

Fixational Eye Movements and Visual Stabilization is an international symposium that is held at the Nobel Forum of Karolinska Institutet, Stockholm, Sweden, on the 21st to 22nd of June, 2010. The aim of the symposium is to bring together the international expertise in the area of fixational eye movements and visual stabilization, both in health and disease.

The symposium is a part of Karolinska Institutet's bicentennial celebration as well as the celebration of the 20th anniversary of the Sigvard and Marianne Bernadotte Research Foundation for Children Eyecare.

The main benefactor of the symposium is the Marcus Wallenberg Foundation for International Scientific Collaboration. Additional support has been graciously received from the Wenner-Gren Foundations.

# Fixational Eye Movements and Visual Stabilization

International Symposium at the Nobel Forum,  
Karolinska Institutet, 21-22 June, 2010



**Karolinska  
Institutet**

**200**  
1810 – 2010 *Years*





THE SIGVARD & MARIANNE BERNADOTTE  
RESEARCH FOUNDATION FOR CHILDREN EYE CARE

# **Marcus Wallenberg Foundation for International Scientific Collaboration**

Marcus Wallenberg Foundation for International Scientific Collaboration is the main benefactor for arranging *Fixational Eye Movements and Visual Stabilization*.

The foundation was founded March 30, 1976 by a donation from the bank SEB in honour of Tech. Dr. Marcus Wallenberg (1899-1982) when the latter resigned as chairman of the bank's board. The Foundation has at its purpose to support scientific research. Foundation funds will be used for the organization of international scientific symposia in Sweden.

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# Monday 21 June

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09:00 Welcome by organizing committee  
Opening remarks by Professor emeritus Torsten Wiesel, Nobel laureate

## **Session 1 Fixational Eye Movements**

Chairman: Jan Ygge; Moderator: Dominik Straumann

*Tiny but mighty: the impact of microsaccades on visual physiology and perception.* Susana Martinez-Conde

Exhibitor's presentation Tobii Technology and Allergan

10:20 Coffee / refreshments

11:00 *Holding the eyes still and aligned during fixations: slow development and frequent dysfunction (strabismus, dyslexia, vertigo).* Zoi Kapoula

*Saccades, microsaccades and saccadic intrusions: the case for a common oculomotor generator and implications for the diagnosis of neurodegenerative disease.* Steven Macknik

*Slow Oscillatory Eye Movements (SOM) During Fixation.* Roberto Bolzani

12:30 Lunch

13:30 *Modeling Oculopalatal Tremor.* Lance M. Optican

*Visually induced ocular torsion.* Tony Pansell

*Presentation of the Nobel foundation by Professor Sten Lindahl of the Nobel Committee*

## **Session 2 Visual Stabilization**

Chairman: Hans van der Steen; Moderator: Susana Martinez-Conde

15:00 *Reaching the end of the line: 3D kinematics at and beyond the motoneurons.* Dora Angelaki

*High speed video recording of eye movements during head movements - the video head impulse test (vHIT). 1. Development.* Ian Curthoys

16:00 Coffee / refreshments

16:30 *The development and application of the video head impulse test (vHIT) - high speed video recording of eye movements during head movements. 2. Applications.* Michael G. Halmagyi

*Fixation monitoring using retinal birefringence scanning in unrestrained subjects.* David Guyton

*Vestibulo-ocular reflex thresholds match perceptual thresholds above 1 Hz.* Daniel M. Merfeld

18:00 Closing and traditional photographing

18:30 Busses leaves to Vasa museum

# Tuesday 22 June

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Continue session 2

09:00 *Saccades, models, membranes and patients: from the clinic to the lab and back.* Stefano Ramat

*TMS perturbs saccade trajectories, unmasking a feedback controller that compensates for the perturbation.* David Zee

## **Session 3 Developmental aspects of fixation**

Chairman: Gunnar Lennerstrand; Moderator: David Guyton

10:10 *Visuo-Vestibular Eye Movements.* Michael C. Brodsky

10:40 Coffee / refreshments

11:20 *The Interaction Between Singular and Non-Singular Arcs in the Control of Slow Eye Movements.* Chris Harris

*Early development of oculo-motor control.* Claes von Hofsten

*Fixation Patterns during Facial Emotion Recognition in Children.* Gustaf Öqvist Seimyr

12:50 Lunch

## **13:50 Session 4 Clinical considerations and treatments regimes in patients suffering from unstable vision**

Chairman: Måns Magnusson; Moderator: Michael C. Brodsky

14:00 *Fixation stability and eye motility in adolescents with congenital or early acquired visual field defects.* Lena Jacobson

*Benefits of four-muscle recession surgery for congenital nystagmus* John Lee

15:00 Coffee / refreshments

15:30 *Ocular counterroll and verticality perception.* Dominik Straumann

*Human Fixation: Higher Level Control and Related Aspects.* Kenneth J. Ciuffreda

Concluding discussion moderated by David Zee

17.00 Buffet

## **Karolinska Institutet, a medical university – 200 years**

Karolinska Institutet is a medical university at the heart of society. We are players in a global arena, also in close collaboration with the health and medical sector and the business community. The strong research profile of Karolinska Institutet places on us a responsibility to take a leading role within the whole field of medical science.

Karolinska Institutet has contributed to improving people's health for 200 years – by constantly seeking new knowledge and by educating the health care personnel and researchers of tomorrow. The global health challenges are extensive. But the prerequisites for finding new and better treatments have never been as promising as today. We are subject to high expectations for the future from the community, from present and future students and – not least – from the general public. We intend to fulfil these expectations.

## **The Sigvard & Marianne Bernadotte Research Foundation for Children Eye Care – 20 years**

The Sigvard & Marianne Bernadotte Research Foundation for Children Eye Care was founded 1989 with the objective of promoting scientific research on children's vision and eye health. The driving force in the creation of the Foundation has been Marianne Bernadotte, Countess of Wisborg, married to the late Prince Sigvard Bernadotte. Her interest in medicine began when she became involved in the development of an advanced wheel chair, the Permobil. Her long dedication to improving visual function in children emerged from a special interest in dyslexia. The Bernadotte foundation has supported paediatric ophthalmology at all universities in Sweden.

