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Original Article

Automated Computerized Neuropsychological Diagnostics in Multiple Sclerosis

Evaluating the MAT-COBI as a Screening Tool

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Abstract: Cognitive deficits are common in multiple sclerosis (MS), necessitating diagnosis and constant monitoring. However, frequent neuropsychological assessments are costly and not always feasible. A computerized assessment of basic cognitive functions could contribute to better patient care in this regard. The primary cognitive inventory of the Memory and Attention Test (MAT-COBI) constitutes such a tool. In this feasibility study, we tested $N = 44$ patients with MS with a standardized neuropsychological assessment consisting of established screening procedures (Brief International Cognitive Assessment in MS [BICAMS] and Brief Repeatable Battery [BRB] and three subtests of the Test Battery of Attentional Performance (TAP). The results of these procedures were considered a gold standard for assessing which patients were cognitively impaired or cognitively unaffected. We also administered the MAT-COBI and compared the results to the gold standard. While the results of an exploratory correlation analysis pointed toward the interpretation that the the MAT-COBI adequately operationalized the basic cognitive domains of attention, memory, and executive, sensitivity was insufficient (32.3 %), while specificity reached 92.3 %. A closer look at the single cognitive domains showed marginal differences across domains (sensitivity ranged from 0–24 %, specificity: 89.5 %-100 %). Based on these results, the MAT-COBI does not appear to be a suitable tool for differentiating between cognitively preserved and cognitively impaired patients with MS. We discuss possible explanations and implications for automated cognitive diagnostics.

Keywords: multiple sclerosis, cognitive screening, BRB, BICAMS, computerized assessment

Automatisierte computergestützte neuropsychologische Diagnostik bei Multipler Sklerose: Evaluation des MAT-COBI als Screeninginstrument

Zusammenfassung: Kognitive Beeinträchtigungen sind ein häufiges Symptom der Multiplen Sklerose (MS), deren Diagnose und Monitoring eine bedeutende Rolle zukommt. Regelmäßige neuropsychologische Untersuchungen sind jedoch kostenintensiv und nicht in jedem Behandlungssetting durchführbar. Eine automatisierte computerisierte Erfassung grundlegender kognitiver Funktionen könnte hier einen wichtigen Beitrag zur Verbesserung der Versorgungssituation leisten. Das kognitive Basisinventar des Merkfähigkeits- und Aufmerksamkeitstests (MAT-COBI) bietet diese Möglichkeit. $N = 44$ Patient_innen mit MS erhielten eine neuropsychologische Diagnostik bestehend aus den etablierten Screeningverfahren Brief International Cognitive Assessment for MS (BICAMS), Kurzform der Brief Repeatable Battery (BRB) sowie drei Untertests der Testbatterie zur Aufmerksamkeitsprüfung (TAP). Die Ergebnisse dieser Verfahren wurden als „Goldstandard" für die Differenzierung von kognitiv beeinträchtigten und kognitiv unbeeinträchtigten Patient_innen herangezogen. Die Patient_innen absolvierten darüber hinaus den MAT-COBI. Die Ergebnisse des MAT-COBI wurden mit dem Goldstandard verglichen. Während die Ergebnisse einer explorativen Korrelationsanalyse darauf hindeuteten, dass die grundlegenden kognitiven Domänen Aufmerksamkeit, Gedächtnis und Exekutivfunktionen im MAT-COBI angemessen operationalisiert wurden, erwies sich die Sensitivität als unzureichend (32.3 %), die Spezifität erreichte einen Wert von 92.3 %. Eine genauere Betrachtung der einzelnen kognitiven Domänen zeigte dabei nur leichte Unterschiede über die einzelnen Domänen hinweg (Sensitivität: 0–24 %; Spezifität: 89.5–100 %). In Anbetracht der Ergebnisse muss konstatiert werden, dass sich der MAT-COBI in seiner vorliegenden Form nicht für die Differenzierung von kognitiv beeinträchtigten und kognitiv unbeeinträchtigten Patient_innen mit MS eignet. Mögliche Gründe hierfür sowie sich ergebende Implikationen für die automatisierte Erfassung kognitiver Defizite werden diskutiert.

Schlüsselwörter: Multiple Sklerose, kognitives Screening, BRB, BICAMS, computergestützte Diagnostik

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Introduction

Multiple sclerosis (MS) is one of the most common neurological disorders. Besides the physical disabilities, cognitive deficits are among the most common symptoms, with a prevalence of 43–72% (Chiaravalloti & DeLuca, 2007; Hansen & Lautenbacher, 2017), the severity of which are subject to substantial interindividual differences. Attention deficits are frequently observed and may range from a slight reduction in information processing speed to extensive impairments in different complex attentional systems such as executive attention control (Hansen & Lautenbacher, 2017). Memory functions are often also affected. Recall and recognition are usually intact, whereas the reception and encoding of information are more prone to be compromised in MS (DeLuca et al., 2014). Finally, executive functions are also frequently affected (Hansen et al., 2017) which may apply to several subdomains such as working memory, fluency, or cognitive flexibility (see Hansen & Lautenbacher, 2017, for an overview). On the other hand, general intellectual abilities are usually unimpaired in persons with MS (pwMS).

