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An exploratory study of temporal integration in the peripheral retina of myopes

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An exploratory study of temporal integration in the peripheral retina of myopes

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ABSTRACT

The visual system takes time to respond to visual stimuli, neurons need to accumulate information over a time span in order to fire. Visual information perceived by the peripheral retina might be impaired by imperfect peripheral optics leading to myopia development. This study explored the effect of eccentricity, moderate myopia and peripheral refraction in temporal visual integration. Myopes and emmetropes showed similar performance at detecting briefly flashed stimuli in different retinal locations. Our results show evidence that moderate myopes have normal visual integration when refractive errors are corrected with contact lens; however, the tendency to increased temporal integration thresholds observed in myopes deserves further investigation.

Keywords: Myopia, temporal visual integration, peripheral retina, peripheral refraction

INTRODUCTION

Myopia is a global problem that affects approximately a billion people worldwide.^{1,2} As a result it is important that we know the mechanisms involved in making an eye myopic and understand the differences in visual perception that occur following the development of the bigger myopic eye. Studies of peripheral refraction have shown that myopes have relative hypermetropic shifts in the periphery while emmetropes have relative myopic shifts.³⁻⁵ This led to the suggestion that the state of image focus in the peripheral retina might be implicated in refractive error development.⁶⁻⁹ These findings have raised the possibility of identifying individuals at risk of developing myopia and eventually the opportunity of preventing its development.

Animal models also suggest that the peripheral retina could have a role in emmetropization and, in particular, in myopia development. An accepted model for emmetropization implies that there is an active feedback mechanism involving the state of focus of the retinal image which drives ocular growth to produce a final refractive state close to emmetropia or, if the habitual viewing distances are relatively short, towards an appropriate level of myopia.^{7,10} Smith et al.¹¹ damaged the central 10° of retina around the fovea in infant monkeys, but left the periphery intact: the animals still developed emmetropia. In other studies from the same group, when a hyperopic defocus was imposed in the periphery, but not in the central 10°, animals developed myopia.¹² Bitzer and Schaeffel¹³ found that blur caused by a lens can alter biochemical signals in the cells of chicken retina, providing evidence that defocus can alter physiology of the cells. In contrast, the same group of authors failed to show an effect of peripheral refraction in the development of a central refractive error.¹⁴ Recent longitudinal studies in humans provide evidence that peripheral refraction is correlated with eye elongation and myopia.¹⁵⁻¹⁷ However, causative effects of the peripheral refraction in myopic development have not been established. Thus, the role of peripheral retina and its optics in myopia development remains under scrutiny.

The temporal processing characteristics of the peripheral retina in myopes have received considerable attention in recent years, in part because there is a lack of understanding of the impact of relative peripheral refractive errors on what the peripheral retina sees. For example, Chen et al.¹⁸ studied retinal function in humans with myopia using multifocal-electroretinogram (mfERG). These studies showed that high myopes have altered temporal responses. However, participants were evaluated only after their refractive error was as high as 9D. Thus, mfERG results might be showing

the effect of refractive error mixed with the effect of neural abnormalities.¹⁹⁻²¹ Evidence that myopes have impaired temporal processing has been provided in a recent study by Kuo et al.²² Using psychophysics, Kuo found significant differences in interstimulus interval between myopes and emmetropes. These results reinforce the notion that myopes might have temporal visual processing deficits. These deficits may be linked to a mixture of factors such as, neural stretching, neural loss and differences in peripheral refraction.

The aim of the present work was to examine whether temporal integration in the peripheral retina is different between myopes and emmetropes. Recent studies using fMRI showed that lens-induced myopia reduces activity in the visual cortex.²³ That added to the evidence already given by visual evoked potentials that amplitude is reduced and latency is increased in myopia.^{24, 25} Based on previous findings, we would predict that myopes might need longer temporal integration than emmetropes at the periphery of the retina. Only low and moderate myopes were included in the study to avoid the possibilities of advanced neural loss, retinal stretching, visible retinal abnormalities or reduction of acuity associated with higher levels of myopia.

METHODS

Participants

We tested the dominant eye of 8 adults (aged 19 to 33 years) with moderate myopia, median -2.0D and standard deviation 1.0D (spherical equivalent ranging from -4.25 to -2.00D, mean cylinder 0.22D) and 8 age-matched emmetropes, mean 0.0D and standard deviation 0.30D (spherical equivalent from -0.63 to +0.75D, mean cylinder 0.37D). Participants were also matched for on-axis astigmatism (differences were investigated with t-test). All participants had best corrected monocular visual acuity in the tested eye of 10/10 or more, no previous eye disease or anisometropia and no family history of eye disease. On-axis refraction was determined through auto-refraction and refined subjectively. The study conformed to the tenets of the Declaration of Helsinki and was reviewed and approved by the Scientific Committee of the School of Sciences of Minho University. All subjects gave their informed consent to participate.

