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CORRESPONDENCE

Putative retinal and cortical potentials from melanopsin sensitive ganglion cells

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To the Editor:

Intrinsically photosensitive retinal ganglion cells (ipRGCs) absorb short wavelength light via the photopigment melanopsin [1]. ipRGCs are critical for photo-entrainment, circadian rhythms, pupillary responses, alertness, and cognition, which persist in blindness or the absence of visual perception [2]. Moreover, Dacey et al. showed that "giant" ipRGSs send signals to the LGN and visual cortex substantiating their role in visual perception [3]. These giant ipRGCs show a unique opponent S-cone off response wherein S cones inhibit ipRGC firing rate while L and M cones enhance it [3]. High contrast stimuli and silent substitution revealed long-latency ERGs from ipRGCs which can be decreased in glaucoma [4]. However, high contrasts can inadvertently stimulate other photoreceptors lessening selectivity of pathway activation. We used selective chromatic adaptation, similar to SWAP perimetry, wherein a blue stimulus, effective for S cones and ipRGCs, was presented on an amber rod and LM cone saturating background to isolate S cone and putative responses from ipRGCs over a 4 log unit luminance range.

Fourteen healthy adults (mean 24.2 ± 1.6 years, 11 females, 3 males) participated in our IRB approved protocol after providing informed consent. A calibrated Ganzfeld (Diagnosys, LLC) was used to fully illuminate the retina with a 200 ms blue flash (448 nm) presented on a constant bright amber background (590 nm, 560 cd/m^2). Simultaneous flash ERGs (DTL fiber electrode at lower limbus of right eye referenced to right earlobe) and VEPs (active electrode 1 cm above inion, referenced to forehead, common ground: left temple) were recorded after 30 s of adaptation to the amber background. Signals from the right eye (left eye occluded) were band-pass filtered (0.612–10 Hz) to isolate low frequency ipRGC responses [4] and recorded in 1000 ms epochs as the average response to 30 artifact free blue flashes (1 flash/2 s). Separate recordings were obtained at four blue intensities spanning 4 log units (16.7–0.0167 cd/m^2). Digital values from all subjects (μV vs. ms) were averaged to compute mean ERG and VEP waveforms. The absence of rod and LM cone ERGs in waveforms and non-recordable ERGs to the ISCEV scotopic flash (0.01 cd/m^2/s) on the amber background confirmed S cone and putative ipRGC response isolation.

Figure 1a shows mean ERGs at the highest luminance and at 100× lower luminance (Fig. 1b). The early small amplitude S cone ERG is followed by a wave of negativity presumed to derive from S cone inhibitory input to giant ipRGCs [3]. A positive response occurs within this negativity representing intrinsic ipRGC light onset or possibly S cone offset responses. The subsequent positivity is likely prolonged spiking by ipRGCs [3]. Figure 1c, d shows flash VEPs with the first positive peak (P1) attributable to ganglion cell input since P1 is selectively decreased in glaucoma and vascular disease [5]. Figure 2 shows mean VEP P1amplitude at four luminances plotted against corresponding ERG negative to positive peaks to index ipRGC activity. The exponential increase ($r^2 = 0.91$) in putative retinal and cortical responses from ipRGCs exemplifies the potential of

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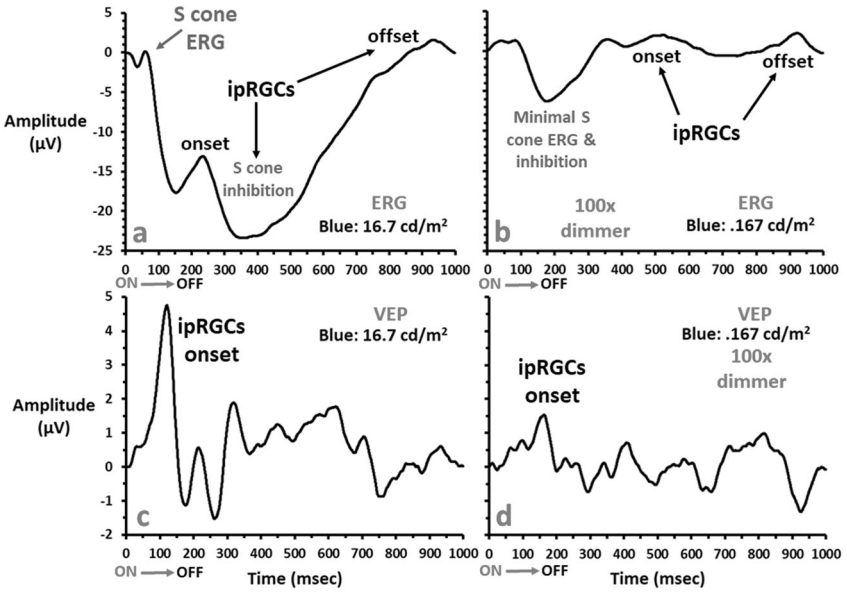

Fig. 1 ERG and VEP Waveforms. a Shows the mean digitized ERG from 14 subjects. The S cone ERG followed by putative components of the ipRGC response are labeled. **b** Shows the ERG at a 100× lower blue flash luminance. **c** Shows the flash VEP at the highest blue luminance and 1d the VEP at 100× lower luminance.

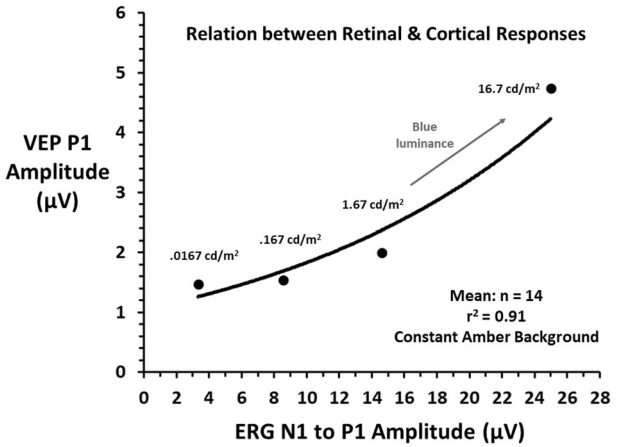

Fig. 2 VEP vs. ERG Amplitudes. The mean VEP P1 amplitude is plotted against the mean ERG negative trough to peak amplitude across a 4 log unit range of luminances.

this novel approach for further revealing their unique functions.

Author contributions The Principal Investigator, JR, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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