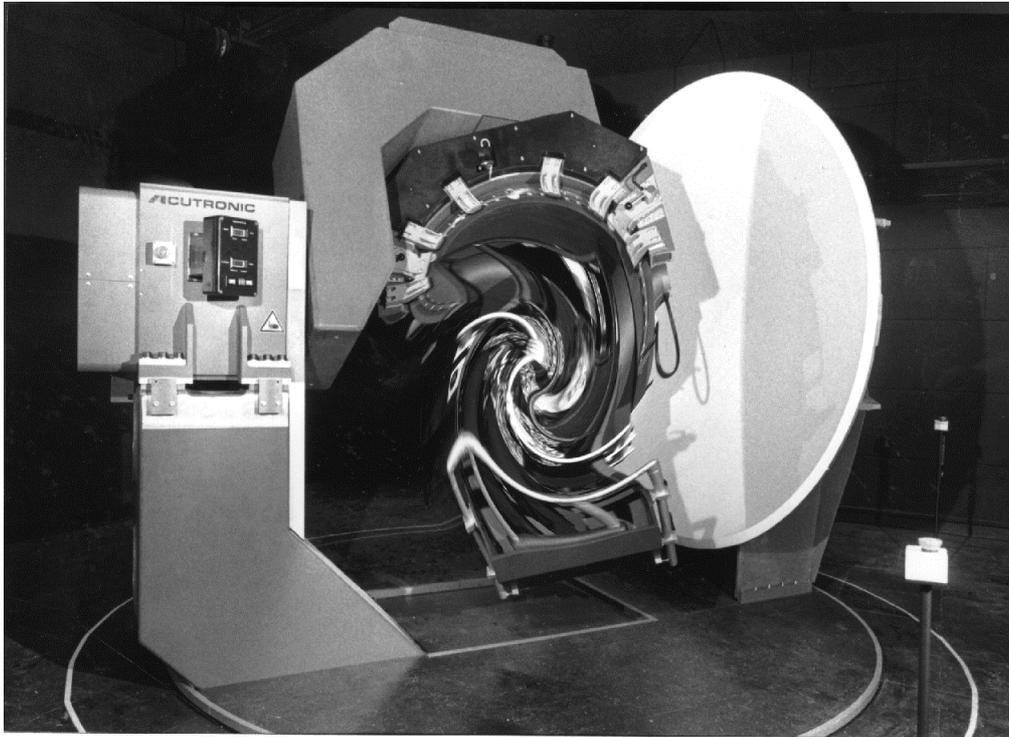


Computational and Experimental Aspects of Rotatory Eye Movements in Three Dimensions



Habilitationsschrift

2000

T. Haslwanter

Mailing Address:

Dr. Thomas Haslwanter
Dept of Neurology
Frauenklinikstr. 26
Zürich 8091
Switzerland
Tel: +41-1-255 5550
Fax: +41-1-255 4507
Email: haslwant@neurool.unizh.ch

Table of Contents

1	SUMMARY	5
2	INTRODUCTION.....	7
2.1	UNDERSTANDING MOVEMENT.....	7
2.2	THE VESTIBULO-OCULAR SYSTEM.....	10
2.3	THE RECORDING OF EYE MOVEMENTS.....	19
2.4	EYE MOVEMENT CONTROL.....	23
3	THE KINEMATICS OF 3-DIMENSIONAL ROTATORY EYE- AND HEAD- MOVEMENTS	27
4	MEASUREMENT OF 3-DIMENSIONAL EYE MOVEMENTS	29
4.1	A THEORETICAL BASIS FOR VIDEO-OCULOGRAPHY	29
4.2	CURRENT TECHNOLOGIES FOR RECORDING 3-DIMENSIONAL EYE MOVEMENTS.....	31
5	EYE- AND HEAD-MOVEMENTS IN HEALTHY SUBJECTS.....	43
5.1	CIRCULAR HEAD SHAKING	43
5.2	OFF-VERTICAL AXIS ROTATIONS (OVAR)	45
5.3	OPTIMIZATION	47
5.4	RAPID HEAD IMPULSES IN HEALTHY SUBJECTS.....	49
6	APPLICATION OF 3-DIMENSIONAL ANALYSIS TECHNIQUES TO THE INVESTIGATION OF PATIENTS	51
6.1	DETECTING FUNCTIONAL DEFICITS IN A SINGLE SEMICIRCULAR CANAL.....	51
6.2	DETECTING TUMORS ON THE COCHLEO-VESTIBULAR NERVE	53
6.3	EFFECTS OF CEREBELLAR ATROPHY ON MULTI-SENSORY INTEGRATION	55
7	VESTIBULAR STIMULATORS – AN OVERVIEW	57
7.1	LINEAR ACCELERATORS & CENTRIFUGES.....	57
7.2	POSTURAL PLATFORMS.....	58
7.3	ROTATORS / TURNTABLES	59
7.4	EXPERIMENTS ON 3D TURNTABLES	65
8	CONCLUSIONS	73
9	REFERENCES.....	75
10	APPENDIX.....	83
10.1	CURRICULUM VITAE.....	83
10.2	LIST OF PUBLICATIONS INCLUDED	85
10.3	ABBREVIATIONS	87

1 SUMMARY

Eye-, head-, and limb-movements in space have many degrees of freedom, and investigations of such movements are correspondingly complex. To simplify experiments and analysis, researchers initially restricted paradigms and recording devices to one-dimensional movements, for example purely horizontal eye movements. This has led to a remarkable understanding of one-dimensional movements, from the muscle mechanics to the underlying neural control system. However, many questions cannot be answered with one-dimensional investigations. Natural movements are executed in 3-dimensional (3D) space, and the control of such movements has to account for the resulting complexities and asymmetries. For example, horizontal and vertical eye movements change the direction of gaze, whereas rotations about the third axis, i.e. the line of sight, leave it unaffected. While the technological foundations for recording 3D movements were already laid in the 60s and 70s, it was not until 1985 that a convenient way to record 3D eye movements was available. At about the same time this technique was extended to animal experiments.

In my research I have built on this recent progress, and tried to turn the basic research findings into useful medical tools. The studies leading to my PhD involved early experiments on the control of 3D eye movements in monkeys. Our group also extended this technique to the recording of combined eye-, head- and arm-movements in humans. My post-doctoral research continued along the same lines: it aimed at improving the underlying technology and methodology for recording 3D eye movements, and extending the techniques to investigations of clinical problems. On the analysis side, I wrote some introductory and overview articles on the underlying questions and principles of 3D movement control and the mathematical tools required for the corresponding data analysis. In collaboration with an engineer I developed the basic algorithms that allow video-based systems to measure 3D eye position by tracking iral patterns. This line of work recently culminated in an international conference on video systems for 3D eye movement recording. In the more medical area of vestibulo-oculomotor physiology of healthy subjects, I have worked on teams concentrating on a better understanding of the peripheral stimulation of the vestibular system, and the control principles that underlie the processing of vestibular signals. The efforts to apply this improved understanding to the medical diagnosis of dizzy patients focused on the development of new tests for vestibulo-ocular pathologies, and on the effects of these pathologies on eye movement control.

The articles presented in this manuscript give a representative overview of the results of these efforts. They include nine reviewed and published articles, two newly written chapters (on eye position recording systems and on vestibular stimulators), as well as a short introduction to the field of vestibulo-ocular research.

Summary

2 INTRODUCTION

"Our nature consists in movement; absolute rest is death."

Blaise Pascal (1623-1662): *Pensées* 1670.

2.1 Understanding Movement

Understanding how our movements are planned, controlled, and executed is a daunting task. On the one hand, any understanding of movement has to be based upon an accurate description of the kinematics and dynamics of the executed movements: the orientation of the eye and the movements of the joints characterize the *kinematical* aspects, and the actual muscle forces that are necessary for these movements give the *dynamics* of the movement. To obtain and to characterize these movements, we need the laws of physics and apply them to the object under investigation – the human body, its limbs, and the sensory input organs. On the other hand, any description of the mechanics of the sensory input and the kinematics of the movement alone does not suffice to “open the black box”, i.e. to understand what is happening in the brain. We need to know the anatomy of the structures involved and their physiological characteristics. We also need accurate tests of patients, since pathological defects of the body can reveal the importance and contribution of the affected individual structures. The truly interdisciplinary scope of this challenge is what makes work in this field so exciting, and the possibility to use the results for better diagnosis and treatment of patients what makes it rewarding.

Starting in the middle of the last century, the interdisciplinary tools necessary to tackle an understanding of movement gradually became available:

- The mathematical formalisms that allow a compact and quantitative description of movements became more refined, and physicians and physicists like Helmholtz (Helmholtz, 1867) and Mach (Mach, 1875) started to apply it to the understanding of the human body.
- New “windows into the brain” were opened: Ramon y Cajal and Golgi used the optical powers of microscopes and new staining techniques to describe the structure and connections of individual nerve cells (Golgi, 1906; Ramon y Cajal, 1892). Eccles and others refined the electrical recording devices to such a point that it was possible to observe the functioning of individual nerve cells (Eccles, 1976). More recently, advances in high technology imaging systems like magnetic resonance imaging (MRI) and positron emission tomography (PET) allow us to see the human brain “at work”, without any surgical intervention.
- Measurement tools have been developed which allow the recording of eye, head, and limb movements with high spatial and temporal resolution.