Apparatus

Peripheral and central refraction was measured using a photo-refractometer (Power Refractor, Plusoptix, Erlangen, Germany) originally designed for foveal refraction. This device has been considered precise in measuring peripheral refraction for myopia below 6D and angles up to 40°.^{9, 26}

Contrast threshold and integration time were measured using custom programs written in Matlab (MathWorks, Natick, MA) and elements of the Psychophysics toolbox^{27, 28} in a PC running windows XP with a NVideo GeForce GTS450 graphics card. The monitor was a Samsung 2233RZ (22", 1680×1050), with a refresh rate of 100Hz and background luminance of 58 cd.m⁻², this LCD monitor has been extensively tested to be used in psychophysics.²⁹

Procedure

During peripheral refraction measurements the subject sat 1m away from the instrument. Fixation targets (black pin button in a white surface) were placed at the same distance and were correctly positioned to measure peripheral refraction at 10°, 20° and 30°, nasally and temporally. Results reported at every angle are the mean of three separate measurements. Fixation targets were held on a flat surface where the central fixation point was in line with the photo-refractometer. For measurements off-axis, subjects turned their eye towards the target and the photo-refractometer remained fixed. This set up required a maximum accommodation on-axis of 1D and a minimum of 0.86D at 30°, reported refraction values have been corrected for the distance. According to Shen and colleagues soft contact lenses do not have a consistent effect on peripheral relative blur³⁰ whilst others showed that axial correction increases the precision of off-axis refractive error measurements.³¹ However, soft contact lens have an effect on relative peripheral refraction (field curvature) that we discuss below. Thus, during measurements participants with myopia were compensated with a spherical contact lens (Focus Dailies®, Ciba Vision Corporation) to correct on-axis refractive error, the power of the lens was the spherical equivalent. By correcting central refractive error we also ensured that the required accommodation was similar in both groups. Refractive measurements were converted into power vectors according to the equations below:

$$M = S + C/2;$$

$$J_0 = -(C/2) \times \cos(2\alpha);$$

$$J45 = -(C/2) \times \sin(2\alpha).$$

where M is the spherical equivalent, S the spherical power, C the cylindrical power and α the cylindrical axis, J0 (vertical/horizontal astigmatism) and J45 (oblique astigmatism) are the power of the two Jackson cross-cylinder components.³²

When measuring contrast thresholds, participants practiced before each data collection session by measuring contrast at one randomly-chosen field position: the practice data was discarded. Participants sat 57cm away from the screen fixating a black dot at the center. The task in contrast threshold and integration time was to report via button press whether a 6° vertical Gabor, centered at the position-of-retina, was tilted 30° to the right or to the left. The perceived size of the Gabor changed slightly with the amount of contrast.³³ The stimulus was presented to the right or to the left of the fixation point according to the position that we wanted to measure. For 30° of fixation the dot was shifted from the centre to avoid the stimulus being presented close to the edge of the screen.

Contrast threshold was measured three times in a random order at 6 positions-of-retina: 10°, 20° and 30° in both the temporal and the nasal retina. Threshold was calculated using Quest, an adaptive psychometric method included in the psychophysics toolbox.³⁴ For testing at 10° and 20° the spatial frequency was set at 4 cycles-per-degree and at 30° spatial frequency was set at 2 cycles-per-degree. These values were calculated to be approximately twice the resolution threshold, for the position-of-retina tested, according to Rovamo et al.³⁵ As shown in Figure 1-A, the target was preceded by a 50 milliseconds (ms) duration cue, exposed for 200 ms, and followed by a blank screen until a response was given. Contrast threshold was measured to determine the contrast of the Gabor to be used when measuring the integration time for each participant at each position of the retina. The use of individual contrast thresholds ensured that the task of visual integration was equally difficult for all participants.

Temporal integration was measured twice in random order in the same 6 positions and conditions described for contrast threshold. Contrast of the Gabor for each subject was set at twice their contrast threshold. In each block, integration time was determined using the method of constant stimuli based on 400 trials per retinal location (80 trials per exposure). As shown in Figure 1-B, the target was preceded by a 50 ms duration cue, exposed for variable periods of 10, 30, 60, 90 and 140 ms, selected in random order, and followed by a noise mask until a response was given.

