

# Temporal visual resolution and disease severity in MS

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## Abstract

### Objective

To examine temporal visual resolution assessed as critical flicker frequency (CFF) in patients with MS and to investigate associations with visual system damage and general disability and cognitive function.

### Methods

Thirty-nine patients with MS and 31 healthy controls (HCs) were enrolled in this cross-sectional study and underwent CFF testing, high- and low-contrast visual acuity, alertness and information processing speed using the paced auditory serial addition task (PASAT), and retinal optical coherence tomography (OCT). In patients with MS, visual evoked potentials (VEPs) and Expanded Disability Status Scale (EDSS) scores were assessed.

### Results

CFF in patients with MS (mean  $\pm$  SD: 40.9  $\pm$  4.4 Hz) was lower than in HCs (44.8  $\pm$  4.4 Hz,  $p < 0.001$ ). There was no significant CFF difference between eyes with and without previous optic neuritis (ON). CFF was not associated with visual acuity, VEP latency, the peripapillary retinal nerve fiber layer thickness, and the combined ganglion cell and inner plexiform layer volume. Instead, reduced CFF was associated with worse EDSS scores ( $r^2 = 0.26$ ,  $p < 0.001$ ) and alertness ( $r^2 = 0.42$ ,  $p = 0.00042$ ) but not with PASAT ( $p = 0.33$ ).

### Conclusion

CFF reduction in MS occurs independently of ON and structural visual system damage. Its association with the EDSS score and alertness suggests that CFF reflects global disease processes and higher cortical processing rather than focal optic nerve or retinal damage.

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## Glossary

**ART** = automatic real-time; **CFF** = critical flicker frequency; **EDSS** = Expanded Disability Status Scale; **GCIP** = ganglion cell and inner plexiform layer; **GEE** = Generalized estimating equation; **HC** = healthy control; **HCVA** = high-contrast visual acuity; **ICC** = intraclass correlation coefficient; **INL** = inner nuclear layer; **LCLA** = Low-contrast letter acuity; **OCT** = optical coherence tomography; **ON** = optic neuritis; **PASAT** = paced auditory serial addition task; **pRNFL** = Peripapillary retinal nerve fiber layer thickness; **RRMS** = relapsing-remitting MS; **RT** = reaction time; **SE** = standard error; **TAP** = Test of Attentional Performance; **TMV** = total macular volume; **VEP** = visual evoked potential.

Afferent visual pathway damage in MS results from acute focal damage, i.e., by optic neuritis (ON) or chronic diffuse damage,<sup>1–3</sup> which leads to visual dysfunction and has a relevant impact on the quality of life of patients.<sup>4</sup> Thus, clinical assessment of the visual pathway by means of high-contrast visual acuity (HCVA), functional assessment by means of visual evoked potentials (VEP),<sup>5</sup> and more recently also structural assessment by optical coherence tomography (OCT) have become integral in diagnosing and monitoring patients with MS.<sup>6</sup>

An intriguing aspect of visual function is the visual temporal resolution, commonly assessed as the critical flicker frequency (CFF).<sup>7</sup> CFF represents the frequency of a pulsed light source, from which an individual perceives the signal as flickering. Braunstein already reported in 1903 that CFF was decreased in optic atrophy and other ophthalmologic conditions.<sup>7,8</sup> From the 1950s onward, CFF was investigated in MS,<sup>9</sup> and decreased CFF was found to relate to ON,<sup>9–11</sup> but independence from ON was also reported.<sup>12,13</sup> Furthermore, higher cortical processes had an impact on CFF in patients with cerebral injuries<sup>14</sup> and hepatic encephalopathy.<sup>15</sup>

Despite these early studies suggesting CFF as a potentially important marker for visual function, it remains unclear how CFF could serve as a marker for monitoring disease severity in MS. Our study is thus aimed at evaluating the potential of CFF measurements by investigating its association with clinical and cognitive assessments and structural visual system damage assessed by OCT.