In 2000, Prince Sigvard inaugurated the Sigvard and Marianne Bernadotte's Research Laboratories for Paediatric Ophthalmology at Karolinska Institutet, St. Erik Eye Hospital. Today some twenty researchers and students are active at the laboratories. The research has resulted in sixteen dissertations for Ph.D. degree.

## **Fixational Eye Movements and Visual Stabilization**

In 2006, a clinician contacted us at the laboratory and wondered why some people have a higher visual acuity than others, could it be due to eye movements? He and his colleagues had announced a contest of best visual acuity. Visual acuity was supposed to correlate with the optical imaging quality of the eye but it turned out that it was not. This issue was the starting point on the research in fixational eye movements that we conduct today. This symposium is therefore the result of a clinical, highly relevant question that probably has a very complicated answer.

Keeping the gaze still is central for our ability to assimilate detailed visual impressions. It is only in a very small area of the retina, the fovea, that we have a sufficient concentration of the type of light sensitive cells that enable us to see with high acuity and discern colours. In order to forward a sharp image via the optic nerve, the incoming light must be focused in the fovea and remain stabilized there for a brief moment. Around the eye there are six muscles whose task it is to both stabilize the gaze, during what we call fixations, and move it around in very fast movements called saccades. The muscles also enable us to follow moving targets and keep the gaze on a target while we ourselves are moving. In order for us to perceive depth, the eyes must synchronize these movements in tandem.

The aim of the symposium is to bring together the international expertise on fixational eye movements and visual stabilization. Apart from covering fixational eye movements and visual stabilization in general, the symposium will focus on developmental and clinical aspects. If we were able to detect deficits in children's fixational eye movements, it might be possible to devise treatments that could make use of the child's neuroplasticity in order to enhance their vision. The clinical aspects concern how we may utilize new measurement techniques and research findings in order to treat patients that experience problems with visual stabilization. Most of the invited speakers have extensive experience of using eye tracking in clinical environments and several have a special interest in children and infants.

The symposium will be part of Karolinska Institutet's bicentennial celebration as well as the celebration of the 20th anniversary of the Sigvard and Marianne Bernadotte Research Foundation for Children Eye care. We strive for the symposium to become a scientifically stimulating environment for lively discussions and future collaborations!

# **Abstracts session 1**

## **Fixational eye movements**

## **Tiny but mighty: the impact of microsaccades on visual physiology and perception**

Susana Martinez-Conde and Stephen L. Macknik  
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When the eyes fixate on something, as they do for 80 percent of our waking hours, they still jump and jiggle imperceptibly in ways that turn out to be essential for seeing. If you could somehow halt these miniature motions while fixating your gaze, a static scene would simply fade from view. Thus fixational eye movements are critical to vision. Moreover, because we are not aware of our fixational eye movements, they are also helping us crack the brain's code for creating conscious perceptions of the visual world. I will present findings on the neural activity generated by fixational microsaccades -the fastest and largest fixational eye movement- in visual neurons, as well as on the perceptual impact of microsaccades.

## **Holding the eyes still and aligned during fixations: slow development and frequent dysfunction**

Zoï Kapoula

IRIS team, CNRS, Paris France

European Hospital Georges Pompidou, Ophthalmology service

Robert Debré Hospital, ENT service, 48 Bvd Sérurier, 75019 Paris, France

A certain level of fixation stability is necessary in order to obtain clear single vision. Stability is particularly important for activities such as reading and working on the computer. And yet, keeping the eyes still during fixation is a highly complex function involving dynamic, sustained, monocular and binocular motor control all of which are dependent on physical depth. Rather than isolating the fixation period per se, we consider fixation as an active process linked to the properties of the preceding saccade. Take for example the case of drift: it is well known that if the saccade pulse-slide-step command signals are not well tailored the eyes will drift and that this drift can be conjugate or disconjugate leading respectively to position errors or depth (vergence) errors.

I will present studies from our group on the normal development of fixational drifts in direction and in depth related to saccade properties. Saccades in young children (<10 years) are disconjugate and they are followed by fixation drifts that are both conjugate and disconjugate. These imperfections decrease progressively with age (via oculomotor learning and visual experience). The improvement is depth specific: at near distance, i.e., reading distance, increased disconjugacy of saccades and of fixation drifts persist until 12 years of age.

I will also review our studies showing that this progressive maturation and improvement with age, particularly with respect to the near distance, occurs at a much slower rate for or is perhaps never fully achieved by several groups of children: in children with dyslexia, children with vertigo symptoms without clinically measurable vestibular deficit and children with strabismus before and after eye surgery.

Slow normal development of fixation stability and fragility in several groups of children indicate the complexity of oculomotor learning mechanisms involved. Learning involves the

cerebellum, brainstem and downstream oculomotor structures as well as cortical oculomotor areas which are the slowest to mature. I will present TMS studies in healthy adults showing that temporary, reversible perturbation of the posterior parietal cortex deteriorates fixation stability in depth leading to transient vergence errors and uncorrelated, increased saccade disconjugacy. Similar results are obtained for isolated fixations and saccades to single targets and for reading saccades and fixations.

I conclude that fixation stability could be better understood when considering previous eye movements. Binocular recording and analysis is essential if we are to assess instability in its integrity and take into account considerations of viewing distance. Determining basic physiologic parameters is also useful in order to assess the interplay between cognitive attention processes and dissociate functional from dysfunctional instability. Dysfunctional fixation instability in children (e.g., dyslexia, strabismus) could require novel training techniques stimulating maturation.

## Slow oscillatory eye movements (SOM) during fixation

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In the eye position recordings during long fixation periods we observed slow oscillatory movements not included in the well known fixation movements: tremor, drifts and micro-saccades. The observed oscillation has a period of about 20 sec and an amplitude smaller than 0.2 deg. To extract the Slow Oscillatory Eye Movements (SOM) component we used a two steps procedure. First by the Fast Fourier Transform (FFT) analysis we evaluated the amplitude and the frequency of the SOM taking the amplitude peak in the frequency range 0.01-0.10 Hz. Then, to have a more defined frequency evaluation, the recorded signal was fitted by a sine function using as starting values the amplitude and the frequency obtained in the first step by the FFT analysis (figure 1). The evaluation of the gaze stability ellipse shows that the SOM area is 20% of the total gaze stability area.

