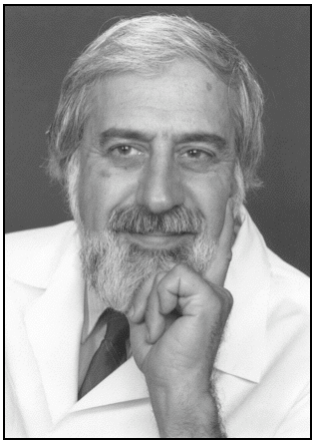
ADVANCES IN UNDERSTANDING MECHANISMS AND TREATMENT OF INFANTILE FORMS OF NYSTAGMUS



A Conference to Honor Louis F. Dell'Osso, Ph.D. and
Celebrate the Opening of the
Daroff-Dell'Osso Ocular Motility Laboratory

May 3-4, 2007

Louis Stokes Cleveland
Department of Veterans Affairs Medical Center
& Case Western Reserve University, Cleveland Ohio

Supported from a Grant from
the Garson Fund of the Mount Sinai Fund of Cleveland, Ohio

Thursday May 3rd, 2007
BRB Research Building – First Floor Lecture Theater

8:30 AM Opening Remarks – John Leigh and Michael Devereaux

Session 1: Basic Concepts of Stable Vision and Gaze
Chair: Robert B. Daroff

8:45 AM *Afferent and efferent contributions to knowledge of eye position*
Martin J. Steinbach, Toronto, Canada

9:30 AM *Perceptual influences of the extra-retinal signals for normal eye movement and infantile nystagmus*
Harold E. Bedell, Houston, TX

10:15 AM Coffee Break

10:45 AM *Perception with unstable vision*
Richard Abadi, Manchester, UK

11:30 AM *Internal and external influences on foveation and perception in infantile nystagmus syndrome*
Larry A. Abel, Melbourne, Australia.

12:15 AM *Perceptual Fading during Voluntary and Involuntary Eye Movements*
Frank A. Proudlock, Leicester, U.K.

12:30 PM Lunch in BRB Lobby

Session 2: New Models and Techniques for Studying Gaze Stability
Chair: Louis F. Dell'Osso

1:30 PM *Alternating Saccades in a Primate Models of Strabismus*
Vallabh Das, Atlanta, GA

2:15 PM *Effects of cerebellar lesions in monkey on gaze stability*
Mark Walker, Baltimore, MD

3:00 PM Tea Break

3:30 PM *Development of visual stabilization devices with potential applications to congenital nystagmus*
Igor Kofman and John Stahl, Cleveland, OH

4:15 PM *Pupil abnormality of the near response in children with the "information technology" syndrome*
Akio Tabuchi, Kawasaki, Japan

4:45 PM Adjourn; Walk back to Glidden House

7:00 PM Special Dinner (Coaches will collect guests at 6:30 pm from Glidden House)

Friday May 4th, 2007
BRB Research Building – First Floor Lecture Theater

Session 3: New Therapies for Congenital Nystagmus
Chair: Michael Devereaux

8:45 AM *Infantile nystagmus: Genetics and pharmacological treatment*
Irene Gottlob, Leicester, UK

9:30 AM *New treatments for infantile and other forms of nystagmus*
Louis Dell'Osso, Cleveland, OH

10:15 AM *Visual and Ocular Motor System Changes After Surgical Intervention in Infantile Nystagmus Syndrome*
Richard W. Hertle, Pittsburgh, PA

10:45 AM *Surgical treatments for acquired forms of nystagmus*
Robert Tomsak, Cleveland, OH

11:15 AM Walk to Louis Stokes Veterans Affairs Medical Center
Tour of Daroff-Dell'Osso Laboratory and Poster Session with Lunch

1:15 AM Return to BRB Building

BRB Research Building – First Floor Lecture Theater

Session 4: Open Papers from Laboratory Alumni and Colleagues
Chair: John Leigh

1:30 PM *Effect of eye exercise on clinical outcome of non-compressive ocular motor nerve palsy*
Anuchit Poonyathalang, Bangkok, Thailand

1:45 PM *Expanding the Original Behavioral Infantile Nystagmus Syndrome Model to Jerk Waveforms and Gaze-angle Variations*
Zhong Wang, Cleveland OH

2:00 PM *Extending the eXpanded nystagmus acuity function to vertical and multiplanar data*
Jonathan Jacobs, Cleveland, OH

2:15 PM *Inertial and non-inertial contributions to the perception of translation and path*
Scott Seidman, Rochester, NY

2:30 PM *The effect of the Duncker visual illusion on smooth arm tracking*
Ari Zivotofsky, Tel Aviv, Israel

2:45 PM *Posterior internuclear ophthalmoplegia of Lutz revisited*
Bernd Remler, Milwaukee, WI

3:00 PM *Divergence insufficiency in patients with hereditary spinocerebellar ataxia*
Patrick Lavin, Nashville, TN

3:15 PM *Neuromuscular junction dysfunction in Miller Fisher Syndrome*
Janet Rucker, Chicago, IL