Since MS often manifests during early adulthood and cognitive impairments tend to manifest early during the course of the disease, the timely assessment and regular monitoring of cognitive function play an important role in disease management (Gold, 2012). This reasoning arises from the fact that cognitive impairments may negatively interfere with cognitively demanding tasks such as employment, vocational training, or academic studies (Flachenecker et al., 2008; Widder, 2009). However, they may also negatively affect other daily activities such as leisure activities or social interactions (Weber et al., 2019).

Nonetheless, a detailed assessment of cognitive functions is often not feasible during clinical routine, which may be ascribed to limited staff and time resources but also a lack of knowledge concerning the involved procedures. To assess the cognitive status of pwMS, widely applied screening procedures such as the Mini-Mental Status Examination (MMSE) (Folstein et al., 1975) or even the somewhat more elaborate Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005) are unsuitable, largely because ceiling effects are easily attained as pwMS may often display only relatively discrete cognitive impairments (Beatty & Goodkin, 1990; Rosca & Simu, 2020). Suitable screening procedures include the Brief Repeatable Battery (BRB; Rao, 1990) or the Brief International Cognitive Assessment in MS (BICAMS; Langdon et al., 2012). Also, because attention deficits are common in MS, computerized assessments such as the Test Battery of Attentional Performance (TAP; Zimmermann & Fimm, 2020) should be considered appropriate to evaluate cognitive performance. A minimal assessment should include the primary attentional domains of intensity and selectivity as well as divided attention (Hansen & Lautenbacher, 2017). However, these procedures require an elaborate initialization and are noticeably more time-consuming than MMSE or MoCA. Also, interpretation of results – especially in marginal cases – requires a certain amount of neuropsychological expertise.

A possible solution in such cases where standardized neuropsychological assessment is otherwise not feasible might be implementing computerized testing procedures, which are noticeably gaining popularity in the assessment of cognitive impairment in pwMS. A recent systematic review identified several of these procedures as having the potential to effectively screen for cognitive impairment (Wojcik et al., 2019). Among them, the Memory and Attention Test (MAT; Adler, Bektas & Eisele, 2008) stands out as it offers the possibility to test a patient without resorting to the resources of clinical personnel at any time during the process, i.e., the test is automated. Once a patient has been introduced to the test and the procedure initiated, further explanations are driven by the program and require no external interference. The program was originally developed in dementia diagnostics (Adler et al., 2012) and has proven to be sufficiently self-explanatory in this context. However, in recent years, its scope has been extended (Adler et al., 2015), including its application in other indications, among others MS (Adler & Lembach, 2015). Also, a shortened version of the MAT (Cognitive Basic Inventory – MAT-COBI) is now available, reducing the duration of testing to approximately 40 minutes and thus qualifying as a screening tool. Furthermore, since the MAT-COBI covers the three primary cognitive domains attention, memory, and executive function that tend to be susceptible to impairment in pwMS, one may suggest that it is suitable for cognitive screening in the context of MS.

The current study therefore evaluates whether the MAT-COBI has the potential to serve as a computerized, largely automated screening tool for identifying cognitive impairment in pwMS.

Materials and Methods

Participants

The ethics committee of the University of Bamberg, Germany, approved the current work. $N = 44$ patients participated in the study, all of whom provided written informed consent to participate before study entry. The patients were recruited during their stay at the Klinikum Bayreuth GmbH, and testing took place during the routine clinical process. Patients had to have a verified diagnosis of MS

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(either relapsing remitting or primary/secondary chronic progressive forms) according to the revised McDonald criteria (Thompson et al., 2018). They were eligible for study entry if between 18 and 75 years. Exclusion criteria involved (1) exacerbation of symptoms during the last 4 weeks, (2) corticosteroid treatment within the last 4 weeks, (3) severe cognitive disabilities, making it impossible to give written informed consent, and (4) severe motor or visual impairments interfering with participating in some of the applied procedures.

Procedure

The neuropsychological assessment was conducted during the routine clinical process. Patients were tested in a quiet, adequately lighted room devoid of distracting objects. Besides the patient and the therapist, no one else was present during testing. Three psychologists (LW, JK, SH) with an average postgraduate work experience in neurology of M = 6.6 years (SD = 3.2) were engaged in obtaining the data for the current project. This occurred under the continuous supervision of a certified clinical neuropsychologist (SH), who was also authorized for clinical training based on regulations of the German Society of Neuropsychology (GNP).

