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Original Article

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

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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 0.20–0.57), 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),[1] and visual function is one of the three most important bodily functions among patients with MS.[2] 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).[3] OCT and MRI detect anterograde neurodegeneration after acute ON as well as retrograde neurodegeneration caused by MS lesions in the posterior visual pathway.[4,5] In fact, impaired integrity of the anterior visual system is now an accepted model to investigate neurodegeneration in MS.[3,6] 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).[1,7] 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.[1] Visual acuity (VA) can be understood as an integration of visual QoL and structural integrity of the visual network.[3] Compared to black-on-white high-contrast (HCVA) charts, low-contrast visual acuity (LCVA) shows a

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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.[8] 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 criteria[15] 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 German collaborative on MS research (http://www.kompetenznetz-multiplesklerose.de). The chart includes 10 rows with three to six numbers. The smallest line with less than two mistakes was recorded as VA (possible values: 1.0, 0.95, 0.9, 0.85, 0.75, 0.6, 0.5, 0.2, 0.1, 0.05). VA5 m charts (http://www.oculus.de) had nine lines with one to 10 letters. Again the smallest line with a maximum of one mistake was defined as VA5 m (possible values: 1.25, 1.0, 0.66, 0.5, 0.33, 0.25, 0.20, 0.14, 0.1). Standard Sloan letter charts (http://precision-vision.com, 12 rows with five letters, distance 2 m) were used according to published guidelines with contrast levels at 2.5% and 1.25%, and the number of correct letters at each contrast level served as the outcome. In addition, the total number of mistakes was calculated by subtracting the number of correct answers for both charts from the total number of letters (120). This additional analysis was implemented to test if a combined analysis of the single Sloan charts might be better than the single charts. The qCSF device presents three bandpass-filtered Sloan letters in each of 25 trials on a 46-inch computer screen at a viewing distance of 4.5 m. A schematic overview of the test and example results is given in Figure 1. Spatial frequency (19 log-equidistant steps between 1.57 and 40.7 cycles per degree of visual angle (cpd)) and contrast (128 log-equidistant levels between 0.2 and 100%) of the rightmost letter were chosen by a Bayesian adaptive algorithm that maximizes expected information gain based on the history of previous trials (for details, see Lesmes et al.[8] and Hou et al. Using 10 AFC to further improve the efficiency of qCSF. *J Vis*, in press; the middle and leftmost letters were displayed at twice and four times contrast, respectively. For each letter, patients' responses were scored as correct, incorrect, or letter not seen by the test proctor using a tablet computer. Because the qCSF estimates contrast-sensitivity thresholds for a large number of spatial frequencies, a good estimate of the entire CSF is obtained after test completion. Median test time was four minutes, which includes time to enter participant details and patch the non-tested eye. Test results included a summary statistic, the area under the log CSF (AULCSF) in the spatial frequency range from 1.5 to 18 cpd (http://en.wikipedia.org/wiki/Degree_(angle)http://en.wikipedia.org/wiki/Visual_angle), and the CSFAcuity, the frequency where threshold contrast is 100%. Additional acuities were calculated at threshold contrast of 2.5% and 1.25%. All participants gave their written informed consent and the local ethics committee approved the study (Ethical Committee of the Board of Physicians in the State of Hamburg, PV4455).