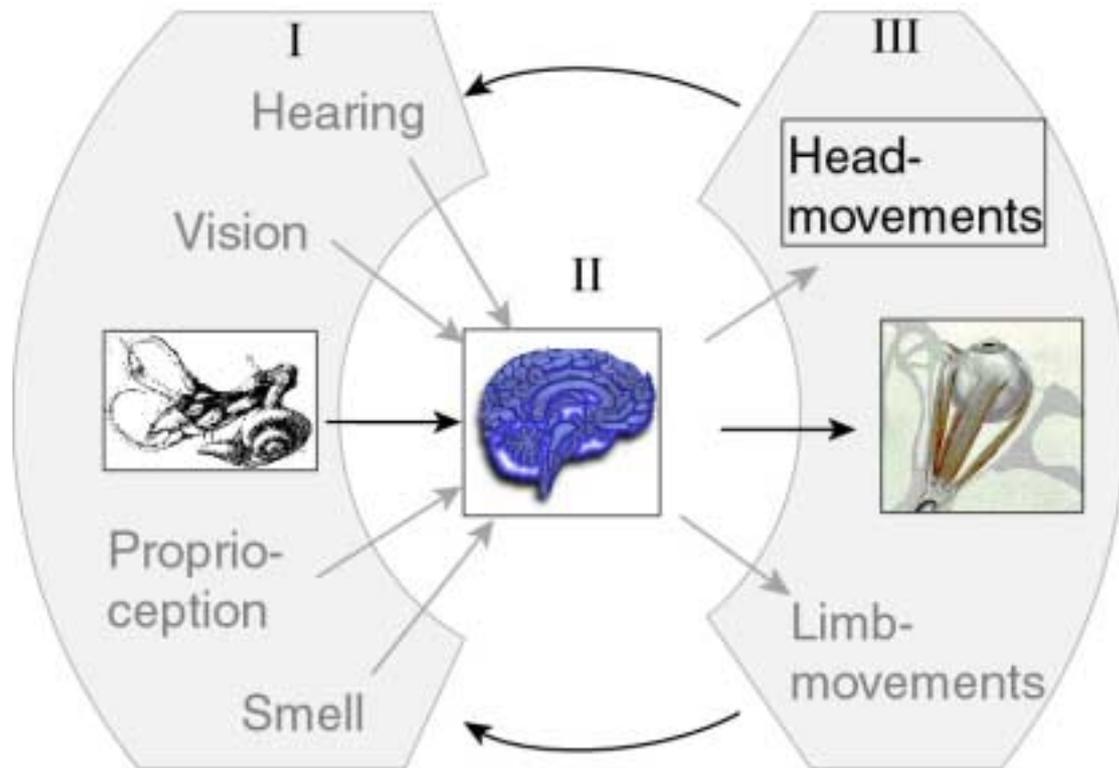


Figure 2-1 Overview

Figure 2-1 presents an overview of the inputs and outputs characterizing human movements. In the work presented below I will concentrate on one subset of movements, 3-dimensional eye- and head-movements and their relation to the inputs from the balance system (indicated by the images and black arrows in Fig. 2-1). Of all types of movement, eye movements are arguably the most accessible ones to scientific investigation. The eye is an object with negligible inertia, and only three pairs of extraocular muscles control its orientation and movement. By comparison, 24 muscles and tendons have to be taken into consideration when simple walking movements in the sagittal plane are modeled (Günther, 1997); note that this is already a 2-dimensional simplification of human walking!) The large number of limb muscles is necessary for two reasons. One reason is the degrees of freedom (DOF) of limb movements: while the eye essentially displays a ball-in-socket behavior, and is thus restricted to only 3 rotatory DOF, leg- or arm-movements have significantly more DOFs. The exact number depends on the type of movement, and which structures are included (for example, the pelvis movement is sometimes also taken into consideration when investigating walking movements of the leg). For efficient multi-joint movements, muscles must be available which move not only one joint but two joints simultaneously. One example is the biceps muscle (biceps brachii), which starts at the shoulder and spans all the way to the forearm. The other reason for the abundance of muscles in legs and arms is the inertia of limbs. While the inertia of the human eyeball is a negligible quantity (Minor et al., 1999a), considerable forces are necessary to accelerate or stop a limb.

The second reason for concentrating on the vestibulo-ocular system is the tremendous importance of eye movements in the diagnosis of neurological, otological and ophthalmologic disorders. Since eye movement control involves many areas of the brain, any improvement in our understanding of the balance system and of the execution of eye movements can have a direct effect on the understanding, diagnosis, and treatment of a number of diseases.

The part of my work presented in this thesis encompasses the whole vestibulo-ocular system indicated in Fig. 2-1 by the black surrounded boxes: the vestibular input, the central processing of these signals, and the measurement and analysis of the resulting eye- and head-movements.

- **I – III)** Chapter 3 describes the analysis tools required for the measurement and analysis of 3-dimensional movements, and covers all areas in Fig. 2-1.
- **I) Vestibular input:** in chapters 5.1 and 5.4 we analyze the stimulation of the vestibular system in healthy subjects, and chapters 0 and 6.2 apply the analysis tools to the diagnosis of dizzy patients. Chapter 7 gives an overview of tools for the stimulation of the vestibular system, focusing especially on 3-dimensional turntables and relevant experiments with them.
- **II) Central processing and planning:** in chapters 5.2 and 5.3 we develop models describing the processing of vestibular inputs and the planning of combined eye-head movements in healthy subjects, and in chapter 6.3 we investigate how the processing of vestibular input is modified by cerebellar atrophy.
- **III) Oculomotor output:** chapter 4.1 provides the mathematical basis for 3-dimensional eye position measurement with video-based systems, and chapter 4.2 gives a state-of-the-art overview of 3-dimensional eye position measurement.

movement (Fig. 2-3; Parameters taken from (Fernandez and Goldberg, 1971). This frequency range covers almost all naturally occurring head movements (Grossman et al., 1988; Viirre et al., 1997).

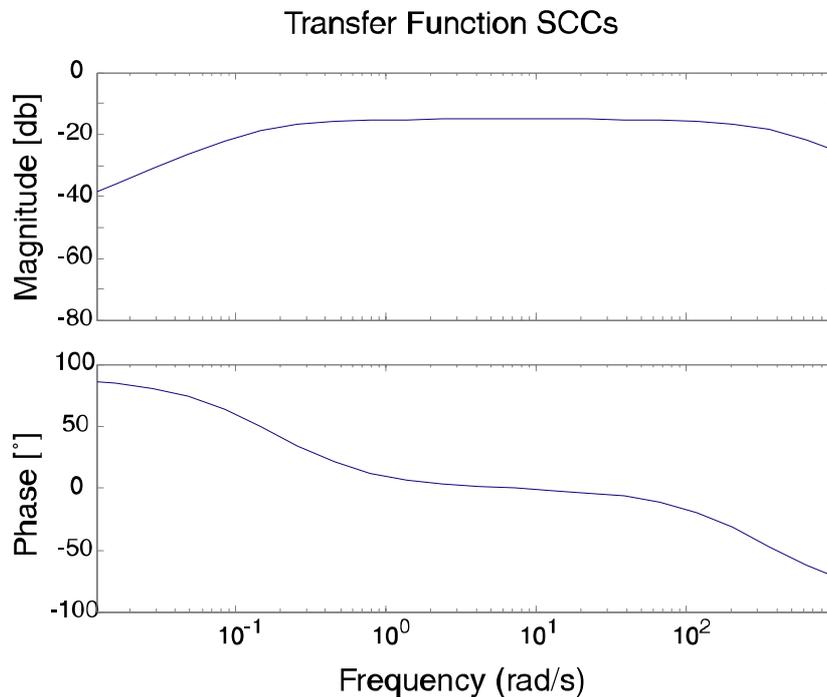


Figure 2-3 Transfer function of the semicircular canals. For naturally occurring head movements (ca. 0.1 Hz – 10 Hz) the semicircular canals transduce head velocity.

The otolith system, in contrast, transduces linear accelerations. The vestibulum contains two otolith structures: the utricle, which is approximately oriented horizontally when the head is upright, and the vertically oriented saccule. Due to the measurement difficulties the exact orientation of these structures is still debated (Maier, 1987). The otoliths constitute the main source of information about our orientation with respect to the earth vertical. Since they also convey information about *linear accelerations*, one of the main challenges of the otolith system is to distinguish between these two signals – a task that we still don't understand completely. The information from the utricle dominates the eye movement response, whereas information from the saccule seems to be mainly used for postural control (Mhoon et al., 1997).

Under most natural situations the signals from otoliths, semicircular canals and the visual system provide a clear indication of our orientation and movement in space. Thereby the vestibular and visual system complement each other: while the vestibular system provides the short latency signals necessary to compensate for fast head movements, the visual system helps out by supplying the sensory signals necessary to compensate for low frequency movements. Sometimes however, the different sensory sources give conflicting information. Such paradigms are called *conflict stimuli*, and often have a highly nauseogenic effect. A good example of such a conflict stimulus is sea sickness: on a rolling ship our balance system continuously indicates movement in changing directions, whereas our visual input is relatively stable since the whole ship is rolling together with us. The opposite effect is achieved when

we sit in a train compartment, and the train next to us starts to move: a powerful visual input elicits a feeling of movement, whereas the vestibular sensors indicate that we are stationary. This strong feeling of movement is actually caused by direct input from the visual system to the vestibular nuclei (Waespe and Henn, 1977). In chapter 5.2 we use such a conflict stimulus, a rotation about an axis tilted with respect to earth vertical, to determine the relative importance of dynamic otolith input for our perception of movement.

While the information from the otolith is the dominant source for our perception of the earth vertical, recent experiments have indicated that also somatosensory input, for example pressure from the soles of our feet or thighs (Yardley, 1990; Anastasopoulos et al., 1999), and maybe even information from our kidneys (Mittelstaedt, 1995) contribute significantly. In the light also the visual input plays an important role for our perception of space.

The articles in chapters 5.1 and 5.4 use the kinematics of 3-dimensional rotations to determine how stimulation of the semicircular canals contributes to our eye movement responses. In chapter 5.1 we use the non-commutativity of rotations to explain the strong feeling of rotation after an abrupt termination of circular head shaking, and the concomitant torsional eye movement patterns. In chapter 5.4 we analyze the stimulation of the individual canals during short but very quick rotatory movements of the head. In chapter 0 we show how this effect can be used to determine a functional deficit in individual semicircular canals. Since the publication of that article this principle has become widely used in medical tests of the peripheral vestibular system. Chapter 6.2 presents another example of how a geometric understanding of the kinematics of eye movements can help in the clinical diagnosis of vestibular problems: sustained eye movements elicited by hyperventilation, i.e. quick and deep inhaling and exhaling of air, can indicate small tumors on the vestibulo-cochlear nerve, even if standard MRIs don't show any signs yet.