3:30 PM *Involuntary version-vergence nystagmus induced by ground plane optic flow: analysis of dynamic characteristics of nystagmus quick phases*
Dongsheng Yang, Pittsburgh, PA

3:45 PM *Neuro-ophthalmological complications of chiropractic manipulation*
Michael Devereaux, Cleveland, OH

4:00 PM *Vergence hysteresis in infantile nystagmus*
Alessandro Serra, Sardinia, Italy

4:15 PM *Using wavelet analysis to evaluate effects of eye and head movements on ocular oscillations*
Ke Liao, Cleveland, OH

4:30 PM *Contributions of electroretinograms to diagnosis in infantile nystagmus*
Elisa Bala, Cleveland, OH

4:45 PM A Summing Up: Robert B. Daroff and Louis F. Dell'Osso

Afferent and Efferent Contributions to Knowledge of Eye Position

Ewa Niechwiej-Szwedo & Martin J. Steinbach
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Toronto, Canada

To stay informed about the position of the eyes in the orbits, the brain has available two extraretinal signals: a copy of the efferent signal (outflow) to the extraocular muscles (EOM) and proprioception (inflow) from the EOM. Palisade endings (PE), associated with the multiply innervated fibers (MIF) of the global layer of EOM, are the putative receptors supplying the inflow eye position signal. Buettner-Ennever's proprioceptive hypothesis for the control of eye movements is based on neuroanatomical tracing studies that identified a distinct set of non-twitch (NT) motoneurons whose activity does not add to the force used to move the eyes. It has been suggested that NT motoneurons could be involved in modulating the gain of sensory feedback from the eye muscles analogous to the gamma-efferent fibres that control the sensitivity of muscle spindles in skeletal muscles. We tested this in a series of studies where the activity of NT motoneurons was altered using the Jendrassik Maneuver (JM). JM facilitates the amplitude of all tendon reflexes, which is likely due to the general up-regulation of the gamma system. We found that the JM perturbation altered registered vergence eye position when observers localized targets in depth. Surprisingly, the JM did not affect higher order perceptual judgments (size constancies), nor did it affect the saccadic system. Overall, our studies provide insight into the putative mechanism involved in the control of sensory feedback from the EOM.

Perceptual influences of extra-retinal signals for normal eye movements and infantile nystagmus.

Harold E. Bedell[1,2], Jianliang Tong[1], Saumil S. Patel[3] & Janis M. White[4]

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The involuntary eye movements in patients with infantile nystagmus (IN) generate rapid to-and-fro motion of the retinal image, which has the potential to produce oscillopsia and the perception of motion smear. In normal subjects, extra-retinal signals can neurally "cancel" the retinal image motion that occurs during eye movements and can reduce the extent of perceived motion smear. Previous studies indicate that extra-retinal signals contribute also to perceived stability in subjects with IN. In addition to "canceling" the to-and-fro motion of the retinal image, extra-retinal signals also compensate partly for changes in retinal-image orientation that occur during the torsional component of IN. We show that extra-retinal signals reduce perceived motion smear in a subject with IN, preferentially for relative target motion in the opposite direction of slow-phase eye movements. A possible mechanism for the reduction of perceived motion smear is a decrease in the duration of the temporal impulse response function during eye movements. Temporal contrast sensitivities measured in normal observers and subjects with IN are consistent with this possibility. Although extra-retinal eye-movement signals have similar influences on perceived stability and clarity in normal observers and subjects with IN, the characteristics of the operative neural mechanisms may not be identical.

Perception with unstable vision

Richard Abadi, Manchester University, UK

Internal and external influences on foveation and perception in infantile nystagmus syndrome

Larry A. Abel, PhD[1] and Linda Malesic, PhD[2], [1]Department of Optometry & Vision Sciences, University of Melbourne and [2]Department of Clinical Vision Sciences, La Trobe University, Melbourne, Australia.

Infantile nystagmus syndrome (INS) is a disorder which, more than many other disturbances of vision, is influenced by a range of both internal and external factors. Manipulation of stimulus characteristics such as contrast have shown that this can provoke oscillopsia—a perception of environmental motion often said to be absent in INS. Rapidly flickering stimuli can also lead to multiply perceived images. Some internal factors, such as variability with gaze position, have been well documented. Others, such as, exacerbation with visual effort, are widely described but have almost never been formally studied. In one study which examined this, the expected relationship was not found, but subjects' comments suggested that an absence of motivation may have been contributory. Although case reports have shown stress or anxiety to exacerbate INS and provoke oscillopsia, systematic studies have been lacking. Similarly, changes in visual function or ocular alignment in adulthood may decrease foveation and elicit oscillopsia in nystagmus patients previously free of this symptom. Future models of INS should incorporate modulatory inputs from the limbic system which represent motivational or stress-related influences as well as limits on the functioning of the mechanisms which compensate for retinal image motion and thus suppress oscillopsia.

