Extrinsic cone-mediated post-receptoral noise inhibits the rod temporal impulse response function

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Received 2 November 2017; revised 17 January 2018; accepted 21 January 2018; posted 22 January 2018 (Doc. ID 312436); published 16 February 2018

We determined how extrinsic white noise correlating with cone inputs to the three primary visual pathways affects both rod-pathway temporal contrast sensitivity and the impulse response function. A four-primary photostimulator provided independent control of rod and cone photoreceptor excitations under mesopic illumination (20 photopic Td). We show that rod-pathway temporal contrast sensitivity uniformly decreases across all temporal frequencies in the presence of cone noise correlating with the inferred magnocellular, parvocellular, or koniocellular pathways. The rod-pathway temporal impulse response functions derived using the Stork–Falk procedure (with a minimum phase assumption) had lower amplitudes in the pathway-specific cone noise. Therefore, cone noise impairs rod-pathway temporal contrast sensitivity without delaying rod-pathway signal transmission.

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OCIS codes: (330.0330) Vision, color, and visual optics; (330.1800) Vision - contrast sensitivity; (330.5510) Psychophysics.
https://doi.org/10.1364/JOSAA.35.000B72

1. INTRODUCTION

Rod-mediated vision typically exhibits a low-pass temporal contrast sensitivity function (TCSF) [1–7] and a monophasic impulse response function (IRF) [8,9]. A rod signal at mesopic light levels can access to all three post-receptoral pathways [i.e., magnocellular (MC), parvocellular (PC), and koniocellular (KC)] either through rod–cone gap junctions (fast pathway) or rod bipolar cells (slow pathway), as evidenced by physiological [10–14] and psychophysical studies (reviewed in Zele and Cao[15]). Therefore, the site of rod–cone and cone–rod interactions in the primate retina may occur at the synaptic junctions between cone bipolar cells and ganglion cells [16]. Recent findings from rabbit retina suggest that the amacrine cells that connect cone bipolar cells with rod bipolarars might also provide a substrate for mesopic rod–cone interactions [17].

Rod contributions to the three post-receptoral pathways vary with retinal illumination, contrast [18], and duration of the rod pulse [18–20]. The three cone post-receptoral pathways at photopic light levels show different TCSF characteristics (shape and cutoff frequency) [21–25] and correspondingly distinct impulse response functions [26,27]. Physiological studies in the primate retinæ show that parasol ganglion cells in the MC pathway exhibit a biphasic IRF [27–29] and bandpass TCSF with a high-frequency cutoff near 100 Hz [21,23,25]. However, the midget ganglion cells in the PC pathway exhibit a monophasic IRF [27–29] and low-pass TCSF with a high-frequency cutoff about 80 Hz [21]. Similarly, the small bistratified ganglion cells in the KC pathway exhibit a monophasic IRF [30,31] and low-pass TCSF, but with a high-frequency cutoff between 50 and 60 Hz [22]. Therefore, these distinct cone post-receptoral temporal filters might differently shape mesopic rod TCSF. Previous studies of the influence of cones on rod signaling (cone–rod interactions) have shown that the adaptation of long-wavelength-sensitive cones or medium-wavelength-sensitive cones can desensitize rod-pathway TCSF when measured for a select range of temporal frequencies (between 7.5 and 15 Hz) [32,33]. The temporal frequency range (up to 15 Hz) can potentially activate both rod pathways as evident from psychophysical [34] and electrophysiological...
studies [32]. Previously, it has been shown that rod–cone interactions [35] are prominent in the inferred MC pathway [36], while there are no such pathway-specific findings available in the literature with respect to cone–rod interactions. Physiological recordings from the macaque retina reveal that the magnitude of cone–rod interactions is less than for rod–cone interactions [16]. However, the magnitude and temporal dynamics of pathway-specific cone–rod interactions have not been determined.