2.2.2 Central processing & planning

While we are constantly aware of our ability to hear, the existence of the vestibular system normally goes by unnoticed. Therefore it may be surprising that the number of afferent nerves from both systems are of the same order of magnitude: an average person has approximately 18'500 vestibular nerve afferents (Naufal and Schuknecht, 1970), and 35'000 cochlear nerve fibers (Spoendlin and Schrott, 1990). So why do we need so many vestibular nerve cells? What is the central nervous system (CNS) doing with the information coming in from SCCs and otoliths? As mentioned above, one of the most important functions of the vestibular system is to compensate for rotatory and translational movements of the head, and thus to stabilize the orientation of the eye in space. The sheer number of vestibular afferents indicates that this task involves some complex information processing. Careful investigation of the eye movements elicited by vestibular signals helps us to understand how the CNS achieves this goal.

2.2.2.1 Three-neuron arc

To get the information about our movement as fast as possible to the eyes, the vestibulo-ocular system uses of the “three-neuron arc” shown in Fig. 2-4. In healthy subjects, this short-cut for vestibular information gets signals within approximately 8 ms from the vestibular periphery through the brainstem and to the eye (Tabak et al., 1997).

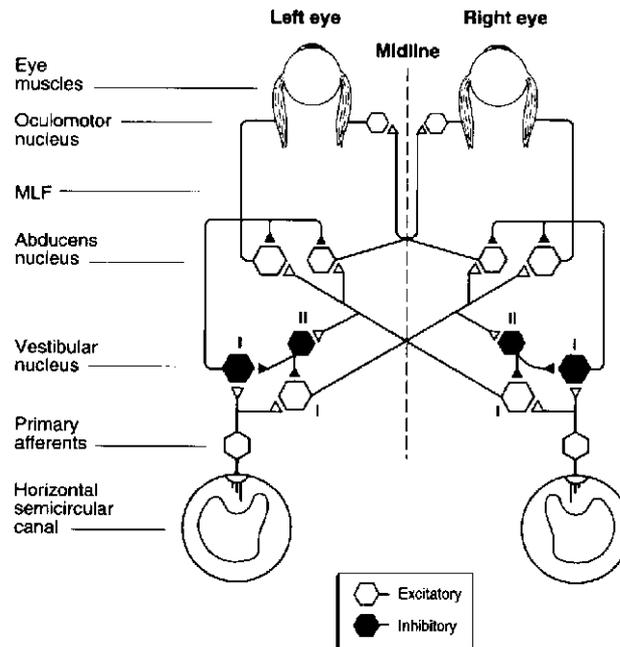


Figure 2-4 The “three-neuron arc” forms the basis for the short-latency oculomotor response to vestibular stimuli.

2.2.2.2 Signal processing in the brainstem

The primary vestibular signals do not provide sufficient information for an adequate compensation of head movements, and are therefore processed further by structures in the brainstem. For example, a mechanism sometimes referred to as *velocity storage* improves the ability of the VOR to transduce the low-frequency components of head rotation (Raphan et al., 1979): when a subject is accelerated on a turntable to a constant velocity, the compensatory eye movements last significantly longer than the mechanical stimulation of the semicircular canals. This behavior cannot be explained by the three-neuron arc. The term *velocity storage* has been chosen since the peripheral signal must somehow be stored or prolonged, to provide a good compensatory eye movement response even though the signals from the canals have already decayed.

In monkeys, where it is possible to actually record the activity of the peripheral vestibular neurons and simultaneously measure eye movements, it has been shown that the canal activity lasts only about 7 s (Carpenter, 1988), whereas the eye movement response decays with a time-constant of approximately 14 s (Tweed et al., 1994a). Fig. 2-5 illustrates the effect of this velocity storage.

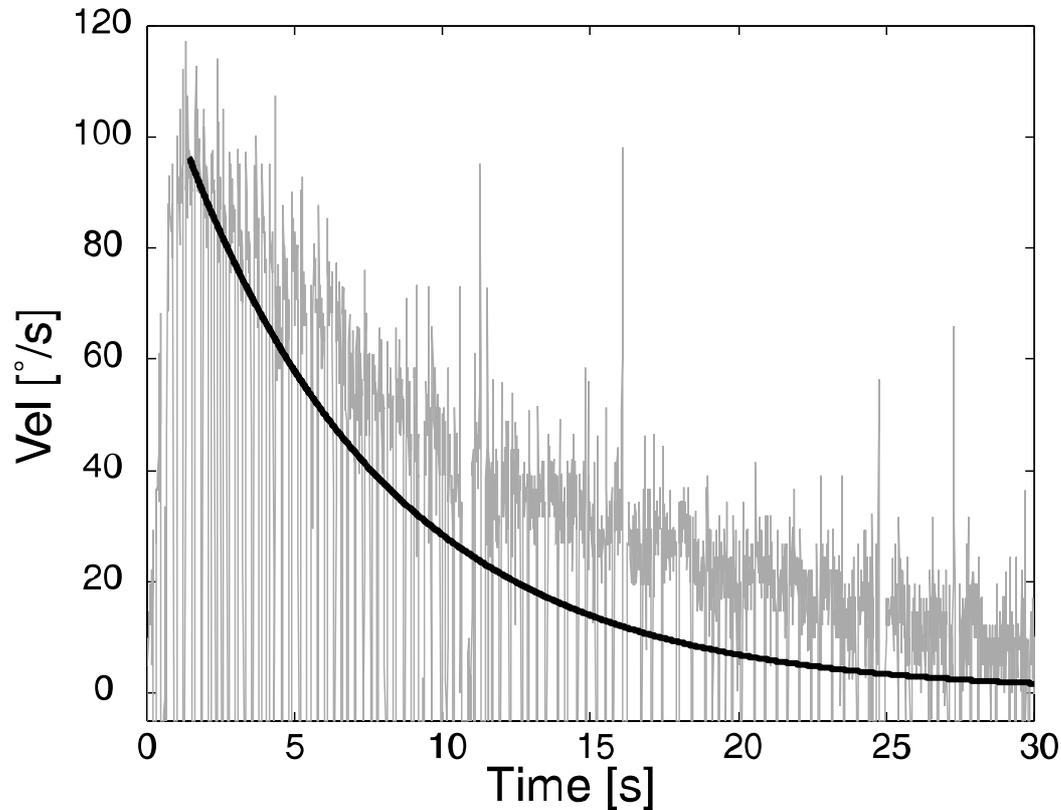


Figure 2-5 Velocity Storage: the gray line represents horizontal eye velocity elicited by a velocity step about a vertical axis. The thick black line indicates the approximate decay of the signal from the semicircular canals.

Experiments in monkeys, where the midline was sectioned at the height of the medulla, have shown that the velocity storage depends on the interconnections between the vestibular nuclei on the left and right side (Katz et al., 1991). Also elimination of vestibular input on one side abolishes the velocity storage (Haslwanter et al., 1995).

2.2.2.3 Cerebellar and cortical connections

Under certain circumstances the signals from the semicircular canals are not only too small but even contradict the signals from the otoliths. In such cases the CNS must use all available information to determine our orientation and movement in space. Such tasks involve contributions from “higher” areas, i.e. from the cerebellum and the cortex. It can be shown that even when the different sensory inputs give contradictory indications about our movement and orientation in space, it is still possible to generate an optimal eye movement response (Merfeld, 1995). One example of a stimulus that produces

conflicting information in otoliths and SCCs is a constant velocity rotation about an axis tilted with respect to the earth-vertical, or *off-vertical axis rotation* (OVAR). In chapter 5.2 we develop a model that is based on “optimal estimator theory”, and that is able to reproduce the experimentally observed eye movements for a wide range of stimulus parameters during OVAR. And in chapter 6.3 we elucidate the role that the cerebellum plays in the processing of dynamic otolith signals in humans. Cerebellar atrophy not only eliminates the ability to determine body rotation from dynamic otolith signals. It also seems to enhance the response of the *linear* vestibulo-ocular reflex (VOR).

Two main subdivisions of the cerebellum play an important role in the control of eye movements: (1) the vestibulocerebellum (consisting of flocculus, paraflocculus, nodulus, and ventral uvula), and (2) the dorsal vermis of the posterior lobe and the fastigial nucleus (Lewis and Zee, 1993). While isolated lesions in these areas are rare in humans, experimental work with animals has been able to elucidate the role of these structures for the VOR. Surgical ablation of the nodulus affects the time constant of eye velocity decay after a rotational velocity step (Waespe et al., 1985; Hess and Angelaki, 1993). The flocculus / ventral paraflocculus area is required for calibrating the magnitude of eye movement responses to a given vestibular stimulus: monkeys with these structures intact are able to adapt to the altered sensory input, e.g. when they are fitted with magnifying or minimizing glasses, whereas lesions reduce or abolish this ability (Zee et al., 1981). Current opinion is divided on the relative contributions of the flocculus and the ventral paraflocculus (Rambold et al., 1999). Other cerebellar structures influence vestibularly evoked eye movements indirectly, like the dorsal vermis through its effect on smooth pursuit.

In contrast to the detailed understanding that we have about the role of the cerebellum, the cortical contributions to vestibular responses are still not well understood. Experiments in cats, humans and monkeys have found a number of cortical areas that respond to vestibular stimuli (Guldin and Gruesser, 1998). Nevertheless, it is still unclear how these areas contribute to our movement- and orientation-perception (Brandt and Dieterich, 1999).

2.2.3 The eye

2.2.3.1 Anatomy of the extraocular plant

The structures of the human eye most relevant for this study are the ones influencing or contributing to its motion, and the ones which allow the measurement of this motion.

The movement of the eye is determined by the activity of the six extraocular muscles, as well as by the mechanical properties of the tissue connecting these structures to the orbit. Comparing the muscle activity to the elicited eye movements in rhesus monkeys, it has been shown that for 1-dimensional movements the extraocular muscles can be described by a third-order model (Robinson, 1964; Fuchs et al., 1988). The biggest unknown factor is the exact path that the extraocular muscles take in the orbit. Recent work based on high resolution MRI scans and on trans-sections of the extraocular plant has revealed that the muscles do not run freely in the orbital globe. Instead, they are connected by collagen

tissue and smooth muscles, sometimes referred to as “muscle pulleys”, to the inner wall of the orbita (Demer et al., 1995).