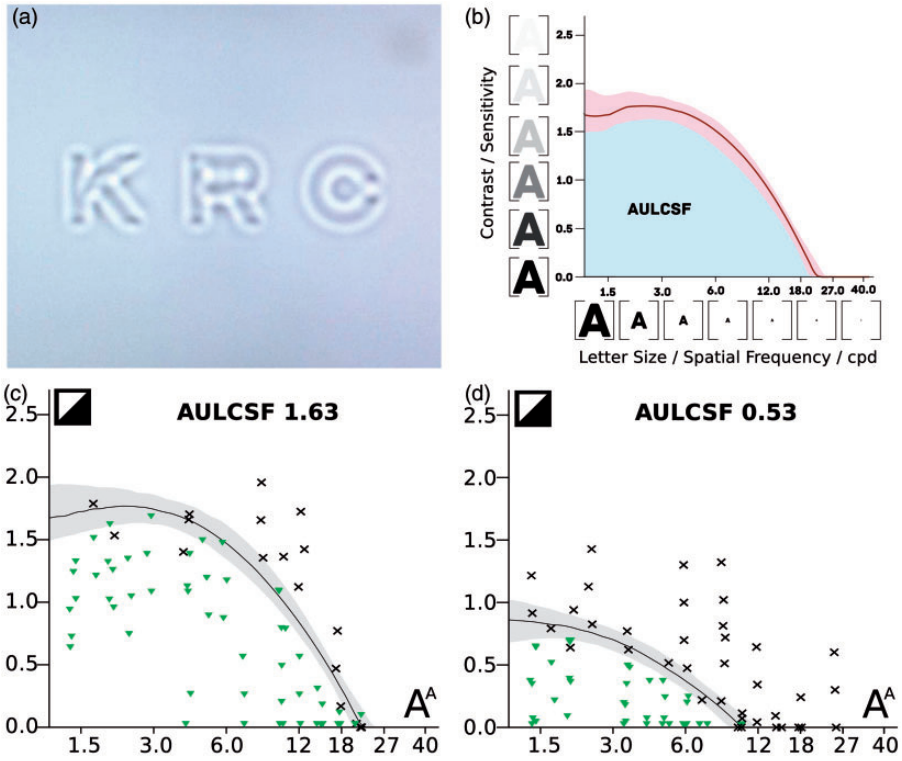

Figure 1. Overview quick contrast-sensitivity function (qCSF)-examination.
(a) Photograph of three bandpass-filtered Sloan letters presented on a 46-inch computer screen at a viewing distance of 4.5 m; (b) Schematic of the contrast-sensitivity function (CSF); x-axis represents spatial frequencies i.e. 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.

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.[17] 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

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* (%)	
CIS	21 (16)
RRMS	93 (71)
SPMS	7 (5)
PPMS	10 (8)
Visual acuity 30 cm mean (SD)	0.9 (0.2)
Visual acuity 5 m mean (SD)	0.8 (0.3)
Sloan charts correct letters mean (SD)	97 (15)
CSF acuity mean (SD)	1.4 (0.2)
AULCSF mean (SD)	1.3 (0.3)

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.

age: 39.6 years) with a predominantly relapsing–remitting disease course (70%). Mean visual acuities at 30 cm (0.9) and 5 m (0.8) were similar (Table 1). There was a comparable moderate correlation of AULCSF and CSFAcuity with Sloan charts ($R^2 = 0.57$ and 0.55) and with VA5 m ($R^2 = 0.47$ and 0.53) but less with VA30 cm ($R^2 = 0.35$ and 0.32; Figure 2).

In comparison to other visual acuity tests, 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. Driving skills and role difficulties were