Neuropsychological Assessment

The neuropsychological assessment included the two most widely-used cognitive screening procedures for pwMS, i.e., BRB and BICAMS, as well as a number of subtests from the TAP. We also applied the MAT-COBI. A detailed description of each procedure can be found below. Table 1 summarizes the complete assessment, where an allocation of procedures to underlying cognitive domains can also be retraced. In many aspects, the neuropsychological assessment applied is congruent with the proposed extensive test battery for pwMS by Hansen and Lautenbacher (2017) and the Minimal Assessment of Cognitive Function in MS (MACFIMS) by Benedict et al. (2006), since BRB and BICAMS together constitute the largest part of the MACFIMS, toward which the extensive test battery proposed by Hansen and Lautenbacher (2017) is also oriented. We did, however, omit several tests concerning executive function. This rationale occurred mainly because of time constraints, as we tried to keep the assessments duration from exceeding 2 hours to reduce potential effects of fatigue. The assessment took place in a fixed order, beginning with the procedures from the BRB, then the BICAMS and the TAP, and concluding with the MAT-COBI. The Symbol Digit Modalities Test (SDMT) is part of both the BRB and BICAMS and was not

Table 1. Neuropsychological assessment

Test/screening battery	Subtests	Cognitive domain
Brief Repeatable Battery (BRB), short form	Symbol Digit Modalities Test (SDMT)	Attention, information processing speed
	Paced Auditory Serial Addition Test (PASAT)	Verbal working memory, information processing speed
	Selective Reminding Test (SRT)	Verbal memory
Brief International Cognitive Assessment in MS (BICAMS)	Symbol Digit Modalities Test (SDMT)	Attention, information processing speed
	Brief Visuospatial Memory Test (BVMT-R)	Nonverbal memory
	California Verbal Learning Test (CVLT)	Verbal memory
Test Battery of Attentional Performance (TAP)	Alertness	Attentional intensity/alertness
	Go/NoGo 1/2	Selective attention/response inhibition
	Divided Attention	Selective attention/executive attention control
Memory and Attention Test – Cognitive Basic Inventory (MAT/COBI)	Attention	Attention
	Executive Function	Inhibition, cognitive flexibility
	Episodic Working Memory	Verbal working memory
	Episodic Short-Term Memory	Verbal memory

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conducted twice, but only once at the beginning of the assessment. The assessment took approximately 2 hours to complete.

Short Form of the Brief Repeatable Battery (BRB)

The Symbol Digit Modalities Test (SDMT) (Benedict et al., 2017): The SDMT assesses information processing speed and attention. Patients must verbally pair numbers and symbols according to a fixed pattern. The outcome score is the number of pairings correctly solved within 90 s.

The Paced Auditory Serial Addition Test (PASAT) (Tombaugh, 2006): The PASAT addresses information processing speed and working memory. Several variants of the PASAT exist. In the variant employed in the BRB, an audio recording of 60 numbers is played to the patient with an interstimulus interval (ISI) of 3 s. The patient must add each currently presented number to the one immediately preceding it and name the result. The performance score is the number of correct calculations.

The Selective Reminding Test (SRT) (Buschke & Fuld, 1974): A test assessing verbal learning and memory, the SRT involves the presentation of a maximum of six trials of a 12-item word list. After the first trial, the examiner only presents those words not recalled on the immediately preceding trial. Presentation is discontinued once a patient has recalled all words from the list on two consecutive trials. Two parameters are considered: (1) long-term storage (LTS): A word is assumed to enter LTS once it has been recalled on two consecutive trials; (2) consistent long-term retrieval (CLTR): If a word is not reported on consecutive trials, it is then assumed that the patient has failed to retrieve it. Only if a word is recalled consistently until the last trial, it is scored under CLTR.

Brief International Cognitive Assessment for MS (BICAMS)

The Symbol Digit Modalities Test (SDMT): see BRB.

The Brief Visuospatial Memory Test (BVMT) (Benedict, 1997): The BVMT assesses learning of a 2×3 array of abstract geometrical shapes. There are three learning trials, where this array is presented for 10 seconds each. After each learning trial, the array is removed and patients have to draw the correct shapes at the correct position (Langdon et al., 2012). Outcome parameters are the number of correctly reproduced shapes in each trial as well as an overall score.

The California Verbal Learning Test (CVLT) (Niemann et al., 2008): Another test assessing verbal learning and memory, the CVLT consists of a 16-item word list that must be memorized over five learning trials. After the presentation of an interference list, a free-recall trial ensues. Only a few of the various computable parameters were included in this study, namely, the number of items recalled in the first and final trials, overall learning, and free recall after interference.

