Characterizing early temporal filters of melanopsin and cones by non-linearities in visual pathway

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I. Introduction

Photophobia is a common symptom in many diseases such as migraine and mild traumatic brain injury (TBI). Therefore, they might all share some certain abnormal changes in the visual pathway, namely, the enhanced sensitivity to light. As suggested by previous studies (Stringham 2003), the discomfort is selectively more severe for the short-wavelength (blueish) than the long-wavelength light. Hence, the effect of different photoreceptors on photophobia might vary.

The intrinsically photosensitive retinal ganglion cell (ipRGC) containing the photopigment melanopsin is a good candidate because its spectral sensitivity is tuned to the short-wavelength region (with the peak roughly at cyan) and ipRGC projects to thalamus which has been suggested to involve in the painful feeling through its connection to trigeminal nerve.

Because the pupillary light reflex (PLR) is controlled by all photoreceptors including ipRGC, it is a useful metric to characterize the temporal transfer function (TTF) of ipRGC. Nevertheless, due to the low-pass property of PLR-controlled system, we cannot obtain significant responses beyond 5 Hz with the sinusoidal flicker stimulus. Owing to the non-linearities of the visual pathway, we can get around the problem by using the amplitude-modulated flicker to measure the TTF of the early photopigment-selective filters (Stockmann & Plummer, 1998).

II. Method

1. Stimuli

The stimuli were uniform disks subtending 27.5° visual angle with the central 5° blocked and the mean light level of 1125 cd/m2. Using the silent substitution method, the light spectral content of the disk is temporally amplitude-modulated to selectively stimulate specific combinations of photopigments (L+M, S, Melanopsin). The formula of the amplitude-modulated stimulus is:

$$A(t) = m[0.5 + 0.5\cos(2\pi f_m t)]\sin(2\pi f_c t)$$

where *A(t)* is the contrast, f_m is the envelope frequency, f_c is the carrier frequency and m is the modulation level. The modulation level was set to 100% for all stimuli. Fig. 1a shows the contrast of the amplitude-modulated flicker as a function of time. The spectral power distributions of the stimuli driving three modulation directions are shown in Fig. 1b with three example spectra: stimulation (black), neutral (gray) and suppression (red).

A digital light synthesizer (Onelight) was used to generate the desired flickering stimuli. The basic mechanism of this system is as follows. Light from an arc lamp is filtered to produce a collimated beam of light which is then passed through a diffraction grating to spatially split the wavelengths contained in the visible spectrum. This wavelength-split light is then projected onto an array of micro-mirrors with each column aligned to a narrow window of wavelength. The micro-mirrors are binary so we can adjust the intensity of wavelength bands by turning on

a certain number of rows in each column. There are 1024 columns and 768 rows. The temporal resolution of Onelight system is 500 Hz.