Figure 1: Stimuli sequence for (A) contrast threshold measurements and (B) temporal integration measurements. In both sequences a beep was presented simultaneously with the target (Gabor).

The integration threshold was computed by fitting a sigmoid function in Origin (V8.5.0, OriginLab Corp., Northampton, MA, USA) and defined as the exposure time yielding 75% of correct responses as shown in Figure 2.

Figure 2: Example of two fitted functions to obtain temporal integration thresholds in two different blocks (10N1 and 10N2) of the same participant at 10 degrees, nasal retina.

Data analysis

In order to test for differences between myopes and emmetropes in our repeated measures design we performed a linear mixed model analysis for each dependent variable.³⁶ In these models fixed factors were “group” and “position-of-retina”. Bonferroni correction was applied for multiple comparisons. “Subjects” was assigned as a random factor, the analysis was conducted in SPSS (IBM Corporation, v21). Correlations were tested to assess associations between outcome measures.

RESULTS

Psychophysical results

Threshold for integration are shown in Figure 3 and summarized in Table 1. The estimated marginal means (EMM) combining all positions measured was 69.8 ms (standard error = 5.8 ms) for myopes and 64.0 ms (standard error = 5.9 ms) for emmetropes. The effect of position-of-retina was statistically significant, $F(5, 144) = 4.19$, $p < 0.001$. The effect of group was not statistically significant ($p = 0.50$). The interaction group×position-of-retina was also not statistically significant ($p = 0.92$).

Comparing the EMM for each position, the mean difference between 30T and 30N was 20 ms ($p = 0.01$), the mean difference between 20T and 10N was 18 ms ($p = 0.037$), the mean difference between 20T and 20N was 18 ms ($p = 0.043$) and the mean difference between 20T and 30N was 26 ms ($p = 0.001$). These results show a significant difference in temporal integration between positions at the nasal and at the temporal retina. Detailed results separated by group and position-of-retina are summarized in Table 1.

The effect of group in contrast sensitivity was not statistically significant ($p = 0.77$), the effect of position-of-retina was statistically significant, $F(5, 262) = 125.3$, $p < 0.001$. The interaction group×position-of-retina was not significant ($p = 0.85$), results are summarized in Table 1.

Figure 3: Integration time for the 6 position-of-retina. On the x axis, T letters indicate positions in the temporal retina and N letters indicate positions in the nasal retina. Differences between 30T and 30N, 20T and 10N, 20T and 20N and between 20T and 30N were statistically significant. The mean values shown are the EMM resulting from the linear mixed models analysis, error bars show the standard error for the EMM.

Table 1: Results for temporal integration and contrast sensitivity separated by position-of-retina and group. In the position-of-retina column numbers indicate eccentricity in degrees, T letters indicate positions in the temporal retina and N letters indicate positions in the nasal retina. The mean values are the estimated marginal means (EMM) resulting from the linear mixed models analysis, SE are the standard errors for the EMMs.

group	position-of-retina	temporal integration (ms)		Log10(contrast sensitivity)	
		mean	SE	mean	SE
emmetropes	30T	68.7	8.0	1.4	0.074
	20T	80.7	8.7	1.3	0.074
	10T	62.9	7.7	2.1	0.074
	10N	58.2	7.5	2.1	0.074
	20N	60.5	7.8	1.8	0.074
	30N	53.5	8.0	2.1	0.074
myopes	30T	80.5	7.8	1.4	0.074
	20T	80.1	7.8	1.2	0.074
	10T	71.2	7.5	2.2	0.074
	10N	66.2	7.8	2.0	0.074
	20N	64.2	7.7	1.8	0.074
	30N	56.5	7.5	2.1	0.074

Refractive results

Results computed directly from the photo-refractometer readings are defined as raw M values. A model with fixed factors “group” and “position-of-retina”, random factor “subjects” was constructed to test the effect of these factors in raw M. As would be expected, the myopic group showed an overall more negative M, $F(5,258)=237$, $p<0.001$, mean difference between groups was 2.25D. The effect of position-of-retina or interaction position-of-retina×group was not statistically significant ($p=0.21$). We ran the same model but now M was normalized by subtracting the central raw M from the raw M of each position-of-retina, results are shown in Figure 4. The effect of group ($p=0.82$), position-of-retina ($p=0.60$) and the interaction group×position-of-retina ($p=0.86$) were not statistically significant.