Here, we evaluate cone–rod interactions using temporal white noise (TWN) that corresponds to the activity of a single post-receptoral pathway [37] to determine how cone activity alters the rod-pathway TCSF and the corresponding IRF in each of the post-receptoral pathways. The use of post-receptoral pathway-specific temporal white noise has advantages in that it contains a range of temporal frequencies (0–255 Hz) that encompasses the high-frequency cutoff for each of the post-receptoral pathways and it allows the functional evaluation of cone–rod interaction specific to each cone post-receptoral pathway. Previous studies of rod–cone interactions have shown that the dark-adapted rods reduce the amplitude and delay the time-to-peak for cone IRFs [35]. The IRF can be used as an analytical tool to describe the change in amplitude and latency of rod and/or cone signals to changes in contrast [29], retinal illumination [8,28], and age-related changes [38,39], mediated via specific visual pathways. Therefore, rod-pathway IRFs are derived from the rod-pathway TCSFs measured in the presence of pathway-specific white noise to reveal the magnitude and latency of pathway-specific cone–rod interactions. This gives insight into how rod and cone signals combine at a mesopic light level to maintain a constant visual percept. In addition, the experimental framework might have applications in the assessment of rod-pathway temporal sensitivity to detect early and subtle rod deficits in acquired retinal diseases that affect both the rod and cone functions.

2. METHODS

A. Observers

Two experienced psychophysical observers (28/M, 22/F) participated in the study. The observers had best-corrected visual acuity (6/6) tested by the Bailey–Lovio logMAR chart and normal trichromatic color vision tested by Farnsworth Panel D-15 and Ishihara tests. The observers had no ocular pathology as examined by slit lamp bio-microscopy and ophthalmoscopy. The research followed guidelines prescribed by the Institutional Human Research Ethics Committee and Declaration of Helsinki. Participants gave their informed consent prior to participation in the study. The second observer was naïve to the research purpose of the experiment. The total testing time (excluding dark adaptation) for each observer was ~15 h.

B. Apparatus and Calibration Procedures

A two-channel Maxwellian-view optical system allowed independent control of individual photoreceptor excitations at constant chromaticity and illuminance [3,40]. The optical system produced a 2° center field with a 13° surround. Each channel consists of four different colored LEDs (namely blue, cyan, green, and red) combined with 10 nm half-bandwidth narrow-band interference filters to produce peak wavelengths at 460 nm, 516 nm, 561 nm, and 658 nm, respectively, which enables the largest level of photoreceptor modulation [40]. The LEDs are connected to a spatial homogenizer via randomly arranged fiber optic bundles, which is then connected to a holographic diffuser. Light from the holographic diffuser is then collimated using a camera lens. The center and surround channels are parallel to each other and a right-angle prism is used to combine the center channel with the surround channel. The light beam from the center channel after the deflection from the prism passes through a photometric cube, which has a mirrored ellipse to generate a 2° circular center field within the 13° surround. The photometric cube is located at one focal length distance from the field lens to produce an image at optical infinity. The voltage to frequency converter, which provides 1 µs pulses, controls the LED light levels and is connected to a Dolby sound card (Revolution 7.1 PCI, M-Audio), which has a sampling rate of 192 kHz. All the software was custom-built using objective-C in an X-code.

