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A smart peek: Processing of rapid visual displays is disturbed in newly diagnosed, cognitively intact MS patients and refers to cognitive performance and disease progression in late stages

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ABSTRACT

Background: MS can reduce the speed of information processing (IPS) leading to a variable pattern of cognitive impairment. To better understand this deficit, a separate evaluation of the sensory, cognitive, and motor speed component is required. Tests using rapid visual displays allow for assessment of separate components of information uptake. We utilized such a test to compare deficit profiles at the earlier and later stage of MS and their relation to cognitive ability and disease progression.

Method: Two groups were evaluated: "Early MS" comprised $N = 24$ patients with disease durations < 2 years; "late MS" $N = 45$ with disease durations > 12 years. Rapid visual displays of letters were utilized to derive individual profiles of visual information uptake according to the 'theory of visual attention' (TVA). The resulting data was then compared with measures of disability, fatigue, depression, IPS, visual-spatial ability, verbal and visual memory.

Results: In the EMS group, where cognitive impairment was the exception, three of the four main parameters of visual information uptake were already modified, i.e. processing rate C, storage capacity K, and iconic memory μ. In LMS an additional elevation of the fourth parameter, i.e., the perceptual threshold t_0 was evident. Threshold values were related to most clinical and cognitive measures.

Conclusions: An early deficit pattern of visual information uptake can be detected at a stage, when performance in tests of IPS is still well-preserved. At later disease stages, a single parameter reflecting the threshold of conscious visual perception may provide a valid estimate of cognitive performance and disease progression.

1. Introduction

Cognitive impairment (CI) can affect patients with multiple sclerosis (MS) from the beginning and is regarded as an important predictor of disease course and functional outcome [1,2]. A large part of CI can be accounted for by measures of information processing speed (IPS) and therefore, the identification of patients at risk for IPS deficits is a main task for current research [1,3]. It has been suggested that for this purpose, novel assessment instruments have to be established that allow a separate evaluation of the underlying sensory, cognitive, and motor speed components under consideration of process purity assumptions [3,4].

Abbreviations: AD, Alzheimer's disease; C, Processing rate; cEMS, with EMS matched control group; CES-D, Center for Epidemiologic Studies Depression Scale; cLMS, with LMS matched control group; EDSS, Expanded Disability Status Scale; EMS, early MS; IPS, information processing speed; LMS, late MS; K, Visual short-term memory capacity; SDMT, symbol digit modalities test; t_0, Perceptual threshold; TVA, theory of visual attention; VSTM, visual short term memory; Weimus, Wuerzburger Erschoepfungsinventar bei MS; μ, Iconic memory

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Tests of visual processing may assess sensory speed deficits within the visual modality. Indeed, different test paradigms with a background in cognitive neuroscience [5–7], ophthalmology [8], or clinical neuropsychology [9–11] have been used to demonstrate impaired visual processing in MS. Approaches involving the use of rapid visual displays are particularly appealing, because the capability to extract information from briefly flashed stimuli may also reflect general cognitive effectiveness as invoked by intelligence research [12–14]. Moreover, tests using rapid displays are free of confounds due to motor impairment and slowed reaction time [15] and the recorded data can be used to deconstruct neuropsychological functions fundamentally different compared to conventional approaches (i.e., performance measures are not directly interpreted, but instead used to mathematically model a function whose properties are then interpreted as latent traits [16]). This allows acquiring cognitive specific deficit profiles of visual processing as shown in over 30 clinical studies [17].

Previous studies revealed a temporal limitation for processing briefly presented stimuli in MS and found this to be associated with slowed IPS and cognitive fatigue [6, 11; see also 18]. However, the samples evaluated in these studies were quite heterogeneous with respect to disease progression and a comprehensive cognitive assessment was lacking.

