

Night vision in aging, AMD, and beyond: basic and clinical aspects

Organizers

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Description

Data accrued over the last 25 years indicate that an important characteristic of vision in aging and AMD is that rod photoreceptors are affected earlier and more severely than are cones. These findings have been comprehensively contextualized as related to changes in the choriocapillaris – Bruch’s membrane – RPE complex that are precursors to characteristic AMD pathology. The overall concept of “night vision testing in AMD” was solidified in 2016 with the results of a well-powered prospective study (Alabama Age-related Maculopathy Study, ALSTAR) (PMID 26522707). Further, in this large cohort of older adults, the ARMS2 AMD susceptibility locus was associated with delayed dark adaptation, even in persons with healthy maculas, just this year (PMID 30389424). Clinicians could be taking advantage of new technology in testing rod function as an early indicator of macular disease and new knowledge on the outer neurovascular unit in their interpretation of clinical imaging. In particular, the presence and distribution of rods and the comparative vision of rods and cones can be used to good effect to dissect mechanisms. Scientists could be directing effort into developing responsive tests of visual function for application to human studies and for addressing clinically relevant aspects of visual function beyond acuity and light sensitivity. All could be using visual functional tests as a readout assay for aging and pathology in the choriocapillaris – Bruch’s membrane – RPE complex. In turn, better knowledge of visual function and explanatory hypotheses that are well-supported in human biology can inform development of rapid and non-invasive tests based on imaging. Finally, this vertically oriented physiologic unit is the front end of the entire visual system, and thus understanding how to probe it functionally can inform the study of many retinal diseases, including diabetic retinopathy.

We expect that the information to be covered is still very new and distributed among different scientific communities not yet aware of their significant synergy and overlap (i.e., visual function testing, retinal cell biology, clinical studies including multimodal imaging). It has really come together only in the last 3 years, due to the outcome of a large prospective study and approval of new devices that expand the range of functional testing of rod vision. We wish to inform investigators using model systems (non-foveate animals, cell culture) interested in accurate human visual neuroscience and up-to-date understanding of visual function and retinal structure in aging and AMD.

Learning objectives

After attending this course, participants will be able to:

- List the layers of AMD pathology impacting macular photoreceptor function
- Compare technologies available for testing rod-mediated visual function
- Explain the major differences between the two retinoid cycles
- Identify experimental strategies to assess rod and cone function in an older patient
- Cite ways to update standardized tests and assessments to include rod-mediated function
- Evaluate critical literature on visual function testing in AMD

Agenda

Presenters and presentations may change.

1 – 1:05pm

Introduction, road map

Christine A. Curcio, PhD, FARVO, University of Alabama at Birmingham, Birmingham, AL

This introduction will provide a verbal and schematic roadmap unifying topics of the course as well as an introduction to the format of the talks and discussion. This course places multidisciplinary research into a new and comprehensive model of visual function and retinal structure in age-related macular degeneration (AMD). Speakers will be introduced in the context of a comprehensive model of cone resilience and rod vulnerability within the outer retinal neurovascular unit, in aging and AMD. The focus will be on clinical and basic science aspects of human rod-mediated vision in these conditions. During the course, synthesis of empirical findings in light of the model, identification of gaps in the model, and new directions are encouraged.

1:05 – 1:22pm

Neuroanatomy and pathology of aging and AMD

Christine A. Curcio, PhD, FARVO, University of Alabama at Birmingham, Birmingham, AL

The snapshot of histology combined with the movie of in vivo imaging has generated new concepts about the fate of photoreceptors in aging and AMD, in the context of the outer retinal neurovascular unit (choriocapillaris, Bruch's membrane, RPE, Müller glia). In the human macula rods out-number cones. In normal eyes, rods decrease 30% over adulthood while cones are stable, according to accurate retinal maps. In late AMD, cones persist. Choriocapillary drop-out with aging and Bruch's membrane change contribute to the build-up of lipids of RPE origin as drusen and basal linear deposit under the RPE in central macula, increasing risk for neovascularization and atrophy. These insights help motivate the development of rod-mediated dark adaptometry as a test of retinoid re-supply via the choriocapillaris, Bruch's membrane, and RPE complex.

New data on the natural history, composition, and topography of soft drusen enable a comprehensive center-surround model: a center of cone resilience (due to Müller glia support) and a surround of rod vulnerability (due to impaired transport). Subretinal drusenoid deposit is a newly appreciated extracellular deposit between photoreceptors and retinal pigment epithelium, abundant at the perifoveal rod ring, that is particularly devastating to rod vision and has its own clinical associations with atrophy and neovascularization. Probing rod and cone structure and function is a means for precisely assessing macular disease mechanisms in the outer retinal neurovascular unit.

