Electronegative ERG or Pseudo-negative ERG?

Letter to Editor.

Prof Graham E Holder*
Department of Ophthalmology
Yong Loo Lin School of Medicine
National University of Singapore
1E Kent Ridge Road
Singapore 119228

ophgeh@nus.edu.sg

Prof Omar Mahroo
UCL Institute of Ophthalmology
11-43 Bath St
London EC1V 9EL
UK

o.mahroo@ucl.ac.uk

*Corresponding author

Editor,

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The recent report of an “electronegative” ERG in a patient with Galloway-Mowat syndrome, by Racine and Golden [1], raises important issues in relation to terminology and also demonstrates the importance of considering in detail the origins of the ERG signals in the interpretation of electrophysiological data.

An “electronegative” or “negative” ERG is one in which the DA 10 a-wave is of normal or near normal amplitude but there is a markedly lower amplitude b-wave such that the waveform is dominated by the negative-going a-wave. It is most commonly a manifestation of inner retinal rod system dysfunction [2]. As stimulus strength is increased in a normal dark-adapted human, the b-wave, predominantly arising in rod On- bipolar cells (BPC), remains of higher amplitude than the rod photoreceptor related a-wave. That a-wave/b-wave relationship is not present in the cone system under photopic conditions where the “photopic hill” phenomenon occurs [3]. The photopic b-wave, derived from synchronised On- and Off- BPC signals, reaches a maximum amplitude with increasing stimulus strength but then, even though the photopic a-wave continues to increase in amplitude due to increased cone photoreceptor activation, the b-wave reduces in amplitude, partly due to an increasing desynchronisation between the On- and Off- BPC contributions [4].

The “photopic hill” phenomenon is, however, not a property of the adaptive state of the retina, but is a physiological property of the cone system, only visible in a normal retina under photopic, rod-suppressing adaptation. It is also observed under dark adaptation in disorders in which rod photoreceptor function is largely lost, such as vitamin A deficiency, fundus albipunctatus relating to variants in *RDH5*, or Oguchi disease [5, 6], as in those disorders all ISCEV Standard dark-adapted ERGs arise via dark-adapted cones. Thus, dark-adapted ERGs in a cone isolated retina can have a b-wave of lower amplitude than the a-wave, mimicking a negative ERG but reflecting totally different underlying mechanisms and cellular origins.

The same phenomenon, a cone system b-wave being of lower amplitude than the a-wave, can also occur in patients with a severe rod-cone dystrophy (RP) when rod function is lost and all remaining ERG signals, under both dark and light adapted conditions, arise in residual cones. Then, however, the a-wave is also profoundly subnormal due to the loss of rod photoreceptor function. Use of a red flash ERG under dark adaptation in such a patient shows detectable dark-adapted cone responses, but no detectable rod system responses, and the changes with increasing stimulus strength reflect the “photopic hill” phenomenon occurring under dark adaptation in the remaining cones (see Figure). The phenomenon does not occur in all patients with severe RP but is relatively common and appears to be evident in the ERGs shown by Racine and Golden. Thus, their findings can be explained by severe photoceptor dysfunction affecting the rod more than cone system, with dark-adapted ERGs reflecting the dark-adapted (and attenuated) cone system response. However, it cannot be excluded with certainty that dysfunction could occur in multiple layers in this condition as single-cell transcriptome studies show *WDR73* may be expressed not only in photoreceptors but also in bipolar cells [7].

Meaningful ERG interpretation requires accurate identification of the cellular origins of the recorded signals, where possible, and then relating those signals to the underlying pathophysiology of the disorder. The dark-adapted red flash ERG, part of the extended protocols (www.iscev.org), is, in our view, extremely valuable if not indispensable to accurate ERG interpretation in routine clinical ERG practice as it provides a measure of dark-adapted cones, not available in the standard ISCEV ERG, and facilitates the identification of signal origins.

As the term negative ERG usually implies dysfunction involving On-BPCs with a normal or near normal rod photoreceptor derived a-wave, confusion can arise from use of the same term when rod photoreceptor function is largely lost. The term “pseudo-negative” ERG has been suggested when the signals arise in dark adapted cones to prevent such confusion in relation to the implied underlying pathophysiological mechanisms [6]. Electrophysiology recording requires utmost precision and attention to detail. The ISCEV stimulus descriptions are unambiguous (DA 0.01, LA 3.0 etc,). We should aspire that waveform terminology should be equally precise.