Figure 4: Variation of normalized M with eccentricity for emmetropes (open symbols) and myopes (filled symbols). On the x axis, T letters indicate positions in the temporal retina and N letters indicate positions in the nasal retina. Error bars show the 95% confidence interval.

Raw J0 values are defined as results computed directly from the photo-refractometer readings. Here we report a statistical analysis of normalized J0 only because raw and normalized produced similar results in our model. Normalization was performed with J0 as described above for M value. A model with fixed factors “group” and “position-of-retina”, random factor “subjects” was run, results are shown in Figure 5 (see also supplementary Table 1 in supplementary results). The effect of position-of-retina was statistically significant, $F(5,276) = 37.5$, $p<0.001$. The effect of group ($p=0.29$) and the interaction position-of-retina×group ($p=0.89$) were both not statistically significant. These results show that astigmatism increases with eccentricity at a higher rate in the temporal retina in both groups.³⁷

We performed for J45 the same type of normalization and statistical analysis that we performed for J0. Results are shown in Figure 6. The effect of position-of-retina was statistically significant, $F(5,276) = 23.2$, $p<0.001$. The effect of group ($p=0.430$) and the interaction position-of-retina×group ($p=0.203$) were both not significant. Pairwise comparisons indicate that J45 in the peripheral retina was small but significantly more negative in positions of the nasal retina than in the temporal in both groups (see also supplementary Table 2 in supplementary results). These results are in line with what has been found by other authors.³⁸

Figure 5: Variation of J0 with eccentricity for emmetropes (open symbols) and myopes (filled symbols). On the x axis, T letters indicate positions in the temporal retina and N letters indicate positions in the nasal retina. Error bars show the 95% confidence interval.

Figure 6: Variation of J45 with eccentricity for emmetropes (open symbols) and myopes (filled symbols). On the x axis, T letters indicate positions in the temporal retina and N letters indicate positions in the nasal retina. Error bars show the 95% confidence interval.

Correlation between outcome measures

We tested for correlation between refractive results (M, J0, J45), contrast sensitivity and temporal integration per each position-of-retina. A negative correlation was found between contrast sensitivity and temporal integration at 10 degrees nasal, $r = -0.54$ ($p < 0.031$). These results indicate that, even when stimulus contrast was optimized by subject and position-of-retina, in this position participants better contrast sensitivity led to lower temporal integration thresholds.

DISCUSSION

In this study we investigated temporal integration thresholds in myopes and emmetropes. We hypothesized that myopes would have different (extended) temporal integration times. However, we failed to find significant differences between myopes and emmetropes for temporal integration in the peripheral retina. We found differences in visual integration amongst positions of the retina and differences in the amount of astigmatism, represented by J0 and J45 in our results. The temporal retina tends to have prolonged integration times when compared with nasal retina and the amount of vertical/horizontal astigmatism was also higher in the temporal retina.

Temporal integration in myopes was not different from emmetropes. We intentionally included only moderate myopes because these are less likely to suffer from other abnormalities of the retina such as stretching and neural loss that people with high myopia can suffer.^{19, 21} Our results for integration time are in agreement with other studies. For example, Hess and Maehara³⁹ measured the delay that the visual system takes to consciously perceive brief temporal events. They found that it takes 67 ms in the fovea and 91 ms at 5° to perceive brief presented visual stimulus. Our results are also in line with other studies showing equal performance of myopes (>6D) and emmetropes, viewing centrally, in tasks such as spatial and dynamic spatial contrast sensitivity and temporal modulation sensitivity.⁴⁰ Conversely, Kou et al. (2012) studied visual processing using visual backward masking and found differences between myopes and emmetropes.²² These results are not in conflict with our study because we were testing a distinct area with a different stimulus. Kuo tested letters parafoveally and we tested Gabors at greater eccentric locations. In addition, our participants were less myopic.

We found a difference in temporal integration thresholds between positions of the temporal and nasal retina. The nasal-temporal asymmetry is hard to understand based on the expected structural changes in myopes versus emmetropes. Different studies found that eye expansion (cornea-to-retina length) with increasing myopia is more pronounced in the nasal side.^{41, 42} As Logan and colleagues observed that this finding counteracts what would be expected based on environmental factors and it remains without explanation.⁴² In contrast, superior performance of the nasal retina has been found in functional studies using electrophysiology⁴³ and psychophysics.⁴⁴⁻⁴⁶ It is known that the nasal retina has more ganglion cells than the temporal retina⁴⁷ and that is the most likely reason for our findings. However, because we used Gabors of different spatial frequencies and contrasts we need to consider our differences between retinal positions carefully. In brief, our results for temporal integration confirmed what was expected for normal observers but failed to show differences between myopes and emmetropes.