Perceptual Fading during Voluntary and Involuntary Eye Movements

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Purpose: Perceptual fading (PF) is a phenomenon in which a target in the visual field fades from view after a certain fading time (FT). PF is reset by microsaccadic eye movements; however, PF has not been investigated during non-fixation eye movements. We compared PF during voluntary eye movements in healthy volunteers and in patients with involuntary eye oscillations caused by nystagmus.
Methods: Twelve healthy volunteers performed a PF task consisting of following an oscillating fixation cross moving with either sine wave (pursuit task) or square wave (saccadic task) profile while viewing a static peripheral spot of low contrast (1.5x threshold). This was compared to FT during a static fixation cross with peripheral spot moving and also when both were moving. FT was also compared in four volunteers with nystagmus.
Results: During pursuit, FT was significantly longer for the static cross + moving target condition compared to the moving cross + static target ($p=0.04$) and moving cross + moving target ($p=0.001$). In contrast, during the saccadic trial, FT was similar for static cross + moving target, and, moving cross + static target tasks, but both were lower than the moving cross + moving target task. FT was more strongly correlated to retinal speed of the PF target during square wave than sine wave tasks. FT was correlated to foveation in the four subjects with nystagmus.
Conclusions: We describe the PF during voluntary eye movements when stimuli are applied at low contrast. Fading time was not simply related to retinal velocity of the target but also to efferent information. Interestingly, patients with involuntary eye movements could also fill–in targets although responses were more variable than healthy volunteers.

Alternating Saccades in A Primate Model of Strabismus

Vallabh E. Das[1,2]
Division of Sensory-Motor Systems[1]*, Yerkes National Primate Research Center, Department of Neurology*[2]*, Emory University, Atlanta, GA 30322.*

Alternating fixation is frequently observed in humans with strabismus. Here we examined this phenomenon in a monkey model for strabismus. An exotropic strabismus was induced in two infant monkeys using an alternate monocular occlusion paradigm for the first four months of life. When the animals were about three years old, we measured binocular eye movements, using the scleral search coil technique, as they performed a visually guided saccade task during monocular or binocular viewing. During binocular viewing, monkeys tended to fixate targets in the right hemifield with their right eye and targets in the left hemifield with their left eye, mimicking patterns of visual suppression in exotropia. An alternating saccade was executed when the target jumped across the midline. There were no significant differences in the amplitude-peak velocity or amplitude-duration main sequence relationships between alternating and non-alternating saccades (monocular or binocular viewing). Saccade latency tended to be greater during binocular viewing than during monocular viewing. Our study establishes a strabismus monkey model useful for studying neural circuits involved in generating alternating fixation and alternating saccade behavior. Further, alternating saccade behavior may be used as a probe to study mechanisms of visual suppression.

Effects of cerebellar lesions in monkey on gaze stability

Mark Walker, Johns Hopkins University, Baltimore

Studies in humans and animals have shown that the cerebellum plays a vital role in calibrating eye movements to maintain gaze stability. Several cerebellar areas have been found to be of particular importance. The oculomotor vermis, acting through the fastigial nuclei, controls the size of saccades. The flocculus and paraflocculus assist fixation and control eccentric gaze-holding; lesions here cause spontaneous (e.g., downbeat) and gaze-evoked nystagmus. They also are responsible to calibrating the gain of the rotational (angular) vestibulo-ocular reflex (VOR).

Here we focus on the function of the cerebellar nodulus and uvula in stabilizing the foveal image when the object of regard is moving (smooth pursuit) and during linear motion of the head (the translational VOR). Eye movements of two rhesus monkeys were recorded using the magnetic field search coil method, before and after surgical ablation of the nodulus and uvula. Key findings included: (1) there was an asymmetric deficit of vertical smooth pursuit – downward, but not upward pursuit was impaired; (2) the vertical translational VOR was reduced, for both upward and downward translation; and (3) the sustained, but not the initial, response to abrupt horizontal translations was impaired. Our results, in combination with prior studies, support a role for the nodulus and uvula in mediating vertical ocular following reflexes, in controlling the horizontal TVOR (possibly acting as an integrator of head acceleration), and in the determination of gravitational orientation.

Development of visual stabilization devices with potential applications to congenital nystagmus

Igor Kofman and John Stahl, Cleveland Ohio

The deleterious consequences of nystagmus include oscillopsia and reduced acuity. Although several medical and surgical interventions have been demonstrated to be efficacious in specific patients/nystagmus types, the treatments are neither universally effective nor always tolerable. Optomechanical devices that stabilize vision by nullifying the image motion produced by the nystagmus have the potential to improve vision in treatment-resistant patients. Such devices may also be used to predict the degree of benefit a patient may expect to receive from a contemplated medical or surgical therapy. A predictive tool would be particularly useful when the contemplated therapy involves significant expenses, risks, or discomforts. Visual stabilization devices can also be applied as research tools to manipulate retinal image velocity and explore its effects on nystagmus waveform and oscillopsia. Optomechanical stabilization systems consist of an eye movement tracking device, a filtering system to extract the pathological movement from the overall eye movement, and an optical or display mechanism (the stabilizer plant) that allows the seen world or displayed images to be oscillated synchronously with the patients nystagmus. Our laboratory has worked to develop a practical, self-contained visual stabilization device. In this chapter we review our experiences with the device, emphasizing the development of the filter and stabilizer plant. Although we focus on the treatment of acquired pendular nystagmus, we also present the effects of visual stabilization in one patient with congenital nystagmus, as an illustration of how a computer-controlled stabilizer might serve as a research tool.

