SUMMER 2010

Point of View
THE EYE RESEARCH INSTITUTE UNIVERSITY OF WISCONSIN–MADISON

No Words Required

Clinical electrophysiology provides a number of non-invasive diagnostic tools for assessing human and animal health. Electrocardiography (ECG) records heart function and alerts us to heart rhythm abnormalities; electroencephalography (EEG) records brain function and helps to diagnose stroke, tumors, and seizure disorders.

James N. Ver Hoeve, PhD, with eye tracking equipment.

Likewise, electroretinography (ERG) measures the function of the whole retina, and the more detailed multifocal ERG (mfERG) simultaneously measures function from over 100 locations on the retina, pinpointing localized retinal dysfunction.

Visual electrophysiology tests can identify function or dysfunction along the entire visual system, from eye to brain. James Ver Hoeve, PhD, senior scientist in the department of Ophthalmology and Visual Sciences and member of the UW Eye Research Institute, brings experience and expertise with these tools to both clinical settings and research applications. Ver Hoeve has been performing and participating in the interpretation of visual evoked potentials (VEPs) and electroretinograms (ERGs) over the past twenty-three years, and has served as director of the UW clinical electrophysiology service since 1997.

En route to his doctorate in experimental psychology with an emphasis in physiological and developmental psychology, Ver Hoeve worked on a number of studies involving responses of premature and full term infants to sensory stimuli. He conducted auditory research on the "startle inhibition," a reflex important for attention, and he tracked mechanisms of early speech perception. His experience interpreting babies' electrophysiologic responses provided a natural platform for studying visual system development. As a postdoctoral fellow in an ophthalmology laboratory, he focused on physiological measures of visual perception including eye movement recordings, electroretinography, and cortical VEP.

"With NIH grant support, I sought to advance and refine the effectiveness of VEP as a method for measuring visual acuity and contrast sensitivity in infants," notes Ver Hoeve, "and I then became interested in applying the VEP method in the clinic." Visual evoked potentials can detect blindness in patients who cannot communicate, can determine if an individual is feigning vision loss, can confirm the presence of an intact connection from eye to brain when the retina is not visible (as in severe cataract), can point to the effect of tumors or compression of the optic nerve, and can discern lesions in the visual pathways characteristic of optic neuritis and multiple sclerosis. "There is so much we can learn," continues Ver Hoeve. "With babies and preverbal children, sweep VEP provides an objective method for measuring visual acuity and is very useful in monitoring children diagnosed with ocular conditions including cataract and strabismus, which require intervention to prevent amblyopia ('lazy eye'). And it is equally valuable in evaluating vision in adults who are unable to respond verbally."

"An important adjunct to VEP is the infrared photorefractor, a camera-like device that allows the operator to know when the infant is looking at the stimulus. Since no verbal input from the subject is required, this technique can be used quite successfully with animals as well," comments Ver Hoeve. "Electrophysiology techniques have clear human and animal parallels, and we have applied clinic methods to the study of various aspects of vision in rabbits, dogs, cats, primates and other species. My research continues to refine and validate new assessment methods in various species."

A strong interest in comparative ophthalmology and in animal models of human disease has engaged Ver Hoeve in numerous research projects, and his current work with fellow ERI members is testament to the value of his electrophysiology expertise and perspectives. Ver Hoeve pairs visual electrophysiology techniques with Ocular Coherence Tomography (OCT) and photography, making him a key campus resource.

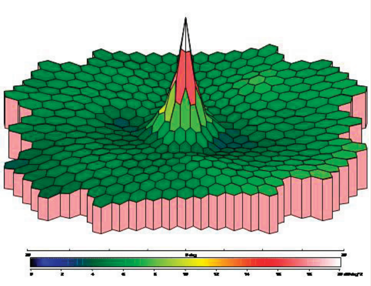
"I sought Jim out when I arrived at UW-Madison in 1993," says ERI member T. Michael Nork, ophthalmologist, "and I have partnered with him ever since. His knowledge and thinking are integrative, and as a clinician-scientist he occupies a middle ground because of his direct experience in both clinical application and research design and conduct." Ver Hoeve aids Nork in studying how photoreceptors are affected in glaucoma and other ocular diseases. Using mfERG with non-human primates allows Nork and colleagues to

Sinusoidal grating - visual stimulus used for sweep VEP testing

How does VEP work? Via three electrodes placed on the scalp, VEP recordings measure the electrical response of the brain's visual cortex to a visual stimulus. In sweep VEP the screen pattern consists of "fuzzy" stripes that alternate contrast (flicker) at a constant rate while the size of the stripes rapidly decreases; computer analysis extracts the brain's response to each pattern size and determines the smallest pattern that elicits a reliable response, all within a ten second presentation.

