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Evidence for M_y-cell Involvement in the Spatial Frequency Doubled Illusion as Revealed by 'a Multiple Region PERG for Glaucoma.

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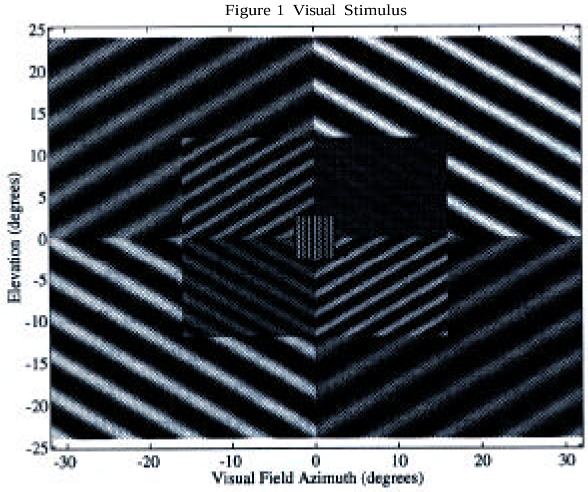
Introduction

Recent evidence suggests that glaucoma leads to early loss of large retinal ganglion cell[1,2] projecting to the Magnocellular layers of the dLGN: the so called "M" retinal ganglion cells. It is necessary for the present study, to appreciate that there are two subgroups of M-cells, the M_x-cells which are quite linear, and the nonlinearly responding M_y-cells, where the subscripts indicate physiological similarities with cat X and Y-cells[3]. In particular the retinal gain control described by Shapley and Victor[4] for cat X and Y cells is strongly expressed in primate M-cells[5]. Except at very low temporal frequencies the quadratic response of Y-cells is larger than the linear response, especially at low spatial frequencies[6], and the gain control effects Y-cells more, especially their quadratic response[7] At least three studies indicate that M_y-cells are larger than M_x-cells[8,9,10]. Therefore, methods for glaucoma diagnosis should perhaps appeal to M_y-cell physiology, e.g. the strong effects of gain control upon their nonlinear responses.

Figure 1 Visual Stimulus



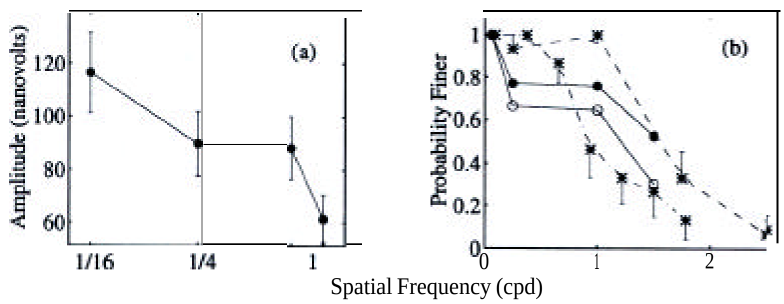
There is an increasing body of evidence suggesting that the frequency doubled (FD) illusion of Kelly[11] corresponds to retinal activity being dominated by M_y-cell responses due to the effects of gain control. The FD effect is that low spatial frequency gratings modulated at high temporal frequencies are seen with twice the original spatial frequency. The mechanism producing the illusion appears to be monocular[12], and was first suggested by Tyler[12] to involve retinal ganglion cells with rectified response components like the M_y-cells. In agreement with this idea the functional form[13] of the rectifier producing the illusion: Response $\propto |\text{Contrast}|^z$ ($z=0.7$), is the same as that producing the characteristic Y-cells[6] response. The spatiotemporal region over which the FD illusion is seen corresponds to where gain control would permit M_y-cell activity to dominate our visual percept. Further support for M_y-cells producing the FD illusion comes from psychophysical investigations in our laboratory showing that the density of the array of units producing the FD illusion is similar to that of the M_y system[14] Also, psychophysical experiments using FD stimuli[15,16] can have false positive and negative rates of about 2% for discriminating glaucoma and normal subjects, as might be predicted if the FD illusion corresponded to M_y-cell function.

Optic nerve transection studies[17] and current source density analysis[18] indicate that in primates the pattern electroretinogram (PERG) is generated by the inner plexiform and ganglion cell layers. Macular[2] as well as peripheral damage occurs in early glaucoma. Taking the above into account we designed a PERG having visual stimuli which were scaled with respect to M_y-cell density on the retina, which exploited the FD illusion, and which had multiple stimulus zones so that we could compare our results with perimetry. A clinical trial with this PERG method showed significant correlation with perimetry[19] and evidence for earlier detection of glaucomatous damage by the new PERG was also provided. The present paper seeks to examine if (1) the spatial frequency roll-off of PERG responses is like that for the FD illusion and (2) whether or not contrast dependent phase shifts characteristic of retinal gain control, most strongly expressed in Y-type cells, are observed for PERGs obtained with FD stimuli. Such results would strongly implicate M_y-cells in the perception of the FD illusion.

