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Contrast sensitivity in relapsing–remitting multiple sclerosis assessed by sine-wave gratings and angular frequency stimuli

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Abstract

Previous studies have shown that multiple sclerosis (MS) affects the visual system, mainly by reducing contrast sensitivity (CS), a function that can be assessed by measuring contrast sensitivity function (CSF). To this end, we measured both the CSF for sine-wave gratings and angular frequency stimuli with 20 participants aged between 21 and 44 years, of both genders, with normal or corrected to normal visual acuity. Of these 20 participants, there were 10 volunteers with clinically defined MS of the relapsing–remitting clinical form, with no history of optic neuritis (ON), as well as 10 healthy volunteers who served as the control group (CG). We used a forced-choice detection paradigm. The results showed reduced CS to both classes of stimuli. Differences were found for sine-wave gratings at spatial frequencies of 0.5, 1.25, and 2.5 cycles per degree (cpd) ($P < 0.002$) and for angular frequency stimuli of 4, 24, and 48 cycles/360° ($P < 0.05$). On the one hand, comparing the maxima of the respective CSFs, the CS to angular frequency stimuli (24 cycles/360°) was 1.61-fold higher than that of the CS to vertical sine-wave gratings (4.0 cpd) in the CG; for the MS group, these values were 1.55-fold higher. On the other hand, CS in the MS group attained only 75% for 24 cycles/360° and 78% for 4.0 cpd of the 100% CS estimates found for the CG at the peak frequencies. These findings suggest that MS affects the visual system, mostly at its maximum contrast sensitivities. Also, since angular frequencies and sine-wave gratings operate at distinct levels of contrast in the visual system, MS seems to affect CS at both high and low levels of contrast.

Keywords: Multiple sclerosis, Angular frequency stimuli, Contrast sensitivity, Psychophysics

Introduction

Multiple sclerosis (MS) is an inflammatory, demyelinating disease of the central nervous system that includes neurodegeneration in its pathogenesis, and it is considered a chronic, immune-mediated neurological disorder (Kornek & Lassmann, 2003; Prinster et al., 2006; Charil & Filippi, 2007; Cohen, 2009; Bendfeldt et al., 2010; Fusco et al., 2010; Havrdova et al., 2010). This disease is more prevalent in North America, Northern Europe, and the Middle East (Mortazavi et al., 2012).

Visual dysfunctions are frequent features of this disease, and optic neuritis (ON) is the most common early clinical manifestation (Glisson & Galetta, 2009). A number of recent studies conducted on MS patients with or without a history of ON assessed visual functions by using Snellen, Pelli–Robson, and Sloan 1.25% and Sloan 2.5% charts, and CS is mainly estimated with the Pelli–Robson chart. In accordance, two studies found impairments of visual acuity in people with MS using the Sloan's tables of letters that involve low levels of contrast (Fisher et al., 2006; Mowry et al., 2009). Indeed, Balcer and Frohman (2010) have argued that the traditional vision test charts that measure visual acuity with high contrast (e.g., the Snellen chart) have been insufficient in detecting subtle visual changes, including when there is no history of ON. But this is not the case when measurements involve the evaluation of visual functions at low levels of contrast (Graves et al., 2013).

In addition, Merle et al. (2010) estimated visual function employing four charts: the visual acuity Snellen chart; the Pelli–Robson chart; the Sloan 1.25% chart; and the Sloan 2.5% chart. The researchers found no differences between volunteers with MS, without a history of ON and the CG, except across both Sloan charts. Besides, they found no significant correlations between the overall average thickness of the retinal nerve fiber layer (RNFL) and the tested visual functions, including CS, for

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the MS non-ON group as compared to the CG. A more recent study by Walter et al. (2012) observed significant thinning of the macular RNFL, even in MS non-ON eyes. However, no differences were found in the ganglion cell layer (GCL), the inner plexiform layer (IPL), or across any of the other retinal layers in the same group.

Contrast sensitivity has been traditionally defined as being the reciprocal of contrast threshold, and a variation in CS over a range of spatial frequencies is described as the CSF (Campbell & Robson, 1968). The CSF is commonly described in logarithmic units of CS as a function of spatial frequency, which are normally expressed in cycles per degree (cpd) of the visual angle (Campbell, 1983). In addition, the CSF reproduces the shape of an inverted letter "U" (Leguire et al., 2011), where the peak refers to a maximum CS in human vision, and attenuation occurs at low and high spatial frequencies.