The Test Battery of Attentional Performance [Testbatterie zur Aufmerksamkeitsprüfung] TAP) (Zimmermann & Fimm, 2020):

Alertness: Motor response times were measured in two conditions. First, patients responded to a cross appearing in the middle of the screen (variable ISI) by pressing a button as quickly as possible (basic attentional intensity, intrinsic alertness). In the second condition, the appearance of the cross was preceded by a warning tone. The latter condition assesses the capability to focus attention on an anticipated event (phasic alertness).

Go-Nogo: Motor response times and response accuracy were measured in the context of a selective response task. Patients were required to press a button in response to a predefined visual target stimulus, while a response had to be inhibited in case of the appearance of a noncritical visual stimulus. The test addresses selective attention and response inhibition.

Divided Attention: This measures motor response times and response accuracy during a task in which visual and auditory stimuli was continuously monitored simultaneously. Patients pressed a button as quickly as possible in the case that randomly moving crosses displayed on a screen formed a square, as well as when a homogeneous sequence of alternating high- and low-pitched tones was interrupted by the consecutive appearance of two tones of the same pitch.

The Memory and Attention Test – Cognitive Basic Inventory [Merkfähigkeits- und Aufmerksamkeitstest – kognitives Basisinventar (MAT-COBI)] (Dynamikos GmbH):

Episodic working memory: Encyclopedia articles of varying degrees of complexity were read to the patient. Directly following that, the patient answered several yes/no questions concerning the previously presented article. The parameter MAT-W represents the number of correct responses in this subtest.

Episodic short-term memory: Short stories with a varying degree of complexity were read to the patient. Following a visual distractor task, the patient answered several yes/no questions concerning the previously presented story. The parameter MAT-S is the number of correct responses in this task.

Attention: Geometrical shapes of differing complexity had to be evaluated regarding deviations from a template. Thus, this test may be considered to assess selective (executive) attention. The base rate of deviation is 20 %. Speed and accuracy of responses were evaluated for three different levels of complexity, yielding an overall performance score for each level (D1, D2, D3).

Executive function: Three different geometrical shapes were displayed in random order. Each shape was associ-

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ated with a specific required response. Besides overall performance (MAT-EX), three parameters can be calculated from the performance in this task: Flexibility (MAT-FL) assesses the ability to shift between response types for varying shapes; endurance (MAT-EN) represents the ability to stick to a currently applying rule in a series of congruent items; and inhibition (MAT-IN) is the ability to inhibit a response if indicated by the appropriate shape.

Statistical Analyses

All statistical analyses were calculated with SPSS 22.0 (IBM).

Several evaluations were implemented to determine the suitability of the MAT-COBI as a tool for cognitive screening in MS. First, descriptive, exploratory two-sided Pearson correlations for all cognitive parameters were computed. Second, estimates of sensitivity and specificity of the MAT-COBI were calculated using crosstabulations. The aggregated results of the extensive neuropsychological testing procedure (short form of the BRB, BICAMS, TAP) served as a gold standard for this evaluation. This procedure is in line with previous studies concerning evaluating the predictive value of cognitive screening tools in MS (Hansen et al., 2015, 2017; Portaccio et al., 2009).

Sensitivity and specificity were derived for several configurations. First, the three underlying different cognitive domains addressed by the extensive testing procedure as well as the MAT-COBI were considered. The three different cognitive domains were conceptualized as attention, memory, and executive function/information processing. Table 2 displays in detail which test parameters were assorted to these domains. Sensitivity and specificity of a respective MAT-COBI subtest in predicting impairment in a corresponding domain of the extensive testing procedure were then determined. A domain of the extensive testing procedure was considered impaired if scores on two or more parameters belonging to that domain fell below the threshold of a percentile rank (PR) < 16. Second, test results of the MAT-COBI as a whole were matched against total results of the extensive test battery, a patient being considered impaired if at least one cognitive domain fell beneath the threshold described above, respectively.

Table 2. Allocation of variables of the MAT-COBI and the extensive testing procedure to cognitive domains

Cognitive domain	MAT-COBI parameters	Extensive testing procedure parameters
Attention	Attention, difficulty level 3	TAP-Alertness, intrinsic
		TAP-Alertness, phasic
		TAP-Go/NoGo 1/2
		TAP-divided attention, auditive
		TAP-divided attention, visual
Memory	Episodic short-term memory	SRT-Long Term Storage
		SRT-Consistent Long Term Retrieval
		CVLT-Trial 1
		CVLT-Trial 5
		CVLT-overall learning
		CVLT-recall after interference
		BVMT-overall learning
Information processing speed/executive function	Episodic working memory	PASAT
		TAP-divided attention, omissions
		SDMT
		BVMT-Trial 1

Notes. BVMT: Brief Visuospatial Memory Test; CVLT: California Verbal Learning Test; MAT/COBI: Memory and Attention Test – Cognitive Basic Inventory; PASAT: Paced Auditory Serial Addition Test; SDMT: Symbol Digit Modalities Test; SRT: Selective Reminding Test; TAP: Test Battery of Attentional Performance.