The physical calibration involved measurement of spectral distribution at 1 nm intervals using a spectroradiometer (StellarNet, Tampa, Florida, USA) and illuminance of each LED obtained using a radiometer (ILT1700 Research Radiometer; International Light Technologies, Inc., Peabody, Massachusetts, USA). The calibration procedure characterizes the relationship between the illuminance of each LED and input voltage. A fourth-order log-transformed polynomial fits the data to generate a voltage illuminance lookup table. The maximum illuminance of the green LED was measured and an observer calibration is used to specify the illuminance of the rest of the LEDs by an observer’s match, which is compared with the theoretical match of 1964 10° standard observer [40]. Individual differences in receptor spectral sensitivities, lens and macular pigment optical densities were compensated for using an observer calibration procedure in which the observer’s match for a mixture of 459 nm and 561 nm relative to the mixture of 516 and 658 nm primary lights is obtained by adjusting the illuminance of the 459 nm light, combined illuminance, and illuminance ratio of 516 and 658 nm lights [40]. The observer match is performed at 7.5° temporal retinal eccentricity where the densities of rods and cones are approximately equal [41,42]. The observer calibration is confirmed by two methods, namely the bleaching test and rod color perception, after 30 min of dark adaptation. The rod stimulus, which is visible easily post-dark adaptation, is not seen until at least 4 min after exposure to a bleaching light of about 10,000 Td [19]. Rod isolation is also confirmed when the rod color percept of an increment stimulus (brighter bluish green) and a decrement stimulus (dark reddish) is matched using the cone excitation values consistent with the literature [18–20,43].

C. Temporal White Noise Paradigm

TWN is characterized by a flat power energy spectrum and random phase distribution [44–46]. In this study, TWN was generated by assigning an amplitude of 0 or 1 to each temporal frequency between 0 and 255 Hz and randomly assigning phase between 0° and 359°. The sampling frequency was
1024 Hz (1.024 samples/ms). The extrinsic noise that correlates with the activity of the MC pathway (+ L + M + S cones), PC pathway (+ L-M cones), and KC pathway (S-cones) was produced by multiplying temporal white noise generated for each of the primary lights with the appropriate cone photoreceptor excitations [37,47]. The Michelson contrast was 8% for LMS noise, 1.4% for + L-M noise, and 16% for S-cone noise, the same contrast values (except for + L-M noise contrast that was halved to fit within the gamut) used previously [37].

D. Psychophysical Paradigm

The rod-pathway TCSF measurements were obtained with and without pathway-specific noise using a temporal three-alternative forced choice (3-AFC) test in combination with a 2-yes and 1-no staircase procedure. There was a 500 ms inter-stimulus interval between each interval of the 3-AFC test. The observer indicated the epoch in which the stimulus was present using a game pad. The rod stimulus was a 2 s Gabor (0° phases offset) modulated between 1 and 14 Hz (as shown in Fig. 1) and presented in a center 2° field. The use of a transient stimulus to elicit cone–rod interactions is supported by previous psychophysical studies that have shown that cone influence on rod-pathway sensitivities is larger for a transient stimulus [48,49] than a steady background. The noise was present in the center and surround fields. The testing was performed at a mesopic light level of 20 photopic Td (∼1.7 log scotopic Td). An auditory beep preceded the onset of each interval. The staircase procedure terminated at 10 reversals and the average of the last six reversals was defined as a threshold, with the final threshold an average of a minimum of three repeats. One set of measurements for all frequencies ranging from 1 to 14 Hz (randomized order) was obtained in each testing session. The observers were dark adapted for 30 min to ensure maximum rod sensitivity before measurements were taken [50].

Rod-pathway temporal IRFs were derived from the rod-pathway TCSFs using the Stork and Falk method with a minimum phase assumption [26]. Kramers–Kronig relations were used to derive a temporal phase spectrum [26] and extrapolation to lower and higher temporal frequencies was done in accordance with the methods described by Swanson et al. [28]. The TCSF data were fitted by Fourier transformation of the estimated IRF with the periodic stimulus.

3. RESULTS

The mesopic rod-pathway TCSFs are low pass with a cutoff at ∼16 Hz. Temporal cone white noise targeting each of the three primary retinogeniculate pathways (LMS, + L-M, and S-cone noise) caused a generalized decrease in rod-pathway TCSF that was constant to ∼10 Hz, with a further reduction at higher frequencies (insets in Fig. 2). The noise attenuated the rod-pathway critical flicker fusion frequency (CFF) by ∼2–3 Hz.