1:22 – 1:39pm

Aging, AMD, rod- and cone- mediated vision

Cynthia Owsley PhD, MPH, FARVO, University of Alabama at Birmingham, Birmingham, AL

This presentation will summarize the vulnerability of rod-mediated vision in aging and early AMD, contrasting it with the comparative resilience of cone-mediated vision. Delayed rod-mediated dark adaptation is the first identified functional biomarker for incident AMD. Delayed rod-mediated dark adaptation will be discussed in terms of its relationship with two of the strongest genetic associations for AMD (*ARMS2* and *CFH*), its association with

structural features of AMD, and its relationship to patient-reported difficulties when engaged in activities under low luminance conditions.

1:39 – 1:56pm

Choriocapillaris: the front end of vision

Robert F. Mullins PhD, University of Iowa, Iowa City, IA

The structure and function of the choriocapillaris will be discussed, especially with respect to supporting mammalian vision. Age- and disease-related changes will be discussed, as will potential therapies to address choroidal dysfunction.

1:56 – 2:13pm

Rod and cone photoreceptor dark adaptation and pigment regeneration

Trevor Lamb, ScD, John Curtin School of Medical Research, Australia National University, Canberra, Australia

I will describe the kinetics of recovery of human visual sensitivity in the scotopic (rod-mediated) and photopic (cone-mediated) systems, as measured psychophysically during 'dark adaptation'. I will also describe the corresponding regeneration of rod and cone visual pigment, as measured by a variety of experimental techniques.

In the photopic system, the desensitisation results substantially from depletion of cone pigment, whereas in the scotopic system, the desensitisation results primarily from the presence of 'free opsin'. In both systems, the kinetics of recovery can be described in terms of the 'rate-limited' regeneration of visual pigment, and I will discuss the likely cellular and molecular mechanisms involved. The slowing of dark adaptation that occurs with aging, and notably with early AMD, will be addressed, with links to other presentations in this course.

2:13 – 2:30pm

Afternoon Break

2:30 – 2:47pm

Second visual cycle (retina-based)

Vladimir Kefalov, PhD, Washington University School of Medicine, St. Louis, MO

This presentation will discuss key electrophysiological experiments for determining the functional significance of the retina visual cycle, the possible mechanisms determining its cone-specificity, its known molecular components, and its potential relevance for visual disorders and current and future therapies.

2:47 – 3:04pm

Monitoring the kinetics of rhodopsin's chromophore in single isolated human rod photoreceptors

Yiannis Koutalos, PhD, Medical University of South Carolina, Charleston, SC

The light detecting chromophore of rhodopsin is 11-*cis* retinal, which is isomerized by light to all-*trans*, activating rhodopsin; all *trans* retinal is subsequently released by photoactivated rhodopsin and reduced to all *trans* retinol. Both 11-*cis* and all *trans* retinal can generate precursors of lipofuscin fluorophores within the outer segments of rod photoreceptors. All-*trans* retinal, all-*trans* retinol, and precursors of lipofuscin fluorophores all emit significant

and distinct fluorescence signals. We have used fluorescence imaging to monitor these signals in single rod photoreceptors isolated from human donor eyes. We find that the enzymatic mechanisms present in human rod photoreceptors efficiently remove physiological concentrations of all-*trans* retinal to prevent the generation of precursors of lipofuscin fluorophores; the primary source of lipofuscin fluorophores in the human retina is 11-*cis* retinal.

3:04 – 3:21pm **Neural circuitry of rod-mediated vision**

Ulrike Grünert PhD, University of Sydney, Sydney, Australia

Vision in darkness (scotopic vision) is mediated by a specific high-sensitivity pathway in the retina. Rod photoreceptors contact rod bipolar cells which transfer the signal to All amacrine cells. The All amacrine cells are crucial interneurons in the rod pathway because they contact both ON-type bipolar cells (through gap junctions) and OFF-type bipolar cells (through glycinergic synapses), thus giving the rod signals access to ON- and OFF-pathways in downstream visual circuits. This connectivity makes All amacrine cells a target for optogenetic induction of light sensitivity to restore vision in retinal diseases. We mapped the three major neurons in the rod pathway (rods, rod bipolar and All amacrine cells) in post-mortem human donor eyes. Our results indicate that in central retina the spatial resolution of scotopic vision is limited by the All amacrine mosaic.