## Methods

### Patients and controls

Forty-two patients with relapsing-remitting MS (RRMS) and 31 healthy controls (HCs) were enrolled in this prospective, cross-sectional pilot study. Inclusion criteria were diagnosis of RRMS according to the 2010 revised McDonald criteria<sup>16</sup> (or HC) and age between 18 and 70 years. Exclusion criteria were any comorbidity (e.g., glaucoma, retinal disease, diabetes mellitus, ophthalmologic surgery), which could influence vision or the retina. Patients with MS were recruited consecutively over 5 years (2012–2017) from the NeuroCure Clinical Research Center, Berlin. HCs were recruited from volunteers.

To match the groups for sex and age, the 3 oldest female patients with MS were excluded before analysis, leading to a final number of 39 patients included in the analysis.

All patients with MS underwent clinical assessment and were scored using the Expanded Disability Status Scale (EDSS).<sup>17</sup> A demographic and clinical overview is given in table 1.

### Standard protocol approvals, registrations, and patient consents

This study was conducted in line with the strengthening the reporting of observational studies in epidemiology statement<sup>18</sup> and was approved by the local ethics committee (EA1/216/11). It was conducted in accordance with the Declaration of Helsinki in its applicable version and applicable German laws. All participants provided written informed consent.

**Table 1** Cohort description

	MS	HC	<i>p</i> Value
Participants, N	39	31	
Sex, male/female (N)	13/26	12/19	0.6 ( $\chi^2$ )
Age/years, mean $\pm$ SD (range)	45.9 $\pm$ 8.4 (27–66)	45.0 $\pm$ 16.1 (20–70)	0.6 (MWU)
Eyes with previous ON, yes/no (N)	28/50		
Time since diagnosis, mo, mean $\pm$ SD (range)	156.8 $\pm$ 92.3 (24–446)		
EDSS, median (range)	2.5 (0–6)		

Abbreviations: EDSS = Expanded Disability Status Scale; HC = healthy control; MWU = Mann-Whitney *U* test; ON = optic neuritis.

## Critical flicker frequency

CFF measurement was performed monocularly using a HEPAtonorm analyzer (nevoLAB GmbH, Maierhöfen, Germany) in a quiet and semidarkened room. The device includes a headset that shields any external light from the participant's eyes and that features intrafoveal visual stimulation with a red luminous diode. The initial light signal of 60 Hz is perceived as continuous by the participant. Participants were instructed to press a stop button as soon as they perceive a flickering signal. When the operator starts the measurement on a hand-held controller, the pulse frequency decreases until it is perceived as flickering. The corresponding pulse frequency is defined as CFF and recorded by the hand-held controlling unit. CFF thresholds were determined monocularly, where each eye was tested 8 times, and the mean CFF (mCFF) value was calculated. All participants underwent a training session with 5 measurements before each initial measurement session.<sup>15,19</sup>

## Visual function parameters

HCVA was assessed with the Functional Vision Analyzer Optec 6500P system (Stereo Optical Co, Chicago, IL), as described previously.<sup>20</sup> Testing was performed monocularly under habitual correction and photopic conditions (85 cd/m<sup>2</sup>) with Early Treatment of Diabetic Retinopathy Study charts in a simulated distance of 20 ft.<sup>20</sup> Low-contrast letter acuity (LCLA) was assessed binocularly with 2.5% contrast Sloan charts in 2 m distance.<sup>21</sup>

Visual evoked potentials (VEP) were tested using the Dantec Keypoint VEP system (Natus Europe GmbH, Planegg, Germany). The P100 latency was measured using a standard black-and-white checkerboard stimulation (15'/50–60', at 1 m) and were recorded from the Oz electrode against a Cz reference electrode according to the 10–20 International System. The P100 amplitude was not analyzed.

## Alertness and cognitive parameters

Because of time constraints, denial by participants and technical issues, only a subset of 17 patients with MS and 20 HCs underwent a selected task from the computerized test of attentional performance (TAP) battery for alertness testing.<sup>22</sup> The tasks consist of a simple visual reaction time (RT) task without an acoustic warning signal, called tonic alertness task (part A) and a visual RT task preceded by an acoustic warning signal, phasic alertness (part B). To measure alertness, several trials were undertaken by alternating part A and part B. The participant was then asked to respond as fast as possible by pushing a button whenever a cross is displayed.<sup>22</sup> Mean RTs from tests without acoustic warning signal were considered a measure of alertness.