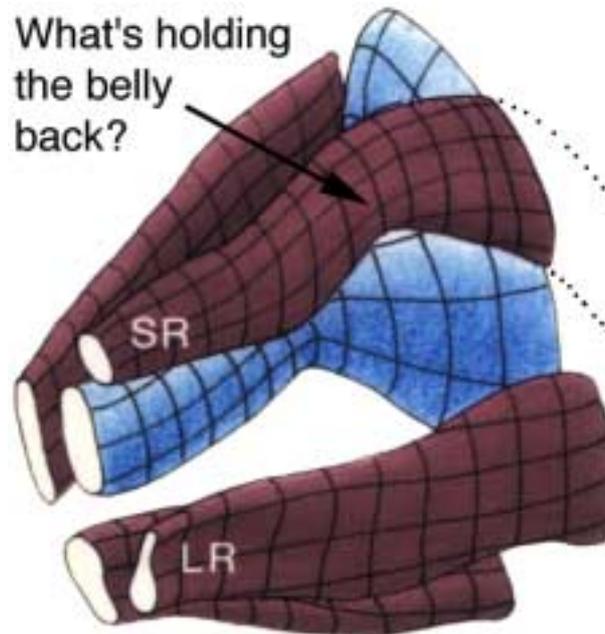


Figure 2-6 Extraocular muscles: LR palsy treated by vertical rectus transposition to the margins of the LR. It can be seen that the belly of the transposed SR is held back. (Courtesy of J. Miller)

These attachments of the extraocular muscles (EOMs) have two important implications. First, they determine the pulling directions of the EOMs (sometimes also referred to as the “functional origin” of the muscles). The exact location of this functional origin is an important factor in transposition of the muscle insertion on the eyeball, a standard operation to correct strabismus (Fig. 2-6). Second, the pulling directions also play an important roll for the control of eye movements. The implications of these muscle pulleys for the control of eye movements are still unclear. One school of thought claims that these pulleys allows the CNS to focus on the control of the *gaze direction*, i.e. the line of sight, and leave the adjustment of the eye rotation about the line of sight to the mechanics of the eye-plant (Raphan, 1998). In fact, recordings of the activity of single neurons in the superior colliculus, a midbrain structure that is very important for the generation of fast eye movements, have shown that at that stage the signal that controls the eye movement is still only 2-dimensional (van Opstal et al., 1991). The other school of thought insists that the eye movement is controlled in all three directions, taking into consideration the effects of the EOMs (Tweed et al., 1998). In their opinion the system accurately controls and executes movements of the eyes, also accounting for the non-commutativity of rotations. Models of combined eye-head movements, which are based on that assumption, can predict the trajectories of complicated eye-head movements precisely, which is impossible if one works with non-commutative control-systems (Tweed et al., 1999). While the first model requires 2 degrees of

freedom for eye movement control, the second model implies a fully 3-dimensional control structure. This question is at the heart of the article in chapter 5.3.

2.2.3.2 Movements of the eye

The two main tasks of the eye are reflected in its movements: the eye has to be able to a) generate a stable image on the retina, and b) to shift the point of interest quickly to a new target. The fast eye movements necessary for target shifts are called “saccades”. Saccades are only used to change the gaze direction, and no visual information is obtained during the saccadic gaze shift. In humans they reach velocities of up to $700^\circ/s$, and are executed in a very stereotyped way. Deviations from the normally fairly fixed relationship between amplitude and peak velocity of saccades, the *saccadic main sequence*, often yield valuable information about the underlying pathological change in the eye movement control system.

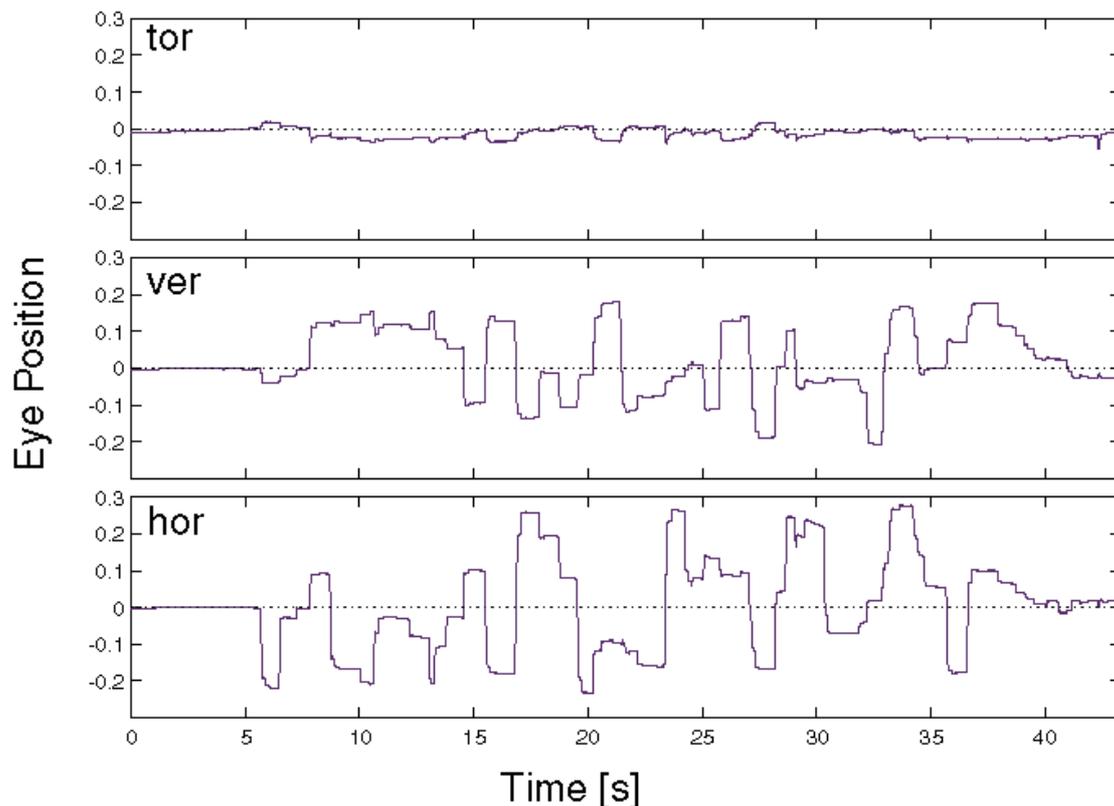


Figure 2-7 Saccades and fixations during voluntary eye movements in a healthy subject.

While saccades that are executed with the head stationary are well understood, combined eye-head movements have only recently become the focus of research. In chapter 5.3 describes the control strategies that are used by the brain to plan and execute large combined eye-head-saccades.

Once the eye has reached its target, the CNS has to ensure that the visual information is clear and does not get blurred by voluntary or involuntary head movements. This is the main task of the *vestibulo-*

ocular reflex (VOR) and of *pursuit eye movements*. The former one compensates for the movement of the head, thereby ensuring a clear image of the fixation object on the retina. The latter one compensates for the movement of an object, and reach velocities of up to $150^{\circ}/s$ in humans. It may be interesting to note here that it is not possible to generate smooth pursuit eye movements without an actual smoothly moving target.

A simple experiment can demonstrate the efficacy of the VOR: take a printed sheet of paper, and hold it about 30 cm in front of your eyes. Now move your head rapidly left and right while trying to read the text on the sheet of paper. You will find that this does not present any serious problem. However, if the head is held stable in space, and the paper is moved with the same speed left and right, it will be almost impossible to decipher anything. The reason for this difference is that in the first case the vestibular input is used to stabilize your gaze direction, while in the second case only visual information is available – which is too slow to compensate fully for the movement of the target.

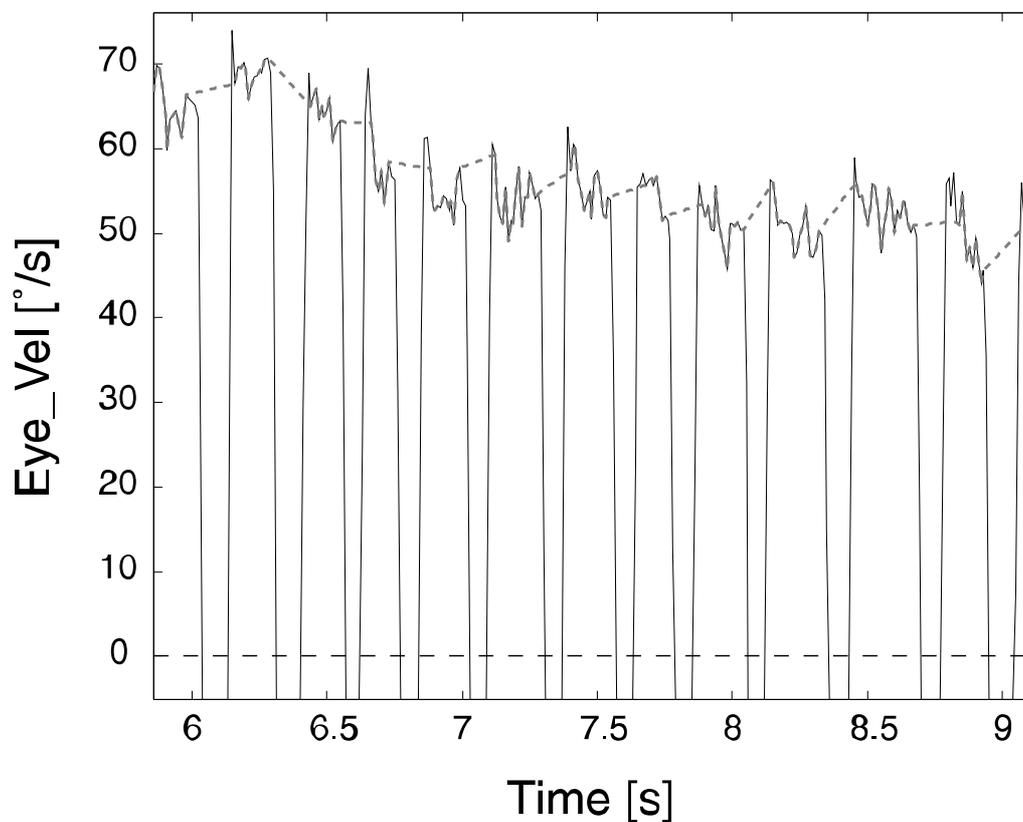


Figure 2-8 Eye velocity during vestibular evoked nystagmus (Magnification of the eye velocity in Fig. 2-5). The gray dashed line indicates the slow-phase eye velocity used during the data evaluation.