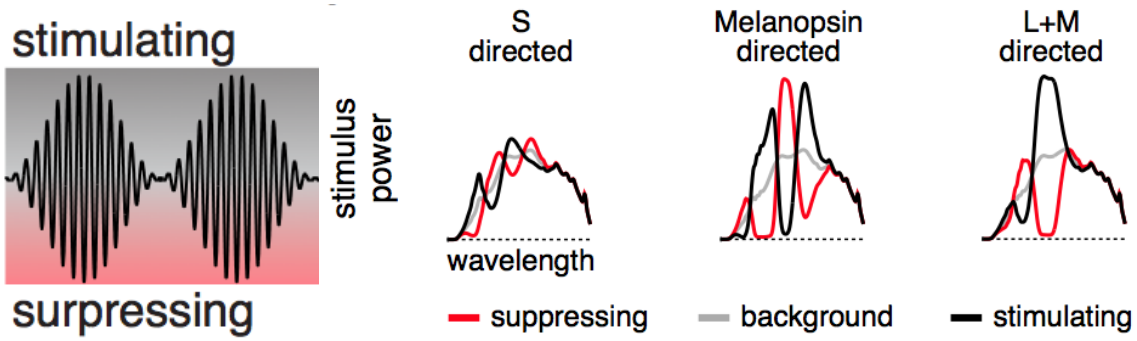


Figure 1

2. *Experimental procedure*

Fig. 2 shows the general setup of the experiment. Subjects' right eyes were pharmacologically dilated with 0.5% proparacaine hydrochloride and viewed the stimuli through a custom-made artificial pupil of 4.7 mm in diameter. The left eyes were tracked by a video eye tracker (Cambridge Research Systems Ltd) to record the pupil diameter at the sampling rate of 50 Hz. A Macintosh computer (MacPro 2.66 quad core, 12 GB RAM) controlled the Onelight system and receives signal from a button box used in the experiment through USB ports. A Windows desktop machine (Dell Optiplex 790, Intel Core i3-2120 CPU @ 3.30GHz and 2 GB RAM) was used to record the pupil data from the eye tracker through the PICOLO frame grabber. The Matlab UDP protocol was employed for the communication between these two computers.

There are 5 blocks for each stimulation direction (L+M, S or Melanopsin) and 17 trials in each block. The first trial in each block was always a 5-minute adaptation period in which the subjects merely viewed the constant background light. After the adaptation trial, the subjects pressed a button on the button box to start a trial and the eye tracker collected 5 seconds of data. If there were more than 5 valid data points, the amplitude-modulated stimuli began; otherwise, a beep tone was played and the subjects would restart the checking process by pressing a button on the button box. We used 4 carrier frequencies (5, 10, 20, 40 Hz) and 1 modulation frequency (0.5 Hz). The carrier modulation contrast was 45% for all stimuli. We also jittered the phase of stimuli by 0, 90, 180 and 270 degree (or 0, 1/4, 1/2 and 3/4 of one envelope cycle). The carrier frequency and phase were counterbalanced in each block so that each trial corresponded to one combination of carrier frequency and phase.

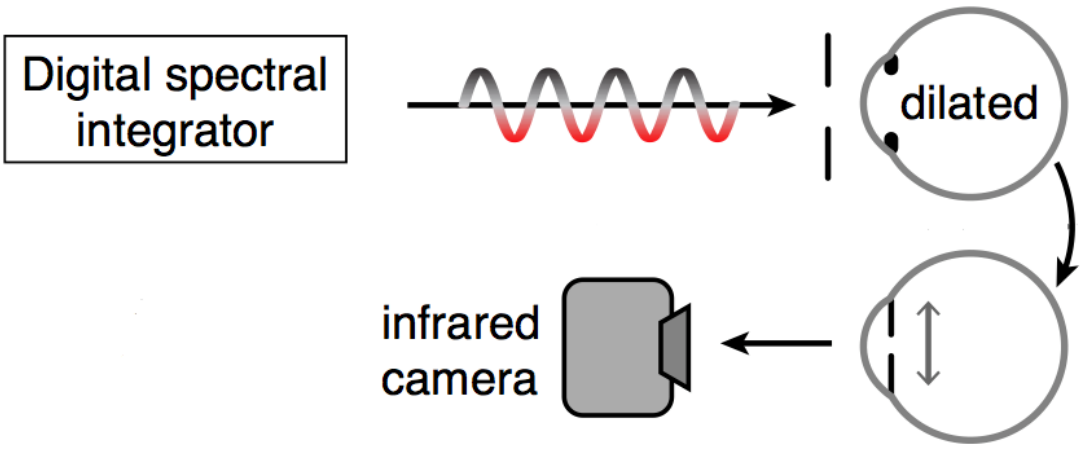


Figure 2

3. Distortion product by nonlinearities

In Stockmann & Plummer (1998), the authors suggested a linear-nonlinear-linear model of the human visual pathway to account for the failure of Talbot-Plateau law in the S-cone pathway. In Fig. 3, the schematic diagram of the model is shown on the left and the frequency representation of the stimulus at various stages is shown on the right. The first linear filter represents early filtering stage of the visual pathway with a gradual roll-off at high frequency. The middle filter demonstrates the nonliniarities in the human visual pathway. Due to this nonlinear property, distortion products are produced at the fundamental and harmonic frequencies of the envelope in the amplitude-modulated stimuli. The last linear filter with steep roll-off at high frequency will filter out the high-frequency component of the amplitude-modulated signal but leave the distortion product intact, especially at the fundamental frequency of the envelope.