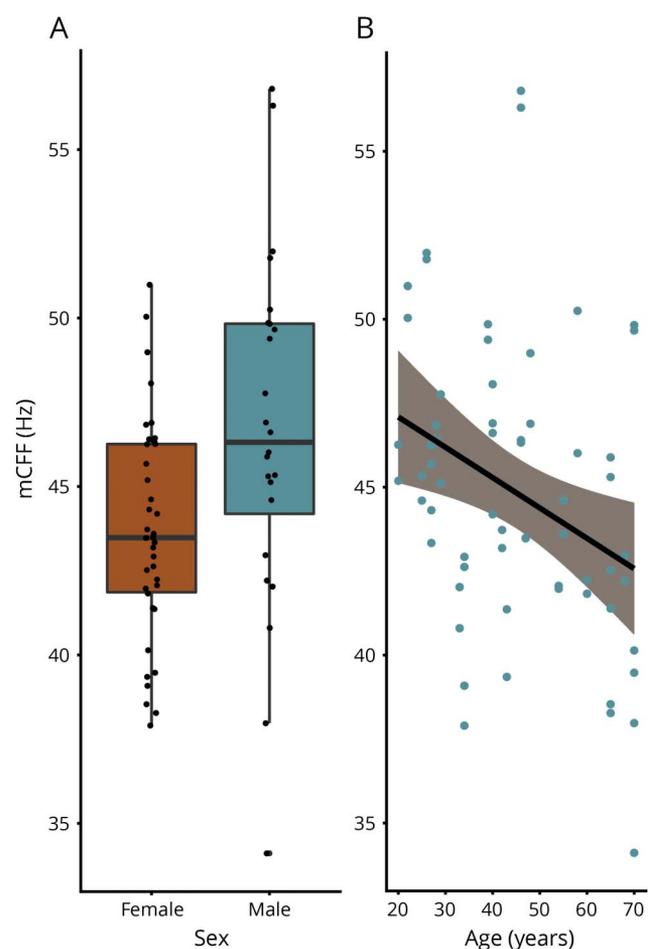
Also because of time constraints, only a subset of 29 patients with MS were tested with the 3-second version of the paced auditory serial addition task (PASAT), a measure of information processing speed.<sup>23</sup> For 14 patients, both alertness and PASAT testing were available.

## OCT and intraretinal segmentation

All participants underwent retinal examination using a spectral domain OCT (Spectralis SD-OCT; Heidelberg Engineering, Heidelberg, Germany) using Eye Explorer 1.9.10.0 and automatic real-time (ART) image averaging.<sup>24</sup> Peripapillary retinal nerve fiber layer thickness (pRNFL) was derived from a standard ring scan around the optic nerve head (12°, 1536 A-scans, 16 ≤ ART ≤ 100) using segmentation by the device's software with viewing module 6.0.14.0. A macular volume scan (25° × 30°, 61 B-scans, 768 A-scans per B-scan, 12 ≤ ART ≤ 15) was acquired for total macular volume (TMV) including all retinal layers from the inner limiting membrane and Bruch membrane, as determined by the device's segmentation software within a 6-mm diameter cylinder around the fovea.

Intraretinal segmentation of combined ganglion cell and inner plexiform layer (GCIP) volume and inner nuclear layer (INL) volume was performed on macular scans with the Johns Hopkins OCT layer segmentation method (AURA Tools

**Figure 1** Critical flicker frequency measurements in healthy controls



Comparison of CFF measurements between female and male HCs (A) and association of CFF measurements with age (B). HC = healthy control; mCFF = mean critical flicker frequency.

version 1.2)<sup>25</sup> combined with in-house pre-processing (cropping of volume scans to 6 × 6 mm) and postprocessing tools (graphical user interface for manual correction of segmentation results). All OCT scans were carefully checked for retinal changes unrelated to MS, sufficient quality,<sup>26,27</sup> segmentation errors, and were manually corrected by a blinded experienced grader if necessary.