The variation of refractive error with position of the retina was similar in both groups. Our results for spherical equivalent or M at peripheral positions of the retina are in line with previous research studying peripheral refraction in children with low myopia¹⁶ or young adults.⁴⁸ Sng et al. (2011) found relative hyperopia in myopes only in one position of the retina - 30° temporal - and no differences at 15° temporal or in equivalent positions in the nasal retina.¹⁶ In this and other studies myopes with moderate and high myopia showed relative hyperopia in all peripheral positions.^{3, 16} Our peripheral refraction measurements were performed with soft contact lens and that can cut the degree of hyperopic field curvature as shown by different authors.^{30, 49} The method we used to measure peripheral refraction might also raise the question whether our relative peripheral refractive error has been affected by accommodation. However, Mathur et al.⁵⁰ have shown that these values would not be significantly altered by using a measuring technique that requires some accommodation. Astigmatism variation, J0 and J45 with position of the retina was also similar for myopes and emmetropes. Other studies also showed that astigmatism is independent of the central refractive error.^{16, 48, 51} We found higher astigmatism in the peripheral retina, which is in line with the findings of others studies summarized by Charman.⁷

Refractive power was not correlated with visual performance. Spherical error was small, similar in different positions of the retina and not correlated with visual performance. That is in agreement with previous findings showing no effect of small spherical errors (close to 2D), for example, in resolution acuity in the periphery. According to Anderson (1996), this happens because the peripheral retina is sampling limited.⁵² There was no correlation but a coincidence that J0 and temporal integration were both higher in the temporal retina than in the nasal retina. These results seem to indicate that astigmatism can impair visual performance. This is in agreement with a recent study by Lewis et al.⁵³ showing that peripheral acuity for low contrast letters can be improved when astigmatism higher than 1D is corrected. It is known that astigmatism can cause strong form deprivation.^{57, 54, 55} It is also known that astigmatism can have a pronounced detrimental effect on critical fusion frequency for small light sources.⁵⁶ Thus, we speculate that astigmatism is contributing to the poorer visual performance of the temporal retina.

This study presents two main limitations: 1) the accuracy of our experimental setup to measure contrast threshold and 2) limited statistical power due to small sample ($n=16$). The reduced accuracy of contrast measurements was mainly due to the range of 8 bits in our graphics card. However, because contrast was just an intermediate measure, we believe that the main outcome of this study, temporal integration thresholds, was not affected by this. To check whether our non-significant differences in temporal integration between groups were due to a lack of statistical power we conducted post hoc power analyses. We used GPower with power ($1 - \beta$) set at 0.80, $\alpha = 0.05$.⁵⁷ The analysis revealed that for the between-groups comparison effect size observed in the present study ($d = 0.18$), an n of approximately 35 would be needed to obtain statistical power at the recommended 0.80 level.

In conclusion, moderate myopes do not show differences in temporal integration in the peripheral retina when compared with emmetropes. Further studies, with more participants and myopes with higher refractive error are desirable to explore whether myopes with relative hyperopia in the periphery show temporal integration deficits.

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SUPPLEMENTARY RESULTS

Supplementary Table 1: Mean differences in dioptres of normalized J0 between positions-of-retina. Values on the table were obtained by subtracting J0 of position-of-retina specified in rows of the first column from J0 corresponding to the position-of-retina specified in the column heading.

	20T	10T	10N	20N	30N
30T	-0.52***	-1.1***	-1.4***	-1.1***	-0.7***
20T		-0.6***	-0.9***	-0.6***	-0.1
10T			-0.3	0.0	0.4*
10N				0.3	0.7
20N					0.5*

*** The mean difference is significant at the 0.001 level; * The mean difference is significant at the 0.05 level

Supplementary Table 2: Mean differences in dioptres of normalized J45 between positions-of-retina. Values on the table were obtained by subtracting J45 of position-of-retina specified in rows of the first column from J45 corresponding to the position-of-retina specified in the column heading.

	20T	10T	10N	20N	30N
30T	0.004	0.073	0.3**	0.4***	0.5***
20T		0.07	0.3**	0.4***	0.5***
10T			0.2*	0.4***	0.5***
10N				0.2	0.2**
20N					0.1

*** The mean difference is significant at the 0.001 level; **The mean difference is significant at the 0.01 level; * The mean difference is significant at the 0.05 level