Many of the experiments described below concentrate on the slow phases of eye movements (chapters 5.1, 5.2, 6.2, 6.3).

2.3 The recording of eye movements

The eye has a number of anatomical structures that facilitate the recording of its movement (Fig. 2-9).

- a) the pupil
- b) pigmentation of the iris
- c) the corrugated surface of the iris
- d) optical refractions at cornea and lens
- e) reflection off the sclera and the iris
- f) an electrical dipole of about 1mV between the cornea and the retina
- g) the structure of the retina

In addition, external marks or measurement devices can be attached to the cornea, and further effects involving the visual system (e.g. afterimages) can aid the determination of the orientation of the eye.

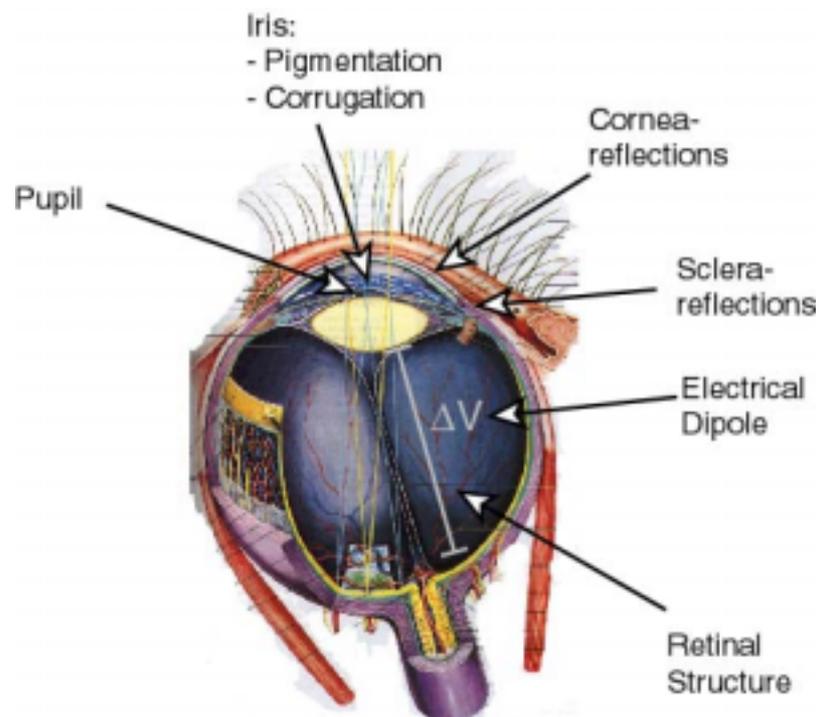


Figure 2-9 Anatomical features of the human eye that lend themselves to eye movement measurement.

2.3.1 Gaze direction

For many applications it is sufficient to determine the gaze direction. Most systems built to that purpose use the effects a) and d)-f) from the list above.

The most obvious feature of the human eye is the pupil (a). Since the eyeball has a radius of about 12 mm, a shift of the pupil by 1 mm corresponds to a gaze shift of approximately 5° . This movement can be tracked, for example by a video based system, and can easily be calibrated.

Another method is to record the reflections of a small illumination light from the refractive surfaces of the eyeball: the front of the cornea, and the front and back of the lens (d). The images of these reflections are called *Purkinje images*, and systems that are based on it *Purkinje trackers*. It is also possible to use the shift of the pupil together with the Purkinje images, to compensate for shifts of the camera with respect to the head.

The *scleral reflection* technique (e) relies on the fact that the dark iris reflects less light than the white sclera. This effect can be used to build cheap infrared systems to record horizontal and vertical eye movements (Ober, Skalar, etc).

Many clinical measurement systems are based on an electrical dipole between the cornea and the retina of about 1 mV (f). While these “electro-oculography” (EOG) systems are prone to a number of artifacts, they are easy to use and have therefore captured a large share of the medical applications market.

A thorough overview of 2-dimensional gaze tracking systems, together with technical details and information relevant for practical use, can be found in (Young and Sheena, 1975). In chapter 4.2 I present an up-to-date overview of current technologies used to record *3-dimensional* eye movements. Since the scleral search coil technique is well established and understood (Collewijn et al., 1985), I will thereby concentrate on video-based systems.

2.3.2 3-dimensional systems

All studies presented in this thesis focus on the full rotatory movements of the eye in space in *three* dimensions. Since the eyeball can execute not only horizontal and vertical movements, but also rotate about the line of sight, the gaze orientation does not determine the orientation of the eye uniquely, but leaves the rotation about the line of sight undetermined.

A simple demonstration of this effect is the following simple experiment: stand in front of a mirror and pick out the exact location of a small vessel in your right or left eye. Then observe the movement of this vessel, while slowly tilting the head to one shoulder. You will find that the eye rotates in the head, trying to maintain its original orientation in space.

Different approaches can be used to record the orientation of the eye in all 3 dimensions:

- The orientation of *afterimages* can be compared to horizontal or vertical lines
- Measurement devices which help to record the eye movement can be attached to the eye (e.g. modified contact lenses)
- The eye orientation can be determined by analyzing images of the eye

Afterimages: Afterimages were already used in the last century for ophthalmologic investigations, and produced the first quantitative information about the orientation of the eyeball in the orbit. Thereby a bright cross is flashed in front of the eye. For a number of seconds an afterimage of that cross remains visible to the subject, and can be aligned with a measurement bar on the target screen (Fig. 2-10). Thereby the ocular torsion can be determined, also for eccentric eye positions. Although this technique is subjective and restricted to stationary eye positions, researchers like Helmholtz, Listing, and Donders were able to find the dominant principles of eye movement control with this technique (Helmholtz, 1867; Donders, 1848) In fact, much recent research has been following closely in their footsteps. But apart from a few exceptions (Probst-Mueller et al., 1996) the technique of afterimages is no longer used.

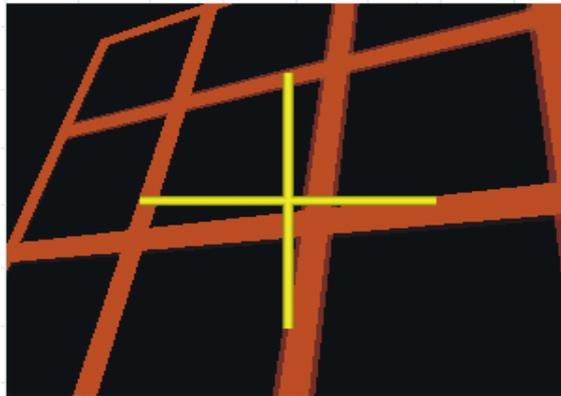


Figure 2-10 Afterimage of a flashed cross, when looking eccentrically at a wall with squares.

Attachments to the eye: At first thought the idea of attaching anything to the eye sounds unacceptable to most people. The eyes, the “windows to the soul”, should remain untouched – after all, isn’t that what the eyelids are good for? The first objective torsion measurement devices relying on this technique were in fact unusual: a straw was glued to the eye, and connected to an intricate leverage mechanism. The other end of this mechanism was covered in ink. The end of the straw produced an eye movement trace on a rotating sheet of paper, similar to the workings of current barometer systems (Ohm, 1928). For understandable reasons this instrument never became very popular, but it was not until the 1960s that a practical objective method to record torsional eye movements was developed. In the first *scleral search coil* experiment in 1963, Robinson attached a bulky contact lens, which contained an embedded wire, to the eye. By electromagnetic induction in the wire loop, a voltage was generated when the subject was placed inside an oscillating magnetic field (Robinson, 1963). As described in detail in chapter 3, this voltage almost directly indicates the orientation of the eye in space. The original approach to generate a suction effect for this contact lens was by means of a mechanical pump. In 1985 Collewijn produced a scleral search coil that holds to the convex cornea through its elasticity: by having a slightly smaller radius than the eye, the rubber annulus containing the search coil flexes backward and automatically generates the suction necessary to keep the annulus firmly attached to the eye (Collewijn et al., 1985). This approach has since become the dominant measurement technique for 3-dimensional eye movements.

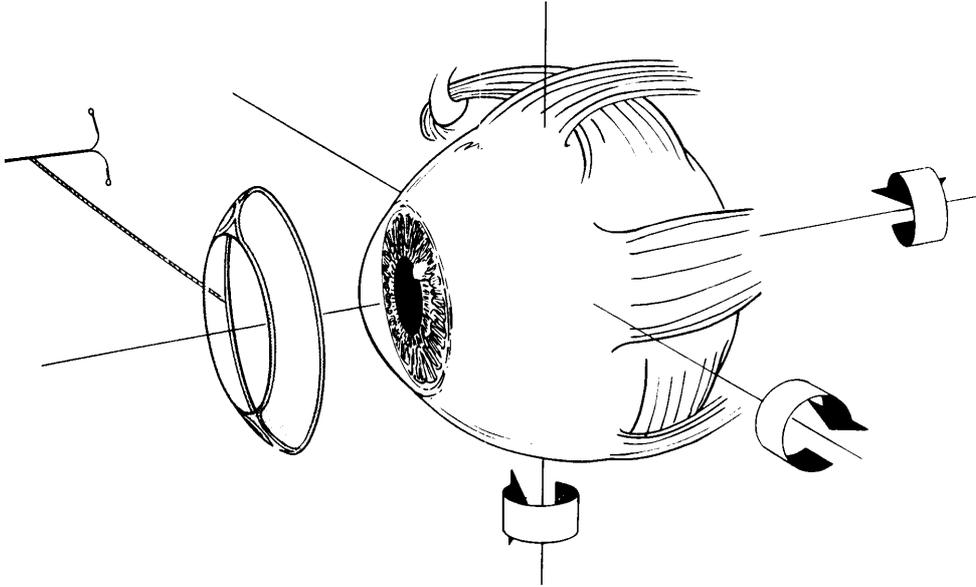


Figure 2-11 Scleral search coil as developed by Collewijn. (Courtesy of Skalar Medical BV, Delft, The Netherlands).