Pupil abnormality of the near response in children with the "information technology" syndrome

Akio Tabuchi, Atsushi Fujiwara, and Mahmoodi Khadija
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"Information technology" syndrome or "Visual Display Terminals (VDT)" syndrome is the complex of eye and vision problems which associated with systemic disorders related to near viewing, for long periods, during which time individuals are exposed to electromagnetic (Computer, Television, cellular phone…) use. Nowadays, millions of children use VDT in school and at home for educations and recreation. Children can experience many of the same symptoms related to VDT use as adults. In healthy eyes, the pupils naturally change size and position as focus shifts from far to near objects during using VDT. In this study, we analyzed a pupil abnormality of the near response, that is convergence, accommodation, and miosis, using by TriIRIS C9000 (Hamamatsu Photonics, Hamamatsu, Japan) in a group of children aged from 13 to 15 years old. We included 129 normal students, excluding those with refractive error. All of them used some kinds of VDTs (Personal computer, TV, TV-Game, Mobile game, Phone). Among 129 students, 101 (78.3%) had normal pupillary response and 28 students (21.7%) had abnormal pupillary response. The pupil abnormality during using of VDT is thought to be mediated by autonomic system disorders that controlled the pupil response during near work. Continuously using of VDT leads to an abnormality in pupillary response.

Genetics and pharmacological treatment of nystagmus: A review of the literature and recent new findings.

Irene Gottlob, University of Leicester, U.K.

New developments in genetics and pharmacological treatment of nystagmus are reviewed. While cases of nystagmus are frequently sporadic, kindreds in which nystagmus segregated as an autosomal dominant, autosomal recessive, or X-linked trait have been reported. Of these, X-linked pedigrees are the most frequent. By linkage analysis, the major X-linked locus for nystagmus (NYS1) was localised to chromosome Xq26-q27. Linkage analysis and DNA sequence analysis performed in 26 families with idiopathic congenital nystagmus (ICN) led to the detection of a novel gene named FRMD7 (FERM domain containing 7) at Xq26.2 in which we have identified 22 different mutations. Mutations in the FRMD7 gene encode a previously unidentified member of the protein 4.1 superfamily. Several drugs have been used to treat acquired nystagmus, however pharmacological treatment has so far not been used in congenital nystagmus. A randomised study showed that memantine (up to 40 mg) and gabapentin (up to 2400 mg) can improve significantly visual acuity in CIN and reduce nystagmus in CIN and in nystagmus associated to ocular disease.

New treatments for infantile and other forms of nystagmus

Louis Dell'Osso, Cleveland OH

Objectives. To translate the past 40 years of infantile nystagmus syndrome (INS) research (i.e., ocular motor recording and control-systems analysis) into a therapeutic approach. Materials and Methods. Our eye-movement recordings use infrared reflection, magnetic search coil, and high-speed digital video systems. Each eye was calibrated during monocular fixation (fellow eye occluded). We analyzed and displayed all data using software developed and written in our laboratory in the MATLAB environment, including the eXpanded Nystagmus Acuity Function (NAFX). Results. Analysis of ~1000 INS subjects over 40 years revealed waveform characteristics that can be exploited therapeutically. Analysis of post-operative INS data suggested that tenotomy and resuture (at the original insertions) of the extraocular muscles in the plane of the IN would improve foveation. The NAFX across normal gaze-angles showed both peak-value increases and NAFX curve broadening. Conclusions. All patients with nystagmus should have eye-movement recording and analysis. The resulting accurate diagnosis and documentation of INS characteristics (undetectable by clinical observation) will identify the best therapy. NAFX analysis allows estimation of post-operative acuities and determination of the most appropriate therapies. This eye-movement based procedure is the first to provide both the physician and patient with a post-therapeutic estimation of specific improvements in visual function not possible from acuity measurements alone.

Clinical and Electrophysiological Results of Eye Muscle Surgery in 53 Patients with Infantile Periodic Alternating Nystagmus (IPAN)

Richard W. Hertle, Dongsheng Yang and Leah Reznick, University of Pittsburgh, PA

Purpose - Of 1,026 evaluations performed between the years 1998-2006 in 506 patients with INS, 78 had ocular oscillations consistent with IPAN. 53 had eye muscle surgery and are the subjects of this report.

Results - Age was 1 to 67 yrs, 57% had pure periodicity, 43% aperiodicity, 42% had albinism, 42% had strabismus, 40% had amblyopia and 32% had other eye disease. All patients had all four horizontal recti operated. In 15% for strabismus alone, 36% for an AHP alone, 13% for strabismus and an AHP and 36% had tenotomy alone. After surgery static AHP and strabimus improved, binocular LogMAR acuity increased from 0.55 to 0.42 ($p < .01$), the periodic cycle average increased from 221 sec to 256 sec ($p < .01$), the null period increased from 11.2 sec to 20 sec ($p<.001$), best foveation increased from 132 msec to 178 msec ($p<0.05$) and 43% changed to a more visually favorable waveform. There were no differences in cycle symmetry about the null period or the four surgical indication groups.