Thus, we investigated the potential of a test using rapid visual displays based on the "theory of visual attention" (TVA) [19] to detect abnormalities in MS, and to function as an index of CI. We examined which of the TVA-based components of visual information uptake are already impaired at an early stage, and how the pattern differs from the late stage. Finally, we assessed how these deficits relate to disease progression and cognitive functioning.

2. Methods

The study was approved by the Ethics Committee of the Saechsische Landesaerztekammer (EK-BR-24/10–1). All participants provided written informed consent.

2.1. Subjects

Seventy-seven patients with a first clinical demyelinating event related to MS or definite MS [20] were recruited from five MS-centers within a time frame of enrolment of 8 months, and assigned to two groups (early MS, EMS, $N = 25$, disease duration < 2 years; late MS, LMS, $N = 52$, disease duration > 12). Patients were individually matched with respect to age at disease onset ($\pm$ 3 years), sex, and education, i.e., after inclusion of one EMS-patient, two matching LMS-patients were recruited. More LMS-patients were recruited to account for the higher variety of structural and cognitive changes at later disease stages. Each site was instructed to recruit sets of 3 matched patients. For this purpose, outpatients were consecutively screened at each site for potential eligibility and matching. When a set was identified, the corresponding patients were invited for inclusion. However, if a site was not able to recruit a full set, the patients' characteristics were entered into a centralized recruitment spread sheet and the other sites were given the opportunity to recruit matching patients to the set. A detailed account of the final recruitment has already been published [21]. Exclusion criteria included a recent relapse or corticosteroid treatment, visual acuity < 0.2, severe fatigue or depressiveness, and exclusion criteria for MRI. One patient withdrew his consent to participate, two patients had insufficient visual acuity, and data from five patients had to be excluded due to initial software problems. Thus, the data of 69 patients (24 in EMS, 45 LMS) are reported in this study (Table 1).

Two individually matched control groups, i.e., "cEMS" and "cLMS" were formed based on a panel of healthy subjects who have been assessed during the course of our studies of visual processing capacity under the same standardized conditions.

Table 1
Clinical and demographic variables.

	Early stage[a]		Late stage[b]	
	EMS	cEMS	LMS	cLMS
N	24	24	45	45
Sex (male: female)	1: 2.43	1: 2.43	1: 2.46	1: 2.75
Age (years)	28.9 (6.7) [20–47]	29.0 (7.1) [20–48]	45.1 (7.9) [32–61]***	44.7 (8.5) [27–60]
Education ≥ 12 years (N (%))	9 (38%)	11 (46%)	11 (24%)	19 (42%)
Age at disease onset (years)	28.0 (7.0) [18–47]		28.2 (6.8) [19–46]	
Disease duration (years)	1.0 (0.8) [0–2]		16.9 (5.4) [10–37]	
EDSS (Median [min-max])	1.8 [0–6]		3.0 [0–8]**	
History of optic neuritis (N (%))	11 (46%)		19 (42%)	
Depressiveness (CES-D)	13.0 (9.9) [1–36]		13.1 (9.0) [0–34]	
Fatigue (Weimus)	19.9 (16.6) [0–50]		26.6 (14.6) [0–51]	
Disease-modifying treatment				
- Azathioprine	–		3 (7%)	
- Interferon beta 1a	8 (33%)		10 (22%)	
- Interferon beta 1b	9 (38%)		13 (29%)	
- Glatiramer acetate	4 (17%)		11 (24%)	
- Natalizumab	1 (4%)		1 (2%)	
- Teriflunomid	1 (4%)		0 (0%)	
- None	1 (4%)		7 (16%)	

Values are displayed as mean (SD) [min-max]. Group differences were tested by using Fisher's Exact Test (sex, education) or independent samples *t*-test (*: $p < .05$; **: $p < .01$; ***: $p < .001$).
EMS = early MS; LMS = late MS; cEMS = with EMS matched control group; cLMS = with LMS matched control group; EDSS = Expanded Disability Status Scale; CES-D = Center for Epidemiologic Studies Depression Scale; g: Weimus = Wuerzburger Erschoepfungsinventar bei MS.
[a] Patients with a disease duration of < 2 years and matched controls.
[b] Patients with a disease duration of > 12 years and matched controls.

