Introducing a new method to assess vision: Computer-adaptive contrast-sensitivity testing predicts visual functioning better than charts in multiple sclerosis patients

JP Stellmann, KL Young, J Pöttgen, M Dorr and C Heesen

Abstract

Background: Impaired low-contrast visual acuity (LCVA) is common in multiple sclerosis (MS) and other neurological diseases. Its assessment is often limited to selected contrasts, for example, 2.5% or 1.25%. Computerized adaptive testing with the quick contrast-sensitivity function (qCSF) method allows assessment across expanded contrast and spatial frequency ranges.

Objective: The objective of this article is to compare qCSF with high- and low-contrast charts and patient-reported visual function.

Methods: We enrolled 131 consecutive MS patients (mean age 39.6 years) to assess high-contrast visual acuity (HCVA) at 30 cm and 5 m, low-contrast vision with Sloan charts at 2.5% and 1.25%, qCSF and the National Eye Institute Visual Functioning Questionnaire (NEIVFQ). Associations between the different measures were estimated with linear regression models corrected for age, gender and multiple testing.

Results: The association between qCSF and Sloan charts ($R^2 = 0.68$) was higher than with HCVA (5 m: $R^2 = 0.5$; 30 cm: $R^2 = 0.41$). The highest association with NEIVFQ subscales was observed for qCSF ($R^2 = 0.20$/$C1510.57$), while Sloan charts were not associated with any NEIVFQ subscale after correction for multiple testing.

Conclusion: The qCSF is a promising new outcome for low-contrast vision in MS and other neurological diseases. Here we show a closer link to patient-reported visual function than standard low- and high-contrast charts.

Keywords: Outcome measurement, multiple sclerosis, visual acuity, contrast vision, Sloan charts

Introduction

Acute optic neuritis (ON) as well as chronic inflammation and neurodegeneration cause visual impairment in multiple sclerosis (MS), and visual function is one of the three most important bodily functions among patients with MS. Recent research activities reveal an improved accuracy for analyzing the structural integrity of the visual system by optical coherence tomography (OCT) and magnetic resonance imaging (MRI). OCT and MRI detect anterograde neurodegeneration after acute ON as well as retrograde neurodegeneration caused by MS lesions in the posterior visual pathway. In fact, impaired integrity of the anterior visual system is now an accepted model to investigate neurodegeneration in MS. However, proclaiming an ecologically valid assessment of visual function is still challenging. Patient-reported outcomes such as the National Eye Institute Visual Function Questionnaire (NEIVFQ) provide measures for vision-related quality of life (QoL). However, the NEIVFQ is not established in clinical trials as the impact of fatigue, motivation or other MS symptoms on the assessment are not yet verified and longitudinal data are lacking. Visual acuity (VA) can be understood as an integration of visual QoL and structural integrity of the visual network. Compared to black-on-white high-contrast (HCVA) charts, low-contrast visual acuity (LCVA) shows a...
better correlation with reading, driving or face recognition in several neurologic diseases.1,8 Recent studies indicate a correlation of LCVA with the retinal nerve fiber layer and cognitive performance in MS.9,10 Even though Sloan charts are the standard assessment for LCVA, they are not yet a standard outcome as normative data, sensitivity to changes and their association with QoL and brain integrity have not been sufficiently proven.3 This might be due to the fact that Sloan charts usually assess selected contrast levels of, for example, 2.5% and 1.25%.11 Because contrast sensitivity varies with spatial frequency, the full contrast-sensitivity function (CSF) as commonly assessed in psychophysics and physiology is a more comprehensive measurement of vision.9 A change in a simple summary statistic, the area under the curve of the CSF, is a sensitive marker for changes in neurologic and ophthalmologic vision.12 However, standard CSF assessment is time-consuming and has not often been applied in MS research.10,13 Computerized adaptive testing would allow for a quick, reliable CSF measurement. The quick CSF (qCSF) method has recently been developed and investigated in ophthalmological diseases but not applied to assess visual impairment in neurologic diseases.8,12,14 We hypothesized that qCSF testing is more closely linked to the NEIVFQ subscales than standard low- and high-contrast letter charts in MS patients.