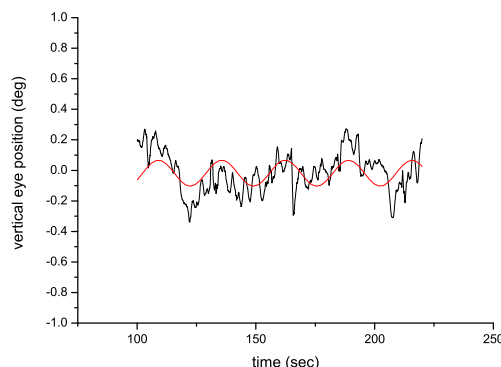


Figure 1. Eye position track and the corresponding sine fitting function

### Is the SOM a real eye movement?

Different artifacts can be hypothesized as possible causes of the observed oscillation:

- Recording technique or band-pass characteristics of the electronic devices
- Blinking
- Some basic physiological activity like breathing or heart activity
- Aliasing due to the sampling frequency or pure noise effect
- Head movements

Some experiments have been conducted to check these possible causes.

To exclude the recording technique artifact we recorded the fixation eye movements by three different methods: infrared system (XY-1000, IOTA Inc.), magnetic search coil (Skalar; SMI) and video oculography (Chronos system). In all recordings we obtained SOM having the

same frequency range. With the infrared system, more than for other techniques, blinking can produce a false eye movement. The blinking frequency has a period similar to the SOM but comparing the oscillation fitting curve to the blinking activity we could exclude that the SOM is related to blinking. The breathing and heart activity, particularly by high resolution eye-tracking systems, are included in the eye position signal but the frequencies of these two physiological functions are outside the range of the SOM. To exclude the aliasing phenomenon we recorded the fixation eye position at different sampling rates (120, 140, 160, 180, 200 Hz). Similar SOM frequencies were still found with no significant change related to the sampling rate. A simulated pure white noise, analyzed by the same procedure used to detect the SOM, did not show any specific frequency peak. Also the head position shows slow oscillations but the frequency and amplitude differed from the SOM signal. Furthermore, the SOM is related not only to the fixation gaze condition. Also in the smooth pursuit recordings, after removing the pursuit movement, the SOM have been found. The first conclusion is that the SOM is not a recording or evaluation artifact.

### **What is the pacemaker for the SOM?**

To check the possible sources of the pacemaker we performed some experiments in binocular and monocular vision conditions and used different types and sizes of target. The comparison between a red dot fixation with image background and a dot fixation with a dark screen background showed some differences in the SOM amplitudes but no difference in the oscillation frequency. The fixation movements in the darkness, without any target and asking the subject to fixate straight ahead, showed large SOM amplitudes with almost the same frequency we have found with the dot fixation. Using different sizes of the target dot we found significant changes for the SOM amplitude and no significant change for the frequency. In all experiments no real horizontal SOM conjugacy has been found while the vertical SOM are almost conjugated. That is true also in monocular vision condition when the movements are recorded in both the two eyes. These results do not show any evidence of a significant effect of the visual feedback on the SOM frequency. Is it due to a general behavior of the muscular tension? The postural stability shows a similar slow oscillation with the highest percentage of the power density in the range 0.01-0.10 Hz. On the other hand the vertical conjugacy of the SOM is in favor of a supranuclear control. In conclusion, the pacemaker should be a muscular supranuclear control not depending on the perception feedback.

## Modeling oculopalatal tremor

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Symptomatic oculopalatal tremor (OPT) is characterized by smooth, aperiodic, ~2 Hz oscillations of the eyes, palate and occasionally other muscles. Oculopalatal tremor develops after a lesion interrupts inhibition of the inferior olivary nuclei by the deep cerebellar or vestibular nuclei. Over time the inferior olive gradually becomes hypertrophic and its neurons enlarge, developing abnormal soma-somatic gap junctions (Ruigrok et al., 1990). Here we look at 3D binocular eye movements in patients and compare their behaviour to the output of our recent mathematical model (Shaikh et al., 2010). This model has two mechanisms that interact to create OPT: an oscillator in the inferior olive and a modulator in the cerebellum. A model of classical delay eyeblink conditioning in the inferior olive (IO) and cerebellum (Hong & Optican, 2008) was adapted to model OPT. This model has adaptable synapses in the cerebellum and gap junctions in the IO. Individual IO neurons fire periodically because of intrinsic membrane pacemaker currents. Gap junctions weakly couple activity within the IO, synchronizing a few neurons. With increased IO coupling, synchronous bursts of activity across many neurons arose. Nonetheless, even with 100% synchronization, the model IO's influence on the eye movement circuit was too small to induce noticeable oscillations. The model explains that noticeable tremors also require cerebellar learning, similar to learning in classical conditioning. In delay eyeblink conditioning, for example, two signals arrive in the cerebellar cortex: one on mossy fibers after a brief tone (conditioned stimulus, CS), and one on climbing fibers after an air puff aimed at the eye (unconditioned stimulus, US). The cerebellar cortical circuitry learns this coincidence and reduces the inhibitory output of the cortex after the CS, but at the expected time of the US. The nearly periodic, synchronous bursts from the IO, arriving in the cerebellar cortex via both climbing and mossy fibers (Carpenter et al. 1972), cause nearly coincident occurrences within the cortex. The learning mechanism responds to these repeated coincidences just as it did to the CS and US in eyeblink conditioning. The learned response amplifies the IO bursts, and smooths them because of the uncertainty in their arrival times. We call this the dual-mechanism hypothesis of OPT. Our model has implications for the treatment of OPT. Simulations show that reducing the influence of the cerebellar cortex on the oculomotor pathway reduces the amplitude of ocular tremor, makes it more periodic and pulse-like, but leaves its frequency unchanged. Reducing

the coupling among cells in the IO decreases the oscillation's amplitude until they stop (at ~20% of full coupling strength), but does not change their frequency. These simulations suggest that drug therapies designed to reduce electrotonic coupling within the inferior olive, or reduce the disinhibition of the vestibular nuclei by the cerebellar cortex, could treat oculopalatal tremor.

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## Visually induced ocular torsion

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Ocular torsion (OT) in response to visual stimulation has been known since the 1930<sup>th</sup> (Brecher, 1934). By rotating a visual stimulus in the frontal plane torsional nystagmus is elicited with a slow phase eye movement in the same direction as the stimulus rotation. This opto kinetic response minimizes the retinal image motion on the retina, which is a prerequisite for a high visual acuity and a stable visual field during prolonged motion. OT in response to a static tilted visual scene was previously demonstrated (Crone, 1975). The eyes slowly shift position in the same direction as the tilted visual scene. The underlying mechanism of this ‘compensatory’ movement certainly has another mechanism than the OKN.