3:21 – 3:38pm **Microperimetry**

Maximilian Pfau MD, University of Bonn, Bonn, Germany

Microperimetry (also termed fundus-controlled perimetry [FCP]) allows for spatially resolved testing of retinal sensitivity over the entire macula area. Besides mesopic testing, novel devices provide scotopic testing protocols including two-color dark-adapted (DA) microperimetry for refined and selective probing of rod function. Since microperimetry compensates for eye movements, it is advantageous in patients with unstable fixation. Recent scotopic microperimetry studies underscore the (previously made) observation that rod dysfunction precedes and exceeds cone dysfunction in intermediate and late-stage age-related macular degeneration (AMD). Moreover, spatial analysis of retinal sensitivity reveals that rod dysfunction is more pronounced in close proximity to AMD-related lesions such as fibrovascular scar tissue or retinal pigment epithelium (RPE) atrophy.

This presentation will (1.) provide an overview of devices available for scotopic microperimetry, (2.) outline the test protocols and results of published as well as ongoing (multicenter) clinical studies and (3.) give an overview of upcoming developments.

3:38 – 3:55pm **Patient-reported outcomes considering low luminance and low contrast conditions**

Robert Finger MIH, MD, PhD, University of Bonn, Bonn, Germany

Patient-reported outcomes research is particularly challenging in early disease stages when little symptoms exist. As particularly low lighting and poor contrast exacerbate many of these symptoms, patient-report needs to capture these specific situations when symptoms occur. To date, many of the available vision-related quality of life (VRQoL) measures do not focus on these situations and include only few items probing these symptoms and conditions under which they occur. Historically, VRQoL instruments have been developed with and for

persons with more advanced disease stages with often considerable loss of vision which is reflected in the final item sets.

In this presentation, we will cover common patient-reported outcomes and concentrate on VRQoL instruments. Details will include how to develop a VRQoL instrument, applicable guidelines and recommendations as well as commonly used available instruments and new developments in this area. Following this we will focus on VRQoL instruments applicable to early disease stages of retinal diseases using early AMD as an example. Advantages and disadvantages of several of the most common and most applicable VRQoL instruments will be discussed followed by their use in research as well as clinical routine and an outlook to future developments in this area.

3:55 – 4:12pm

Diabetic retinopathy, childhood, nutrition, and retinal physiology

L. Michael Larsen MD, DMSc, University of Copenhagen, Copenhagen, Denmark

Diabetes can lead to both reversible and chronic tissue damage in the retina in a decade-long protracted process. Functional instability linked to short-term fluctuations in glycemia can be observed, however, well ahead of the first retinal microaneurysm. Intriguing abnormalities of dark adaptation and electrophysiology in diabetes have parallels in the adaptation to chronic hypoxia at high altitude and some other metabolic challenges. This suggests the existence of a general adaptation of the retina to changing metabolic circumstances and a failure to reach such stability in the ever-changing context of unstable glycemia in diabetes. Dark adaptometry is an attractive method of examining the metabolic condition of the retina and may have a role in clinical practice. Standardized examination protocol should take into account that dark adaptation changes rapidly with glycemia. The demonstration in clinical trials that poor metabolic control is a risk factor for diabetic retinopathy events decades later supports that much can be gained by optimizing metabolic control in childhood.

4:12 – 4:29pm

Night driving in aging and AMD

Joanne M. Wood BSc, PhD, Queensland University of Technology, School of Optometry, Brisbane, Queensland, Australia

Nighttime driving is challenging for all drivers, particularly for older adults and for those with eye diseases, such as AMD. This presentation will provide an overview of the challenges of nighttime driving, the difficulties reported by older drivers both with and without AMD, and associations with visual function.

4:29 – 4:46pm

Imaging retinal densitometry

Tom H. Margrain BSc Optom, PhD, Cardiff University, Cardiff, Wales, United Kingdom

High fidelity Imaging Retinal Densitometry (IRD) is a new technique that facilitates the measurement of rod and cone visual pigment synthesis rates across the central retina. This presentation will describe the technology and the algorithms that facilitate the extraction of rod and cone visual pigment signals in human eyes.

In healthy controls, the spatial distribution of rod and cone visual pigments is consistent with histological descriptions of photoreceptor topography. Examination of the temporal characteristics of photopigment regeneration supports the hypothesis that pigment

regeneration is rate-limited for cones and rods but only after the distorting effects of Metarhodopsin III are accounted for. Data from people with early and intermediate stage AMD is distinct from age-matched controls and highlights the potential value of the technique as an objective biomarker

4:46 – 5pm

Wrap up

Cynthia Owsley PhD, MPH, FARVO, University of Alabama at Birmingham, Birmingham, AL

Review of the day and key take-away messages.