2.2. Assessment of visual information uptake

Efficiency of visual information uptake (visual processing capacity) was assessed by using a simple psychophysical task, whole report of rapidly displayed letter arrays, in combination with a TVA-based modeling of the individual test performance (Fig. 1). This procedure has been employed in several previous studies and a detailed description can be found there [e.g. 22]. The task lasted approximately 30 min and included 24 pre-test trials to adjust individual exposure durations, followed by 192 experimental trials. The individual exposure durations were determined for each subject with respect to the same criterion, i.e., an average of 20% correctly reported letters per trial and an average accuracy of 80%. This was done to assure sufficient visual acuity and to permit comparable baseline performance for all subjects. Four independent parameters were computed that constitute the efficiency of visual information uptake (see Fig. 1): the minimum exposure duration where conscious visual processing starts (perceptual threshold, t_0); the number of visual objects that can be processed per second (processing rate, C); the number of visual objects that can be maintained in parallel within visual short-term memory (VSTM storage capacity, K); and the additional time a visual percept is available for processing due to visual persistence, in unmasked compared to masked presentations (iconic memory buffering, μ). Congruent testing conditions and procedures were assured by intensive training of examiners before the project started.

2.3. Assessment of cognitive performance

Aspects of information-processing speed, verbal memory, visual memory, and visuo-constructive abilities were assessed on a separate

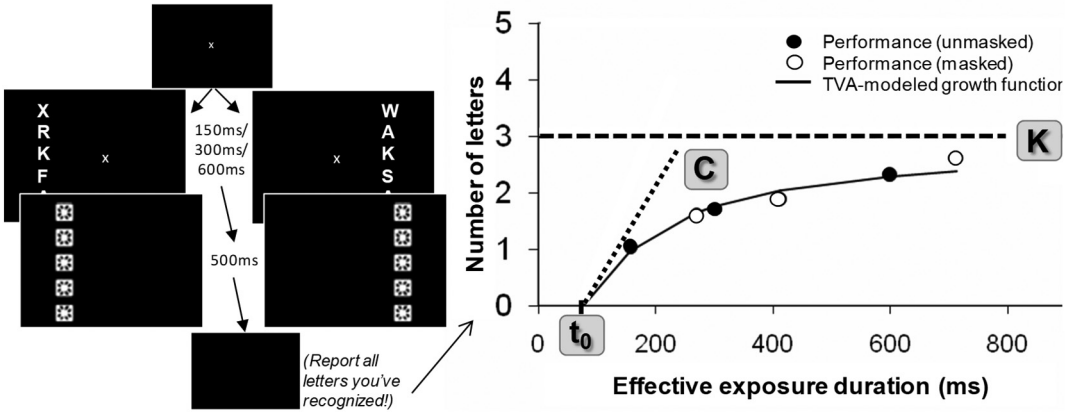

Fig. 1. Assessment of the efficiency of visual information uptake. (Left): Rapid visual displays consisted of five random letters that appeared either on the left or right side of the screen at three predetermined exposure durations. Patients verbally reported all letters they had identified and the next trial was initiated by the experimenter. (Right): The mean number of correctly reported letters was modeled as an exponential growth function according to a maximum likelihood method. The resulting curve was characterized by the three parameters reflecting visual processing capacity: The slope at the curves' origin determines the processing rate (C), the asymptote determines visual short-term-memory storage capacity (K); the origin determines the perceptual threshold (t_0). Performance difference between unmasked and masked trials determined iconic memory buffering (μ).

Table 2
Cognitive assessment battery.