Image-based systems: The newest approach to measuring the 3-dimensional orientation of the eye in space is *video-oculography* (VOG). From images like the one in Fig. 2-12 the horizontal, vertical and torsional orientation of the eye can be determined. Originally this approach was restricted to recording ocular torsion while looking straight ahead. In chapter 4.1 we develop the mathematical tools necessary to obtain accurate torsion values for general eye positions.

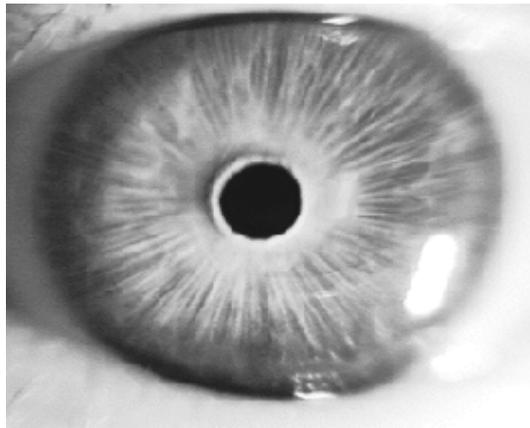


Figure 2-12 Image of pupil and iris, as used for video-oculography.

In chapter 4.2 I document the state-of-the-art of video-oculography and outline approaches for solutions to the remaining problems.

2.4 Eye movement control

Our understanding of the way the brain controls movements of the eyes has advanced considerably due to new experimental findings that elucidate the functioning of the brain during well controlled behavioral tasks. These experimental findings are complemented by improvements of our understanding of the way the different sensory input signals get processed to elicit the observed eye movements.

2.4.1 Experimental findings

Experimental work with animals has provided a wealth of information about the functional role of the individual regions of the brain. Many of these results rely on *single cell recordings*. This technique allows monitoring the activity of a single cell while the animal executes carefully controlled movements or other tasks. Using this approach, we have obtained a reasonable understanding of the role the brainstem and midbrain play in the generation and execution of eye movements. Once a hypothesis is developed about the functional contribution of a certain brain area, it can be tested by *micro-stimulation* or by temporary or permanent *inactivation* of this area. In the former case, a small electrical current is applied to the region under investigation. This current stimulates the surrounding tissue. Careful observation of the elicited movements allows confirmation or rejection of the hypothesis that was put forward based on the results of the previous single cell recordings.

Single-cell recording results have to be complemented by *inactivation* of small areas of the brain to determine the dependence of the task execution on the area under investigation. For example, stimulation of the *superior colliculus* elicits saccades of an accurately defined magnitude and direction. Surprisingly, though, inactivation of the colliculus does not eliminate saccades permanently. Only if a second, cortical brain area, the *frontal eye fields*, also gets inactivated, is the generation of saccades abolished. Inactivation studies can be *temporary* or *permanent*. Temporary inactivation of the brain area under investigation is achieved by injecting a small amount of the neurotransmitter used for communication between the nerve cells in this area. Thereby this area gets “inactivated” until the concentration of the injected substance has become so small that it does not interfere with the normal signal transmission between these cells.

Since many brain functions possess a highly redundant organization, temporary inactivation only provides information about the acute effects of changes in that area. Luckily, such acute effects can often be compensated, and the original task can be taken over by other brain areas. Such compensations are most strikingly shown by improvements that can often be observed in patients after a stroke attack. To study the underlying re-organization of the brain it is necessary to *permanently* inactivate small regions of the brain. This is usually achieved by injecting minute amounts of neurotoxic substances into the brain areas that are to be inactivated. By observing how the CNS adapts to such a lesion over time, we can learn how the CNS re-organizes the way sensory signals get processed and motor-commands generated.

Single cell recordings have been extremely helpful in our efforts to understand the CNS in general, and the VOR in particular. Nevertheless, investigations in animals cannot completely replace experiments with human subjects: recent experimental evidence shows that while short latency responses are almost identical in man and monkey, responses that require higher order processing often reveal remarkable differences. For example, monkeys can use a dynamic, purely otolith input during rotations about tilted axes to accurately reconstruct their movement in space, and generate appropriate compensatory eye movements in response (Angelaki and Hess, 1996). In chapter 5.2 we show that humans employ quite different strategies to respond to dynamic otolith stimuli. Similar differences have shown up in other experiments (Angelaki and Hess, 1994a; Fetter et al., 1996). An outline of new behavioral experiments that can be used to investigate the vestibulo-ocular system is given in chapter 7.

In testing the effects of functional inactivation of small brain areas in humans, behavioral experiments are sometimes complemented with modern imaging techniques that allow us to obtain valuable information from patients who have had strokes or tumors, or who have suffered from degenerative diseases. Today CT (computer tomography) images can reveal anatomical details down to a resolution of 0.1 mm, and MRI images, which have the advantage that they don't require X-rays, permit a visualization of the brain structure down to less than 1 mm (Minor, 2000). In chapter 6.3 we study the role of the cerebellum in the processing of dynamic otolith signals by recording 3-dimensional eye movements in patients with cerebellar atrophy during rotations about tilted axes.

2.4.2 Analytical tools

A boost in our analytical understanding of the information-processing properties of the brain was provided by application of a more quantitative way of formulating predictions and hypotheses that was championed by Robinson, Young, and others from the 60's onward. Especially the tool of *control theory* allowed to investigate the role that feed-back and feed-forward can play in the processing of sensory signals at a new qualitative and quantitative level. In oculomotor research, the techniques of control theory were applied to adaptation (Young and Oman, 1969), smooth pursuit eye movements (Robinson, 1965; Young et al., 1971), saccade generation (Robinson, 1964), periodically alternating nystagmus (Leigh et al., 1981) and many other areas. One advantage of control systems is that they allow us to use behavioral data to investigate the function of the underlying system. In chapter 5.2 we show how a 3-dimensional control system can be used to explain the formation of our perception of motion and orientation from the combination of sometimes contradictory information from different vestibular inputs.

Studies of the global properties of movement control are complemented by investigations of the information processing at the level of single neurons. For example, Angelaki has shown how a combination of the spatial and temporal properties of vestibular neurons can be used to determine the rotatory movement in space from dynamic otoliths signals (Angelaki, 1992). Subsequent observations have shown the existence of neurons with just such properties (Bush et al., 1993; Angelaki et al., 1993).

Introduction

A radically different approach to describe the architecture and function of the central nervous system is provided by *artificial neural networks*. Artificial neural networks try to simulate the distributed organization of the human brain, by representing it by a large number of simple individual units that are interconnected with varying strengths. The information processing properties of the network are modulated by changing the connection strengths between the individual units or “neurons”. For example, Anastasio used a *recurrent neural networks* to describe how connections within the vestibular nucleus might be changed to adapt to a unilateral vestibular loss (Anastasio and Bower, 1992; Anastasio, 1992); Cartwright and Curthoys tried to use the anatomical knowledge about the organization of the vestibulo-ocular system to explain observed neural activation patterns after surgical unilateral labyrinthectomy (Cartwright and Curthoys, 1996).

Another improvement in our understanding of the vestibulo-ocular system was brought about by the introduction of vector descriptions of rotations, such as *rotation vectors* and *quaternions*. While these tools had been invented more than century ago (Hamilton, 1899; Rodrigues, 1840), their application to oculomotor problems (Haustein, 1989) (Tweed and Vilis, 1987) simplifies the investigation of global properties of rotational movements of eye, head, and arms (Straumann et al., 1991). Chapter 3 covers in detail the mathematical implications of application of these tools.

Introduction

3 THE KINEMATICS OF 3-DIMENSIONAL ROTATORY EYE- AND HEAD- MOVEMENTS

Published as: *T. Haslwanter. Mathematics of Three-Dimensional Eye Rotations. Vision Res 35:1727-1739, 1995.*

The kinematics of movements in 3-dimensional (3D) space often have unexpected implications: while a translation of an object first 1m to the left and then 1m up brings the object into the same final location as a translation with the opposite sequence, first 1m up and then 1m left, this “commutativity” does not hold for rotations. To make things even harder, many texts do not clearly distinguish between rotations of objects and rotations of coordinate systems, and a range of different representations of rotations is used to quantify rotatory movements.

In this article I start out by describing the most common parameterization of rotations, i.e. rotation matrices. Through combinations of two or more of these rotation matrices arbitrary rotations in space can then be characterized. Especially the *scleral search coil technique* is particularly suited to for evaluation with rotation matrices, since the normalized coil voltages correspond directly to the elements of a rotation matrix. I proceed to show how vector based descriptions of rotations, *quaternions* and *rotation vectors*, relate to the rotation matrices.

I proceed to cover questions specific to vestibulo-ocular research. If a subject looks around, the *rotation vectors* or *quaternions* describing the eye positions line up nicely along a plane. This property, called *Listing’s Law*, allows a convenient global characterization of 3-dimensional eye positions. I describe the dependence of this *Listing’s Law* on the reference position used for the description of eye movements, and how eye position and eye velocity are determined by Listing’s Plane. In the last part of the paper I show how the formulas developed in the first chapters can be used to analyze combined eye-head movements.

4 MEASUREMENT OF 3-DIMENSIONAL EYE MOVEMENTS

The *magnetic- or scleral-search-coil-technique* is a well-established technique to record 3-dimensional eye positions in research environments. But its semi-invasive nature has prevented its application in standard clinical diagnosis. To overcome this problem, different research groups have tried to develop accurate video-based systems for recording 3-dimensional eye position. In chapter 4.1 I develop the algorithms required to determine the correct torsional eye positions from iral patterns, and in chapter 4.2 I given an overview of the state-of-the-art of image based 3D video-oculographic (VOG) systems.