Discussion - IPAN as part of INS is 15% in our population. Surgery on the eye muscles of these patients improves multiple ocular motor and visual system functions.

Surgical Treatments for Acquired Forms of Nystagmus

Robert L. Tomsak, MD, PhD
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Case Western Reserve University School of Medicine

Three patients with acquired nystagmus were treated with eye muscle tenotomy.

1. The first patient had acquired pendular nystagmus (APN) from MS and underwent bilateral medial rectus tenotomies and bilateral lateral rectus recessions to also correct exotropia. Eye movements were recorded by the scleral search coil technique at three times: before surgery, after surgery, and after surgery and treatment with memantine. Following surgery, APN decreased by ~50% and the expanded nystagmus acuity function (NAFX) increased by 34%. Measured Snellen acuity increased 100% from 0.125 OD and OS to 0.25. Saccades were unaffected. After treatment with memantine, APN was damped further by 69% and NAFX was improved an additional 9%; Snellen acuity increased 60% to 0.4.

2. The second patient had unilateral APN caused by MS. Pre- and post-tenotomy eye movements were studied using digitized video recordings. The horizontal recti were tenotomized and reattached in only the APN eye. This resulted in damping of the nystagmus by 66%, and Snellen acuity increased 100% from 0.2 to 0.4.

3. The third patient had downbeat nystagmus (DBN) of undetermined etiology, oscillopsia, and vertical diplopia from skew deviation; he preferred a chin-down (upgaze) head position to diminish symptoms. Pre- and post-tenotomy eye movements were recorded by a high-speed digital video system. Asymmetric superior rectus recessions were done to address head position and hypertropia and were combined with tenotomy and reattachment of both inferior recti. Surgery resulted in movement of the NAFX peak from 10 deg up to primary position, and NAFX values were improved by 17%. Vertical NAFX values increased across the –10 deg to +5 deg vertical range. Foveation time per cycle increased from 88 ms to 178 ms (102%). Vertical component amplitude was reduced by 46% and frequency was unchanged at ~3 Hz. Visual acuity was improved from 20/25 to 20/20, and the hypertropia was improved.

Conclusions: Eye muscle tenotomy appears to have salutary effects on acquired nystagmus of differing etiologies and different neuroanatomic sites of origin; this supports its hypothesized proprioceptive mechanism of action. The addition of memantine in one patient with APN augmented the effects of tenotomy.

Effect of Eye Exercise on Clinical Outcome of Non-Compressive Ocular Motor Nerve Palsy

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Objective: To study the effect of eye exercise on non-compressive ocular motor nerve palsy treatment in addition to medical treatment.
Background: Treatment of ocular motor nerve palsy by occlusion, prism and botulinum toxin injection are used to reduce diplopia symptoms. To reduce recovery time, the use of eye movement exercises has been introduced.
Method: Patients with ocular motor nerve palsy were randomly instructed to move their eyes back and forth in directions of paresis 100 times a day. Time from onset to normal fusion was recorded and compared between an exercise and non-exercise group.
Results: Eleven patients had cranial third nerve palsy, twelve had sixth nerve palsy and one had both third and sixth nerve palsy. All patients were treated with oral aspirin or other anti-platelet therapy. The eye exercise group included nine patients and non-eye exercise group had fifteen patients. The eye exercise group had an average recovery time of 3.8 weeks as compared to the 25.5 weeks for the non-exercise group.
Conclusion: Patients who performed eye exercises had shorter recovery times from double vision than patients who were only given medical treatment. However, since our sample size was very small, other parameters could possibly be responsible for the results that were seen.

References

1. Everhard-Halm YS, Koornneef L, Zonneveld FW. Conservative therapy frequently indicated in blow out fractures of the orbit. Ned Tijdschr Geneeskd. 1991; 135(27):1226-8.
2. Kawahira K, Shimodozono M, Etoh S, Tanaka N. New facilitation exercise using the vestibulo-ocular reflex for ophthalmoplegia: preliminary report. Clin Rehabil. 2005; 19(6):627-34.

Expanding the Original Behavioral Infantile Nystagmus Syndrome Model to Jerk Waveforms and Gaze-angle Variations

Z.I. Wang, L.F. Dell'Osso , and J.B. Jacobs, Cleveland, OH

Objectives. To expand the behavioral Ocular Motor System (OMS) model for Infantile Nystagmus Syndrome (INS) by: 1) incorporating jerk and jerk with extended foveation waveforms with a unifying mechanism for both pendular and jerk waveforms; 2) incorporating idiosyncratic variation of IN amplitude with gaze angles. Materials and Methods. Ocular motor recordings of humans, using infrared reflection, high-speed digital video, and magnetic search coil systems, were used as templates for the computer simulations. All simulations and analyses were performed in MATLAB Simulink environment. Results. Examinations of eye-movement data during different states of attention suggested that pendular and jerk INS waveforms came from the same underlying smooth-pursuit-system oscillation. Simulation of unidirectional jerk waveforms, required a resettable neural integrator in the pursuit pre-motor circuitry. Alexander's law relationships were used to produce desired INS "null" positions and sharpness. At various gaze angles, these Alexander's law relationships influenced the IN slow-phase amplitudes differently, thus mimicking the same gaze-angle effects observed in INS patients. Conclusions. The simulations of a robust behavioral OMS model demonstrated that both pendular and jerk waveforms can be generated by the same pursuit-system instability. Alexander's law output effectively modulates the nystagmus variation at different gaze angles.