While OKN has been shown to correlate with the semicircular canal system activity, it is tempting to assume that torsion in response to a static tilted visual stimulus correlates to the otolith system responsible for sensing the gravito-inertial direction. This has been proposed earlier but not further elaborated (Crone 1975). The authors’ hypothesis was that if the torsional response to a static visual tilt is related to the gravito-inertial vestibular system, then a visual stimulus with spatial clues important for maintaining body posture will induce a larger torsional response compared to a similar stimulus lacking spatial information.

In this presentation we will describe the influence of spatial information in a tilted visual scene on the generation of OT. We will present some preliminary results from an ongoing study where we investigate the influence of conflicting visual information of tilt position and image motion by a torsional step-ramp stimulus.

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# **Abstracts session 2**

## **Visual Stabilization**

## Reaching the end of the line: 3D kinematics at and beyond the motoneurons

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Strong debate has centered around whether three-dimensional movement kinematics, such as the half-angle rule and ocular counterroll, are determined either neurally by brainstem circuits (Tweed & Vilis 1987; Tweed et al. 1994) or mechanically by the positioning of orbital pulleys (Quaia & Optican 1998; Demer 2002). But a test to definitively distinguish between these two hypotheses has yet to be made. Recently, we showed that stimulation of the abducens nerve from an upright orientation results in eye movements that obey the half-angle rule (Klier et al. 2006). The fact that the half-angle rule is implemented by the eye plant has also been supported by recordings from extraocular motoneurons (Ghasia et al. 2005).

While eye movements such as pursuit and saccades, that re-direct gaze when the head is stationary, follow the half-angle rule, other eye movements that stabilize the visual image during head movements, such as static ocular counterrolling, the vestibulo-ocular and optokinetic reflexes, do not obey Listing's law (Crawford and Vilis, 1991; Angelaki, 2003). More recently we have examined stimulation-induced eye movements across different horizontal eye positions and during static roll tilts.

During static roll tilts, the eyes undergo ocular counterroll (a roughly 10% tilt-dependent change in torsional eye position that is in the opposite direction of the head tilt). But, it is unclear whether ocular counterroll is due to active neural commands sent to either (1) a fixed oculomotor plant (Crawford et al. 2003), or (2) a plant whose pulleys change their configuration with ocular counterroll (thereby affecting the pulling direction of the eye muscles) (Demer & Clark 2005).

We stimulated the abducens nerve (stimulation parameters: train frequency = 500 Hz, train duration = 50 ms, current < 50  $\mu$ A) as rhesus monkeys fixated visual targets, at various vertical and horizontal eccentricities (a 5x5 grid spanning 50° horizontally and 50° vertically), at 5 different static roll tilt angles (0°,  $\pm$ 45°,  $\pm$ 90°). The static roll tilt induced ocular counterroll that offset Listing's plane away from 0 torsion (either CW with CCW tilt or CCW with CW tilt). By stimulating so late in the oculomotor pathway, we essentially

bypassed any neural circuits that could potentially contribute to the implementation of the half-angle rule.

We found that (1) the half-angle rule is generally conserved across horizontal eye positions (i.e., torsional velocity tilted out of Listing's plane by half the angle of eye elevation), and (2) stimulation-induced eye movements from different roll tilt angles showed similar offsets as their corresponding Listing's planes (i.e., the stimulation-induced eye movements shifted fully with ocular counterroll). Thus, in summary, the pulleys appear to change their configuration with ocular counterroll thereby acting as a Listing's plane gimbal capable of maintaining the half-angle rule at different static roll tilts. On-going experiments investigate the results of electrical stimulation of the abducens nerve during the roll (torsional) vestibulo-ocular reflex. One hypothesis that is being investigated is that the departure of the vestibulo-ocular reflex from the half-angle rule is mediated by the same mechanism as static ocular counterroll: Torsional neural signals change the configuration of the extraocular muscles (pulleys) dynamically such that the 'default' half-angle rule is no longer obeyed.

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## High speed video recording of eye movements during head movements - the video head impulse test (vHIT). 1. Development

Ian S. Curthoys, Hamish G. MacDougall, Michael Halmagyi, Leigh A. McGarvie, Andrew P. Bradshaw, Konrad P. Weber  
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During head rotations, the compensatory eye movement in relation to the head movement indicates vestibulo-ocular performance (VOR gain). It is specifically slow phase eye velocity (SPV) which is measured because saccades are driven by different circuitry from that which drives the vestibular slow phase. So to get accurate measures of VOR gain we need to identify saccades and remove them.

The early studies of VOR used low frequency sinusoidal rotation but such stimuli do not measure VOR unambiguously since a patient with bilateral surgical vestibular loss could generate SPV to such stimuli. This patient could not generate SPV during the first 100ms of a brief unpredictable, passive, high acceleration head rotation and so this “head impulse” stimulus has become a standard. If the VOR is not adequate then usually there has to be a corrective saccade at the end of the head impulse rotation and that corrective saccade is the head impulse sign. Nowadays we call that an “overt saccade”. In clinical use it is a subjective measure and depends on many parameters (such as the angular extent of the head rotation and the acceleration) and can be difficult to detect.

Some clinicians failed to see any overt saccade even in patients with known unilateral vestibular loss. We now know some patients with unilateral and even bilateral loss can generate saccades **during** the head rotation which are not detectable by observers and so we call these “covert saccades”. They also occur when the patient is asked to make an active yaw head rotation. Because of the covert saccade, gaze finishes on target and no overt saccade is necessary and any peripheral vestibular deficit is concealed. A covert saccade removes retinal smear by virtue of the very high velocity saccadic eye rotation together with the fact that saccadic suppression is operating to depress vision during the saccade.