Therefore, we can characterize the high-frequency range of the early filter by varying the carrier frequency while fixing the envelope frequency as shown in Fig. 4. From previous works, we know that the pupillary control system at the late filtering stage shows little sensitivity beyond 5 Hz. Hence, if we vary the carrier frequency from 5 Hz to 40 Hz and keep the envelope frequency at 0.5 Hz, we will be able to identify the early filter in this frequency range.

4. Checking for nonlinear artifacts in devices

To make sure that the distortion product is only due to the nonlinearities in the human visual pathway and not some artifacts in the devices, we measured the amplitude-modulated stimuli generated by the Onelight using a colorimeter (Klein K10-A, Klein Instruments Inc.). The sampling rate of the Klein K10-A is 256 Hz.

The amplitude-modulated stimulation of the luminance L+M channel was used with envelope frequency of 1 Hz and 4 carrier frequencies of 10, 20, 40 and 80 Hz. The measured frequency spectra for L+M and Mel direction are shown in Fig. 5. It is clear that there is no power at 1 Hz and a clear signal at the carrier frequencies for the L+M direction. Due to some splatter in the stimulation, we still see some power along the Mel direction but it is not significant compared to L+M (9.5% compared to 48%).

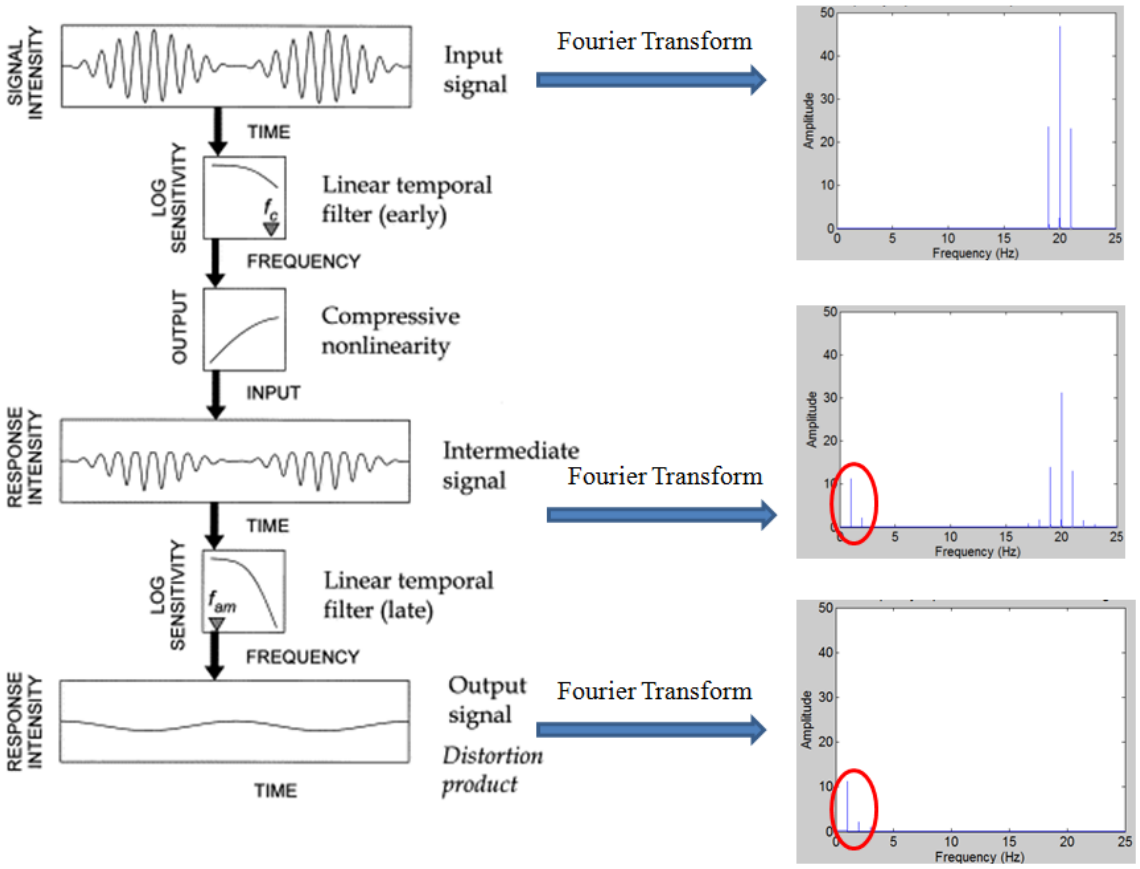


Figure 3

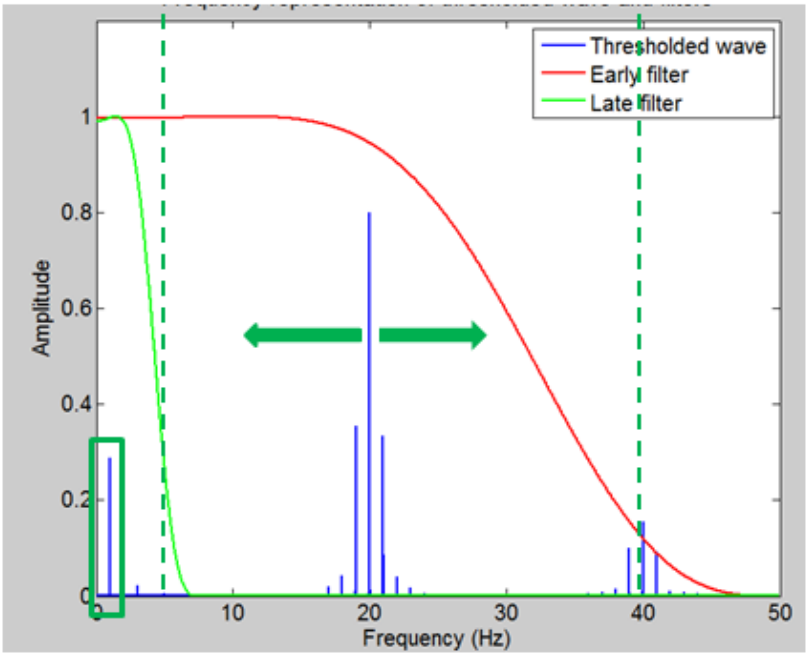


Figure 4

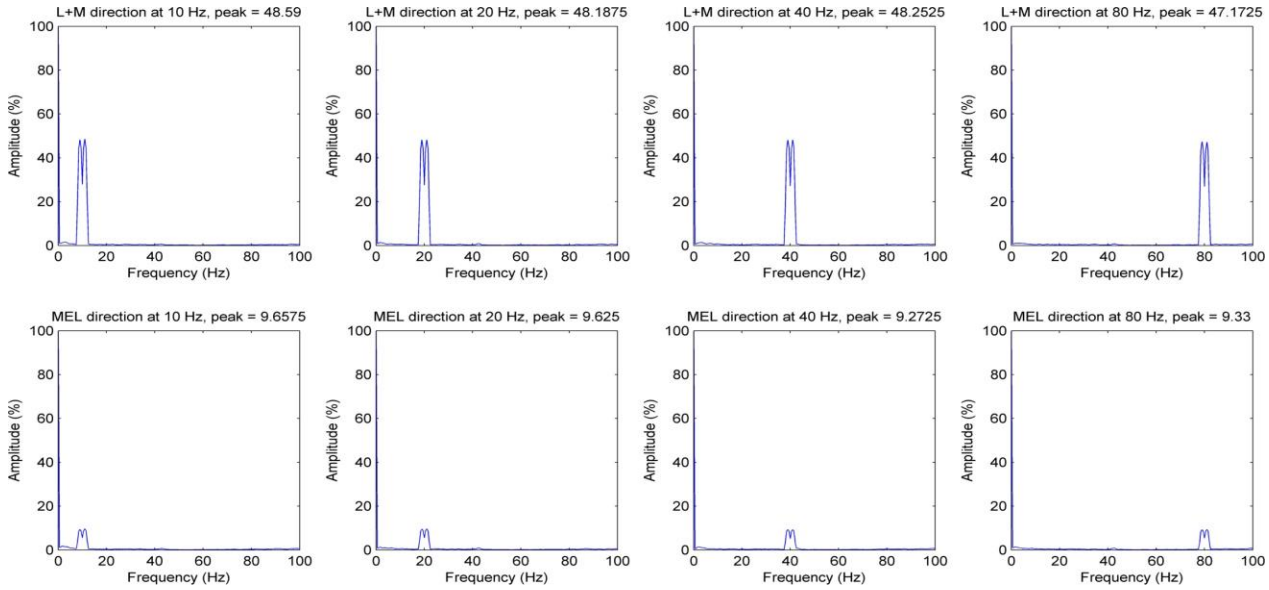


Figure 5

5. Data analysis

The pupil diameter data were preprocessed by removing the spikes and outliers and then smoothed by a Savitzky-Golay filter. To correct for the phase jitter of the modulation in the experiment, each time series is then aligned back to the zero phase position and is normalized