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Results

Study Population

Table 3 reviews the demographic and clinical information of the study sample. The ratio of patients suffering from secondary progressive variant MS was relatively high (43.18%), which is in line with the relatively high mean disease duration (*M*: 13.5 years). Approximately two-thirds of the study sample were female (31/44). Educational degrees were divided approximately equally between the three basic German graduation certificates. Most patients (86.36%) were receiving disease-modifying therapy.

Descriptive Intercorrelations

The electronic supplementary material [ESM] 1 displays the results of the descriptive intercorrelations.

Concerning the attention-domain parameters of the MAT-COBI, significant correlations were found for the attention task (difficulty level 3) with SDMT ($r = .409^{**}$) as well as parameters of the divided attention-task of the TAP (visual response times: $r = -.471^{**}$; auditory response times: $r = -.403$), and also response times on the intrinsic alertness test of the TAP ($r = .330^{*}$). Out of the attentional domain, significant correlations were also found with several parameters of the memory domain (CVLT-total learning: $r = .324^{*}$; CVLT-recall: $r = .351^{*}$; BVMT-Trial 1: $r = .338^{*}$). The other difficulty levels of the attention task showed markedly less significant (Level 2) or no significant (Level 1) correlations with other parameters of the extensive assessment.

Initially, the episodic working memory and the episodic short-term memory parameters of the MAT-COBI were assorted to the memory domain. While the short-term memory parameter showed several significant correlations with other parameters of the neuropsychological assessment (SRT-LTS: $r = .503^{**}$; SRT-CLTR: $r = .576^{**}$; CVLT-Trial 5: $r = .531^{**}$; CVLT-overall learning: $r = .500^{**}$; CVLT-recall: $r = .542^{**}$; BVMT-overall learning: $r = .429^{**}$) and also significantly correlated with the SDMT ($r = .457$) and the PASAT ($r = .340^{*}$), the working-memory parameter only correlated with BVMT-overall learning ($r = .396^{**}$) within the memory domain. However, correlations with parameters from other domains were also found for the working-memory parameter of the MAT-COBI. Concerning attention, this was SDMT performance ($r = .365^{**}$). In the domain of executive functions, MAT-COBI working memory also correlated with the PASAT ($r = .318^{*}$).

Finally, executive function parameters of the MAT-COBI included flexibility, endurance, and inhibition as well as an overall-performance parameter. Concerning the latter, significant correlations were found with the PASAT ($r = .443^{**}$) as well as with several memory (SRT-LTS: $r = .374^{*}$; SRT-CLTR: $r = .369^{*}$; CVLT-Trial 5: $r = .328^{*}$; BVMT-overall learning: $r = .378^{*}$) and attention parameters (SDMT: $r = .315^{*}$). The other MAT-COBI executive function parameters showed significant correlations among each other and especially with the overall parameter (MAT-flexibility: $r = .968^{**}$; MAT-endurance: $r = .967^{**}$; MAT-inhibition:

Table 3. Demographical and clinical characteristics of the sample

Sex	Male/female (*N*)	13/31	
Age (years)	(*M*/*SD*/Md/R)	52.1/10.4 /52.5/28–71	
MS-type	RRMS	22	50.00%
	SPMS	19	43.18%
	PPMS	3	6.82%
EDSS	(*M*/*SD*/Md/R)	4.8/2.1/4.0/1.0–8.5	
Disease duration (years)	(*M*/*SD*/Md/R)	13.5/9.6/11.0/0.1–35.0	
Education	HS	14	31.82%
	MR	18	40.91%
	Abi	12	27.27%
Disease-modifying	Yes	38	86.36%
Therapy	No	6	13.64%

Notes. RRMS: relapsing-remitting MS; SPMS: secondary progressive MS; PPMS: primary progressive MS; HS: Hauptschule; MR: Mittlere Reife; Abi: Abitur; *M*: mean; Md: median; R: range; *SD*: standard deviation.

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.719**) as well as with select other parameters from other cognitive domains. However, because no normative data exist for these parameters as of yet, their relevance for determining the predictive value of the MAT-COBI in further data analysis is limited.