The CSF became one of the main tools used in the theoretical and clinical analysis of sight or vision structure (Adams & Courage, 2002). It has been used to characterize the response of the human visual system to elementary stimuli. And the most frequently used stimuli are vertical sine-wave gratings, which consist of spatially periodic stimuli (Cornsweet, 1970; Campbell & Maffei, 1974; Schwartz, 2004; Díez-Ajenjo & Capilla, 2010), and are defined in a cartesian system of coordinates. According to the literature, this pattern is mostly processed in the striatal (primary) areas of vision (Wilson et al., 1997; Wilkinson et al., 1998).

A research by Regan et al. (1977) presented the first results on decreased CS in MS, for the authors observed the decline in CSF exactly at the peak of sensitivity in human vision. This was also observed in a similar way, in the research of Sisto et al. (2005) using the CSV-1000 test, but with high frequencies (12 cpd and 18 cpd). In the study by Logi et al. (2001), participants with MS needed greater contrast to detect vertical sine-wave gratings, as compared to horizontal ones, when CS to spatial frequencies of 0.5, 1, 3.7, 5, 10, and 20 cpd were tested.

But, the evaluation of the specific characteristics of visual damage, or loss, is highly dependent, in part, on the spatial configuration of the stimulus pattern used in the measurements (Flanagan & Markulev, 2005). Thus, a resumption of research methods that used vertical sine-wave stimuli (e.g., Regan et al., 1977) is needed to compare the results obtained with angular frequency stimuli that are processed by different groups of neurons.

An angular frequency stimulus is defined in a polar system of coordinates (Simas, 1985; Simas & Dodwell, 1990; Gallant et al., 1993). This type of stimulus is dimensionless and independent of the distance from the observer. In this stimulus, contrast varies in accordance with angle, and angular frequencies are always given by an integer number of cycles per 360°. According to Simas (1985), the angular frequency stimulus is the result of adding an orthogonal component to the target stimulus, which is presented as radial J_0 (circular and symmetrical), as introduced previously by Kelly (Kelly, 1960; Kelly & Magnuski, 1975).

Simas et al. (1997) measured the CSF for angular frequency stimuli and vertical sine-wave gratings and compared their respective maximum contrast sensitivities. They found that the CS for angular frequency stimuli was 1.6-fold higher than that for vertical sine-wave gratings. This is probably due to the fact that patterns in polar coordinates are integrated at the post-striatal visual areas (Wilkinson et al., 2000).

There are only a few theoretical and clinical studies that have been conducted with stimuli defined by polar coordinates, particularly among MS patients. The effects of MS on CS in response to angular frequency stimuli are unprecedented in the literature on MS. Therefore, the objective of this study was to evaluate CS in adults with relapsing–remitting MS by measuring the CSF using sine-wave vertical gratings and angular frequency stimuli.

Materials and methods

Participants

This research was submitted to and approved by the Committee of Research Ethics. Volunteer participation required the signing of a consent form. The study included 20 volunteers (21–44 years old, with an average age of 30.8 ± 8.2 years), 10 of whom were diagnosed with clinically definite MS (McDonald et al., 2001; Polman et al., 2005) and of the relapsing–remitting clinical form (Lublin & Reingold, 1996). None of the subjects had ON, as verified by MRI, neuro-ophthalmologic assessment, and data from the patients' medical records. All patients were referred to the experiments during the symptom remission phase.

A selection of volunteers with the clinical form of relapsing–remitting MS is established based on the fact that over 85% of cases begin the course of this disease with this clinical expression (Courtney et al., 2009).

According to the epidemiological data from the Health Secretary of the State of Paraíba, there are 66 people with MS in the city of João Pessoa, Paraíba, Brazil. This study could only draw 46 people who were eligible to participate in the experiments; among the total of 66 individuals, two people were under 20 years and 18 were over the age of 50 years. Of the 46 adults eligible for the survey, there were a total of 25 adult respondents. However, 15 of these individuals were removed based on the following exclusion criteria: the presence of ON, cataract, strabismus, nystagmus, depression, smoking, peripheral neuropathy, glaucoma, and a visual acuity of 30/40.