as percent signal change relative to the mean pupil diameter of each subject. The resulting time series were then regressed on the cosine and sine waves of envelope frequency to extract the amplitude at that frequency. The amplitude data are then averaged across trials for each carrier frequency and stimulated channel to obtain the TTF.

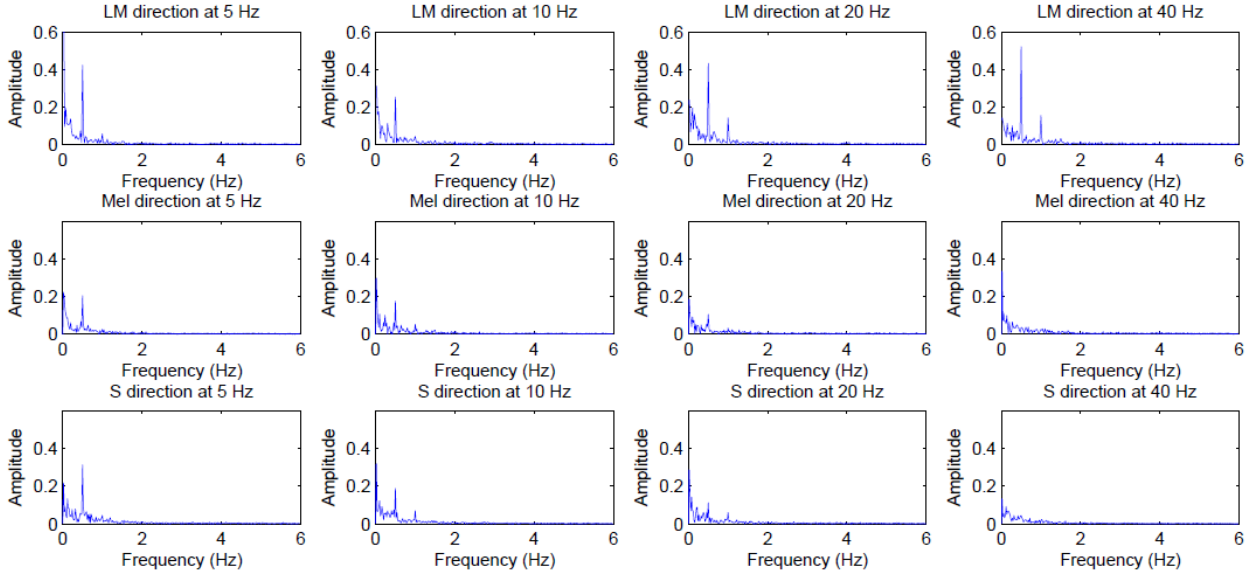
III. Result

As a check for the signature of the product distortion, the frequency spectra of the averaged pupil diameter data are computed. Fig. 6 presents the result for 2 subjects LL and MS. The row indicates carrier frequency and the column indicates the stimulation direction. The distortion product at 0.5 Hz can be seen clearly for low carrier frequencies and vanishes at high frequencies. A notable feature is the distortion product at the harmonic frequency 1 Hz in some cases but it is not robust.