Methods

Patients and data acquisition

Between July 2014 and January 2015, we recruited 131 consecutive patients at the MS Outpatient-Clinic and Day Hospital at the Institute of Neuroimmunology and Multiple Sclerosis (INIMS), University Medical Centre Hamburg-Eppendorf, Germany. All participants had a clinically isolated syndrome (CIS) suggestive of MS or a definite diagnosis of MS based on the revised McDonald criteria15 and did not report any other ophthalmological disorder. All patients underwent an assessment of visual function in the same room under the same ambient light conditions and in the same order. The assessment included HCVA (Snellen charts) assessment at a distance of 30 cm (VA30 cm), an HCVA at 5 m (VA5 m), low-contrast Sloan charts (Sloan) and the qCSF system. All tests were performed for each eye separately. Subsequently, patients were asked to fill out the extended version of the NEIVFQ (version 2000, 39 items). The neurological status of all patients was assessed by trained neurologists with the Expanded Disability Status Scale (EDSS).16 VA30 cm was measured with a pocket chart provided by the
Statistics
We performed descriptive statistics as means with standard deviation (SD) or as frequencies. NEIVFQ subscales (general health, general vision, ocular pain, near activities, distance activities, social functioning, mental health, role difficulties, dependency, driving, color vision, peripheral vision) were calculated according to the published guidelines (https://www.nei.nih.gov/sites/default/files/nei-pdfs/manual_cm2000.pdf). We decided on appropriate regression models for analyzing correlations between assessments by investigating data distribution. Except for CSFAcuity, all measures showed skewness to the right, and we used polynomial fitting with two degrees of freedom to adjust for skewness. We compared different vision tests with each other and examined their association with disability levels. The association between vision tests and NEIVFQ subscales was explored with linear models adjusted for gender and age. To gain one value per participant for both eyes, we calculated minimal (i.e. worse eye), mean and maximal (i.e. better eye) values of each test for both eyes. To assess a ceiling effect, we calculated as well a linear model including all vision tests. \( R^2 \) values from the best qCSF outcome were then compared with the ceiling model and to quantify the agreement, we calculated the differences of \( R^2 \) between the best and the ceiling model. In addition, we investigated whether the complete qCSF as measured by the AULCSF shows a better association with the questionnaire than qCSF acuity at selected contrast levels according to Sloan charts (i.e. 1.25% and 2.5%). \( P \) values were corrected for multiple testing using the Bonferroni method and considered statistically significant if below 0.05. All analyses were performed with Statistics in R 3.0.0.

Results
Cohort
We recruited 131 patients representing a typically mildly disabled MS cohort (mean EDSS: 2.3; mean