Domain	Test[a]	Concept
Information-processing speed	Alertness	Reaction to a simple visual stimulus after an auditory or no cue
	Divided attention	Reaction to competing auditory and visual stimuli
	Flexibility	"Set-shifting" task that requires reactions to complementary visual target stimuli on an alternate basis from trial to trial
	SDMT[b]	Substitution task in which nine numbers have to be paired with abstract symbols as rapidly as possible according to a provided key
Visuo-constructive abilities	ROCF	Copying a complex figure.
Verbal memory	AVLT	Learning a list of orally presented nouns with immediate and delayed retrieval
	VLT	Recurring recognition test of non-words
Visual memory	ROCF	Delayed free reproduction of a previously copied figure (memory component was unannounced)
	DCS	Learning nine different geometric figures and the order they are presented at over the course of three trials
	NVLT	Recurring recognition test of geometric and irregularly shaped figures

SDMT = Symbol Digit Modalities Test; ROCF = Rey-Osterrieth Complex Figure Test; AVLT = Rey Auditory Verbal Learning Test; VLT = Verbal Learning Test; DCS = Diagnosticum fuer Cerebralschaedigung; NVLT = Nonverbal Learning Test.

[a] Tests were performed in the following fixed order: AVLT (learning), ROCF (copy), alertness, divided attention, flexibility, AVLT (recall, recognition), ROCF (recall), DCS, VLT, and NVLT.

[b] The SDMT was applied at a follow-up assessment 4.25 years after the original evaluation.

day, two weeks before or after the assessment of visual processing capacity (Table 2) [21]. Composite scores were computed by averaging the z-normalized results of the corresponding tests after correction for age, sex and education [21].

Additionally, results of the symbol digit modalities test (SDMT), one of the most commonly utilized screenings for information-processing speed and cognitive impairment in MS [23], were obtained from 56 patients (20 EMS, 36 LMS) who agreed to a follow-up assessment performed 4.25 years after the initial evaluation. The SDMT data was used to investigate correlations between efficiency of visual information uptake and performance on the SDMT 4.25 years later.

Measures of physical disability (EDSS), depressiveness (CES-D), and fatigue (Weimus) were applied to assess disease progression. Weimus is a validated, two-dimensional questionnaire of MS-related fatigue (focus on motor and cognitive fatigue). It comprises 17 items that were derived from three widely used scales (i.e., Fatigue Severity Scale, the Modified Fatigue Impact Scale, MS-specific Fatigue Severity Scale) and were selected based on a comparison of item properties acquired in one sample. In this study the raw sum score was analyzed.

2.4. Statistical analyses

Statistical analyses were performed with SPSS (Version 20). Group differences were evaluated by using independent samples t-test after verifying normal distribution. To increase statistical power, associations to clinical and demographic variables were evaluated in a pooled sample including all patients and by using Spearman's rank correlation or independent samples t-test. Associations to cognitive measures were analyzed by using Pearson correlation. The relative contribution of TVA-based parameters to the cognitive outcomes was analyzed by using stepwise regression analyses including clinical and demographic variables as predictor variables in block 1 and the TVA-based parameters in block 2.

3. Results

3.1. Efficiency of visual information uptake

Processing rate C, visual short term memory capacity K, and iconic memory μ were significantly lowered in both MS groups compared to controls (Table 3), with relatively strong effect sizes for the two memory parameters in the group EMS. In contrast, the perceptual threshold t_0 was only elevated in LMS, but not in EMS.

Differences between EMS and LMS were significant with respect to the parameters t_0 (perceptual threshold; d = 1.2, $p < .001$), C (processing rate; d = 0.6, $p < .05$) and μ (iconic memory; d = 0.5, $p < .05$), but not with respect to K (visual short term memory capacity; $p = .647$). However, differences between the two control groups cEMS

Table 3
TVA-based visual processing capacity in early and late stages of MS.