Prof Graham E Holder
Department of Ophthalmology
Yong Loo Lin School of Medicine
National University of Singapore
1E Kent Ridge Road
Singapore 119228

ophgeh@nus.edu.sg

Prof Omar Mahroo
UCL Institute of Ophthalmology
11-43 Bath St
London EC1V 9EL
UK

o.mahroo@ucl.ac.uk

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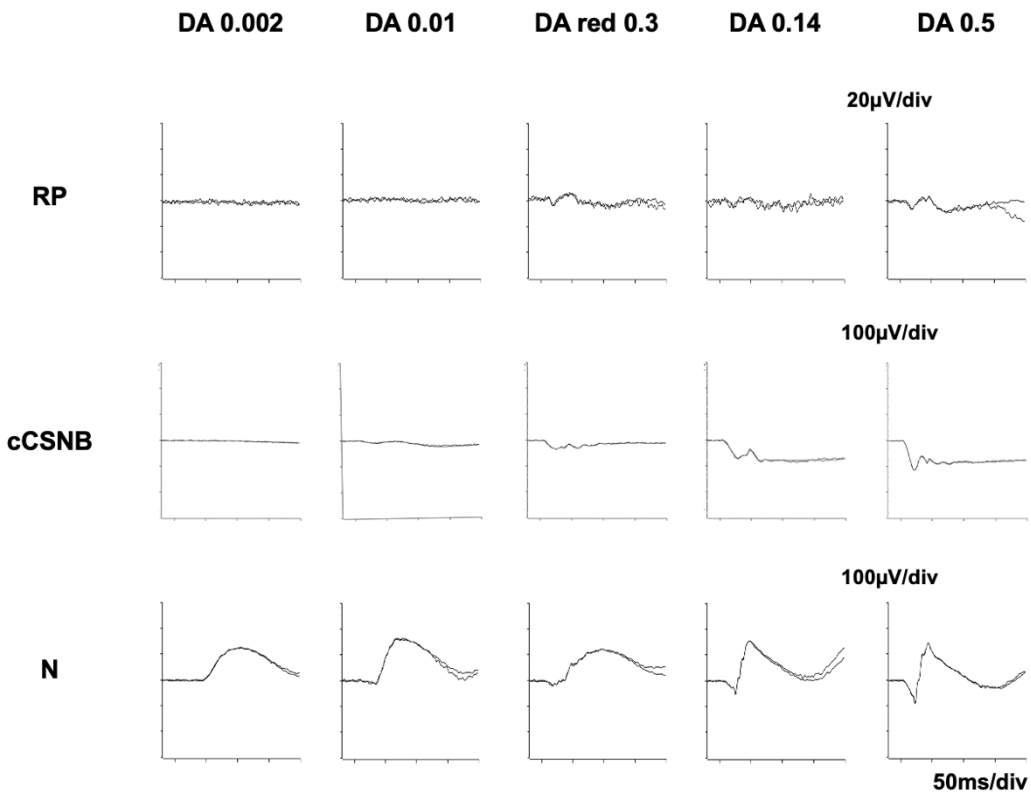
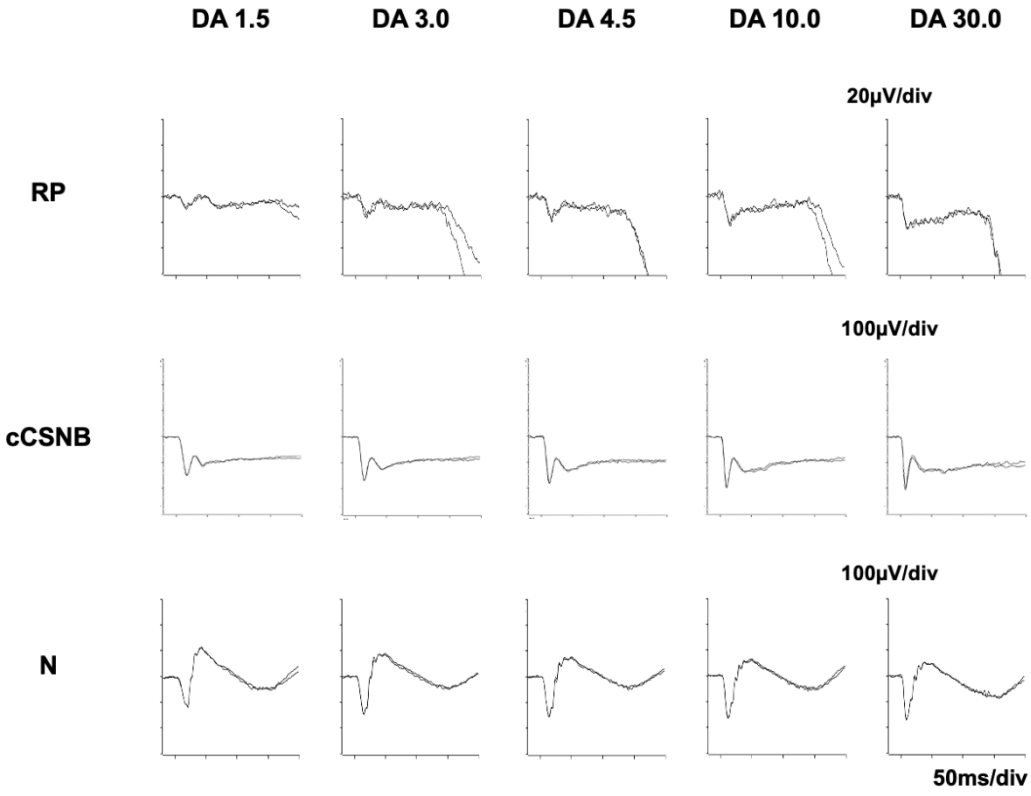
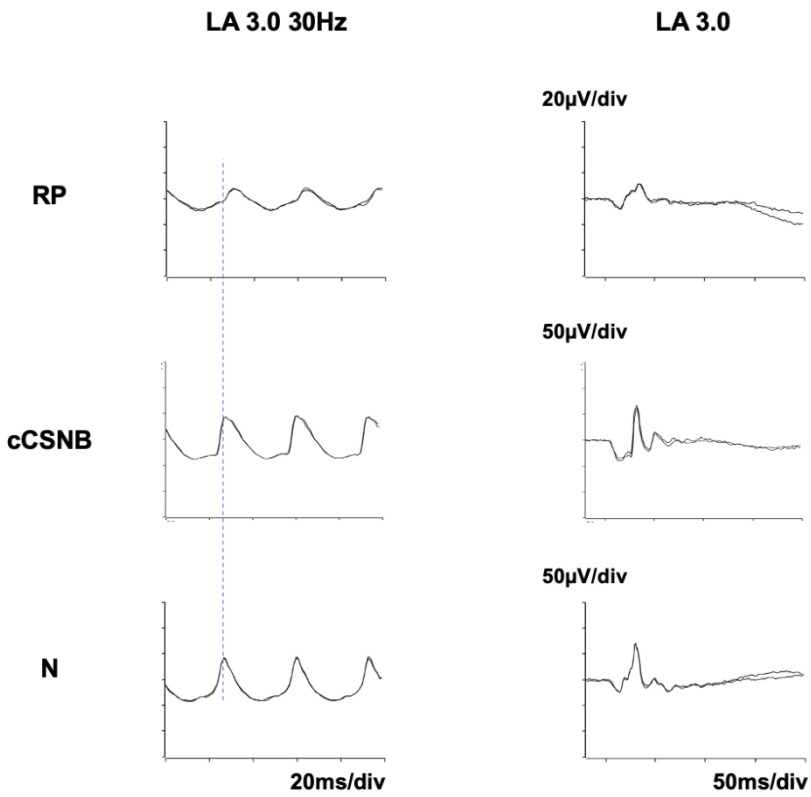
Legend to Figure:

Full field ERGs from one eye of a patient with moderately severe retinitis pigmentosa (rod-cone dystrophy), one eye of a patient with “complete” congenital stationary night blindness (cCSNB), and a normal control (N). All stimuli are white (Diagnosys Espion) other than the red flash. In the RP patient, note the undetectable DA 0.01 response; the absent rod component in the dark-adapted red flash ERG; and the development of a pseudo-negative ERG (reduced b:a ratio accompanied by a profoundly subnormal a-wave) with increasing stimulus strength. This is consistent with the “photopic hill” phenomenon revealed in remaining dark-adapted cones by the absence of detectable rod function. Note the delayed and subnormal flicker ERG in keeping with generalised retinal cone system dysfunction. The data from the RP patient should be compared with those in cCSNB. Note the gradual increase in dark-adapted a-wave amplitude in the CSNB patient with all a-wave amplitudes being similar to those in the normal control, and the failure of the CSNB b-wave to rise above the a-wave at any stimulus strength, also visible in the dark-adapted red flash ERG.

Calibrations refer to the entire row in which they appear; note the differences in calibration between the RP patient compared to the cCSNB and the normal (N).


DA 0.002
DA 0.01
DA red 0.3
DA 0.14
DA 0.5
20μV/div
RP
100μV/div
cCSNB
100μV/div
N
50ms/div


DA 1.5
DA 3.0
DA 4.5
DA 10.0
DA 30.0
20μV/div
RP
100μV/div
cCSNB
100μV/div
N
50ms/div


LA 3.0 30Hz
LA 3.0
20μV/div
RP
50μV/div
cCSNB
50μV/div
N
20ms/div
50ms/div