Figure 1. Overview quick contrast-sensitivity function (qCSF)-examination.
(a) Photograph of three bandpass-filtered Sloan letters presented on a 46-inch computer screen at a viewing distance of 4.5 m; (b) Schematic of the contrast-sensitivity function (CSF); x-axis represents spatial frequencies i.e. decreasing size of the letters; y-axis represents decreasing contrast; red line: CSF, light red area: confidence interval of the CSF, blue area: area under the log CSF (AULCSF). (c), (d) Example of qCSF results from a patient with a first optic neuritis, unaffected left eye (c) with a visual acuity at 5 m = 1.0, (d) acute optic neuritis left eye with a visual acuity of 0.66.
The association between Sloan charts (1.25%, 2.5% and correct letters on both charts) and the subscales of the visual function questionnaire turned out to be weak (Figure 3(a)). They failed to explain patient reported visual function after correcting for multiple testing (Figure 3(b)). AULCSF from the better eye was the overall best predictor for NEIVFQ subscale scores followed by the mean value of both eyes (mean $R^2 = 0.43$ and mean $R^2 = 0.40$). In comparison to a linear model including all vision outcomes, the AULCSF alone had better $R^2$ values for mental health and color vision. Overall, $R^2$ from the AULCSF was similar to the ‘‘all-outcome’’ model as the mean difference between the two models was 0.04, i.e. the AULCSF explained only 4% less of the variance than the full model. Low-contrast acuities extracted from the qCSF at contrast levels according to Sloan testing (2.5% and 1.25%) were less correlated with NEIVFQ than the whole curve (mean $R^2$ at 2.5% contrast = 0.14 and 0.02 at 1.25 contrast, $p < 0.01$). VA30 cm of the better eye was a better predictor than HCVA at 5 m of the better eye (mean $R^2 = 0.32$ and mean $R^2 = 0.21$). For all outcomes the visual acuity of the better eye was more predictive for visual function than the worse eye. None of the outcomes was significantly associated with general health, dependency and ocular pain. The only tests weakly associated with driving were mean AULCSF and AULCSF from the better eye ($R^2 = 0.20$ and $R^2 = 0.23$). The overall highest correlation was found for AULCSF and color vision ($R^2 = 0.57$).

**Discussion**

Measurements of the whole CSF obtained with the quick CSF method within four minutes demonstrate a much better correlation with self-reported visual function in MS than established low- and high-contrast letter charts. Sloan charts, which have repeatedly been recommended as a more valuable tool to detect visual impairment in MS 1,11 were not significantly associated with the NEIVFQ in our cohort and performed worse than HCVA. Without any adjustment for multiple testing, the correlation between Sloan charts and NEIVFQ was comparable to two previous studies investigating the association between selected low-contrast vision levels with the NEIVFQ. 9,18 In addition, the AULCSF was significantly associated with most of the subscales from the NEIVFQ.

### Table 1. Descriptive statistics.

| Patients ($n$) | 131 |
|----------------|-----|
| Gender female/male $n$ (%) | 92 (70.2)/39 (29.8) |
| Age mean (SD) | 39.6 (11.7) |
| EDSS mean (SD) | 2.3 (1.6) |
| EDSS median (range) | 2 (0–6.5) |
| Disease duration in years mean (SD) | 7.8 (8.4) |
| Disease course $n$ (%) | 21 (16) |
| CIS | 93 (71) |
| RRMS | 7 (5) |
| SPMS | 10 (8) |
| PPMS | 0.9 (0.2) |
| Visual acuity 30 cm mean (SD) | 0.8 (0.3) |
| Visual acuity 5 m mean (SD) | 97 (15) |
| Sloan charts correct letters mean (SD) | 1.4 (0.2) |
| CSF acuity mean (SD) | 1.3 (0.3) |
| AULCSF mean (SD) | 0.57 |

EDSS: Expanded Disability Status Scale; CIS: clinically isolated syndrome; RRMS: relapsing–remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis, PPMS: primary progressive multiple sclerosis; CSF: contrast sensitivity function; AULCSF: area under the log contrast sensitivity function; for details, see Methods section. Data as mean (SD) if not indicated differently.
associated only with the AULCSF, even though the correlations were moderate. Beside contrast vision, color vision was just recently recommended as an important read-out for diffuse neurodegeneration in MS. Remarkably, the AULCSF was highly associated with patient-reported color vision. Overall, AULCSF seems to be more closely linked to patient-relevant visual functioning than any established measure and is a promising new parameter for visual impairment in neurological diseases.