The other 10 volunteers, all of which were without neurological or ophthalmological damages, were randomly selected for participation in the control group. The volunteers in the control group were chosen based both on their similarity to the ages of the experimental group (20–44 years; mean age of 28.6 ± 6.8 years), and on their occupation equivalent: graduation and high school students, or commerce employees.

The characteristics and additional clinical information about these volunteers are shown in Table 1.

Both groups had no prior knowledge of the tests, and they attended the same training session prior to the experiments. All volunteers showed satisfactory performance on tests of color vision with Ishihara plates, in addition to 20/20 visual acuity, and normal or corrected to normal vision. The latter factor was measured with Rasquin's "E" optotypes presented at high contrast, 600 cm away from the screen, monocularly (Rubin et al., 2000).

Equipment

The stimuli were presented on a 19-inch LG video monitor (cathode ray tube), which was driven by the video processor, BITS + + (Cambridge Research Systems, Rochester, United Kingdom), to increase the linear dynamic range of contrast levels. The screen luminance calibration and the gamma correction were made with a Color Cal photometer (Cambridge Research Systems).

An achromatic, static, and circular stimulus with a visual angle diameter of 4.7° was presented at the center of the display. The

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Table 1. *Clinical characteristics of participants with multiple sclerosis*

Participants	Age	Sex	EDSS[a]	Time of disease from diagnosis	Location of lesions[b]
1	28	M	3.5	1 year and 8 months	Periventricular lesions, sem iovais centers, and joint calososeptalperitrigonal
2	32	M	1.5	9 years	Periventricular lesions, sem iovais centers, and joint calososeptalperitrigonal
3	21	M	2.0	4 months	Supratentorial and periventricular lesions, especially in the corona radiata, in the center semioval; calososeptal junction, occipital lobe, posterior parahippocampalgyrus and the frontal lobe in the perisylvian region. Other lesions in the midbrain, pons, medulla, and cerebellar hemispheres
4	21	F	3.5	3 years	Periventricular lesions in central semioval, in the corona radiata, in subinsulares regions, in posterior arms of the internal capsule, in the middle cerebellar peduncles.
5	44	F	2.0	1 year	Periventricular lesions, in the semioval center, and at the calososeptal junction. Spinal cord injuries between C3 and C4
6	28	F	3.0	2 years and 6 months	Lesions at the semioval center, and in the calososeptal junction
7	32	F	1.5	3 years	Semioval lesions in the center and perpendicular to the corpus callosum, showing irregularities in the calososeptal junction
8	39	F	1.0	5 months	Periventricular lesions at the calososeptal junction. Spinal cord injuries between C2 and C6
9	21	F	2.0	4 months	Periventricular lesions, bilaterally, at the semioval center, in subcortical regions of both cerebral and cerebellar hemispheres
10	42	F	3.0	16 years	Periventricular lesions, in the semioval center, in the corpus callosum, and in the cerebellar hemispheres

[a]EDSS = expanded disability status scale (Kurtzke, 1983).
[b]Records obtained by magnetic resonance imaging, with T_2 – weighted gadolinium-enhanced and T_1 – weighted techniques.

vertical sine-wave gratings had spatial frequencies of 0.5, 1.25, 2.5, 4, 7.5, 10, and 20 cycles per degree and the angular frequency stimulus had spatial frequencies of 1, 2, 4, 24, and 48 cycles/360°. We also used a gray circle at mean luminance as the noise stimulus in the forced-choice procedure (Fig. 1).

Experimental procedures

We employed a psychophysical forced-choice method (Wetherill & Levitt, 1965) to evaluate the CS within a detection paradigm, in which the volunteer had to choose between two stimuli—one containing the test frequency (sine-wave grating or angular frequency stimulus) and the other at mean luminance (noise). This method is based on the probability of correct consecutive choices made by the participant. So, following three consecutive correct responses, contrast is decreased by 20% and, following each error, contrast is increased by 20%. Measurements of the CSF were carried out binocularly (Rubin et al., 2000) at a distance of 300 cm from the monitor display, in photopic conditions, with a mean luminance of 41.05 cd/m^2.