To get quantitative measures of VOR gain during a head impulse has, up to now, required the speed and accuracy of search coil measures. For many years we have tried to develop a simple VOR gain measure using video methods. Many problems have had to be overcome, the most

significant being to prevent goggle (and thus camera) slippage. Now small, fast, lightweight, video cameras can detect small fast eye movements. To solve the slippage problem goggles which comfortably fit snugly around the orbital rim are used. There is an inertial sensor in the goggles which detects 3D angular velocity and 3D linear acceleration to provide the head movement measures. This vHIT system has been validated by comparing it to simultaneous measures from search coils and the VOR gain results are very similar

The challenges which have to be faced are the detection and removal of saccades and the measurement of VOR gain. As a result of many measures we question whether it is adequate to calculate VOR gain as eye velocity/head velocity at a single arbitrary latency or point (e.g. peak velocity or peak acceleration). We consider a new measure – the area under the desaccaded eye velocity curve, divided by the area under the head velocity curve, may be a measure which is more functionally significant and less subject to artifacts.

## **The development and application of the video head impulse test (vHIT) - high speed video recording of eye movements during head movements. 2. Applications**

G. Michael Halmagyi, Hamish G. MacDougall, Ian S. Curthoys, Leigh A. McGarvie, Andrew P. Bradshaw, Konrad P. Weber  
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The use of this new vHIT method and the direct comparison of video and search coil recordings has raised many basic matters. Whereas the usual measure of vestibular performance has been VOR gain, it seems that the number and amplitude of saccades may be a complementary indicator: inadequate VOR requires more saccades, be they overt or covert, for gaze to remain on target.

Covert saccades are of special interest. Now we have been able to measure a very large number of patients we realize that covert saccades are quite common. But the questions we seek to raise are;

- what triggers such a covert saccade?

The covert saccades during active head rotation are probably due to pre-programming.

However it is very puzzling what could generate them during passive unpredictable head rotations.

- why do some patients learn to generate these and others do not learn?
- could covert saccades really be of value in vestibular compensation – is it that patients who have good vestibular compensation use these covert saccades, whereas poorly compensated patients do not? We do not have adequate data on this question at present

The recordings of a patient with total bilateral surgical deafferentation were exceptionally valuable since this patient generated short latency covert saccades during the head rotation. But since he had no vestibular function the trigger for his saccades could not be due to any vestibular input. It was not anticipation or prediction since the patient was 100% correct even over a long series with unpredictable head rotation directions. One possibility is cervical input acting as a trigger, but the latency of such input seems long

vHIT has been valuable for demonstrating the return of vestibular function in a patient with vestibular neuritis who was tested during the acute phase and then later at recovery. Testing during the acute phase would be very difficult if search coils had been used.

In a recent study we demonstrated how VOR measures could be valuable in signalling gentamicin vestibulotoxicity. That study used head impulses with search coil recordings with considerable difficulty. vHIT allows this kind of measurement even at the bedside in patients.

Finally the high speed and high resolution of this simple vHIT system allows for detection of oculomotor pathophysiology with head stationary or slowly moving which cannot be detected by the naked eye or by low speed video procedures.

## **Fixation monitoring using retinal birefringence scanning in unrestrained subjects**

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By taking advantage of the birefringence of the Henle nerve fibers emanating radially from the fovea, the projection of the fovea into space can be detected directly using changes in the polarization of retro-reflected light from the fundus. By scanning a small spot of polarized near-infrared light from a 795 nm laser diode in a 3-degree circle on the retina, characteristic signals can be obtained from analysis of the reflected light. A visible fixation spot is provided exactly in the center of the circular scan, such that when the eye fixates on the visible spot, a periodic signal of polarization fluctuation at twice the scan frequency ( $2f$ ) is obtained using fast Fourier transform (FFT) analysis. When the fovea is directed to any other point, the predominant frequency in the signal is equal to the scanning frequency ( $f$ ). The normalized ratio of the  $2f$  signal strength to the  $f$  signal strength yields a robust indication of foveal fixation, currently obtained at 2 or 3 Hz depending upon the scanning frequency. Accuracy is approximately  $\pm 0.5$  degree.

The optical noise from reflections from the optics, cornea, sclera, and lids has been minimized, along with simplification of the electronics to a single detector, by using a spinning half wave plate to rotate the axis of polarization striking the eye at a fractional frequency of the scan frequency. By proper choice of frequencies, the digitized periodic signal obtained may be shifted by one scan period and subtracted from itself prior to FFT analysis, yielding a differential polarization signal at the fractional frequencies of interest. The scanning frequency and harmonics of the scanning frequency are subtracted out, eliminating much of the noise from reflections.

The corneal birefringence is approximately seven times greater than the birefringence of the Henle fibers radiating from the fovea. The corneal birefringence is relatively constant across the pupil, however, and by manipulating the polarization state of the light entering the eye, it is possible to essentially bypass the effect of the corneal birefringence over the range of corneal retardations and azimuths that have been documented in a large database of human eyes.

We have designed, constructed, and tested several models of our foveal fixation monitor: a binocular version for the detection of strabismus in infants and children, a no-moving-parts version that proved to have a poor signal-to-noise ratio, and a monocular version for potential monitoring of fixation stability in patients with attention deficit disorder.

The primary advantage of our fixation monitoring technology is the direct detection of the anatomic fovea, without the calibration steps required by other methods of eye fixation monitoring and tracking that use reflections from external structures. A secondary advantage is the large exit pupil, approximately 40 x 40 mm for each eye, that facilitates hand-held maintenance of alignment with the eyes of an unrestrained child.

The primary disadvantage of our technology is the slow "frame rate," currently only 2 to 3 Hz. Future development will address ways to increase the temporal resolution of fixation detection using retinal birefringence scanning and also will explore approaches to eye tracking.

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## **Vestibulo-ocular reflex thresholds match perceptual thresholds above 1 Hz**

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How the brain processes signals in the presence of noise impacts much of behavioral neuroscience. Recent studies have shown that variations in smooth pursuit are predominantly due to sensory, not motor, contributions. Analyses of smooth pursuit noise/variability (e.g., Osborne et al., 2005) and comparisons of perceptual and motor thresholds (e.g., Stone and Krauzlis, 2003) support this conclusion. We set out to generalize these findings to another sensorimotor system - the vestibulo-ocular reflex (VOR). Specifically, we set out to determine if horizontal VOR thresholds evoked by yaw rotation match perceptual thresholds across a broad frequency range.