4.1 A theoretical basis for video-oculography

Published as: *T. Haslwanter and S. T. Moore. A Theoretical Analysis of Three-Dimensional Eye Position Measurement Using Polar Cross-Correlation. IEEE Trans Biomed Eng 42:1053-1061, 1995*

Video-based systems offer the only alternative to the uncomfortable and semi-invasive scleral search coil technique to record 3-dimensional eye position. So already in the 70s researchers developed techniques that allow the determination of ocular torsion from video images (Nakayama, 1974). The technological drawbacks of these early systems, high prices, low resolution, and time-intensive data analysis have gradually been reduced by the dramatic developments of video- and imaging-technology and the processing power of computers. To automate the analysis of the video images, Hatamian and Anderson introduced the *polar cross-correlation* technique, where the light-dark pattern of the iris along a circular line around the center of the pupil is compared to that with the eye in the reference position. One of the main limitations of that technique was that it only works for looking straight ahead. During eccentric eye positions, for example looking to the left, the algorithms led to systematic, significant measurement errors. In the first part of the paper we extend the polar cross correlation technique to allow correct 3-dimensional eye position measurement even for eccentric eye positions. By incorporating the spherical geometry of the eye, we show how systematic measurement artifacts can be eliminated by calculating the correct location of the sampling area for the iral light-dark pattern. The recording of 3-dimensional eye positions with VOG systems is inherently more complicated than recordings with the scleral search coil technique: while the latter one measures the spatial orientation of a solid object, the dual search coil, VOG systems have to determine the orientation of a physiological object, the eye-ball. The accuracy of these measurements is thereby determined not only by the measurement algorithms, but also by the physical and physiological properties of the eye. In the second part of the paper we use simulations to estimate the errors induced by these properties into the measurement process. The simulations show that while some effects, e.g. the optical distortion of the

Measurement of 3-dimensional eye movements

iral image by the cornea, have only a negligible influence on the measurement, other parameters, e.g. the angle between the optical and visual axis of the eye, have to be investigated further to guarantee high precision video recordings of eye movements.

4.2 Current technologies for recording 3-dimensional eye movements

The line of sight is controlled by the horizontal and vertical orientation of the eye. For understanding the movement of the eye, however, also the torsional eye movement component must be known.

Advances in ophthalmology, otology, and neurophysiology have raised important questions that can only be answered by knowing the rotatory movement of the eye in all three dimensions (Fetter and Haslwanter, 1999).

Currently the only firmly established way of recording 3-dimensional eye movements is the dual search coil technique. But based on recent advances in video- and computer technology, video-based systems have made significant progress and are increasingly used for scientific investigations. Many researchers, however, are still unsure of the qualities and weaknesses of 3D video systems, and don't know how to judge its accuracy. Below I present a survey of the state-of-the-art in 3D video-oculographic systems, and compare the strength and weaknesses of video-based systems with the search coil technique. I will also try to point out crucial steps in the analysis, and important points to be kept in mind during the operation of such systems.

4.2.1 Video Based Systems

4.2.1.1 Basic design

The basic elements for the data acquisition are shown in Fig. 4-1. An image of the eye is projected through a lens onto the image plane.

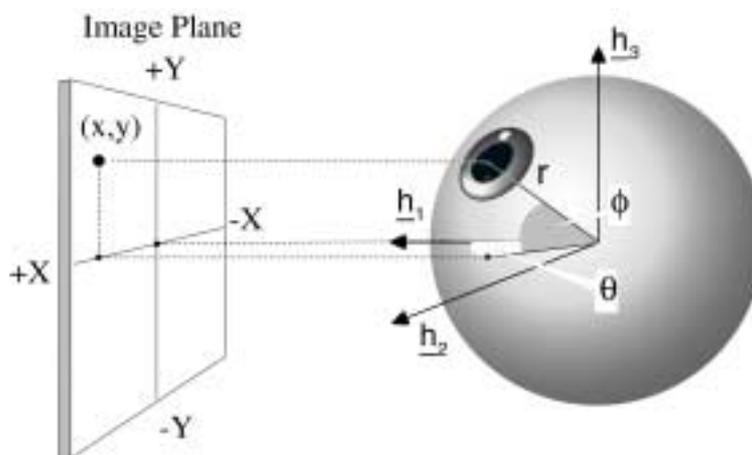


Fig. 4-1 Image acquisition in video-based systems. Note that the effect of the camera lens is ignored in this simplified sketch.

From this image of the eye its original orientation has to be reconstructed. Most systems first find the horizontal and vertical eye position, or *gaze direction*, by tracking the center of the pupil. In a second step the rotation of the eye about the gaze direction is determined. While the scleral search coil technique measures the orientation of the search coil directly from by voltages induced in the search coil (Haslwanter, 1995), video-oculographic (VOG) systems have to use information extracted from the 2-dimensional image to determine gaze direction and ocular torsion.

4.2.1.2 Hardware

The essential hardware elements making up a VOG-system are shown in Fig. 4-2

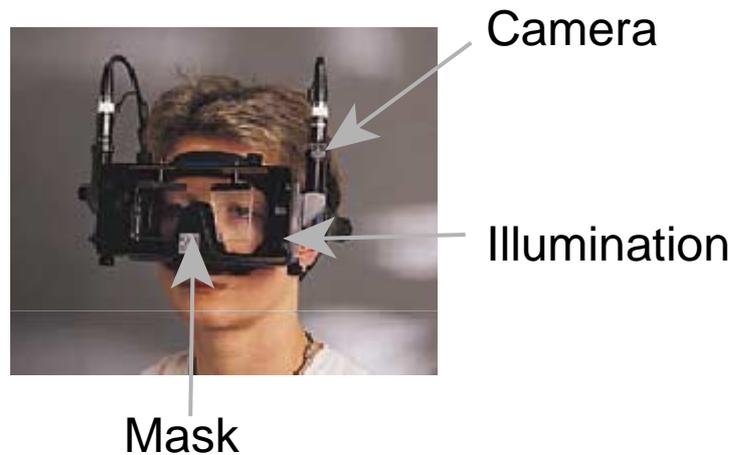


Fig. 4-2 Critical hardware elements of image acquisition.

HEAD MASK

The average radius of the eye is about 6mm, and a shift of the camera by only 1mm appears in the image like a gaze shift of more than 5°! It is therefore important to keep the orientation of the camera stable with respect to the head. Since muscles and connective tissue can move with respect to the bone, there are two ways to achieve a stable head-mount. One can either try to minimize the contact points, and choose them such that they have as little slippage as possible with respect to the head. The mask in Fig. 4-3 is attached to the head only at the nose-ridge and at the temples.

Alternatively one can use as large an area as possible for the attachment of the mask to the head.

Favorable experiences have been made with thermoplastic materials, molded to the shape of the face (Figs. 4-4 and 7-6). The current costs of one mask are between 5.- and 30.- US\$, but no experience has yet been made with the extensive re-use of masks, e.g. for routine investigations of patients.

Vacuum cushions which adjust themselves to the head of the subject have gone out of vogue, since their edges and pressure points can cause discomfort.

Measurement of 3-dimensional eye movements



Fig. 4-3 Head mask with few attachment points to the head (Courtesy of Dr. Kingma and I. de Jong, University Hospital Maastricht, Netherlands).

To improve the stability of the camera with respect to the head, most groups that do *not* routinely test patients do use a bite bar. An alternative is a *tooth-clip*, a holder that is firmly attached to the teeth of the subject. Such a tooth-clip eliminates the requirement to keep pressing the teeth together. Head masks should allow binocular vision, and a *field of view* (FOV) of at least $\pm 45^\circ$. In a recent “Neurolab” experiment, robust optokinetic responses have been achieved with a field of view of this extent. Only “vection experiments”, which use large-field moving visual inputs to elicit a feeling of movement in the subject, might require an even larger FOV.



Fig. 4-4 Head mask, made from thermoplastic material (Courtesy of Mill Reschke and Scott Wood, NASA).

ILLUMINATION

A critical ingredient for a good image quality is a proper illumination of the eyeball. Almost all research groups have started to use front-on illumination (between 5° and 20° from the straight-ahead direction). Older systems used infrared (IR)-illumination with grazing incidence-angle. Since the main iral features from IR light are generated by crypts of the iris, a grazing incidence-angle produces iral patterns that change as the eye rotates about the line of sight. With front-on illumination, or with visible light (where the structure of the iris is determined by the pigmentation of the iris stroma), this problem is eliminated. Front-on illumination also has the advantage that over the whole measurement range the eye is evenly illuminated, and no shadows of the eyeball degrade the image. While most researchers require a system that records eye position within a horizontal range of approximately $\pm 30^\circ$ and a vertical range of $\pm 20^\circ$, a number of groups are mainly interested in the torsional component of eye movements while looking straight ahead. Especially for clinical diagnostics, a lot of important information can be gathered while subjects are looking straight ahead. This restriction greatly facilitates the eye position measurement.

Front-on illumination has the disadvantage that iral patterns deteriorate with increasing wavelength. At the same time, the wavelength has to be long enough that the subject cannot see the illumination light. This is especially important for medical tests, where the movement of the eye should be measured while the patient has no visual fixation points. These two constraints restrict the wavelength to about 940 nm. Apart from the “invisibility”, IR light has the advantage that the pupil border is much sharper than in the visible light, which makes it easier to detect the gaze-direction.

Care has to be taken with the intensity of the illumination, since too strong an illumination can cause irreversible defects of lens and retina. The NASA-limits for the illumination intensity are 10 mW/cm². According to the “German industry standard “ (DIN IEC 60825), the time integral of the illumination intensity with pulsed light has to be significantly below that of continuous illumination. It also distinguishes between point sources and distributed light sources. Therefore the limit can lie anywhere between 0.7 mW/cm² and 620 mW/cm², depending on the exact properties of the light source. Special care has to be taken with patients with facial paralysis: since they cannot blink, the cornea is fairly dry, and they are therefore more sensitive to higher intensity illuminations. An overview of this topic has been presented by (Thalmeier, 1999).

While it is simpler to illuminate the eye continuously, pulsed illumination has a number of advantages:

- a) Not only does the eyes tolerate higher illumination intensities when the illumination is pulsed. Also the IR LEDs (light emitting diodes) can tolerate a higher level of current (and therefore give more light) if they are pulsed compared to when they are continuously illuminated.
- b) With pulsed light it is possible to avoid stray reflections when binocular recordings are made (i.e. the left eye is only sampled when the left illumination is on, the right eye only when the right illumination is on). Trials with polarizing filters to the same purpose have shown that up to 70% of the light are lost with these, and that they are difficult to adjust.
- c) Another advantage of pulsing (or shuttering) is that the image of the eye is not blurred as much by eye motion, which is particularly important in torsion measurements using iral patterns. A recent investigation has shown that with an illumination time of 20 ms, the torsion

measurement using iral signatures becomes impossible at eye velocities as low as 60°/s (Schreiber, 1999). An exposure time of 4 ms or less should be sufficient for all types of eye movements that are of interest for VOG.