Participants were subjected to successive discriminations between pairs of stimuli presented at the center of the monitor screen. The order of stimulus presentation was random. Prior to each experimental session, volunteers were instructed to press the left button of the mouse (or number 1) when they perceived the test stimulus in the first presentation and the right button (or number 2) when they perceived the test stimulus in the second presentation. The experiments were only initiated when participants acknowledged that they fully understood the procedure. Each stimulus was presented for 2 s, with intervals of 1 s between stimuli. The intervals between the trials lasted a minimum of 3 s, starting only after each response was made by the participant. The experimental sessions, for each test frequency, began with contrast levels set at suprathreshold levels. The number of presentations needed to estimate the contrast threshold varied depending on the correct responses and errors made by the observer, and it also depended on the criteria of five maxima and five minima per session. Two measures for each frequency were obtained for all volunteers (those with MS and those in the CG), always on different days.

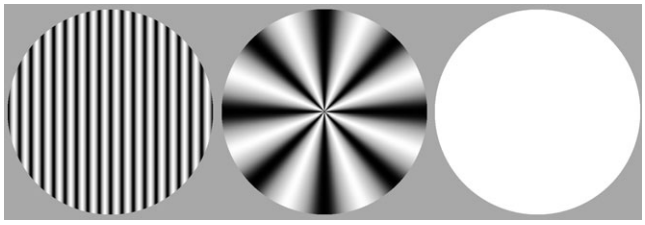


Fig. 1. Examples of visual stimuli used: vertical sine-wave grating in cpd; angular frequency in cycles/360°; and neutral at mean luminance.

Results

Fig. 2 shows the CSF for the detection of vertical sine-wave gratings for the MS group and the CG. The CSFs showed similar profiles: maximum sensitivity occurred at 4 cpd for both groups. On average, the CS of the MS group reached only 66%, 74%, 70%, 78%, 85%, 85%, and 96% for spatial frequencies of 0.5, 1.25, 2.5, 4, 7.5, 10, and 20 cpd, respectively, when compared to the CS estimates of the CG. Results from *t*-tests comparing the independent groups for each pair of spatial frequencies showed significant differences at 0.5, 1.25, and 2.5 cpd ($P < 0.002$).

Fig. 3 shows the CSF for the angular frequency stimuli in the MS group and the CG. The curves also presented similar profiles. Participants with MS reached only 85%, 77%, 68%, 75%, and 75% of the CS for the CG to detect angular spatial frequencies of 1, 2, 4, 24, and 48 cycles/360°, respectively. Results from the *t*-tests for the independent groups showed significant differences at angular spatial frequencies of 4, 24, and 48 cycles/360° ($P < 0.05$).

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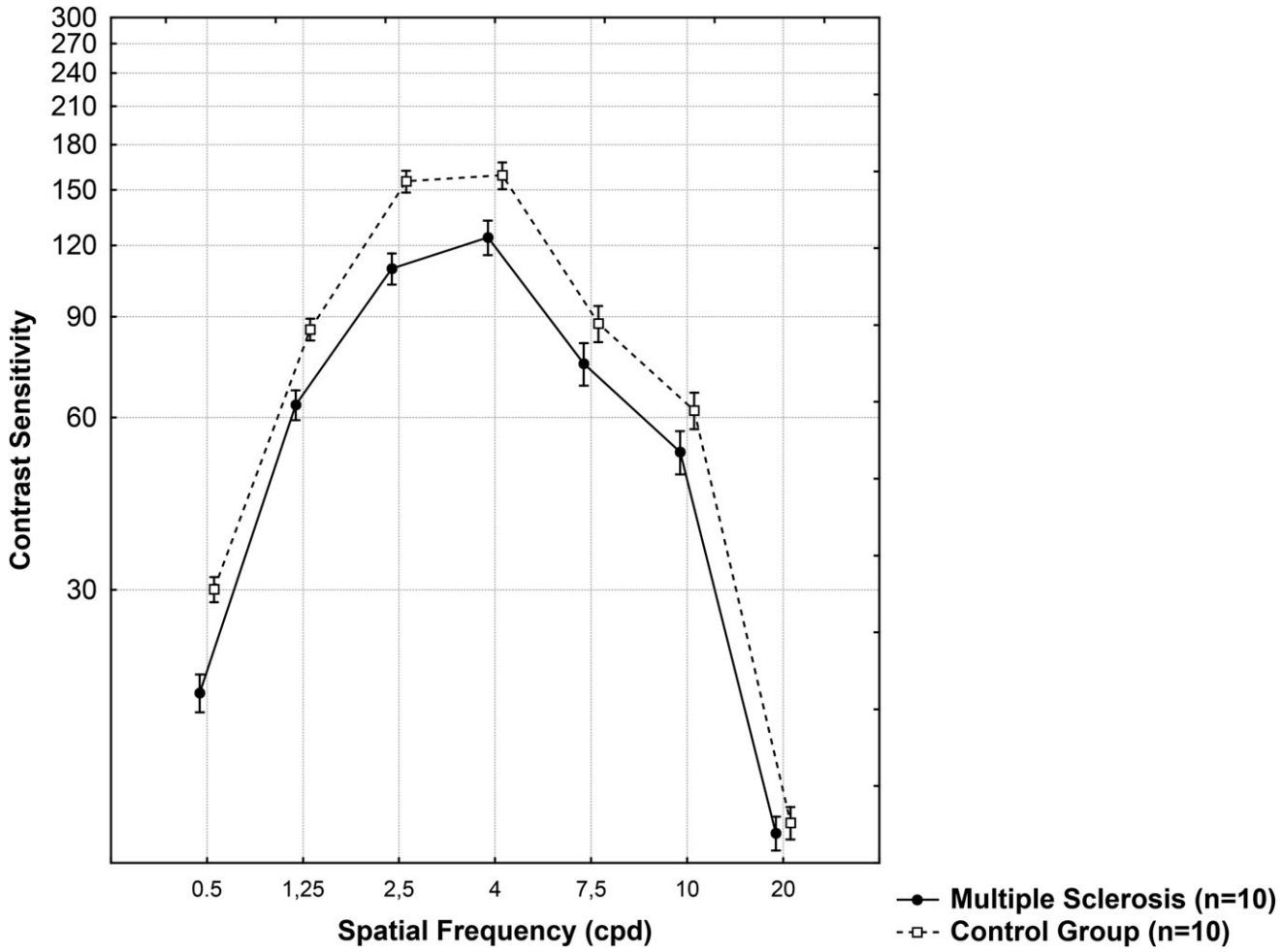