Only one paper (Seemungal et al., 2004) has previously quantified VOR thresholds – reporting VOR thresholds of  $0.5^\circ/\text{s}$  that were significantly less than perceptual thresholds ( $1.2^\circ/\text{s}$ ) evoked by the same angular velocity ramp stimuli. Other studies using single cycle sinusoidal accelerations have shown that yaw angular velocity perceptual thresholds are roughly constant between about 0.5 and 5.0Hz (Grabherr et al., 2008) but increase substantially as frequency decreases below 0.5Hz (Benson et al., 1989; Grabherr et al., 2008). These dynamic effects can be modeled with a high-pass filter having a cut-off frequency of 0.3Hz that is substantially above the cut-off frequency of the semicircular canals ( $\sim 0.05\text{Hz}$ , e.g., Fernandez and Goldberg, 1971). This finding does not match VOR “velocity storage” findings that show that the VOR can be mimicked by a high-pass filter having a cut-off frequency ( $\sim 0.01\text{Hz}$ ) substantially below the canal cut-off frequency.

In this study, we measured the VOR using search coils in rhesus monkeys. Single cycles of sinusoidal angular acceleration were applied over a broad range of frequencies (0.2, 0.3, 0.5, 1, 2, and 3Hz) with the stimuli amplitude near-threshold. The direction of eye movement (left or right) was determined. A psychometric function was fit for each animal at each frequency with a Gaussian cumulative distribution function. The fit parameters gave a measure of the standard deviation of the underlying noise, which is directly proportional to threshold. At 2Hz and 3Hz, we found VOR thresholds that averaged about  $0.5^\circ/\text{s}$ , which matched perceptual thresholds at these frequencies, which is consistent with the hypothesis that

sensory noise determines both VOR and perceptual thresholds. However, we also show that VOR thresholds diverge dramatically from perceptual thresholds at frequencies below 0.5Hz. This demonstrates that the bandwidth over which the VOR can be used to directly assay sensory noise is restricted to frequencies above 0.5Hz. The dramatic difference between VOR and perceptual thresholds below 0.5Hz suggests that at least one different dynamic neural mechanism affects perceptual thresholds.

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## **Saccades, models, membranes and patients: from the clinic to the lab and back**

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Traditional models of the saccadic mechanism simulate normal saccades well, but are challenged by clinical disorders, as they often do not represent the specific anatomical and physiological detail needed to model clinically important abnormalities. Here we consider the example of high-frequency saccadic oscillations, which has provided new insights into the neurobiology of saccades and driven the development of a new model and explanation of oscillations.

Saccadic oscillations are unwanted back-to-back saccades occurring one upon the other producing a high-frequency oscillation of the eyes (usually 15-30 Hz) that disrupts vision. These may occur transiently in normal subjects: around the orthogonal axis of a purely horizontal or vertical saccade, during combined saccade-vergence gaze shifts or during blinks. Some normal subjects can induce saccadic oscillations voluntarily ('voluntary nystagmus'). They are called ocular flutter when purely horizontal and opsoclonus when multidimensional. The classical explanation of oscillations is based on a delay in the local feedback loop around the high-gain amplifier representing the burst neurons. The duration of the delay ( $\tau$ ) is the hypothetical mechanism controlling the frequency of the oscillations so that  $f \approx 0.25/\tau$ .

Recent findings, though, have questioned the validity such model since:

- Individuals can produce oscillations of different amplitudes with little change in frequency; oscillations span a large range of frequencies, although it tends to be fixed within a given subject.
- A patient with surgical ablation of the FN, a putative relay station of the local feedback loop still produced saccadic oscillations.
- A mother and daughter with microsaccadic oscillations and limb tremor ( $\mu$ SOLT) even during fixation, which are amplified when OPN discharge is modulated.

The new mathematical model of saccadic brain stem control of horizontal saccades includes many details of the circuitry based on current anatomy. It represents the OPN, the bilateral EBN and IBN forming two positive feedback loops, and the VI nucleus. Each population of neurons is modeled by representing the membrane as a high pass filter showing adaptation,

which causes these neurons to show post-inhibitory rebound (PIR): at the offset of inhibition there is a rebound in the membrane potential allowing the cell to fire spontaneously. Human saccadic burst neurons express subtypes of ion channels carrying  $I_T$  and  $I_h$  which are responsible for PIR.

In humans, the premotor circuit is potentially unstable due to the high gain of the output nonlinearity of the burst neurons and to the positive feedback loops coupling EBN-IBN and IBN-IBN. If the burst neurons are not inhibited by the OPN and are not driven to produce a saccade, such latent instability may lead to high-frequency, conjugate oscillations (i.e. horizontal oscillations during a vertical saccade). In patients, either an increase in neural excitability or a reduction of OPN inhibition can cause instability and oscillations.

We hypothesize that ocular flutter and opsoclonus are related to alterations in the membrane properties of the neurons that generate saccadic bursts. We also propose that the level of activity in OPN may play a role in the genesis of saccadic oscillations. However, the properties of the oscillations and the ease with which the system can be made to oscillate depend critically on membrane properties of the burst neurons (PIR).

## **TMS perturbs saccade trajectories, unmasking a feedback controller that compensates for the perturbation**

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We applied a single pulse of transcranial magnetic stimulation during a saccade and observed that it perturbed the trajectory of the eyes, causing them to slow down or pause. This response was similar to that seen with direct stimulation of omnipause neurons (Keller et al., *Vis. Neuroscience*, 1996) or stimulation of the rostral superior colliculus (Munoz et al., *J. Neurophys.* 1996). Sensory stimulation, stimulation of the supraorbital nerve and noise bursts also induce pauses in saccades (Becker, *Contemporary Ocular Motor and Vestibular Research* 1993; Goossens et al., *J. Neurophys.* 2010). We found that despite the TMS induced perturbation to the eye trajectory, the saccades were corrected and the eyes stopped accurately at the target.

We tested five healthy human subjects while they performed visually guided saccades and triggered TMS with respect to the onset of saccades. TMS was applied to the head using a Magstim 200 stimulator with a maximum output of 2.2 Tesla, connected to a figure of eight magnetic coil, each loop having a diameter of 7cm. The stimulation strength varied from 50% to 60%. Eye movements were measured using the magnetic search coil technique. Subjects made saccades following a red laser target, rear projected onto a screen 1m away.