### Statistical analysis

Statistical analyses were performed with R version 3.1.2 including geepack package 1.2-0. For demographic comparisons between patients and HCs, the Pearson  $\chi^2$  test for sex and nonparametric Mann-Whitney *U* test for age were used. Generalized estimating equation (GEE) models with working correlation matrix “exchangeable” and corrected for age and sex were used for group comparisons and associations involving eye-related measurements to account for within-subject intereye effects. GEE results are given with regression coefficient (B) and standard error (SE). All measurements were treated as continuous variables, and groups were stratified within patients with MS in ON and non-ON eyes. For the assessment of the test-retest reliability, the intraclass correlation coefficient (ICC) and its 95% confidence intervals were estimated using the R ICC package.<sup>28</sup> As suggested in a previous study, we considered an ICC greater than 0.9 as high and as moderate if between 0.8 and 0.9.<sup>29</sup> Statistical significance was established at  $p < 0.05$ . A correction for multiple comparisons with the Bonferroni-Holm method was performed for all correlation analyses.<sup>30</sup>

### Data availability

All data of this study will be shared by request from any qualified investigator.

## Results

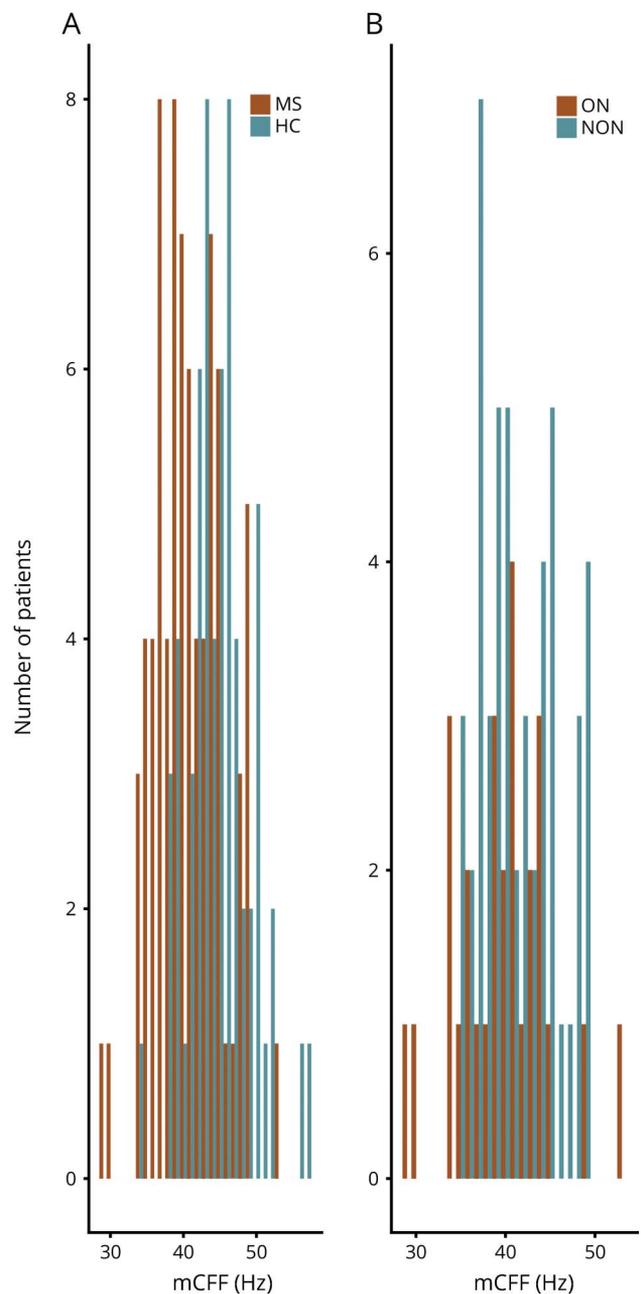