	MS	control	d	p
Early stage MS				
Perceptual threshold t_0 (msec)	11.8 (12.8)	9.09 (16.3)	0.2	0.518
Processing rate *C* (elements/s)	20.66 (5.7)	26.12 (11.6)	0.6	**0.045**
VSTM capacity *K* (number of elements)	2.59 (0.50)	3.41 (0.70)	1.3	**0.000**
Iconic memory μ (msec)	102 (40.3)	142 (48.6)	0.9	**0.003**
Late stage MS				
Perceptual threshold t_0 (msec)	46.8 (39.3)	24.8 (30.9)	0.6	**0.004**
Processing rate *C* (elements/s)	17.15 (5.9)	20.55 (8.1)	0.5	**0.025**
VSTM capacity *K* (number of elements)	2.53 (0.51)	3.15 (0.61)	1.1	**0.000**
Iconic memory μ (msec)	79 (45.3)	151 (58.0)	1.4	**0.000**

Results are displayed as mean (SD). Group differences were tested by using independent samples t-test. Cohen's d effect sizes are provided for group differences (≤0.2 small; ≤0.5 moderate; ≤0.8 large).
TVA = Theory of visual attention; VSTM = visual short term memory.
Significant group differences are highlighted by p-values in bold.

and cLMS were also significant with respect to the parameters t_0 (d = 0.6, p < .05) and *C* (d = 0.6, p < .05), but not with respect to μ (p = .547) and *K* (p = .114).

3.2. Associations with clinical and demographic variables

Age was found to be associated with perceptual threshold t_0 and to a lesser extent with processing rate *C* (Table 4). Education was found to be associated with t_0 as well, whereas sex was not associated with any of the visual parameters.

With respect to the clinical variables, no associations with optic neuritis and depressiveness were evident (Table 4). However, a series of significant correlations with the perceptual threshold t_0 was apparent including EDSS, disease duration, and fatigue (Table 4; see Table e-1 for separated analyses in EMS and LMS). Also, a weak correlation between processing rate C and disease duration was found (Table 4). When including age as a covariate the correlation between t_0 and EDSS remained significant (Table 4).

In healthy controls, the following associations with demographics were evident: age with perceptual threshold t_0 (r_s = 0.437, p < .001), and with processing rate *C* (r_s = −0.315, p < .01), education with t_0 (mean ± SD: ≥12y: 11.4 ± 22.7 vs. < 12y: 25.5 ± 29.8; p < .05).

3.3. Associations with cognitive performance

In the EMS group, cognitive performance appeared to be well-preserved, i.e., differences from the healthy control group were not significant in this sample (Table 5). The correlation analyses (Table 5) revealed a significant weak correlation between verbal memory performance and the perceptual threshold t_0. Additionally, a weak correlation between visual memory performance and t_0 was found to be borderline significant (p = .088). In the regression analysis t_0 remained to be a significant predictor (standardized β = −0.580, p < .01) of verbal memory (p < .001, adj. R^2 = 0.463) additionally to sex (standardized β = −0.56, p < .01).

In the LMS group, cognitive performance was significantly lowered compared to the healthy control group with respect to information-processing speed, verbal and visual memory (Table 5). The correlation analyses (Table 5) revealed moderate correlations between performance in each of the four cognitive domains and the perceptual threshold t_0. Additionally, a weaker correlation between information-processing speed and processing rate *C* was found. Regression analyses confirmed t_0 as an independent predictor of performance in information-processing speed, visual memory, and visuo-constructive abilities even after controlling for all clinical and demographic variables (Fig. 2).A detailed analysis of the association with information-processing speed (Table 6) revealed that the correlation with perceptual threshold t_0 was evident in those tests that went beyond simple reaction time, i.e., divided attention and flexibility. Moreover, within these tests, the correlation was apparent in measures of reaction time as well as accuracy for visual and auditory stimuli, and remained significant even after correction for EDSS and age (Table 6). In contrast, the correlation with alertness did not reach significance for t_0, but in this case for processing rate *C*.