The rod-pathway IRFs derived from the TCSF data in the control condition are monophasic with an average time to peak of 36.5 ± 1.5 ms (Fig. 3). In temporal white noise, the amplitudes of the rod-pathway IRFs decreased by more than 20% (Table 1) whereas the time to peak was longer, but all within 4 ms of the control condition. The Fourier transformations of the rod-pathway IRFs for each condition are shown as solid lines in Fig. 2.

4. DISCUSSION

Our results indicate that noise corresponding with the activity of the three post-receptoral pathways will decrease mesopic rod-pathway TCSF (Fig. 2) but the effect on the latency of rod-pathway signal transmission is negligible (Fig. 3). Rod-pathway TCSFs in the control condition were low pass, consistent with past reports [1–7], and the rod CFF (∼16 Hz) was in agreement with studies using stimulus fields up to 6° diameter and measured at similar retinal eccentricities [3,51]. It is possible to achieve higher mesopic rod CFFs (up to ∼26 Hz) with larger fields at more peripheral retinal eccentricities (e.g., 16°) [4,52]. Physiological recording in macaque retina shows that the TCS functions of the cone inputs to the three pathways are different [21,22,53,54]. Here, the cone–rod interactions reveal similar levels of attenuation of the rod-pathway temporal contrast sensitivity function irrespective of the pathway-specific noise. Given this, we speculate that the locus of the cone–rod interaction is retinal and could involve multiple loci. Physiological recordings from macaque retina indicate that the site of cone–rod interactions likely occurs at the common synaptic circuit between cone bipolar and ganglion cells [16]. The attenuation of the rod-pathway TCSF by pathway-specific

Fig. 1. Temporal profile of the rod Gabor stimulus presented in a three-alternative forced choice test. A 2 s duration (8 Hz) rod Gabor stimulus is shown in the first interval of a three-alternative forced choice (3-AFC) in (a) the control condition (without noise) or in (b) the presence of temporal white noise that correlates with the cone signals. The vertical dotted lines indicate the 500 ms inter-stimulus interval (ISI).
noise could be due to the interaction of the rod-pathway signal with the cone noise, initially from a high-frequency attenuation at the photoreceptor level [55,56] followed by low temporal frequency attenuation at the post-receptoral site, possibly between cone bipolar cells and ganglion cells [57]. We observed a uniform decrease in the rod-pathway TCSF. For temporal frequencies up to 10 Hz, the LMS cone noise data for the inferred MC pathway parallels the rod/cone response ratio of MC cells in the macaque retina that are close to unity at 20 Td, the adaptation level of this study [54]. Rod suppression of cone signals is strongest for stimuli mediated via the MC pathway [36], whereas the current study indicates that the cone–rod interactions are present, and of similar magnitude, in the MC, PC, and KC pathways. The design of the study is not intended to test whether there is a cross talk between the post-receptoral pathways, when pathway-specific noise is introduced. However, this inference of cross talk between post-receptoral pathways can be made from another study conducted by Hathibelagal et al. [58], where we showed that noise introduced in any post-receptoral pathway can affect rod contributions to all the post-receptoral pathways.

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Fig. 2. Temporal contrast sensitivity functions for control (no noise) and noise conditions. The left panels (a)–(c) show the temporal contrast sensitivity functions (mean ± SD) for observer 1 (O1) and right panels (d)–(f) for observer 2 (O2). The rod control temporal contrast sensitivity functions (open circles) are included in all the panels to allow comparison with the rod data measured in pathway-specific noise (solid triangles). The solid (control) and dashed (noise) lines represent the contrast sensitivity functions derived by the Fourier transformation of the estimated temporal impulse response functions with the periodic stimulus. The horizontal lines (solid for control and dashed for noise conditions) indicate the instrument gamut limit. The panel inserts show the sensitivity ratio of control/noise at each temporal frequency.

Fig. 3. Effect of extrinsic cone noise on rod-pathway temporal impulse response functions. The left and right panels show the data for observers 1 and 2, respectively. The rod control IRF (solid lines) is included in each panel for comparison with the rod IRF measured in noise (dashed lines). The rod noise IRF is normalized to the maximum amplitude of the control condition for each observer. The time to peak ($t_p$) is included.