### CFF in HC

HC had an mCFF of  $44.8 \pm 4.4$  Hz. There was no mCFF difference between female and male HCs ( $43.70 \pm 3.24$  vs  $46.6 \pm 5.3$  Hz,  $B = 1.7188$ ,  $SE = 4.06$ ,  $p = 0.67$ ) (figure 1A), but lower mCFF was associated with higher age ( $B = -0.090$ ,  $SE = 0.043$ ,  $p = 0.036$ ) (figure 1B) in HC. Also, in HC, there was no association between mCFF and HCVA ( $B = 2.30$ ,  $SE = 1.99$ ,  $p = 0.34$ ), mCFF and LCLA ( $B = 0.029$ ,  $SE = 0.078$ ,  $p = 0.71$ ), or VEP P100 latency ( $B = 0.044$ ,  $SE = 0.042$ ,  $p = 0.29$ ). Likewise, alertness did not correlate with mCFF ( $B = -0.011$ ,  $SE = 0.0093$ ,  $p = 0.25$ ). Mean results are presented in a supplemental file (table e-1, [links.lww.com/NXI/A65](https://links.lww.com/NXI/A65)). The test-retest reliability in HC was high, with an ICC value of 0.91 (0.87–0.94).

### CFF in MS

mCFF in patients with MS was lower than in HC ( $40.9 \pm 4.72$  Hz,  $p < 0.001$ ). There was no difference between ON and non-ON eyes ( $39.7 \pm 5.22$  vs  $41.5 \pm 4.33$  Hz,  $p = 0.094$ ) (figure 2). mCFF was also not associated with visual function as determined by HCVA, LCLA, VEP latencies, and retinal OCT parameters pRNFL (global and papillomacular bundle),

**Figure 2** Critical flicker frequency measurements



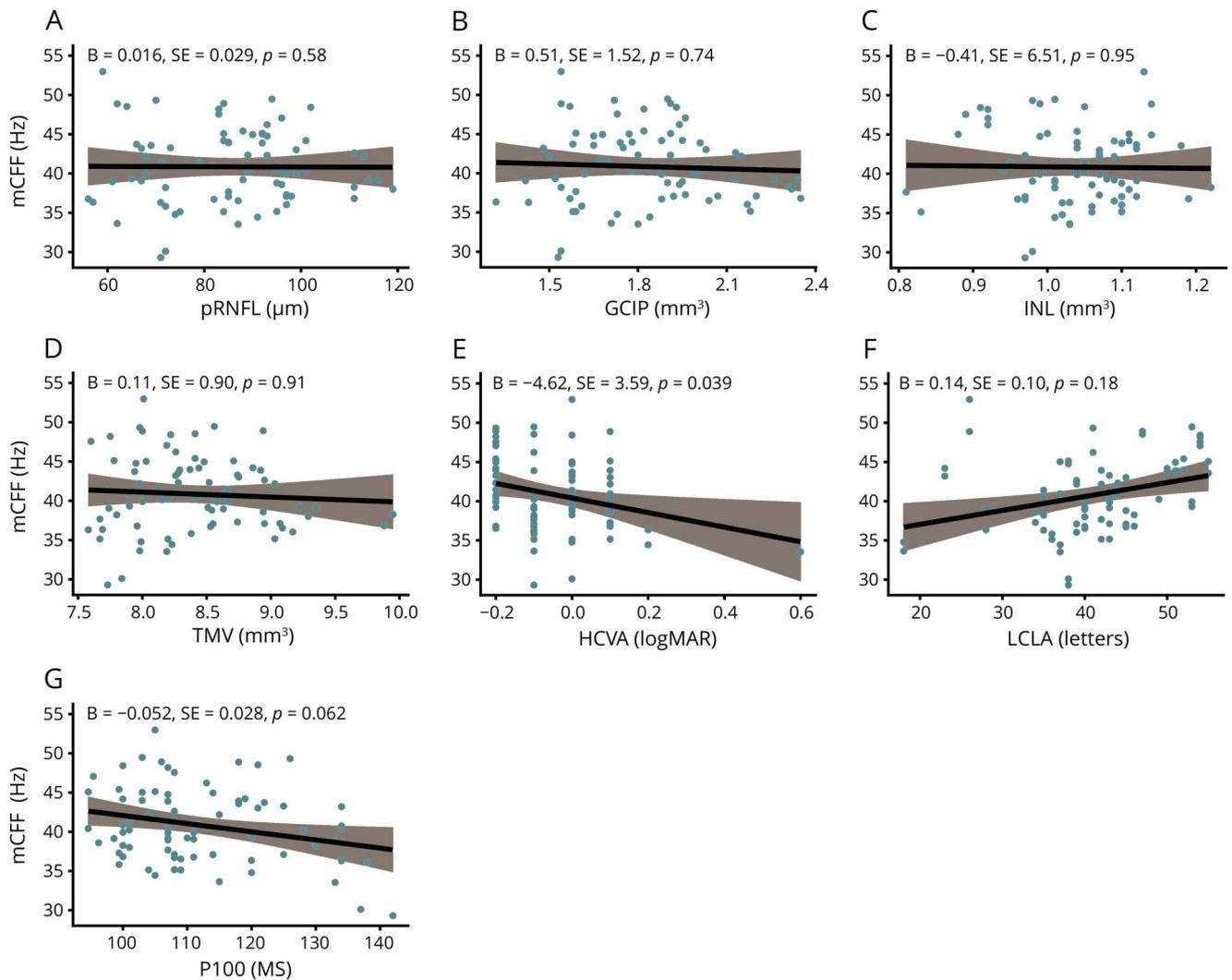
Comparison of CFF measurements between HCs and patients with MS (A) and comparison of CFF measurements between eyes with optic neuritis (ON) and eyes without ON (NON) in patients with MS (B). HC = healthy control; mCFF = mean critical flicker frequency.