Extension of the eXpanded Nystagmus Acuity Function to Vertical and Multiplanar Data

Jonathan B. Jacobs and Louis F. Dell'Osso, Cleveland, OH

Objectives. To update and extend the functionality of the eXpanded Nystagmus Acuity Function (NAFX), allowing for its application to biplanar nystagmus and improving its predictive value in clinical evaluations. Materials and Methods. The original NAFX was based on foveation times taken from a "tau surface," an array whose values were calculated for each combination of position and velocity limits of a "foveation window." For the updated NAFX, we replaced the empirical surface with a mathematically defined surface that matched the original, but without the idiosynchratic irregularities due to the waveforms of the subjects used for its calculation. For biplanar data, we have investigated combining horizontal and vertical eye-movement data into a single radial vector. Age-related relationships were incorporated for more accurate individual visual acuities. Results. Using the same uniplanar patient data, we verified that the updated NAFX yielded equivalent results as the original NAFX for the foveation window limits we tested. For biplanar data, the NAFX values were also comparable to those from uniplanar data of the same magnitude. Conclusions. The new version of the NAFX allows greater accuracy in predicting visual acuity for subjects of all ages, for both uniplanar and biplanar nystagmus. This will allow researchers and clinicians to select the best therapies for a wider range of nystagmus patients.

Inertial and non-inertial contributions to the perception of translation and path
Scott H. Seidman, University of Rochester, NY

The ability to determine the path of travel, or "path integration", has been reported to be robust in humans, and has been attributed to an accurate double integration of acceleration signals transduced by the otolith organs to yield path information. Vestibuloocular responses to translational motion, however, are most robust at high frequencies of motion, and become somewhat feeble at frequencies typically used in the study of path integration; this observation puts the otolith origin of path integration phenomena in doubt. To determine if path integration behaviors might be mediated by cues of motion of a non-inertial nature, such as vibration and noise that might accompany translational motion, we measured the perception of motion on two different apparatus: one that minimized non-inertial cues of motion, and a second that dissociated non-inertial cues from actual motion.
When non-inertial cues are minimized, we observe a variety of high-pass phenomena in the perception of translation, including a decay in magnitude during constant velocity travel, and decreasing magnitude accompanied by increasing phase leads as the frequency of sinusoidal translation decreases. When cues are dissociated from motion, the perception of translation is heavily influenced by the non-inertial cues. We conclude that otolith mechanisms are not sufficient to drive path integration behaviors.

The Effect of the Duncker Visual Illusion on Occluded Smooth Arm Tracking

Ari Z. Zivotofsky[1], Adi Bercovich[1,3], Jason Friedman[2], Eva Kelman[1], Elinor Shinhertz[1], and Tamar Flash[2]

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Motor systems are required to perform coordinate transformations in order to accurately translate the visual information utilized in the execution of the desired task. These transformations can be affected by the presence of a visual illusion. The Duncker Illusion, also known as induced motion, is an illusion of motion that occurs in the presence of background movement. Previous studies have shown that certain aspects of the ocular motor system are influenced by this illusion in the same manner as the perceptual system is influenced. The present study examined the effect of the Duncker Illusion on hand tracking movements. Eight subjects were required to track with their hand using arm movements the trajectory of a smoothly moving target without the benefit of visual feedback. Our results show that in a significant number of trials with the illusion, the hand-tracking trajectory differed significantly from its control condition in the direction opposite that of the illusion. This is explainable by positing that there were ocular following type eye movements generated by the flow-field movement that in turn influenced the arm tracking. This presents another instance of a motor system whose control system is impervious to influence by a visual illusion.

Posterior INO of Lutz revisited

Bernd F. Remler and R. John Leigh

In 1923 Anton Lutz proposed the existence of a posterior INO, i.e. a prenuclear palsy of the lateral rectus, analogous to the medial rectus palsy of "anterior INO". His innervational model postulated direct supranuclear projections to the 3rd nerve nucleus with collaterals to the 6th nerve nucleus. Despite the faulty anatomical concept "Posterior INO of Lutz" has persisted as a label for prenuclear abduction deficits.

This case report regards a 50yo man who presented with insidious onset diplopia on rightward gaze. His examination demonstrated a minimal abduction deficit and esodeviation OD, which increased on rightward gaze. After initially negative imaging, a small midbrain lesion evolved in the supranuclear region of the R 3rd nerve nucleus. The lesion and ocular motor findings have remained nearly unchanged over >2 years. An eye movement recording confirmed the abduction deficit, but saccadic velocities were in the normal range. Vertical gaze was intact.