Fig. 2. Curves of CS of participants with MS and of healthy participants for vertical sine-wave gratings. The error bars are standard errors of the mean for each frequency.

Also, for the CG, measurements of the CSF yielded a maximum CS to angular frequency stimulus at 24 cycles/360°, which was 1.61-fold higher than the maximum CS to vertical sine-wave gratings at 4.0 cpd. This ration was only 1.55 for the MS group.

Discussion

This study compared the CS in adults with relapsing–remitting MS to the CS of healthy adults by measuring the CSF for two classes of spatial frequency stimuli: vertical sine-wave gratings and angular frequency stimuli. Participants with MS showed reductions in CS for sine-wave gratings at spatial frequencies of 0.5, 1.25, and 2.5 cpd and for angular spatial frequencies of 4, 24, and 48 cycles/360°. Thus, visual impairment was found at the low and middle range for sine-wave gratings and at the high range for angular frequency stimuli. Also, the objective to verify whether these changes are already seen in the initial course of the disease was attained—the response to that question is positive.

The present results are also in agreement with those from several studies, which have shown the presence of subclinical changes in the visual systems of people with MS (Sisto et al., 2005; Balcer & Frohman, 2010). And the results of the present study also reproduced the important observations made by Regan et al. (1977) regarding CS in MS.

Moreover, there are no studies to date that assessed the CS to angular frequency stimuli in MS. Thus, we chose to measure the CSF for vertical sine-wave gratings, to allow for comparisons with previous studies.

The findings of the present study also showed a ratio of 1.61 between the maximum sensitivities for the angular frequency stimuli and that for sine-wave gratings, as measured by the CG, and as found in previous studies (Simas et al., 1997). This can be better observed when comparing the performance of volunteers, as shown in Fig. 2 with those presented in Fig. 3, where a higher range of the logarithmic scale for CS to angular spatial frequencies was observed. Also, the measured CSF for sine-wave gratings by the CG replicated those found in the literature (e.g., Campbell & Robson, 1968; Campbell & Maffei, 1974).

We conclude that it is necessary to expand upon the research pertaining to how the CSF behaves in different clinical forms of MS, and the correlation of those psychophysical results with the clinical ones, in order to determine the implications of high- and low-contrast visual impairments in activities of daily living.