Two recent reviews on the visual system in MS highlighted the importance of a valid assessment tool for LCVA and the need to develop better outcome measures for future trials. Apart from the link to real-life visual functioning, LCVA might even serve as an outcome for brain network integrity as LCVA has been, for example, linked to retinal nerve fiber thinning and cognitive performance in MS or disability in Parkinson’s disease. Considering that CSF correlates with functional
MRI (fMRI) activation and fMRI changes are associated with short-term adaption to contrast vision,\(^\text{21,22}\) MRI as well as OCT might help to clarify the association of AULCSF with structural and functional integrity of visual tracts and cortex. Owing to the cross-sectional design of our study, the sensitivity to changes in MS cannot be answered yet. However, a study in children with early-onset blindness due to bilateral cataracts could show improvements after cataract surgery even in individuals.\(^\text{12}\) Such improvements are known to be associated with neuroplasticity in the visual cortex.\(^\text{23}\)

![Figure 3](image)

**Figure 3.** Association of visual tests and patient-reported visual function. (a) Barplot with sums of $R^2$ values for NEIVFQ subscales (b) Table/heat map showing $R^2$ values after Bonferroni correction (n.s. = not significant). $R^2$ from linear models with a polynomial fitting to adjust skewed distribution of tests and corrected for gender and age. $P$ values corrected for multiple testing according to Bonferroni. All: $R^2$ values from a linear model including all visual tests as reference for ceiling effect. NEIVFQ: National Eye Institute Visual Functioning Questionnaire; min: minimal/worse eye values; max: maximal/better eye values; CSFAcuity: acuity from contrast-sensitivity function; AULCSF: area under the log contrast-sensitivity function (for details, see the Methods section); VA30 cm: high-contrast visual acuity at 30 cm; VA5 m: high-contrast visual acuity at 5 m. Sloan: sum of correct letters at, 2.5 and 1.25% contrast charts, Sloan 2.5 and Sloan 1.25: correct letters for single-contrast levels.
and not by ophthalmic examination. This could have biased our findings, which is a limitation of our study. However, as the impact of a history of ON seems not to affect the correlation between contrast vision and QoL, this cross-sectional analysis was not controlled for historical ON. However, especially in upcoming longitudinal studies this moderator variable should be controlled for. For all investigated tests, visual assessment of the better eye was much more predictive for self-reported visual function than assessment of the worse eye. Future testing should address how testing of each eye compares to binocular testing and test-retest reliability. In our cohort we observed a superiority of a short distance test at 30 cm over the 5 m Snellen chart in its association with NEIVFQ even though 5 m HCVA charts are recommended for MS visual function scoring (www.neurostatus.net). This effect may be explained by the spectrum of visual acuity steps assessable from the charts used in this study. While the pocket chart allowed a differentiation of seven VA steps between 1.0 and 0.5, our Snellen charts are divided into only three steps. As our cohort was only mildly disabled with a mean HCVA above 0.8, Snellen charts were not able to reflect the variance at this level of visual functional impairment. Considering the high sensitivity of the AULCSF in a mildly disabled cohort, the AULCSF is expected to be even more exact and useful when assessing more severely disabled patients. However, this assertion still needs confirmation. Here, we looked only at univariate measures of the CSF; multivariate analysis has the potential to further improve results.

Conclusion
The qCSF method is a promising new outcome for visual impairment in MS and other neurological diseases. It has proven a closer link to patient-reported visual function than standard low- and high-contrast charts.

Funding
This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest
MD holds equity in Adaptive Sensory Technology, the manufacturer of the qCSF system. The qCSF device was provided to INIMS free of charge; no further compensation was granted.

Acknowledgments
Mary Lou Jackson kindly provided methodological guidance and advice. We thank Michael Hauck for initiating the project.