"Posterior INO of Lutz" has been attributed to a disconnection between the PPRF and the abducens nucleus. Midbrain lesions are also associated with abduction deficits suggesting that internuclear connections between the 3rd and 6th nerve nuclei may exist. However, other anatomical concepts could account for our patient's findings including loss of supranuclear medial rectus inhibition. A functional and anatomical classification should replace the diagnosis of "Posterior INO of Lutz" because variable anatomical locations are associated with prenuclear abduction deficits.

Divergence insufficiency in patients with hereditary spinocerebellar ataxia
Patrick Lavin, Nashville, TN

Divergence insufficiency is characterized by five criteria: 1) acquired uncrossed horizontal diplopia at distance, but not near; 2) comitant esotropia at distance; 3) full ductions; 4) normal abducting saccades, with no signs of abducens palsies; 5) reduced or absent fusional divergence.
Unfortunately, the terms divergence insufficiency (DI) and divergence paralysis (DP) are used interchangeably. Bruce (1935) distinguished between "divergence insufficiency" in which an otherwise healthy patient develops sudden onset esotropia at distance, and "divergence paralysis" which is associated with underlying neurological diseases. DI can be distinguished from divergence paralysis which occurs as a result of bilateral abducens palsies in patients with severe head injuries, intracranial hypertension, intracranial hypotension, brainstem tumors, craniocervical junction abnormalities, and Fisher's syndrome. Patients usually have bilateral abduction deficits, horizontal diplopia at distance, and quantitatively slowed abducting saccades. DI can be difficult to distinguish from DP in those recovering who go through a phase during which the esotropia becomes comitant with full ductions, mimicking DI; however, quantitative abducting saccades are generally slowed.
DI generally occurs in patients who otherwise appear neurologically normal; occasionally, it occurs with Chiari I malformations, midline cerebellar degeneration and sedation (diazepam). The association of DI and hereditary spinocerebellar degeneration is not well known; the purpose of this study is to report the association of DI with hereditary spinocerebellar ataxia in six patients and discuss their management.

Neuromuscular Junction Dysfunction In Miller Fisher Syndrome

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Introduction: Miller Fisher syndrome (MFS) consists of a triad including ophthalmoplegia, ataxia, and areflexia with a self-limited monophasic course. Anti-GQ1b antibodies are present in up to 90% of patients. It is considered a variant of Guillain-Barre, with the primary pathology considered to be peripheral nerve demyelination. Methods: A 43 year old man with an acetylcholine receptor antibody-negative diagnosis of myasthenia gravis for a 3 month monophasic illness 15 years prior presented with binocular diplopia. Electrophysiologic studies prior to neuro-ophthalmologic evaluation revealed a decremental response to repetitive stimulation. Relapse of myasthenia gravis was the working diagnosis. Neuro-ophthalmologic examination and literature review were performed. Results: Examination revealed diffuse bilateral ophthalmoplegia, bilateral pupillary light-near dissociation, and areflexia. Cerebellar function was normal. Cerebrospinal fluid was normal. Anti-GQ1b antibodies were positive. Recurrent MFS was diagnosed. Primary neuromuscular junction pathology in MFS is reported electrophysiologically and pathologically in a mouse diaphragm / phrenic nerve model upon exposure to human GQ1b antibodies. Three human cases of GQ1b positive MFS with abnormal single fiber EMG and two with incremental responses to repetitive stimulation are described. Conclusion: The patient in this case report brings to light a developing recognition in the human clinical literature of neuromuscular dysfunction in MFS, which is well-founded in basic science studies. Systematic evaluation of neuromuscular junction physiology should be performed in MFS patients to advance understanding of this process.

Involuntary version-vergence nystagmus induced by ground plane optic flow: analysis of dynamic characteristics of nystagmus quick phases

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We used a new ground plane motion stimuli displayed on a computer monitor in the ground plane to induce involuntary version-vergence nystagmus. Eye movements were recorded with a search coil system. The involuntary version-vergence nystagmus had both vertical version and horizontal vergence components. Quick phases of both vergence and version components were analyzed. Backward motion induced monophasic divergent quick phases and upward versional quick phases. Forward motion induced biphasic divergence-convergence quick phases and downward versional quick phases. A time dissociation of about 20 ms between version velocity peak and convergence velocity peak was observed. Vergence peak time had a dependence on version peak time. Linear relationships between vergence peak velocity and versional saccadic peak velocity were demonstrated under binocular viewing conditions, but not monocular viewing conditions. Our data support the hypothesis that the vergence system and the saccadic system can act separately, but interact with each other whenever they occur simultaneously.
Keywords: nystagmus, vergence, eye movements, optic flow