3.4. Associations with follow-up performance in SDMT

Twenty patients from the EMS group agreed to the follow-up assessment. The mean (± SD) number of correct answers in the SDMT was 62.7 (± 10.1) (mean corrected T-value: 53.8 ± 9.66). No significant correlations were evident between follow-up SDMT performance and the efficiency of visual information uptake.

Fifty-six patients from the LMS group agreed to the follow-up assessment achieving an average of 49.1 (± 15.6) correct answers in the SDMT (T-value: 47 ± 15). The follow-up SDMT performance was found to be strongly correlated with the perceptual threshold t_0 (r = −0.608, p < .001) and moderately with the processing rate *C* (r = 0.312, p < .05). After correction for EDSS and age the correlation with t_0 remained significant (r = −0.466, p < .01), but not the correlation with *C* (r = 0.252, p < .1).

Table 4
Associations between visual processing capacity and clinical and demographic variables in all MS patients (*N* = 69).

	t_0	*C*	*K*	μ
Age	***0.541*****	−**0.385****	0.008	−0.234†
Sex (female vs. male)	32.2 (34) vs. 40.7 (43)	18.2 (6) vs. 18.9 (6)	2.5 (0.5) vs. 2.6 (0.4)	91 (46) vs. 78 (42)
Education (≥12y vs. < 12y)	**17.3 (22) vs. 41.7 (39)***	19.5 (6) vs. 17.9 (6)	2.5 (0.6) vs. 2.6 (0.5)	102 (38) vs. 81 (46)†
EDSS	**0.415**** **(0.330****)**	−0.210† (−0.040)	0.112	−0.198
Disease duration (years)	**0.374**** (0.101)	−**0.276*** (−0.025)	0.041	−0.223†
Optic neuritis[a] (no vs. yes)	34.3 (37) vs. 35.0 (36)	19.1 (7) vs. 17.4 (5)	2.5 (0.5) vs. 2.7 (0.5)	82 (41) vs. 94 (49)
Depressiveness (CES-D)	0.197 (0.114)	−0.090 (−0.012)	0.149	0.025
Fatigue (Weimus)	**0.324**** (0.236†)	−0.159 (−0.054)	**0.250***	−0.009

Associations with continuous variables were tested by using Spearman's rank correlation (in parentheses age-corrected partial correlations), those with dichotomous variables by comparing group means (SD) using independent-samples *t*-test (†: p < .10; *: p < .05; **: p < .01).
t_0 = Perceptual threshold; C = Processing rate; K = Visual short-term memory capacity; μ = Iconic memory; EDSS = Expanded Disability Status Scale; CES-D = Center for Epidemiologic Studies Depression Scale; Weimus = Wuerzburger Erschoepfungsinventar bei MS.
Significant correlation coefficients are highlighted in bold.
[a] Presence of optic neuritis in the patients' clinical history.

Table 5
Cognitive performance in early and late MS and its correlation to visual processing capacity.

	Mean (SD)[a]		significance[b]		Correlation to visual processing capacity[c]			
	HC	MS-patients	d	p	t_0	C	K	μ
Early stage MS								
IPS	−0.02 (0.4)	0.13 (0.6)	0.3	0.310	−0.167	0.318	0.101	−0.048
Visuo-constructive abilities	−0.02 (1.0)	−0.02 (1.1)	0.0	0.987	−0.153	0.133	−0.011	0.206
Verbal memory	−0.03 (0.7)	−0.11 (0.7)	0.1	0.684	**−0.461***	0.122	0.007	0.244
Visual memory	−0.03 (0.6)	−0.10 (0.7)	0.1	0.701	*−0.356†*	0.007	0.156	0.250
Late stage MS								
IPS	0.04 (0.5)	−0.59 (0.9)	0.9	0.001	**−0.504****	**0.310***	0.134	0.108
Visuo-constructive abilities	0.12 (0.8)	0.00 (1.2)	0.1	0.570	**−0.661****	0.113	0.059	*0.231*
Verbal memory	−0.05 (0.8)	−0.48 (0.9)	0.5	0.021	**−0.359***	0.053	−0.181	−0.066
Visual memory	−0.03 (0.5)	−0.46 (1.0)	0.5	0.021	**−0.534****	*0.227*	−0.003	0.095

