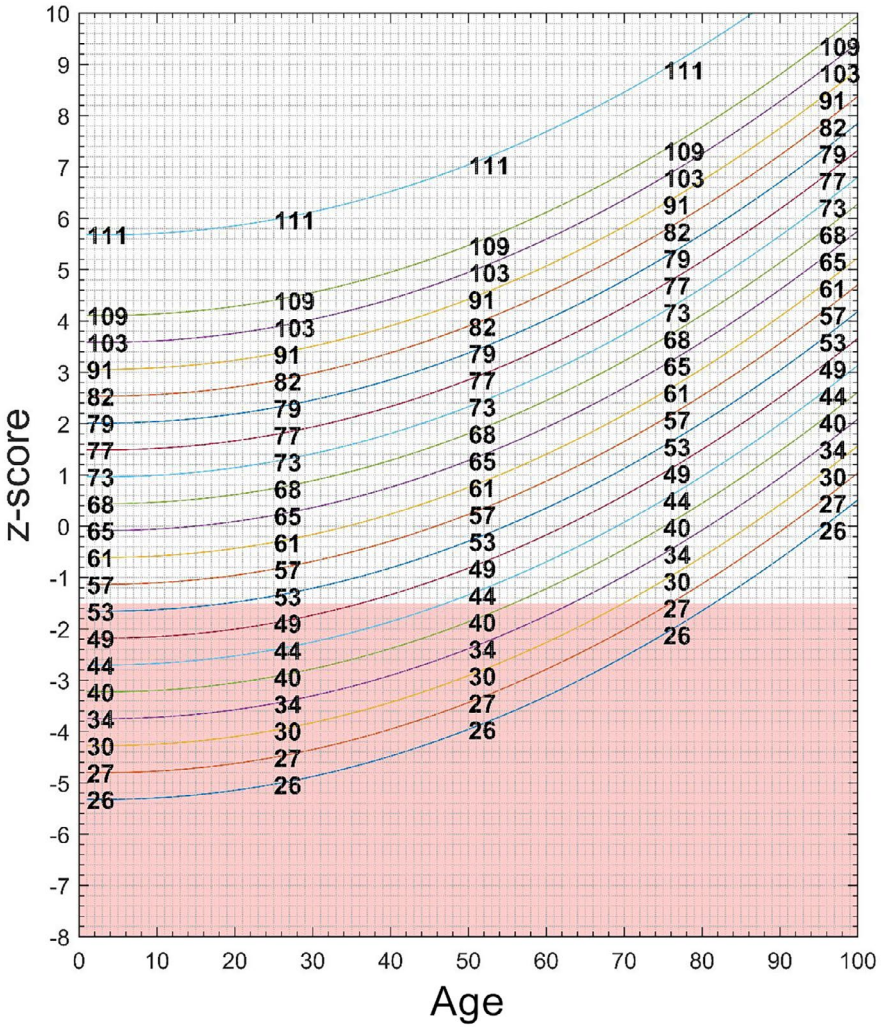


FIGURE 3 Nomogram for the Symbol Digit Modalities Test, for a female patient with education level 4 (years of school ≥12, A-levels/university).

TABLE 6 Maximal error within an age bin calculated for the different cognitive tests for various age bins.

	Age, years										
Cognitive test	**18–21**	**26–29**	**34–37**	**42–45**	**50–53**	**58–61**	**66–69**	**74–77**	**82–85**	**90–93**	**98–101**
SDMT	0.086	0.124	0.162	0.201	0.239	0.278	0.316	0.354	0.393	0.431	0.470
VLMT	0.200	0.171	0.142	0.113	0.084	0.056	0.027	0.009	0.038	0.067	0.096
BVMT-R	0.140	0.134	0.127	0.121	0.115	0.108	0.102	0.095	0.089	0.081	0.075

Abbreviations: BVMT-R, Brief Visual Memory Test-Revised; SDMT, Symbol Digit Modalities Test; VLMT, Verbaler Lern- und Merkfähigkeitstest.

BICAMS was introduced in 2012 [4] as a sensitive and user-friendly screening tool for daily routine application in MS care. In reality, however, neurologists still focus on the EDSS as the major component of the established neurological diagnostic process and, in so doing, disregard the fact that cognition is not sufficiently captured by this standard neurological assessment tool. The EDSS is the standard method of measuring the impact of MS during the neurological clinical examination [19]. It is calculated in a somewhat convoluted manner, based on functional systems and ambulation ability (see neurostatus.net, neurostatus scoring definitions version 04/10.2). Only one of the seven functional systems (cerebral or mental functions) used in the calculation takes cognition into account, and this is based purely on a subjective clinician impression, with a classification of either 'normal'; 'mood alteration only'; 'mild'; 'moderate or marked decrease in mentation'; or 'dementia'. This explains why the main determinant of the EDSS is physical ability, and also explains the discussion and related doubt about the existence of purely cognitive relapses. The latter was eventually resolved by a prospective multicentre study showing multiple occurrences of a significant decrease in SDMT score *without* any change in EDSS score [20]. These findings may have increased the willingness of neurologists to additionally apply neuropsychological screening tests during their consultation hours, but so far regular implementation has not been achieved [21]. The reasons for this are manifold. In German-speaking countries (Germany, Switzerland and Austria), for example, clinicians see a large number of patients during their consultation hours, and time is already very limited. Within this limited time, many issues need to be addressed, including talking to the patient about their experiences in the interval between consultations, documenting disease signs during the neurological examination, evaluation of effects and side effects of treatment, interpreting follow-up brain and spinal cord magnetic resonance imaging, planning further treatment and follow-up, discussing these elements with patients and the family members they bring along, completing diverse administrative forms, prescribing disease-modifying and symptomatic medication and producing letters for referrers. In addition, appropriate reimbursement for neuropsychological screenings is often not given.