Methods

Subjects: This study employed 9 normal subjects from a larger study group of 86 subjects used in our clinical trials.
Visual Stimuli and analysis: The face of the monitor was divided in 9 "zones "or "regions" as shown Fig. 1. Each region contained an achromatic (6500° K) sinusoidal grating with a mean luminance of 45 cd m^{-2}. A fixation spot was presented in the centre of the monitor. In the spatial frequency dependence experiments the grating orientation was like that in Fig. 1. In all other experiments all gratings had horizontally oriented stripes. In the basic method the inner zone contained a 3/4 c.p.d. grating, the middle and outer zones contained 1/4 and 1/8 c.p.d. gratings respectively. Thus, grating scale increased with eccentricity. Fig. 1 represents 1 frame of our video sequence but where the spatial frequency has been doubled to illustrate the perceived pattern. Spatial frequency was varied such that the spatial frequencies of all regions were scaled by *en ensemble* by: 0.25, 1, 2, 4 or 6. To permit extraction of responses to the different regions while recording with one electrode the contrast of each stimulus region was sinusoidally modulated in time, each region at a slightly different frequency (hence Fig. 1 shows different contrasts in different zones due to asynchronous temporal modulation of the zones). The video frame rate was 101.50 Hz (non interlaced) and a single stimulus sequence contained 4096 frames of video providing an overall stimulus duration of 40.354 s. The PERG signals were typically amplified 10 times and sampled at 4 times the video frame rate, and synchronous with frame onset. Response components were extracted by the fast Fourier transform (FFT), the run length providing a temporal frequency resolution ΔF of 0.0248 Hz.

Figure 2 - Spatial Frequency Dependence



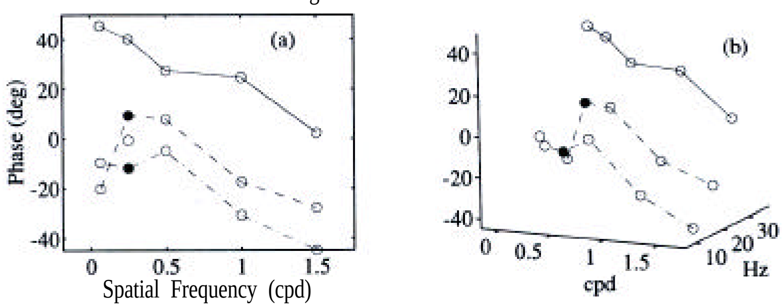
For the FFT signal extraction process to work we needed to have an orthogonal design i.e. it was necessary for all 9 frequencies $\{f_1, f_2, \ldots f_9\}$ to contain an integral number of cycles over the 4096 video frames. Since we are interested in the second harmonics it was also necessary that no two sum frequencies $\{ f_i + f_j \}$ should equal any of the 9 second harmonic frequencies. If sum frequencies, $f_i + f_j$, appeared in the record they would represent interaction or light scattering between the stimulus zones. The actual stimulus frequencies were integer multiples of $\Delta F * \{ 889, 893, 898, 904, 911, 921, 935, 947, 955 \}$. Alternative temporal frequencies where created by subtracting 225, 375, 525, 675 from the 9 frequency indices. In general we ran several repeats of the 40 s stimulus sequence. The FFT was computed for each sequence and the complex Fourier transfer coefficients were averaged. We extracted the second harmonics $\{ f_i + f_j \}$; the interaction frequencies $\{ f_i + f_j \; i \neq j \}$ and all the remaining "noise" frequencies in the band $2f_1$ to $2f_9$ The significance of a frequency component is related to its amplitude, which is the modulus of the Fourier transform coefficient at that frequency, A(f). A test of significance for a particular frequency can be done as follows. Under a null hypothesis of no signal, the real and imaginary parts of the Fourier Transform coefficients, Real(A(f)) and Imag(A(f)) are independent normal variates with zero mean and some variance σ^2. The squared modulus of the coefficient, $|A(f)|^2$ is then σ^2 times a Chi-squared variate on 2 degrees of freedom. An estimate σ^2 of s^2 is obtained from frequencies not in the set of second order stimulus frequencies, and a one-sided F-test can be done for the significance of the extra signal amplitude at the second harmonic frequencies. For large n the F-test is closely approximated by a Chi-squared test, the test statistic being $|A(f)|^2 / s^2$ with 2 degrees of freedom. Only significant PERG amplitudes ($p < 0.05$) are reported on here and p values < 0.001 were common.