Table 1. Summary of the Average CFF and IRF Parameters in the Noise and Control Conditions

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Control</th>
<th>LMS</th>
<th>Noise + L-M</th>
<th>S-Cone</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Amplitude</td>
<td>N/A</td>
<td>22.7</td>
<td>23.1</td>
<td>26.1</td>
</tr>
<tr>
<td>Latency (ms)</td>
<td>(36.5, 38, 35)</td>
<td>41 (42.4, 41, 39)</td>
<td>40 (42.2, 41, 39)</td>
<td>39.5 (42.2, 39.5)</td>
</tr>
<tr>
<td>CFF (Hz)</td>
<td>16 (15, 17)</td>
<td>13 (12, 14)</td>
<td>13.5 (13, 14)</td>
<td>13 (12, 14)</td>
</tr>
</tbody>
</table>

*Individual observer values are in the parentheses.

*Percent amplitude decrease relative to control.
The mesopic rod-pathway IRFs derived from the contrast sensitivity data were monophasic with a 36.5 ms time-to-peak amplitude, consistent with the previous behavioral data at 20 photopic Td [8]. Investigations of cone–rod interactions with a transient or flickering stimuli have consistently found that cone activity decreases rod flicker sensitivity [32,33,49,59]. Cone–rod and rod–cone interactions have different effects on mesopic vision [15,60]. Cone–rod interactions decrease the rod CFF by only ∼2–3 Hz (Fig. 2), whereas the cone-mediated CFF is inhibited by rod-pathway signals by ∼6 Hz [36]. This is consistent with the physiological recordings in macaque retina which show that rod–cone interactions are of greater magnitude than cone–rod interactions [16]. Rod pathways have a slower temporal response than cones [13,34,54,61], and therefore any inhibitory effects of these interactions on rod or cone signaling vision might be expected to be different if they are in some way to benefit vision to maintain stable and uniform visual percepts during transitions between the signals arising from the two photoreceptor classes. The larger inhibition of the cone CFF by rod pathway (rod–cone interaction) will minimize the difference in their respective temporal responses [35,62] while cone–rod interactions would require lesser attenuation, as observed here. That cone noise attenuates the amplitude of the rod-pathway IRF (<20% decrease) may be an intrinsic mechanism to suppress rod sensitivity at high mesopic light levels [33] without affecting the timing of the rod-pathway signals.

Recent studies of the physiological basis of mesopic rod–cone interactions in rabbit retina proposed that the suppression of rod-pathway activity could also involve amacrine cell motifs that connect cone bipolars with rod bipolars [17]. It is known that the AII amacrine cell is functional in mesopic illumination in both primates (macaques) [54,63,64] and non-primates (mice, guinea pig, salamander, and rabbit) [65–68] in two distinct pathways, one via gap junctions (rod → cone → ON/OFF cone bipolar → amacrine cell → OFF ganglion cell) and the second involving the rod-bipolar cell pathway (rod → rod bipolar → amacrine cell → ON/OFF cone bipolar → ON/OFF ganglion cell). The increase in the receptive field size of small bistratified ganglion cells in response to white noise stimulation matches the rod-pathway mediated inputs to the amacrine cell pathway [53]. The implication of the amacrine cell pathway in cone–rod interactions is not inconsistent with the synaptic circuit between cone bipolar and ganglion cells [16] because the AII amacrine cells can transmit rod-pathway signals to ganglion cells via cone bipolars. However, based on the available psychophysical and physiological data, it is not possible to differentiate between amacrine cell pathway or rod–cone gap junctions; therefore, the role of rod–cone gap junctions in mesopic cone–rod interactions cannot be ruled out.

Funding. Australian Research Council (ARC) (ARC-DP140100333).

Acknowledgment. A. J. Z. and B. F. received funding from the Australian Research Council.

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