Overall, the parameters of the MAT-COBI showed significant intercorrelations with such parameters of the extensive neuropsychological testing procedure which assessed similar cognitive domains. This finding points toward a sufficient convergent validity of the MAT-COBI parameters with the parameters of the extensive testing procedure.

Crosstabulation

We examined the predictive value of the MAT-COBI in comparison to the gold standard of the extensive neuropsychological assessment. In particular, we used crosstabulations to calculate sensitivity, specificity, and accuracy, implementing these calculations in two steps: First, we calculated a separate analysis of the predictive value for the three cognitive domains attention, memory, and executive function; second, we also calculated sensitivity, specificity, and accuracy for a global cognition parameter including all cognitive domains.

We then aligned the parameters of the MAT-COBI to the parameters of the extensive neuropsychological assessment, based on hypothetical assumptions concerning the underlying cognitive domains. These were supported by the results of the descriptive intercorrelations. We excluded some parameters of the extensive testing procedure because of redundancies, ambiguities, or reduced interpretability. Similarly, not all parameters of the MAT-COBI proved to be meaningful in the previous statistical analyses. Therefore, we chose only one parameter of the MAT-COBI to represent each cognitive domain. The parameters in question exhibit a sufficient proximity to their respective cognitive domains, both regarding statistical aspects and content. Table 2 provides an overview of the allocation of parameters to cognitive domains for the analyses of the predictive value. Because the executive function parameters of the MAT-COBI currently lack normative data, they could not be included as a binary variable (cognitively impaired: Yes/No) in the crosstabulations. Therefore, we chose the working memory parameter of the MAT (MAT-W) to represent executive functions.

We considered patients cognitively impaired if they met the following criteria:

1. A result was generally considered impaired if patients scored a percentile rank (PR) of <16 on that parameter.
2. MAT-COBI: A cognitive domain was considered impaired in case a PR of <16 on the test parameter aligned with the domain in question. A patient was considered impaired on the global cognition parameter if at least one cognitive domain was impaired.
3. Extensive testing procedure (gold standard): Because of the relatively larger number of test parameters, at least two test parameters of a cognitive domain had to fall below PR 16 for this domain to be considered cognitively impaired. Analogous to the MAT-COBI, a patient was considered impaired on the global cognition parameter if at least one cognitive domain was impaired.

Table 4 displays the results of the crosstabulations, including sensitivity, specificity, and accuracy of the MAT-COBI compared to the extensive testing procedure. The specificity of the MAT-COBI proved to be very high in all cognitive domains and the global cognition parameter (specificity: 89.5–100 %). This implies almost no false-positive classifications because of the MAT-COBI. At the same time, the sensitivity of the MAT-COBI turned out to be very low compared to the gold standard, reaching 24 % and 15 %, respectively, in the attentional and executive function domains. Furthermore, it failed to identify any cognitively impaired patients in the memory domain. The results were somewhat improved for the global cognition parameter, where the MAT-COBI reached a sensitivity of 32.3 %. The overall accuracy for the global cognition parameter reached a value of 50 %.

In summary, the results of the crosstabulations pointed toward a limited sensitivity and specificity of the MAT-COBI compared to the extensive neuropsychological assessment employed in our study.

Additional Analysis

Additional statistical data regarding the factor structure of the neuropsychological examination and the way the subtests of the MAT-COBI group themselves to factors can be found in ESM 2.

Discussion

This study served to assess the MAT-COBI as a cognitive screening tool in MS. Computerized assessments of cognitive functions have been gaining popularity in recent years (see Wojcik et al., 2019, for an overview concerning computerized assessment tools in MS). Such programs are available in the form of applications for the clinical practitioner – as is the case with the MAT-COBI – and self-assessments for patients and other interested groups (i.e., personal cognitive health applications). However, the empirical evaluation of such instruments is an ongoing process and remains an object of scientific interest.

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Table 4. Crosstabulations concerning the predictive value of the MAT-COBI in comparison to the extensive testing procedure

a. Attention					b. Memory				
		MAT-COBI					MAT-COBI		
		Impaired	Unimpaired				Impaired	Unimpaired	
ETP	Impaired	6	19	25	ETP	Impaired	0	17	17
		Sens: 24.0 %					Sens: 0.0 %		
	Unimpaired	2	17	19		Unimpaired	0	27	27
			spec: 89.5 %					Spec: 100 %	
		8	36	44			0	44	44
				acc: 52.3 %					acc: 61.4 %
c. Information processing speed/executive function					d. Global cognition parameter/all domains				
		MAT-COBI					MAT-COBI		
		Impaired	Unimpaired				Impaired	Unimpaired	
ETP	Impaired	3	17	20	ETP	Impaired	10	21	31
		sens: 15.0 %					Sens: 32.3 %		
	Unimpaired	0	24	24		Unimpaired	1	12	13
			Spec: 100 %					Spec: 92.3 %	
		3	41	44			11	33	44
				acc: 61.4 %					acc: 50.0 %

Notes. MAT-COBI: Memory and Attention Test – Cognitive Basic Inventory; ETP: extensive testing procedure; sens: sensitivity; spec: specificity; acc: accuracy.