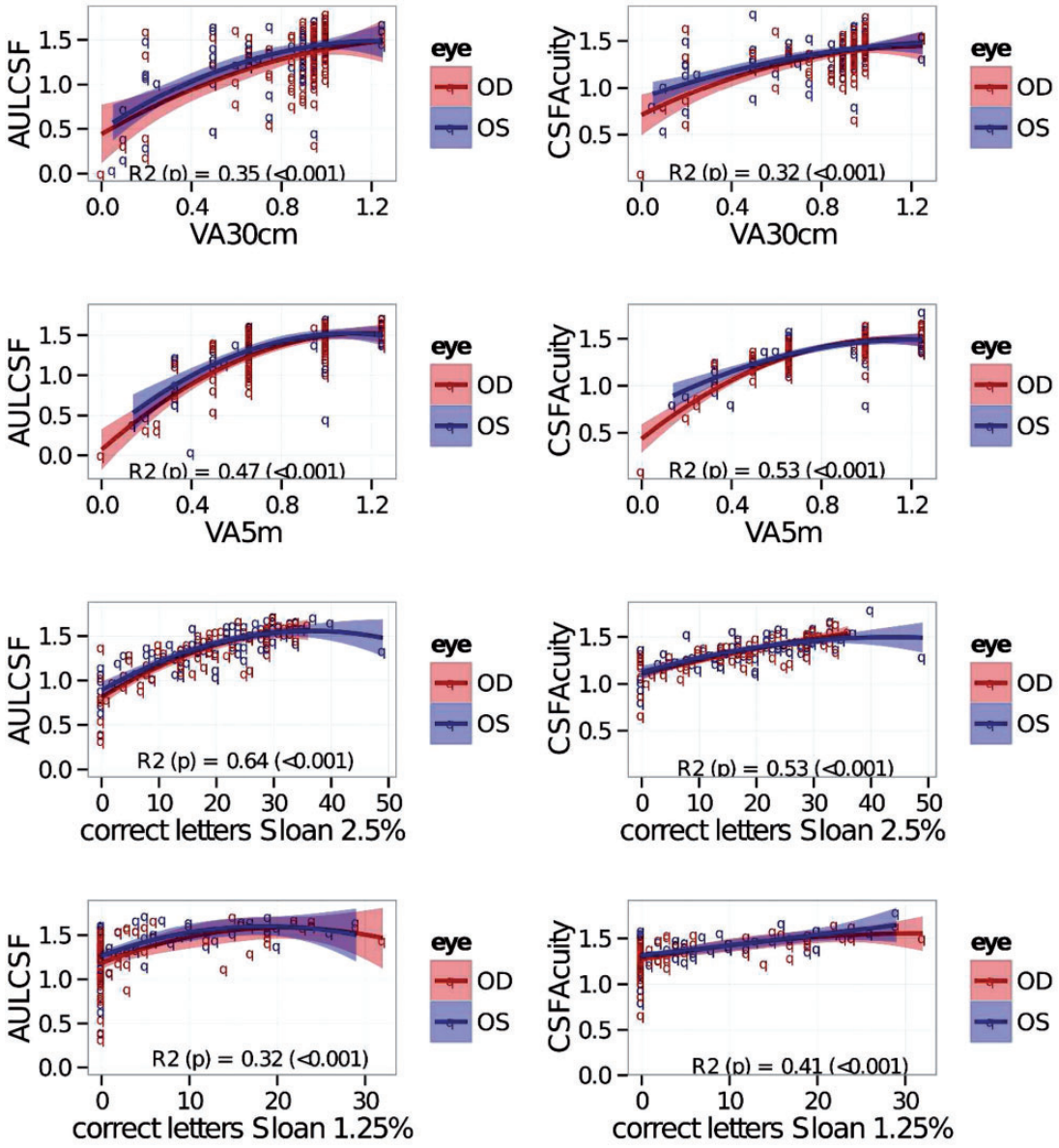

Figure 2. Adaptive contrast-sensitivity function and standard letter charts.
CSFAcuity: acuity from contrast-sensitivity function at 100% contrast; AULCSF: area under the log contrast sensitivity function (for details, see the Methods section); VA30 cm: high-contrast visual acuity at 30 cm; VA5 m: high-contrast visual acuity at 5 m. Sloan 1.25% and 2.5%: correct letters on Sloan charts with 2.5% and 1.25% contrast.

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.[3] 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.[1,3] 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.[10,19,20] Considering that CSF correlates with functional