Finally, a novel contribution of the present study is the fact that the use of angular frequency stimuli detected losses in volunteers with MS, without a history of ON over a higher and wider range of

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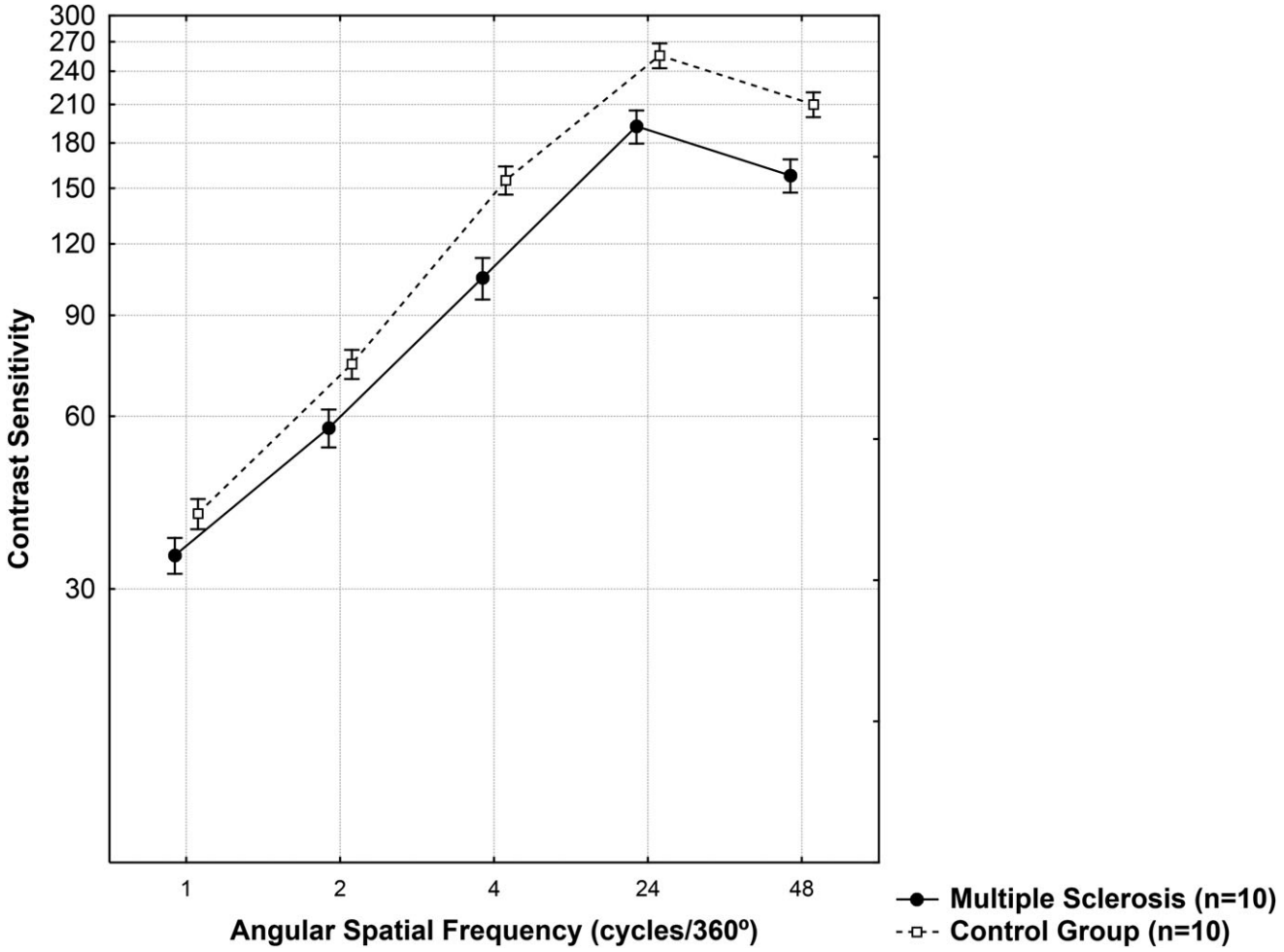


Fig. 3. Curves of CS of participants with MS and of healthy participants to angular frequency stimuli. The error bars are standard errors of the mean.

maximum CS, at high and low angular spatial frequencies. Further, we should also investigate whether the use of angular frequency stimuli allows for detection of loss of visual functions in MS prior to those detected with sine-wave gratings.

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Competing interests

The authors declare that they have no competing interests.

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