GCIP, INL, and TMV (figure 3). Mean results are presented in a supplemental file (table e-1, [links.lww.com/NXI/A65](https://links.lww.com/NXI/A65)). The test-retest reliability was moderate, with an ICC value of 0.89 (0.85–0.92).

### CFF and disability

We then investigated whether CFF was associated with overall disability, alertness, and information processing speed in MS patients. Here, overall disability was found as higher EDSS scores, which was inversely correlated with lower

**Figure 3** Critical flicker frequency measurements and visual function in MS



Association of CFF measurements with structural and visual functional parameters: pRNFL (A), GCIP (B), INL (C), TMV (D), HCVA (E), LCLA (F), P100 (G). After Bonferroni-Holm correction, no *p* value remained significant. GCIP = ganglion cell/inner plexiform layer; HCVA = high-contrast visual acuity; INL = inner nuclear layer; LCLA = low-contrast letter acuity; mCFF = mean critical flicker frequency; pRNFL = peripheral retinal nerve fiber layer; TMV = total macular volume; VEP = visual evoked potential.

mCFF ( $r^2 = 0.26$ ,  $B = -1.77$ ,  $SE = 0.50$ ,  $p = 0.00036$ ) (figure 4A). Moreover, lower mCFF was associated with worse alertness ( $r^2 = 0.42$ ,  $B = -0.048$ ,  $SE = 0.014$ ,  $p = 0.00042$ ) (figure 4B), but not with information processing speed, assessed by PASAT ( $B = 0.063$ ,  $SE = 0.065$ ,  $p = 0.33$ ). After Bonferroni-Holm correction, the associations between mCFF and alertness and between mCFF and EDSS remained significant. The SD of the CFF measurements was not associated with alertness ( $B = 0.0015$ ,  $SE = 0.0035$ ,  $p = 0.68$ ).