The results of the current work support the conclusion that the cognitive domains of attention, memory, and executive function have been largely adequately operationalized in the MAT-COBI, which can be derived from the results of the descriptive intercorrelations. We reported significant correlations between parameters that may be assumed to measure the same cognitive domain. For instance, we observed highly significant correlations between the highest-difficulty parameter of the MAT-COBI attention task and several parameters of the TAP and the SDMT. Also, the short-term memory parameter of the MAT-COBI showed highly significant correlations with all parameters of the word-list-learning tests employed in the gold standard. The picture is somewhat less clear for the executive function parameters of the MAT-COBI, though most of them show at least significant correlations with performance on the PASAT (see ESM 1 for comparison).

Based on these descriptive results, we implemented an analysis of the predictive value of the MAT-COBI using crosstabulations. To this end and based on both hypothetical assumptions concerning underlying cognitive domains and the results of the correlational analysis, information processing- and executive function-related variables were clustered in a single domain for this step of the statistical analysis. This course of action also appeared necessary because normative data for the executive function parameters of the MAT-COBI (flexibility, endurance, inhibition, overall performance) have not yet been made available.

While the specificity of the MAT-COBI compared to the gold standard proved to be very high, the sensitivity turned out to be very low (see Table 4 for a comparison). This finding emerged equally for all analyzed cognitive domains and the global cognition parameter, including all cognitive domains. The pattern was most pronounced in the memory domain, where the MAT-COBI could not identify even one of the patients identified as cognitively impaired by the gold standard. But even in the attention domain, where the MAT-COBI reached its best result regarding a single cognitive domain, sensitivity turned out to be as low as 24 % and thus still insufficient. Sensitivity was only slightly improved for the global cognition parameter, reaching 32.3 %. This result seems especially noteworthy, as the MAT-COBI

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turned out to identify cognitive impairment in only 25% of examined patients, while the gold standard identified 70.5% of patients as impaired in at least one cognitive domain. As pointed out in the Introduction, long-standing data on cognitive impairment in pwMS imply prevalence rates of cognitive impairment ranging from 43–72% (Chiaravalloti & DeLuca, 2007; Hansen & Lautenbacher, 2017). Thus, even though procedural differences between diagnostic approaches such as varying cut-off scores, the procedures or patient subgroups may influence prevalence estimates, the results from the gold standard used in the current work are well in line with the contemporary literature. On the other hand, the results of the MAT-COBI seem to be uncharacteristically low concerning the prevalence of cognitively impaired patients. This finding seems odd, as a previous study involving the MAT identified several parameters that indicated a cognitive decline of pwMS compared to healthy controls (Adler & Lembach, 2015). Among them were episodic short-term memory, episodic working memory, and the level 3 difficulty of the attentional task – all of which are embedded in the MAT-COBI as used in the current work. The study by Adler and Lembach (2015) also identified approximately 20% of pwMS as cognitively impaired. However, some methodological differences between this study and our study must be pointed out. First, while we compared two diagnostic approaches, Adler and Lembach (2015) compared the results of healthy controls (HC) to those of pwMS. Second, the latter authors used a considerably more conservative cut-off score of 2 *SD* below the mean. Third, they reported the rate of cognitive impairment only for the short-term memory parameter, which lay at 20.2%. Fourth, they employed the MAT, while we resorted to the shorter MAT-COBI. These differences somewhat impede a comparison of results, though one may suggest that they do not necessarily contradict each other: The three parameters mentioned (episodic short-term memory, episodic working memory, and attention level 3) range among the best predictors for cognitive decline in MS in the study by Adler and Lembach (2015). It therefore makes sense to consider the MAT-COBI, which basically consists of these three parameters, suitable for cognitive profiling in MS.

However, comparing the results of the MAT-COBI with the results from an established gold standard, as in the current study, suggests that the MAT-COBI is unsuitable as a screening instrument for cognitive impairment in pwMS. This is largely because a screening tool should identify as many conspicuous test performances as possible and therefore avoid type II errors. On the other hand, possible false-positive classifications may then be rectified in an extensive testing procedure following the screening (see Hansen & Lautenbacher, 2017, for comparison). Yet, the results of the current work indicate that the MAT-COBI is prone to such errors of omission in the investigated context. Therefore, we suggest that the MAT-COBI can differentiate between pwMS and HC on a population level, as indicated by the study of Adler and Lembach (2015). Still, it seems unsuitable to differentiate between cognitively impaired and cognitively unimpaired pwMS on an individual level.