HC = healthy controls; t_0 = Perceptual threshold; C = Processing rate; K = Visual short-term memory capacity; μ = Iconic memory; IPS = information-processing speed.
Significant correlation coefficients are highlighted in bold.
[a] Composite scores were computed by averaging the z-normalized results of the corresponding cognitive tests after correction for age. Sex and education.
[b] Group effects between patients and individually matched controls were assessed by using the *t*-test. Cohen's d effect sizes are provided (≤0.2 small; ≤0.5 moderate; ≤0.8 large).
[c] Pearson correlation coefficients (†: $p < .10$; *: $p < .05$ **: $p < .01$).

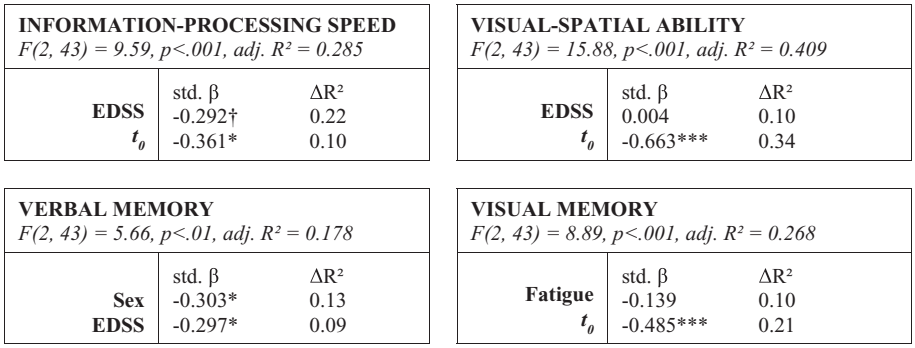

Fig. 2. Stepwise regression analyses of cognitive performance in late stage MS.

4. Discussion

Cognitive and visual deficits are common in MS [24], can occur in early disease [25], rank first among the most burdening symptoms as perceived by patients [26], and share a considerable proportion of common variance [27]. The present study assessed, based on the theoretical framework of TVA, separate components of visual processing within one and the same task and related them to cognitive performance in early and late stage MS.

Even at an early stage, where cognitive performance was still well-preserved, MS patients already showed significant modifications in three of the four parameters reflecting the efficiency of visual information uptake, as modeled by TVA: i.e. iconic memory, VSTM storage capacity, and processing rate. The later stage was characterized by a quantitative increase of parameter deviations, as well as by a qualitative change, i.e. the emergence of an elevated perceptual threshold. Taken together, these results suggest a staged decline: Efficiency of visual information uptake is reflected by a set of parameters, as defined by TVA. Part of this set (in particular the parameters reflecting temporary maintenance) is affected by the disease from early on, while the

Table 6
Pearson correlations (corrected partial correlations) between tests assessing different aspects of information-processing speed and visual processing capacity in late stage MS.

		TVA-based parameters			
		t_0	C	K	μ
Alertness	Reaction time	−0.201† (0.059)	0.303* (0.237†)	−0.157	−0.077
Divided attention	Reaction time visual	**−0.393** (−0.297*)**	0.218† (0.208†)	0.232†	0.222†
	Reaction time auditory	**−0.387** (−0.278*)**	0.078 (0.067)	**0.312***	0.130
	Errors	−0.355** (−0.247†)	0.280* (0.231†)	−0.161	−0.052
	Omissions	**−0.296* (−0.291*)**	0.106 (0.091)	0.130	0.180
Flexibility	Reaction time	−0.369** (−0.245†)	**0.285* (0.262*)**	0.134	0.047
	Errors	−0.359** (−0.211†)	0.194 (0.111)	0.082	0.039