## Discussion

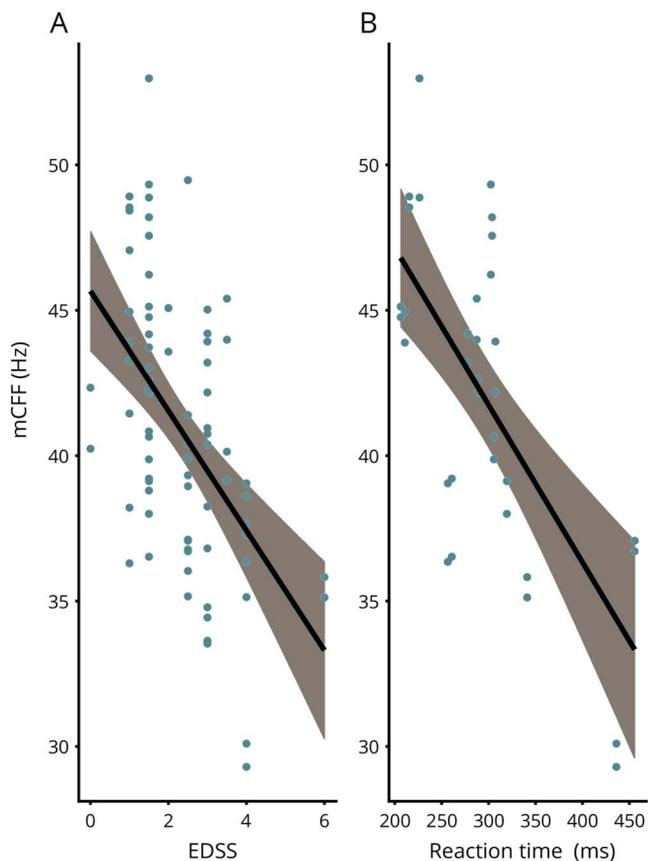
In this study, we investigated the visual temporal resolution by means of CFF assessment in patients with MS. Key findings are as follows: (1) CFF is reduced in MS compared with HC; (2) CFF is not or only weakly associated with structural and functional measures of afferent visual system damage in MS;

and (3) by contrast, CFF is associated with alertness and clinical disability.

Previous studies consistently reported impaired CFF in MS and ON.<sup>9,10,12</sup> Some investigators interpreted these results as support for cortical damage causing impairment at the central perceptual-discriminative level.<sup>9,31</sup> Thus, they recommended CFF as a general measure of cortical processing capacity.<sup>32</sup> On the other hand, neuroaxonal degeneration in the retina and the visual pathway of patients with MS could affect CFF as well.<sup>9</sup>

Perception of high-frequency stimuli has been suggested to be influenced by retinal ganglion cells.<sup>32</sup> Furthermore, cells of the magnocellular system are confirmed to be more sensitive to higher temporal frequency stimulation than cells of the parvocellular system.<sup>33</sup> Thus, we postulated that CFF could

**Figure 4** Critical flicker frequency measurements in patients with MS



Association of CFF measurements with the EDSS (A) and with reaction time in MS (B). EDSS = Expanded Disability Status Scale; mCFF = mean critical flicker frequency.

reflect integrity of the magnocellular retinal cells' ability to detect higher frequency stimuli,<sup>34</sup> and damage of magnocellular retinal ganglion cells might specifically cause decreased CFF. However, our results show no significant association of CFF with any afferent visual system marker, indicating that retinal neuroaxonal retinal damage had no or only negligible influence to CFF in patients with MS.<sup>34,35</sup> These findings could be explained by effects being small and masked by other associations. However, neuroaxonal retinal damage and demyelination of our MS cohort seem to be comparable to other MS cohorts regarding OCT and VEP measurements.<sup>36,37</sup>

By contrast, our results showed that lower CFF values are associated with longer RTs in a test of alertness, whereas there is no association with CFF SD. This suggests that the association of CFF with alertness is not caused by impaired alertness reducing the ability to comply with the CFF assessment. Tonic alertness refers to a cognitive control of wakefulness and arousal in the absence of a warning and is part of the domain of attention.<sup>38</sup> It is based on the activation of frontoparietal and partly thalamic regions of the right hemisphere.<sup>38</sup> Alertness was shown to be impaired after

appearance of right hemispheric lesions,<sup>38</sup> and we could report an association with MS-related fatigue in an earlier study.<sup>39</sup> This suggests that impaired CFF reflects damage to higher cognitive areas involved in alertness and cognition. Contrarily, the PASAT, which focuses on information processing speed, the cognitive domain most commonly affected in MS, showed no association with CFF in our study.

CFF also correlated with overall disability as represented by the EDSS score. Studies from the 1950/1960s already suggested an association of CFF with general disease disability, but did not investigate this systematically.<sup>9,40</sup>

CFF measurements from our HC are in line with previous studies regarding the mean CFF and an increase of CFF with age.<sup>41</sup> However, although 1 study found sex differences in CFF, this difference was not significant in our study.<sup>42</sup> The ICC values for CFF measurements in HC and MS showed that this method produces reliable results.