When applied during a saccade, TMS induced reductions in saccade velocities with a latency of 65ms after the TMS. This reduction in velocity lasted around 29ms, after which the saccade resumed toward the target. On average, the resumed movement took the eyes to a final location that was 0.5deg further than control saccades. Not all interrupted saccades resumed movement. Perhaps these saccades ended close enough to the goal (less than 1.35deg away) so that they did not require a correction. Given that the pauses occurred at a long delay of 65ms after TMS, the saccade had to be of sufficient duration to observe any effect from TMS. For saccades of long duration (>100ms), we observed that TMS applied early in the saccade transiently slowed the eyes, creating double peaked velocity profiles, whereas TMS late in the saccade could pause the eyes.

The effect of TMS was nonspecific to the brain region as similar perturbations occurred for saccades in all directions and regardless of where we applied the TMS: top of the head, the cerebellum, or the parietal cortex. The sound of TMS alone (i.e., coil discharged at least 0.3meters away from the head) could also induce pauses, although less frequently. Blinks were present on many TMS trials, but were not necessarily associated with pauses. There were trials with blinks but no pauses, and trials with very small blinks but very clear pauses. We speculate that TMS likely engages the “startle” circuits of the brain,

In summary, we found that a single pulse of TMS during a saccade perturbed the eye’s trajectory, causing a reduction in velocity, or an outright pause. This perturbation was corrected within the same change in gaze with compensatory motor commands that brought the eyes near the target. As this correction occurred even without visual input (in conditions where the target was removed), it appears that the correction to the perturbation is due to an internal feedback process that has an estimate of the current state of the eye. Our findings further emphasize that TMS can have non specific, presumably “startle”effects on motor behavior, and these effects should be taken into account when interpreting the effects of TMS on brain function.

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# **Abstracts session 3**

## **Developmental aspects of fixation**

## **Visuo-vestibular eye movements**

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Visuo-vestibular eye movements are unique eye movements that develop almost exclusively in the setting of infantile strabismus. They are generated by asymmetrical binocular visual input which leads to consist of dynamic movements such as latent nystagmus in the yaw plane, and tonic deviations such as dissociated vertical divergence in the roll plane, primary oblique muscle overaction in the pitch plane, and dissociated vertical divergence in the roll plane. These movements are the inverse of those produced by vestibular imbalance in the same planes, suggesting that these visual reflexes permit the eyes and ears to function together as complementary balance organs in lateral eyed animals. In lower animals, the accessory optic system shows maximal sensitivity for optokinetic movements in the planes of the semicircular canals, providing a neurological substrate for visuo-vestibular eye movements in humans.

## **The interaction between singular and non-singular arcs in the control of slow eye movements**

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Plasticity is a core function of human behaviour, whether it be at the synaptic, behavioural, or cognitive level, or whether it be reversible adult ('physiological') plasticity or irreversible developmental plasticity. It implies the existence of a meta-controller that guides developmental/adaptive control towards some 'desired' or 'optimal' end-state. Eye movements are stereotyped behaviours that are par exemplar.

Optimal control theory provides a powerful over-arching (non-linear) mathematical framework for understanding how behaviour can be controlled to produce desirable state trajectories. We introduce the mathematical concepts of 'singular' and 'non-singular' control as hypotheses for the existence of slow and fast eye movements, based on the assumption of a zeros-compensated plant, and proportional noise at high motor command levels. In singular control (fixation, smooth pursuit, slow vergence, nystagmus slow-phases), we propose that control is essentially kinematic, where visual Lagrangians can be optimised unconstrained by neural signals. In non-singular control (gaze/eye saccades), neural noise limits performance and imposes a speed accuracy trade-off (main sequences). A fundamental problem confronting oculomotor control (and our understanding of it) is how to join non-singular to singular arcs optimally. For example, the end-point variance of a saccade leaves uncertainty in the initial conditions of the subsequent fixation or slow-phase, which then influence the next saccade/quick phase, and so on.

We examine experimentally and theoretically human optokinetic nystagmus as an example of a velocity-position conflict that is intermediate between the canonical physiological 'steady' fixation and pathological 'unsteady' infantile nystagmus. We reveal hitherto unappreciated complexity in joining quick phases and slow phases. We propose that (non-singular) quick-phases have a strong influence over (singular) slow-phases, and that a holistic approach is required to understand oculomotor control.

## Early development of oculo-motor control

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While ability to perform saccades is fairly well developed at birth, the ability to perform smooth adjustments of gaze direction is not. The vestibularly governed response (VOR) is only partly functional and the visually guided smooth pursuit (SP) is not functional (Rosander & von Hofsten, 2000). From about 6 weeks of age, however, a very consistent improvement takes place and within 2 months SP becomes adult-like (von Hofsten & Rosander, 1997). During this developmental period the head also contributes increasingly to gaze stabilization. The problem, however, is that head tracking induces VOR that needs to be inhibited if head movements are going to contribute to gaze stabilization. The inhibition of VOR is dependent on ability to perform SP. SP predicts the motion it tracks but the head does not. This creates a problem for the early tracking and in certain situations the head and the eyes may move out of phase and counteract each other. The neural control of SP in young infants seems to be primarily situated in the Parietal-temporal-occipital junction or MT+ region. Its activation from motion increases over age as SP improves. The activation from visual motion does not seem to originate in the occipital region but rather from collicular-pulvinar loop (Rosander et al. 2007; Wattam-Bell et al. 2010). Very premature infants show dramatic delays in the oculo-motor system. They have very bad SP at 2 months corrected age but these delays are possibly overcome later in development. At 10 months corrected age our data indicate that their SP does not differ from typically developing infants.

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## Fixation patterns during facial emotion recognition in children

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As social beings, our ability to understand emotions is very important for communication with others. The aptitude to recognize emotions appears to be innate; infants prefer to look at stimuli resembling faces and are able to imitate facial expressions after just a few days. By a few months of age, children are able to express emotions of their own and use them for communication. Recognition of facial emotions facilitates our learning of the mental processes of others and supports the development of social skills. Faces appear to have a special status in our visual system, not only are we biased to look towards them; we are also very fast when performing the fixation patterns required for processing them.

Inattention to faces is an early developmental sign of Autism Spectrum Disorders (ASD) that can be detected as early as by one year of age. All children with ASD demonstrate deficits in social interaction, verbal and nonverbal communication, and repetitive behaviours or interests. It is well known that children with ASD exhibit a deviating eye movement pattern when recognizing facial expressions. The cause of the differences is however disputed. Eye movement tracking may potentially be used as an early screening device for ASD, but before it can be used as such we need a better understanding of fixation patterns during facial recognition in children with a normal development

In this talk, I will present results from an ongoing eye movement study where 25 normally developing children (~10 years) have looked at images with five facial emotions (neutral, happy, sad, angry, and scared). Emphasis will be put on the analysis of the time course of fixations performed during recognition.