Despite these circumstances, awareness of the value of neuropsychological data in the context of MS diagnosis and long-term monitoring of pwMS has increased [22]. As the number of practising clinical neuropsychologists is not sufficient to provide patients with prompt neuropsychological examinations [23], screening by neurologists would at least allow monitoring of cognitive status on a more regular basis. BICAMS was developed precisely for this purpose [4] and now needs further promotion to become an integral component of standard clinical care.

With this aim, we collected normative data on BICAMS on a large number of healthy German-speaking control subjects and have provided easily applicable age- and education-corrected look-up tables and nomograms for the three neuropsychological tests to be used in standard clinical care. This will also help to convince clinicians that the application of one single test (most often the SDMT) is insufficient. Neurologists tend to select only one short screening test if they include cognitive assessment in their evaluation at all. For many years this single measure was the Paced Auditory Serial Addition Test (PASAT), which was included in a proposed composite outcome measure for clinical trials, the MS functional composite (MSFC), designed to replace the EDSS with a three-dimensional measure including the timed 25-foot-walk test and 9-hole peg test, next to the PASAT [24]. In recent years, the SDMT has replaced the PASAT for reasons of tolerability, handling and sensitivity. While the SDMT is certainly one of the most sensitive test measures to assess cognitive processing speed in MS [12, 25] and is the test most often recommended [26], it only captures one, albeit very relevant, cognitive domain and does not allow any conclusions to be drawn about the cognitive profile or cognitive ability of a person per se [27]. Moreover, in the context of BICAMS it has convincingly been shown in a study by Bätge et al. that single application of the SDMT is insufficient to obtain a reliable picture of the cognitive status of patients and that a two-test combination (SDMT and BVMT-R) at least, or preferably the complete BICAMS battery, should be considered [28].

The provision in this study of normative data for the three subtests of BICAMS might reduce the barriers to application of more than one neuropsychological test. Up to now, those normative values have not been available for German-speaking countries, leading to the need to transform raw values either to age- and education-corrected *z*-values or to rely on normative data from other countries, which has led to a critical attitude towards the regular use of BICAMS.

In summary, the present study could lead to a significant increase in the regular use of BICAMS in daily clinical routine by providing users with age- and education-corrected nomograms and look-up tables. With this tool it will be possible for clinicians to quickly detect whether a patient deviates from the norm in processing speed as well as in verbal and visuo-spatial short-term

memory and learning, or not. The tool also allows for single test evaluation if, for convincing reasons, only one domain is to be assessed.

This study has some flaws. We acknowledge the substantial heterogeneity in our sample regarding age and education level. Specifically, our sample includes a high concentration of participants in the younger (20–29 years) and older (50–69 years) age groups, with a relatively low number of middle-aged participants (30–49 years). This age distribution may affect the generalizability of our findings to all individuals with MS in German-speaking countries. The underrepresentation of subjects with lower education levels further limits the applicability of our results. However, we note that there is a societal trend towards higher education levels, as evidenced by similar normative studies [29, 30].

Despite these limitations, we assume that the effect of age on cognitive function within the 20- to 60-year age range would follow a linear trajectory, based on established observations in cognitive aging literature [31]. Therefore, the lack of middle-aged participants should not significantly compromise the validity of our linear model. Furthermore, our sample probably reflects the demographics of patients typically attending specialized MS clinics, which often attract younger patients recently diagnosed with MS and older patients managing long-term symptoms, as well as individuals with higher educational attainment.

AUTHOR CONTRIBUTIONS

I. K. Penner: Conceptualization; investigation; funding acquisition; writing – original draft; methodology; writing – review and editing; visualization; formal analysis; supervision; project administration; validation; software; resources. **J. Baijot:** Writing – original draft; methodology; visualization; writing – review and editing; software; formal analysis; validation. **M. Filser:** Investigation; writing – review and editing. **S. Bätge:** Investigation; writing – review and editing. **L. Raithel:** Investigation; writing – review and editing. **E. Toth:** Investigation; writing – review and editing. **A. Renner:** Investigation; writing – review and editing. **G. Nagels:** Methodology; writing – original draft; visualization; writing – review and editing; software; formal analysis; validation.

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CONFLICT OF INTEREST STATEMENT

I. K. Penner declares honoraria for speaking at scientific meetings, serving at scientific advisory boards and consulting activities from Adamas Pharma, Almirall, Bayer Pharma, Biogen, Celgene, Sanofi-Genzyme, Janssen, Merck, Novartis, Roche and Teva, and research support from the German MS Society, Celgene, Novartis, Roche and Teva. Guy Nagels is supported by a personal grant appointed by the Fonds Wetenschappelijk Onderzoek (FWO), Flanders (1805620N) and is a shareholder in icometrix, a company providing tools to support clinical care. The other co-authors have nothing to disclose.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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