Values represent correlation coefficients. Partial correlation reflect corrections for those clinical and demographic variables that were significantly correlated with TVA-based parameters (t_0: controlled for age and EDSS; *C*: controlled for age). Correlations were tested one-sided (†: $p < .10$; *: $p < .05$ **: $p < .01$.).
t_0 = Perceptual threshold; C = Processing rate; K = Visual short-term memory capacity; μ = Iconic memory.
Significant correlation coefficients are highlighted in bold.

remaining component (threshold) is affected not before substantial disease progression has occurred.

Threshold values had a significant relationship to EDSS scores and to cognitive measures, in particular impaired IPS and visual memory, but were unaffected by history of optic neuritis. These results suggest the perceptual threshold to be responsive to disease severity which is in close correspondence to a recent study by Ayadi et al. [28]: These authors reported a similar pattern of results when looking at critical flicker frequency (CFF) which was associated with EDSS and a visual response time measure, but not with optic neuritis. CFF was also not related to visual acuity, VEP latency, and OCT measures. Therefore, the authors concluded that CFF reflects global disease processes and dysfunctional cortical processing instead of damage at the level of the optic nerve or retina.

In connection with these findings, the increase of the perceptual threshold t_0 observed in our study might also reflect impaired cortical function. Results from Alzheimer's patients [22] support such a "cortical interpretation" of parameter t_0. They show that the perceptual threshold is affected at an early disease stage ("mild cognitive impairment"), where cortical damage prevails [29]. A role of cortical function for quick visual information processing has also been demonstrated in MS patients: For example, V2 atrophy has been identified to significantly influence visual processing speed [30]. And a recent study found MS patients to have difficulties in processing visual information quickly in a rapid visual presentation task. This impairment was also attributed to a temporal-processing limitation in the sensory visual system in MS [6].

In contrast to the increase of the threshold value as estimated by TVA, changes of processing rate C and VSTM storage capacity K may be more related to white matter damage. Evidence in favor of this assumption comes from a TVA-based analysis of individual differences in the parameters K (VSTM storage capacity) and C (processing rate) in healthy young subjects. Inter-individual variability was closely linked to structural differences within frontal-parietal association pathways [31] of the periventricular white matter. This neuroanatomical region is well known to be typically affected by MS-related neuropathology.

Similar as suggested by Fielding et al. [32] for the oculomotor system, analysis of the visual processing system based on TVA may, thus, be able to disclose dysfunction within cortical networks. The visual processing system, in particular the postgeniculate section, is intricately involved in cognitive networks, with a large part of the cerebral cortex being responsive to visual input [33]. Structural and functional changes within this system [34,35] may represent an exemplar case of network dysfunction that can be mapped by TVA based assessment. Importantly, the resulting picture is one of an incremental change, possibly reflecting two pathophysiological processes, i.e. white matter and grey matter changes that appear to be differentially pronounced depending on the disease stage.

As a major limitation of our study, we cannot discriminate which parameter is more related to lower level, and which one is more related to higher level processing stages of the visual hierarchy. In particular, although history of optic neuritis was not associated with our results, they might nevertheless be affected by visual acuity differences [36]. However, even as a global measure, combining visual and cognitive aspects of visual information uptake, we would suggest that the TVA-based assessment provides meaningful results: It is able to identify a reduction of processing efficiency even at an early disease stage, when cognitive performance is still well-preserved. At later stages, a single parameter reflecting the threshold of conscious visual perception may provide a valid estimate of cognitive ability and disease progression. If parameter changes at the early disease stage would have predictive value for the later stage, this could open a window for early intervention. Therefore, further studies are required to monitor the longitudinal development of parameter changes, assess their relationship to neuro-ophthalmologic measures, and disclose neuroanatomical associations.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jns.2019.04.031.

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