# **Abstracts session 4**

## **Clinical Aspects of Visual Stabilization**

## **Fixation stability and eye motility in adolescents with congenital or early acquired visual field defects**

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Malformations of the brain, pre-, perinatal and early acquired brain damage may involve the posterior visual pathways and/or visual cortex and cause cerebral visual impairment. The visual field (VF) outcome depends on localisation and extension of the lesion, but also on at what stage of maturity the visual system was injured. Insults near term or in the more mature brain tend to cause more severe restriction of the visual field than malformations arising in the first or second trimester and periventricular white matter damage occurring early in the third trimester. This may be a consequence of reorganisation of the visual system by bypassing the lesion in the ipsilateral hemisphere or maybe by interhemispheric reorganisation in the very immature brain. In addition, ocular motor problems such as difficulties to maintain fixation, strabismus, nystagmus and defect saccades and smooth pursuit movements and paroxysmal deviations may also be a result of pre- and perinatal brain damage.

The functional visual field may be described as a product of the “neurological” visual field and the eye movements. The long time consequences of congenital or early acquired VF defects have not been well described. It is common that VF defects in children with brain damage remain undetected. This may partly be due to effective compensation mechanisms.

To better understand the practical problems caused by early acquired visual field defects we studied fixation, eye alignment and scanning. The visual field function was assessed with confrontation technique, Goldmann perimetry, Visubit/Rarebit and Esterman computerized perimetries. Fixation during perimetry was in two cases registered with a video tracker from Chronos. To illustrate our findings five cases with different patterns of cerebral pathology causing VF defects will be presented. The functional VF outcomes in these cases were, besides by plasticity of the immature brain that may rewire the posterior visual pathway in some cases, also modified by nystagmus, exotropia and automatic scanning.

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## **Benefits of four-muscle recession surgery for congenital nystagmus**

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**Introduction** Conventional Anderson-Kestenbaum surgery was described around sixty years ago for congenital nystagmus with null zone and compensatory head posture. In 1960 Bietti and Bagolini suggested recession of all four horizontal rectus muscles for nystagmus without a compensatory head posture. More recently von Noorden (1991) and Helveston (1991) published series showing improvement in visual acuity with this surgical approach.

**Material and methods** Between 1997 and 2002 we operated on 18 consecutive patients aged 16 to 51 years (mean 32). Twelve were male and 6 female. All had congenital nystagmus with no other detectable ocular or systemic condition. Sixteen had demonstrable binocular function and stereopsis. Preoperative best corrected vision ranged from 6/9 to 6/60. All underwent recession of all four horizontal rectus muscles. We asked all patients to fill in and return a postal questionnaire regarding perceived benefit of the surgery.

**Results** Postoperative best corrected vision was 6/9 to 6/36. Nine patients (50%) gained one line of Snellen visual acuity. Six patients showed improved stereopsis, 7 were static, 5 slightly worse. All showed bilateral limitation of adduction and 16/18 also showed bilateral limitation of abduction. All patients experienced significant postoperative pain up to 2 weeks post-op. One patient had a scleral perforation, with no further sequelae. One had decompensation of exophoria to exotropia, and one developed exotropia. One had persisting asthenopic symptoms for around 6 weeks post-op. Fourteen of eighteen questionnaires were returned. Eight patients were glad they had had surgery, 3 indifferent, and 3 displeased. Eight reported no change in their daily lives, 2 said computer screens were easier to see, 2 reported increased confidence in eye contact. One reported that their nystagmus was less variable when stressed. One reported being more tired since surgery.

**Conclusion** Although half of patients stated that they were glad they had opted for surgery, the maximum gain of one line of Snellen acuity was obtained in only 8 patients. Seven of fourteen patients stated in their questionnaires that a desire to drive was one of the reasons for having surgery, but to date, none have obtained a driving licence. We conclude that the procedure confers minimal visual benefit.

## Ocular counterroll and verticality perception

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Changes of the static whole-body position in the roll plane influence the torsional position of the eyes (static ocular counterroll) and the perception of earth- and body-verticality.

Recordings of ocular counterroll (OCR), subjective visual vertical (SVV) and subjective visual longitudinal body axis (SVLBA) in healthy human subjects at different whole-body roll positions were analyzed in terms of accuracy (deviation from full compensation), precision (intra-individual variability), and hysteresis (directional effect of whole-body roll displacement). While the accuracy of OCR modulates roughly sinusoidally (largest deviations in the 90 deg side positions), the accuracy of SVV and SVLBA is dominated by the A-effect. The precisions of OCR and SVV as a function of roll position, however, modulate in parallel, suggesting a common otolith input. OCR shows hysteresis, i.e., in the upright position after a quasi-static 360 deg roll, there is residual ocular torsion in the direction of the previous OCR. In contrast, SVLBA is “leading” whole-body roll position, possibly as a visual consequence of OCR hysteresis. In conclusion, OCR and verticality perception as function of whole-body roll are similar in terms of precision (related to the common otolith input), but differ in terms of accuracy and hysteresis (both related to vision in the perceptual tasks).

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## **Human fixation: higher level control and related aspects**

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Traditionally, and in the context of the early bioengineering control systems models employing internal neurological feedback control, the human fixational eye movement system responds to two primary types of oculomotor errors to maintain accurate eye position during attempted fixation---position and velocity. This can account for much of its control ability under most normal viewing conditions. However, under some 'unusual' normal viewing conditions, and in some types of abnormal clinical oculomotor conditions (e.g., nystagmus, strabismus), various types of "higher level fixational control" can be exhibited involving visual, auditory, and/or tactile feedback information.

In this presentation, several examples of such higher level control, in both normals and abnormals, will be described, along with their clinical implications. This will include the 'fixation versus hold' paradigm, oculomotor auditory feedback, external visual feedback, and proprioception.

## Organizers

The symposium is arranged by the Sigvard & Marianne Bernadotte research laboratories for paediatric ophthalmology at St. Erik Eye Hospital and Karolinska Institutet. The organizing committee is headed by Professors Jan Ygge and Gunnar Lennerstrand.

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