References
1. Balcer LJ, Miller DH, Reingold SC, et al. Vision and vision-related outcome measures in multiple sclerosis. Brain 2015; 138(Pt 1): 11–27.
2. Heesen C, Böhm J, Reich C, et al. Patient perception of bodily functions in multiple sclerosis: Gait and visual function are the most valuable. Mult Scler 2008; 14: 988–991.
3. Martínez-Lapiscina E, Sanchez-Dalmau B, Fraga-Pumar E, et al. The visual pathway as a model to understand brain damage in multiple sclerosis. Mult Scler 2014; 20: 1678–1685.
4. Klistorner A, Sriram P, Vootakuru N, et al. Axonal loss of retinal neurons in multiple sclerosis associated with optic radiation lesions. Neurology 2014; 82: 2165–2172.
5. Gabilondo I, Martínez-Lapiscina E, Martínez-Heras E, et al. Trans-synaptic axonal degeneration in the visual pathway in multiple sclerosis. Ann Neurol 2014; 75: 98–107.
6. Sühs KW, Hein K, Sättler MB, et al. A randomized, double-blind, phase 2 study of erythropoietin in optic neuritis. Ann Neurol 2012; 72: 199–210.
7. Mowry EM, Loguidice MJ, Daniels AB, et al. Vision related quality of life in multiple sclerosis: Correlation with new measures of low and high contrast letter acuity. J Neurosurg Psychiatry 2009; 80: 767–772.
8. Lesmes L, Lu Z, Baek J, et al. Bayesian adaptive estimation of the contrast sensitivity function: The quick CSF method. J Vis 2010; 10: 1–21.
9. Schinzel J, Zimmermann H, Paul F, et al. Relations of low contrast visual acuity, quality of life and multiple sclerosis functional composite: A cross-sectional analysis. BMC Neurol 2014; 14: 31.
10. Wieder L, Gäde G, Pech LM, et al. Low contrast visual acuity testing is associated with cognitive performance in multiple sclerosis: A cross-sectional pilot study. BMC Neurol 2013; 13: 167.
11. Balcer LJ, Galetta SL, Polman CH, et al. Low-contrast acuity measures visual improvement in phase 3 trial of natalizumab in relapsing MS. J Neurol Sci 2012; 318: 119–124.
12. Kalia A, Lesmes LA, Dorr M, et al. Development of pattern vision following early and extended blindness. Proc Natl Acad Sci U S A 2014; 111: 2035–2039.
13. Vieira-Gutemberg JG, Mendes-Santos LC, Cavalcanti-Galdino MK, et al. Contrast sensitivity in relapsing–remitting multiple sclerosis assessed by
sine-wave gratings and angular frequency stimuli. *Vis Neurosci* 2014; 31: 1–6.

14. Dorr M, Lesmes LA, Lu ZL, et al. Rapid and reliable assessment of the contrast sensitivity function on an iPad. *Invest Ophthalmol Vis Sci* 2013; 54: 7266–7273.

15. Polman CH, Reingold SC, Banwell B, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the “McDonald criteria.”. *Ann Neurol* 2011; 69: 292–302.

16. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: An Expanded Disability Status Scale (EDSS). *Neurology* 1983; 33: 14–44.

17. Greenland S. Dose-response and trend analysis in epidemiology: Alternatives to categorical analysis. *Epidemiology* 1995; 6: 356–365.

18. Jasse L, Vukusic S, Durand-Dubief F, et al. Persistent visual impairment in multiple sclerosis: Prevalence, mechanisms and resulting disability. *Mult Scler* 2013; 19: 1618–1626.

19. Lin TP, Rigby H, Adler JS, et al. Abnormal visual contrast acuity in Parkinson’s disease. *J Parkinsons Dis* 2015; 5: 125–130.

20. Saidha S, Syc SB, Durbin MK, et al. Visual dysfunction in multiple sclerosis correlates better with optical coherence tomography derived estimates of macular ganglion cell layer thickness than peripapillary retinal nerve fiber layer thickness. *Mult Scler* 2011; 17: 1449–1463.

21. Leguire LE, Algaze A, Kashou NH, et al. Relationship among fMRI, contrast sensitivity and visual acuity. *Brain Res* 2011; 1367: 162–169.

22. Kwon M, Legge GE, Fang F, et al. Adaptive changes in visual cortex following prolonged contrast reduction. *J Vis* 2009; 9: 20.1–20.16.

23. Martins Rosa A, Silva MF, Ferreira S, et al. Plasticity in the human visual cortex: An ophthalmology-based perspective. *Biomed Res Int* 2013; 2013: 568354.