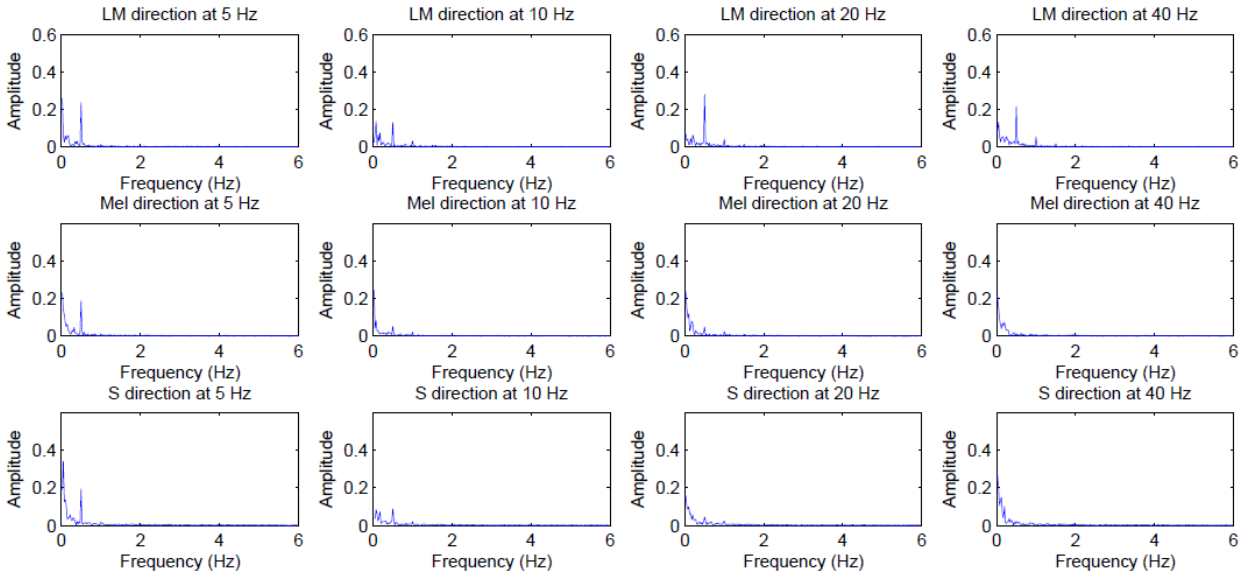
The TTFs of three stimulation directions (L+M, S or Melanopsin) are shown in Fig. 7. The general shapes of TTFs are quite consistent across the two subjects. Specifically, the filtering properties of Mel and S channel are quite similar which might imply a common early filter for these two pathways. In contrast, the shape of L+M filter is distinct from the others, especially at higher frequencies (20 and 40 Hz). An interesting feature of L+M TTF is the dip at 10 Hz which is consistent for both subjects. A subject reported that at 10 Hz, the L+M stimulus turn from chromatic to achromatic. So it might be the effect of the L+M-S channel.

Due to the high amplitude at 40 Hz of L+M TTF, we ran more experiment at this frequency and at 80 and 160 Hz of carrier frequency to full characterize this channel. The iso-channel stimulation was also added to test the combined effect of all channels. The result is shown in Fig. 8. The L+M TTFs of two subjects show a roll-off at higher frequencies. Also, the Iso

channel TTF appears to follow the shape of L+M channel but with lower amplitude, especially at low frequencies as in subject LL. So it appears to reflect the combination of L+M, S and Mel channel.