The Neuro-Ophthalmologic Complications of Cervical Manipulation
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Cervical manipulation, specifically chiropractic manipulation, is an important cause of vertebral basilar and rarely carotid artery distribution strokes. The mechanism of action of vertebral artery distribution strokes is vertebral artery dissection at the level of the atlas as a result of rotation and extension of the head, which can occur in association with chiropractic manipulation. The vertebral arteries are tethered as they pass through the dura. Rotation of the atlas around the axis can lead to stretching of the vertebral artery on the side opposite the direction of head rotation, with a resultant intimal tear, and ultimately occlusion with thrombus formation and embolization. Neuro-ophthalmologic findings are a common and at times relatively isolated feature of strokes secondary to chiropractic manipulation. This is a more frequent occurrence than commonly recognized. A variety of neuro-ophthalmologic disturbances have been recognized including visual field defects due to posterior cerebral artery distribution embolic strokes and oculomotor disturbances due to strokes anywhere in the brain stem, but most commonly in the medulla. Strokes induced by therapeutic manipulation of the neck are not rare. Patients, particularly young patients with significant stroke risk factors presenting with vertebrobasilar strokes should be questioned as to whether they have undergone cervical manipulation. Patients should be routinely instructed to avoid chiropractic neck manipulation.

Vergence hysteresis in infantile nystagmus

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Objectives. To investigate the previously observed hysteresis (higher eXpanded Nystagmus Acuity Function (NAFX) during divergence than convergence) effects of multi- and single-step vergence on visual acuity in a subject with Infantile Nystagmus Syndrome (INS). Materials and Methods. Eye movements were measured using a high-speed digital video system during fixation of targets at 0º, stepping in from far to near (60D) and back out (5 or 20 sec/fixation) as well as during single steps (1-5 seconds per fixation). Results. Higher values of NAFX were achieved at far if the previous near target was fixated for 5 seconds. Single steps between near and far (1 and 3 sec/fixation), did not improve the following far NAFX. Double near shifts (F-N-F-N-F), yielded some improvement in far NAFX values in one of two trials with 3-second fixations. Hysteresis was still present for 5-second fixations of multiple-step targets, whereas the NAFX values were high at almost all near targets for 20-second fixations; hysteresis was observed only at far. Conclusions. For better visual acuity at far, a fixation of ≥5 seconds of a near target is required. The time-dependent improvement of visual acuity during convergence or divergence may reflect the time required by the pulleys to reduce the plant's responsiveness allowing better vision.

Using Wavelet Analysis to Evaluate Effects of Eye and Head Movements on Ocular Oscillations

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Insights into the pathogenesis of certain ocular oscillations are provided by determining whether eye or head movements can perturb or "reset" the nystagmus. When the oscillations are regular and sinusoidal, this poses few problems, since the oscillations prior to the perturbation can be compared with those following. However, when the ocular oscillations have an inherent randomness to them, such as the ocular oscillations of oculopalatal tremor (OPT), such comparisons often will not determine whether the perturbation has phase-shifted the nystagmus. We applied complex wavelet analysis to data from two patients with OPT and checked whether vestibular stimuli induced a change in nystagmus amplitude or phase. The nystagmus signal was only present in levels 6-8 (about 1-3 Hz) of the wavelet decomposition. Statistical analysis indicated that, within these levels, there was no change in the energy before or after head rotations. For each head perturbation, we selected two nystagmus cycles prior to a head rotation and shifted them by two peaks to predict what the nystagmus would have been without the perturbation. We compared the prediction with the two cycles that followed the rotation. The phase difference between the cycles before and after head rotation was determined by wavelet coherence analysis. Because OPT is an aperiodic signal, small phase shifts between any sets of two nystagmus cycles are expected, but the rate of change of phase shift is low (< 1000 deg/s). However, at the time of the head perturbation rate of change of phase was large (> 2000 deg/s). We found that head perturbations caused significant ($p < 0.05$) rates of change of phase shift in both patients, confirming our hypothesis that the mechanisms generating OPT receives vestibular inputs.

Multifocal Electroretinographic Study of Patients with Oculocutaneous Albinism and Infantile Nystagmus Syndrome

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Purpose: Some patients with infantile nystagmus syndrome (INS) have an afferent defect that may be the limiting factor for visual acuity. We used the multifocal electroretinogram (mfERG) to quantify retinal function in INS patients with oculocutaneous albinism.

Methods: We recorded mfERGs from two patients, using a standard stimulus (scaled array with 103 hexagons covering the central 45°). Recordings were made under continuous fundus monitoring, allowing us to re-record segments with insufficient fixation. Quantification of nystagmus waveforms was made using the eXpanded Nystagmus Acuity Function (NAFX).

Results: Useable data were obtained from 3 of 4 eyes. One eye could not be recorded due to large-amplitude nystagmus. In the usable recordings, analysis with concentric ring averages showed reduced response amplitude only in the central areas, with normal response amplitudes peripherally. Implicit times were normal at all locations.

Conclusions: Our results are consistent with anatomical studies indicating that albino retinas do not develop a central area of high cone density, and suggest that the potential for good central vision is limited in these patients, in agreement with a recent pediatric study (Kelly & Weiss, AJO 2006;141:1156). We determined that, for one patient, this underdevelopment–rather than the nystagmus–was the limiting factor, and she was less likely to receive enough increase in visual acuity to warrant surgery.