The fact that sensitivity was very low in this context, while specificity, on the other hand, was very high, suggests that ceiling effects may have been reached in at least some of the employed procedures. Therefore, it might be possible that the test items employed are too simple or that cut-off scores are set too low to reasonably differentiate between cognitively impaired and unimpaired pwMS. This conclusion is supported by the fact that 38.6% of patients were classified as impaired in the memory domain by the gold standard, while the MAT-COBI didn't classify a single patient as cognitively impaired. Furthermore, in the attention domain, the gold standard identified 45.5% of patients as impaired, while the first two difficulty levels of the attention task in the MAT-COBI were also not at all sensitive to cognitive impairment. Only in the highest difficulty level (D3) were 13.6% of patients classified as impaired. This result is noteworthy as difficulties in tasks relying on information processing speed often manifest in pwMS who otherwise exhibit only slight cognitive impairment (Hoffmann et al., 2007; Keune et al., 2019).

It is conceivable that the original conceptualization of the MAT as a diagnostic tool for patients suffering from cognitive decline because of gradually advancing neurodegenerative diseases, especially Alzheimer's disease (AD) (Adler et al., 2008, 2012), may weaken its usefulness as a screening instrument in MS. At least compared to more advanced stages of AD showing clinical symptoms, cognitive deficits often present in a much more subtle form in MS (Charest et al., 2020; Messinis et al., 2018). At the very least, the results of the current work suggest that the MAT-COBI cannot necessarily be easily transferred to an automated assessment of cognitive functioning in pwMS.

As a general conclusion, we therefore note that one ought to be cautious when applying automated procedures in routine clinical practice. These procedures must be carefully validated, both conceptually in terms of convergent validity with other established measures as well as across patient groups to be examined. This prerequisite, however, does not appear to be satisfied regarding the procedure at hand, putting its usefulness as a cognitive screening tool for pwMS into question. Furthermore, employing the MAT-COBI as a second-stage tool based on its high specificity also does not appear feasible. First, our results strongly imply that, on an individual level, the MAT-COBI cannot effectively differentiate between cognitively unimpaired pwMS and pwMS presenting light symptoms

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of cognitive impairment. Second, the usefulness of the MAT-COBI as part of an extensive testing procedure would largely depend on the availability of norms for its various parameters to allow meaningful conclusions regarding cognitive profiles.

Finally, we should note the composition of our sample. Though a relatively large number of people with SPMS were included in the sample, pointing toward a more advanced stage of the disease, we do not necessarily consider this a shortcoming. Cognitive deficits may manifest at any stage of the disease (DeSousa et al., 2002), underscoring the need for sensitive screening tools of cognitive dysfunction early on in the diagnostic process. Even though the severity of symptoms is loosely associated with disease duration (Amato et al., 2006), many patients should present with at least mild cognitive deficits even in the early stages of the disease. Thus, although we consider our interpretation of the results regarding the MAT-COBI to be generalizable in a group of newly diagnosed pwMS, we cannot rule out that base rates of cognitive impairment would have been lower in such a group. However, it stands to reason that these would have been lower in both diagnostic approaches and therefore do not influence sensitivity and specificity.

There are several limitations to the current study that should be considered. First, the sample size was relatively small; we cannot rule out the influence of random effects that may have affected the generalizability of the results. Second, the normative data for the executive function parameters of the MAT-COBI were still not available when data collection was implemented; consequently, several test results that might have suggested cognitive impairment may have been lost to our analysis of sensitivity and specificity. Third, we applied the neuropsychological assessment in a fixed order. Since both physical and cognitive fatigue are common symptoms in pwMS, we cannot rule out that the order in which the tests were presented might have affected participants' performance. A randomized application would have been preferable and should be implemented in future studies regarding this issue along with an objective evaluation of fatigue using, for example, a standardized questionnaire.

Nonetheless, we consider our results unambiguous. Even though the MAT-COBI appears to be a valid and reliable diagnostic tool in which the basic cognitive domains attention, memory, and executive function have been adequately operationalized, currently it cannot be recommended as a screening tool for cognitive impairment in MS. Again, this points to the fact that the often subtle cognitive deficits in MS are easily overlooked. While a computerized procedure is generally desirable for cognitive screening in MS, our results suggest the necessity of a different and possibly more cognitively demanding approach.

Electronic Supplementary Material

The electronic supplementary material (ESM) is available with the online version of the article at https://doi.org/10.1024/1016-264X/a000359

ESM 1. Correlations of select parameters of the complete testing procedure, sorted by cognitive domains (Table)

ESM 2. Factor solution of the principal component analysis (Table)

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