Hexagonal array - visual stimulus used for mfERG

How does ERG work? The traditional full-field ERG measures summed activity of the retinal cells located at the back of the eye (the photoreceptor rods and cones) to a brief flash of light via a contact lens electrode placed on the surface of the cornea. In mfERG, the subject fixates on a visual display containing an array of 103 hexagons that increase in size from the center outward. During the stimulation, the display flickers as each hexagon goes through a unique sequence of alternately black and white presentations. The computer recording cross-correlates the multiple ERG recordings taken at each sequence change, reflecting the retinal response of each of the 103 corresponding stimulated areas.



A 3-D plot of mfERG responses, reflecting the response density distribution across the stimulated retinal area. In healthy eyes, the peak is generated by the cells in the fovea, where response density is highest.

track changes in glaucomatous eyes over an extended course of time, with the goal of finding a marker of glaucoma before there is visual field loss.

In related work, ERI member Gillian McLellan, veterinary ophthalmologist, benefits from Ver Hoeve's role as a co-sponsor of her NIH clinician-scientist career development award. States McLellan, "As the electrophysiologist, Jim himself is the most important system component. His ability to differentiate artifact from actual abnormality and to troubleshoot problems with electrodes or equipment stems from his vast experience and enhances the clarity of our data." Utilizing VEP, full-field and mfERG, and OCT, McLellan measures retinal and brain function in a cat model of glaucoma and observes disease progression and structural changes over time, as well as monitoring the efficacy of treatments under investigation.

ERI member Ian Duncan, veterinary neurologist, takes advantage of Ver Hoeve's electrophysiology expertise using pattern ERG and pattern VEP to monitor indications of demyelination (loss of the outer sheath of a neuron) in an animal model. This study supports Duncan's work on recruiting stem cells to repair central nervous system damage after myelin loss, which may bring significant insight to mitigating multiple sclerosis and related diseases. Affirms Duncan, "Jim brings to bear extensive background knowledge of published scientific literature along with his broad practical and experiential knowledge, meeting technical challenges and interpreting data. I appreciate his patience, persistence and adaptability."

As co-principal investigator of a grant focused on developing biology-inspired imaging systems, Ver Hoeve partners with ERI members Hongrui Jiang, electrical and computer engineer, Chris Murphy, veterinary ophthalmologist, and Li Zhang, computer scientist, to understand the biology of visual systems at simple and complex levels. Specific vision features from the animal world may be applied to engineered micro cameras and instruments. For example, hawks and other predator birds have two foveas. This adaptation to the central areas of sharpest vision in the retina enhances visual comparison of movement and depth. The research team is working to design an intelligent camera vision system with similar structural and functional features.

While advancing new clinical management strategies for human and veterinary patients is only one component of Ver Hoeve's collaborative efforts, it is the primary focus of his consulting work with the Comparative Ophthalmic Research Laboratories (CORL) and its industry partner, Covance. ERG testing is essential to drug efficacy and safety evaluation, as the FDA now mandates that electrophysiology be employed in drug toxicity studies—whether drugs are designed to affect ocular function or are intended for other purposes such as cancer or arthritis. "Even when potential drugs are not targeting the eye directly, the eye can be affected," explains Ver Hoeve. "The eye is a directly observable part of the central nervous system with a high rate of blood flow and a complex and fragile chain of biochemical processes needed for electrical activation by light; thus focusing on the eye is an efficient way to monitor the side effects of many kinds of drugs. As CORL is demonstrating, imaging and electrophysiology studies of the eye are serving an increasingly important role in the development of safe pharmaceuticals."

Ver Hoeve epitomizes the collaborative spirit of the ERI, functioning at the hub of multidisciplinary partnerships with fellow ERI members working to gain critical knowledge about the science and art of vision and apply it to the treatment of eye disease and prevention of blindness.

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