Our study has several limitations. Sample sizes of <40 in both MS and control groups might have been insufficient to detect small effects. This is particularly important for a potential effect of a previous ON on the CFF, which was not significant in our study, but gave a low *p* value indicative of a potential power issue. Moreover, the subsets with available TAP and PASAT tests were even smaller, and differences in sample size due to some technical problems and time restrictions in the assessment of the measurements may have resulted in a selection bias potentially weakening our conclusions. We therefore might have missed an association of CFF to information processing as assessed by PASAT. It should also be noted that exclusion of the 3 oldest patients has to be regarded critically because higher age is associated with decreased CFF and impaired visual parameters potentially influencing our findings in regard of the absence of associations between CFF and visual parameters. All visual parameters were measured monocularly except the LCLA because of unavailability at the beginning of the study, potentially reducing the validity of its comparison to monocularly measured CFF values. We did not perform MRI in our study, so we have no information on the association of radiologic disease activity and CFF. Likewise, we have only cross-sectional measurements, so the dynamics of CFF in context of the disease course and any causal inferences remain unclear. It is important to note that most previous studies on CFF in ON and MS were published in the 1950–1970s.<sup>11–13</sup> Thus, test procedures regarding CFF and other parameters might differ, making comparison of our results to these previous ones difficult. The interpretation of the findings of this study is mostly based on the absence of association with functional and visual parameters. Therefore, we believe that adding MRI and conducting longitudinal observations would be the next step in validating CFF measurements in MS.

Our study showed that visual temporal resolution as assessed by CFF is impaired in patients with MS independent of visual and structural visual system damage. Whether CFF

can serve as a marker for overall disease activity warrants further investigation.

### Author contributions

N. Ayadi: assessed CFF data, performed statistical analysis, and drafted the manuscript. J. Dörr: conceived the study and critically revised the manuscript. S. Motamedi and K. Gawlik: analyzed OCT data and critically revised the manuscript. J. Bellmann-Strobl, J. Mikolajczak, and A.U. Brandt: contributed to data interpretation and critically revised the manuscript. H. Zimmermann: contributed to the design of the study and data interpretation and drafted the manuscript. F. Paul: contributed to the design of the study and data interpretation and critically revised the manuscript.

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### Disclosure

N. Ayadi reports no disclosures. J. Dörr served on the advisory boards of Bayer, Novartis, Sanofi Genzyme, and Merck Serono; received travel funding from Novartis, Sanofi Genzyme, Biogen, and Bayer and speaker honoraria from Novartis, Merck Serono, Sanofi Genzyme, Biogen, and Roche; and received research support from Novartis and Bayer. S. Motamedi has a patent pending for method for estimating shape parameters of the fovea by optical coherence tomography. K. Gawlik has a patent pending for retinal image analysis. J. Bellmann-Strobl received travel funding and speaker honoraria from Bayer, Sanofi-Aventis/Genzyme, Merck, and Teva. J. Mikolajczak received travel funding and/or speaker honoraria from Teva, Biogen, Bayer, and Novartis. A.U. Brandt has a patent pending for perceptive visual computing based motor function analysis, MS biomarker, and retinal image analysis; serves on the executive board of IMSVISUAL; received research support from Novartis, Biogen, BMWi, BMBF, University of California, Irvine, and The Guthy Jackson Charitable Foundation; and holds stock or stock options held in Motognosis and Nocturne. H. Zimmermann received speaker honoraria from Teva and Bayer and received research support from Novartis. F. Paul served on the scientific advisory boards of Novartis and MedImmune; received travel funding and/or speaker honoraria from Bayer, Novartis, Biogen, Teva, Sanofi-Aventis/Genzyme, Merck Serono, Alexion, Chugai, MedImmune, and Shire; is an academic editor of *PLoS One* and an associate editor of *Neurology: Neuroimmunology & Neuroinflammation*; consulted for Sanofi Genzyme, Biogen, MedImmune, Shire, and Alexion; and received research support from Bayer, Novartis, Biogen, Teva, Sanofi-Aventis/Genzyme, Alexion,

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