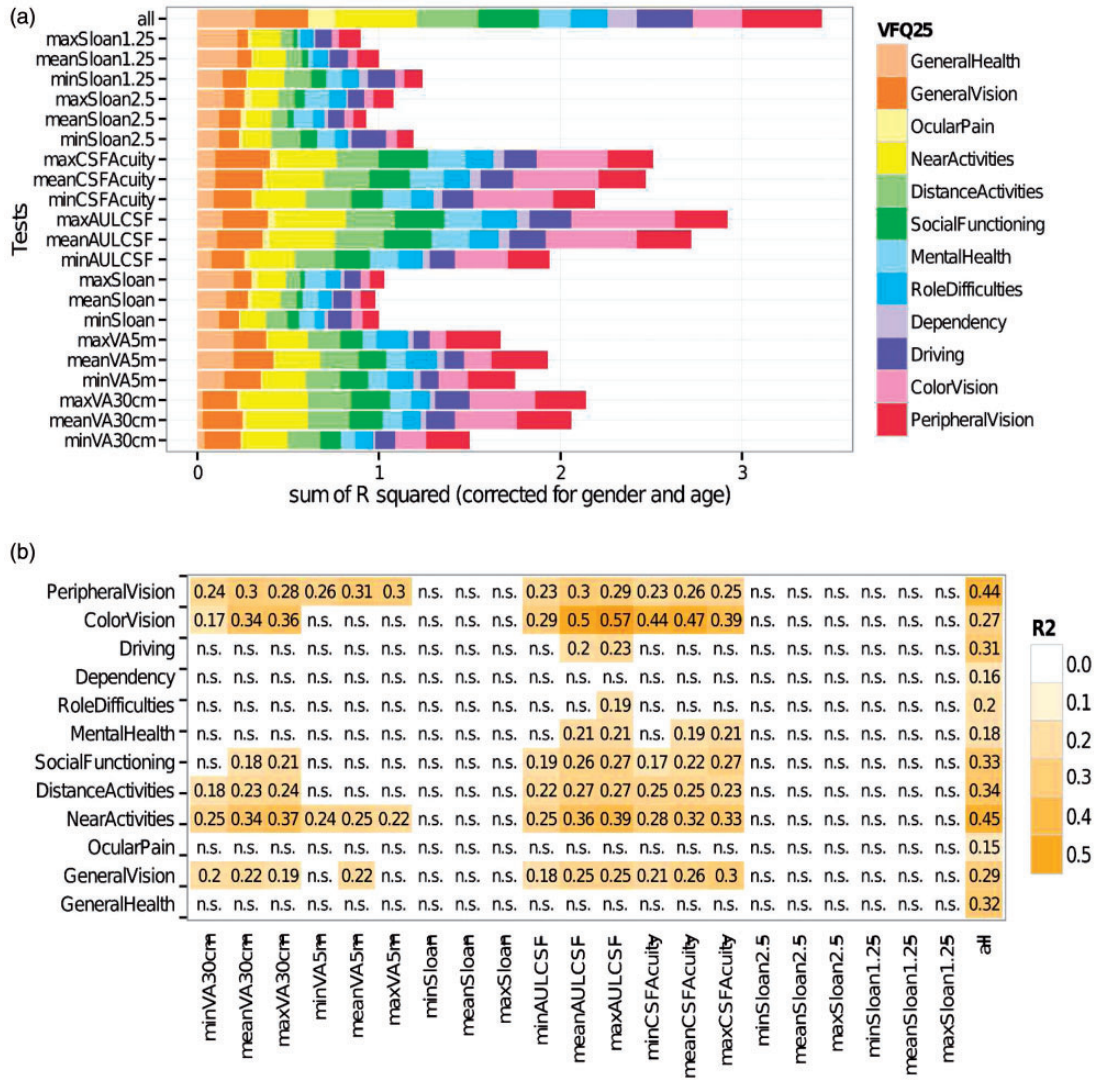

Figure 3. Association of visual tests and patient-reported visual function.
(a) Barplot with sums of R^2 values for NEIVFQ subscales (b) Table/heat map showing R^2 values after Bonferroni correction (n.s. = not significant).
R^2 from linear models with a polynomial fitting to adjust skewed distribution 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.

MRI (fMRI) activation and fMRI changes are associated with short-term adaption to contrast vision,[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.[12] Such improvements are known to be associated with neuroplasticity in the visual cortex.[23] Visual impairment caused by ocular diseases such as refraction errors was determined only by patient interviews

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.

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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.

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