Results

As pointed out by Tyler[12] the expectation is that local generators of the FD illusion would respond at twice the stimulus frequency. Normal PERG signals are mainly second harmonics (the phase of second harmonics are also doubled, thus phases from eye regions viewing dark and bright regions will differ by 2π rather than π and so add) but nevertheless a finding of no strong second harmonics while viewing FD stimuli would preclude the involvement of the retina and M_y-cells. All subjects showed strong PERG amplitudes during FD stimulation.

One characteristic of the FD illusion is that the illusion fades with increasing spatial frequency. We therefore examined if the PERG components had any particular spatial frequency dependence. We tested 9 subjects with visual stimuli where the spatial frequencies of the grating patterns of all regions were scaled up or down compared to Fig. 1. The temporal modulation frequencies were the highest described in Methods, and had a central frequency of 0.0248*911 = 22.59 Hz. Fig. 2a,b summarises the results for 4 test patterns. The spatial frequencies shown correspond to the frequencies of the middle 4 stimuli because this region compares well with previous psychophysical methods[11,12,13] There is a marked roll-off in mean PERG amplitude of the central 4 regions, as a function of increasing spatial frequency (Fig. 2a). All stimulus regions behaved in the same way. In separate experiments (where subjects judged apparent spatial frequency of temporally modulated gratings against an unmodulated standard) we measured the probability of seeing the FD illusion as a function of spatial frequency at retinal eccentricities of 2.52° (Fig. 2b, dashed) and 10° (Fig. 2b, dashdot), which span the eccentricities of the middle 4 stimulus regions. Fig. 2b shows two scaled versions of Fig. 2a where either the baseline noise has (open circles), or has not (solid circles) been subtracted prior to scaling.

Figure 3 - Phase Difference



Our next experiment sought to examine whether phase shifts characteristic of the gain control so strongly expressed in Y-cells, and which acts very strongly upon their quadratic response[6,7]. could be observed in our PERG records. More specifically Shapley and Victor[7] showed that the properties of the nonlinear Y pathway could, to a first approximation, be described by a classical linear/static nonlinear/linear (LNL) sandwich model. The main departure from this model was a parametric dependence on contrast of the phase lag produced by the leading linear filter[7]. For a multiple frequency input this translates into a phase advance for sum frequencies ($f_i + f_j$) but not difference frequencies ($f_i - f_j$). If the FD illusion were due to the dominance of retinal activity of Y-cells whose activity was enhanced by gain control one would therefore expect phase advances of second harmonic responses ($f_i + f_j$) as a function of increasing contrast which would be particularly large in the spatiotemporal region where the FD illusion is seen. To that end we tested at a range of spatial scales, temporal frequencies, at 2 contrasts: 0.4 and 0.8. Figure 3a,b shows that the difference in phases obtained at the two contrasts are characterised by increasing phase advances as temporal frequency and grating period increase. (The spatial frequencies indicated are those of the middle 4 regions, the temporal frequencies are the middle output temporal frequency of the 9 second harmonics: solid line 33.95, dashed 26.51, dashdot 19.08, single pt 11.64 Hz). The largest advances correspond to the spatiotemporal region where the FD illusion is seen, and where gain control is expected to effect Y-cell physiology most. The figures shown represent the median phase difference for the nine stimulus regions. The results for each stimulus region were very similar to Fig. 3. There are, however, systematic differences in the behaviour of the 9 retinal regions measured (not shown). In particular contrast dependent changes were largest for superior retina and some interesting naso-temporal differences were also observed. Another set of experiments (not'shown) using a broader range of contrasts suggests different contrast gain control strategies operate in central versus peripheral retina.

Discussion

The PERG results obtained with this particular selection of spatial and temporal frequencies has previously been shown to be strongly correlated with glaucomatous damage[19], and these PERG results are also strongly correlated with accurate psychophysical tests for glaucoma which are also based on the FD illusion[16]. The spatial frequency roll-off of the PERG signal in this spatio-temporal region is similar to that for the FD illusion and in line with the expectation for Y-cell nonlinear response[6]. Most importantly contrast dependent phase advances characteristic of contrast gain control acting upon the nonlinear response components of Y-like retinal ganglion cells[7] was most strongly observed from PERG responses to stimulation in the spatiotemporal region where the FD illusion is observed. These results when taken conjunction indicate that the FD illusion is likely to be produced in the human retina by M_y-cells. Since M_y-cells appear to be the largest retinal ganglion cells[8,9,10] it is not surprising that results obtained with tests based on the FD illusion are strongly correlated with glaucomatous damage,

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