a) Subject LL



b) Subject MS

Figure 6

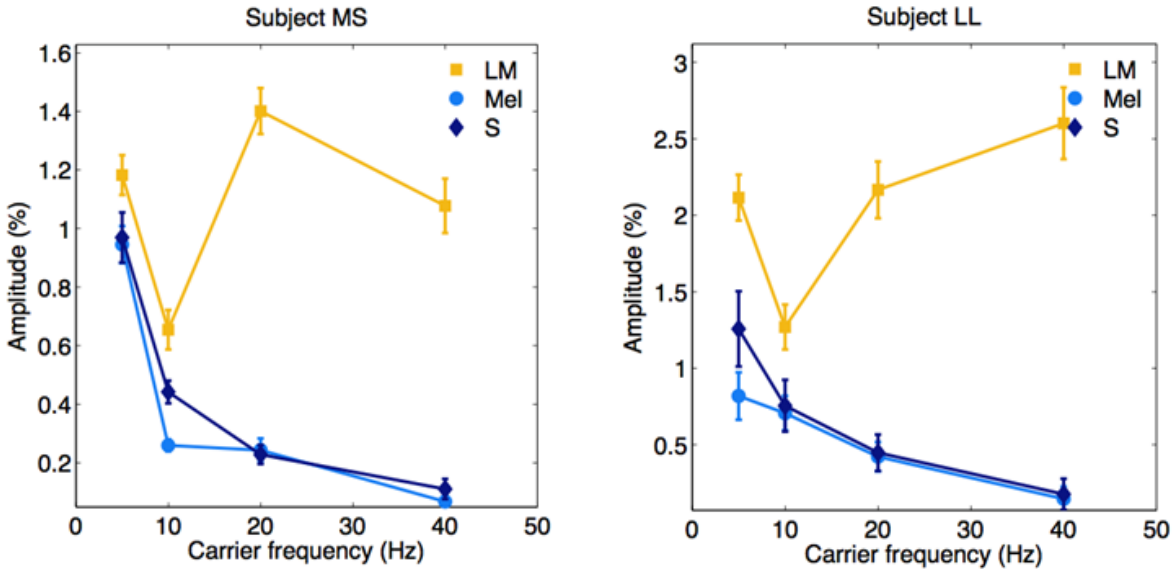


Figure 7

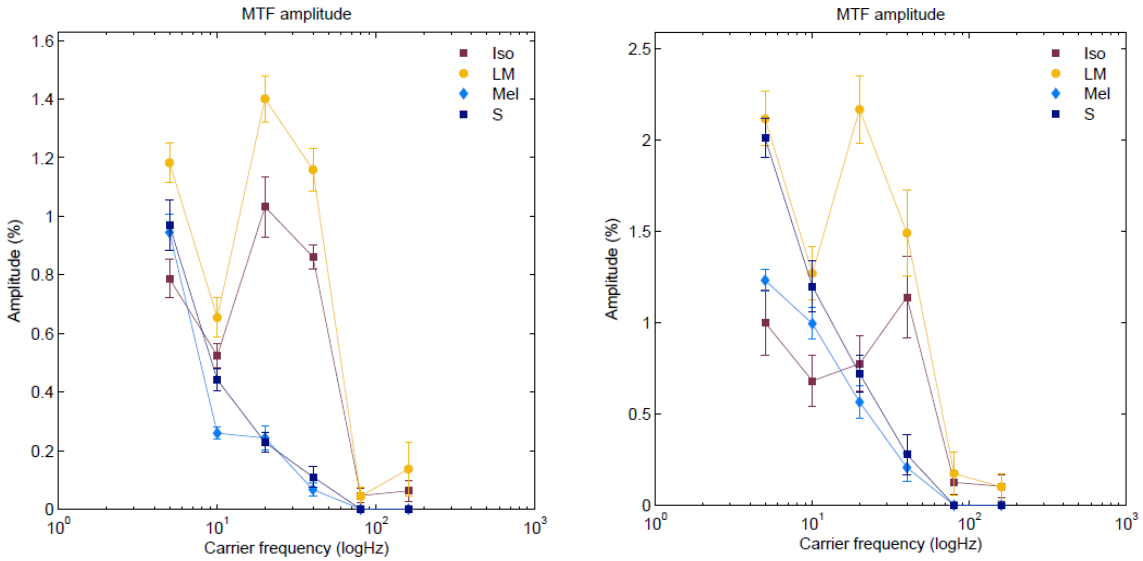


Figure 8

IV. Discussion

The clear distortion product found in the experiment shows that the nonlinearity appears after an early filtering stage and demonstrates the usefulness of the amplitude-modulated flicker as a proxy to study to properties of early processing in visual pathway such as the retinal circuitry. Furthermore, the result hints at interesting features of the early filters for different photoreceptors' pathway. Specifically, the similarity of S and Mel TTFs might indicate some early processing shared by these two photoreceptors. On the other hand, the dip of L+M TTF may be due to separate early mechanisms of the luminance channel. Finally, the shape of iso channel could be the combination result of L+M, S and Mel channels both in amplitude and phase and further investigation into the phases of all the channels may be able to explain this.

Reference:

Stockman A., Plummer D. J. (1998). Color from invisible flicker: A failure of the Talbot-Plateau law caused by an early "hard" saturating nonlinearity used to partition the human short-wave cone pathway. *Vision Research*, 38, 3703–3728.

Stringham, J. M., Fuld, K., & Wenzel, A. J. (2003). Action spectrum for photophobia. JOSA A, 20(10), 1852-1858.