However, care has to be taken to avoid overexposure of the iris in case the pulsed diodes switch to continuous illumination. When determining the location of the illumination source, one should keep in mind that the IR diodes used for illumination of the eye can literally explode. This has already happened in three cases (in two different laboratories).

CAMERA

Early VOG systems used photographic film to capture the image of the eye (Diamond et al., 1979). The next generation of VOG systems was already completely digital. Due to the limited computational power of early PCs and workstations, these systems could not evaluate the data in real time. Instead they had to be stored on an intermediate medium (VCR- or “Betacam”-systems), and then handle the data-analysis off-line. This limited the sampling rate to 50 Hz (set by the PAL-standard in Europe) or 60 Hz (NTSC, in the USA), with no option of a real-time data display. Only expensive custom-made, dedicated hardware could acquire images faster. While it has been shown that under certain conditions saccade dynamics can be determined with sampling rates as low as 60 Hz (Enright, 1998), most researchers believe that saccade-evaluation requires sampling rates of 150-200 Hz. For the analysis of slow-phase eye movements, sampling rates have to lie between 50 Hz and 100 Hz. For the real-time display of the data, which is especially important in clinical applications, visualization at a rate of 25/30 Hz is sufficient.

Currently, the most common technology employed for acquiring video images are *charge coupled devices* (CCDs). With such standard CCD cameras it is only possible to acquire full images, yielding sampling rates of 25/30 Hz (interlaced, frame frequency), or 50/60 Hz (non-interlaced, field frequency), corresponding to the European CCIR/PAL and North American EIA/NTSC TV standards. In contrast, with *complementary metal oxide semiconductors* (CMOS) it has become possible to read out defined sections of the image, and image lines and pixels can be randomly accessed under program control. This technique allows acquisition of regions of interest to be sampled at much higher rates (200 - 400 Hz) (Clarke and Krzok, 1996). CMOS cameras have the additional advantage of a higher sensitivity for larger wavelengths, as well as a larger dynamic range.

A further improvement in image acquisition can be obtained by employing CMOS sensors with on-chip parallel pixel processing and/or allocating a *field programmable gate array* (FPGA) to the programmable CMOS sensor. This approach eliminates the need of a frame grabber and the excessive data transfer rate that is required for high-speed acquisition of whole images. Furthermore, it facilitates preprocessing of the regions of interest in each image, e.g. for pupil edge detection.

4.2.1.3 Software

In most systems the first step is to find the center of the pupil. If the gaze-direction is known for a number of eye orientations, the locations of the center of the pupil allow *calibration* of the system, i.e. determining measurement parameters like the radius of the eyeball and the location and orientation of the camera with respect to the head. With these parameters established, the ocular torsion can then be determined.

PUPIL DETECTION

Since the torsion measurement depends on the accurate finding of the center of the pupil, the quality of the pupil location is very important. The simplest approach, a *center of gravity* algorithm that determines the mean horizontal and vertical position of the visible part of the pupil, is not sufficient: in many subjects part of the pupil is hidden by a drooping upper eyelid, and the center of the visible pupil area does not constitute the actual center of the pupil. The biggest challenge is to eliminate the parts of the pupil circumference that contain no information about the pupil center. Such artificial borders can be caused by reflections of the illumination lights from the cornea, by eyelids, eyelashes, and by shadows of the cornea. A number of different solutions exists. “Growing circles” are used (Sung and Reschke, 97 A.D.), empirical curvature algorithms and ellipse fits (Zhu et al., 1999), as well as iterative approaches (Groen et al., 1996). Although the accuracy of the center location is very important, especially for the determination of ocular torsion, the different approaches are about equally satisfactory.

The size and location of the pupil can fluctuate depending on the lighting conditions (Wyatt, 1995). The *limbus*, i.e. the border between pupil and sclera, on the other hand is not affected by the surrounding lighting. But efforts to use the limbus instead of the pupil edge to determine the gaze direction have failed, as the edge of the limbus is not clearly enough defined for accurate detection. The biggest problem in finding the gaze direction is a possible slippage of the camera.

CALIBRATION ALGORITHMS

For accurate VOG recordings the following parameters have to be determined at the beginning of an experiment:

- a) Radius of eyeball
- b) Location of the pupil center in the image when the eye is in the reference position (usually looking straight ahead)
- c) Rotation of the camera with respect to the head
- d) Horizontal and vertical rotation axis of the eye

The horizontal and vertical orientation of the camera does not have a big effect on the accuracy of VOG systems and may be discarded or kept at a fixed value (Moore et al., 1996).

As with most other systems, the accuracy of the calibration determines the quality of the recording. Therefore it may be surprising that so far no completely satisfying calibration procedure has been

developed. Difficulties can arise because of inaccuracies in the determination of the experimental parameters. For example, the exact distance between the camera and the eye depends on the shape of the head of the subject. This might be circumvented by using the fixed focal length of the camera, since the iris is only in focus when it is exactly at a certain distance from the lens.

Another inherent problem is the low fixation accuracy of untrained subjects. The variability can be as large as $\pm 0.5^\circ$, although this can go down to $\pm 0.1^\circ$ in trained subjects. These inaccuracies, as well as other variable parameters such as the distance between subject and target screen, induce some inherent variability in the determination of the calibration parameters.

Different procedures have been tried to increase the accuracy of the calibration. The most successful approaches are based on numerical minimization procedures. These procedures use a number of target points at well defined locations, and calculate the calibration parameters as a best fit to the recorded eye positions (Schreiber, 1999; Peterka and Merfeld, 1996).

For search coil systems it has been possible to work out calibration algorithms that do not require knowledge about the exact orientation of the eye, but only require a number of different, but otherwise arbitrary fixation points (Bartl et al., 1996). Similar efforts have been made with VOG systems. They rely on the fact that a round pupil becomes elliptical when the subject does not look exactly straight at the camera. In theory it is possible to use this effect for the calibration of the system (Van der Glas et al., 1999; Zhu, 1997). In practice, however, implementations of these algorithms have so far proven ineffective because of the variability of the human pupil.

Other external information could perhaps be used to determine some of the calibration parameters of video systems. For example, the diameter of the iris correlates closely with the diameter of the eyeball. This effect can be used to estimate the approximate radius of the eye. Alternatively, the radius of the eye could be determined from MRI images or other ophthalmologic procedures. However, these approaches might be too laborious and expensive for standard applications. A simpler solution might be simultaneous recordings of the eye from different angles. This could be achieved by using multiple cameras, or by inserting a beam-splitter into the image path (Thalmeier, 1999).

TORSION MEASUREMENT

For the determination of ocular torsion from video images either discrete structures on the iris or sclera can be used, or, alternatively, larger iral patterns. Hatamian and Anderson have introduced a technique to use the light-dark pattern on the iris along a circle about the center of the pupil to determine ocular torsion (Hatamian and Anderson, 1983). This technique, originally designed to determine ocular torsion while the subject looks straight ahead, has in the meantime been expanded to allow torsion measurements in arbitrary eye positions (Moore et al., 1996; Haslwanter and Moore, 1995). Further extensions, which rely on the use of multiple patterns, even allow the compensation of small errors in the detection of the center of the pupil (Groen et al., 1996). Without these improvements the torsional eye position values are not reliable.

The location of iral structures or patterns depends not only on the 3D orientation of the eye, but also on the dilation of the pupil. When the pupil is dilated, all patterns will be located at the edge of the iris.

During contraction of the pupil, the iral patterns do not contract along a radial line, but follow a “swirling” path, similar to the shutter of a camera. This implies that a simple linear scaling of the iral patter, which is sometimes used to compensate for the contraction and expansion of the pupil, is not sufficient for an accurate determination of iral patterns.

To avoid this problem, some newer systems rely on markers placed on the conjunctiva. Thereby marks are placed with standard surgical markers outside, but close to the limbus, since the conjunctiva is not fixed with respect to the eyeball. The marks remain well detectable for 30-40 min. A local anesthetic is commonly used for the cornea, since it is important to get the marker onto the sclera, i.e. to get through the tear liquid film. These markers eliminate physiological noise caused by the contraction and dilation of the pupil.

NEURAL NETWORKS

A radically different approach to VOG has been developed by Guillemant. It uses a combination of supervised and dynamic learning to identify the pupil, and iral patterns for the measurement of ocular torsion (Guillemant et al., 1995). This approach has the advantage that image artifacts like reflections of the illumination lights from the cornea and occlusions of the pupil by drooping eyelids are implicitly dealt with by the algorithm, and do not have to be identified separately. While only little has been published about the underlying algorithms, this approach might be able to handle non-linear problems in the image processing, which can for example be caused by contraction or expansion of the pupil.

4.2.1.4 Physiological Questions

Scleral search coil signals indicate the orientation of the coil in the magnetic field. These measurements may be made more difficult by engineering obstacles (e.g. constant offsets induced in the measurement setup), but they are not affected by physiological characteristics of the subject, e.g. the shape or size of the eye. In contrast, the results of 3D VOG systems are directly affected by the anatomy of the subject tested. One of the obvious parameters, mentioned above, is the radius of the eyeball. But also other effects can play a role.

Center of rotation: The eye does not show a “ball-in-socket” behavior, but instead rotates about points that depend on a) the direction of the rotation, and b) the eye position (Fry and Hill, 1962). To account for this complex behavior, some current eye models for the interpretation of VOG data assume a different axis of rotations for horizontal and vertical eye movements. In these models the eye movement is described in a Helmholtz- or Fick-system, and the displacement between the two axes of rotation is labeled “d” (Schreiber, 1999; Kopula, 1996). If this effect is not taken into consideration, the radius indicated for the eyeball will depend on whether the calibration data were taken from horizontal or from vertical eye movements.

Pupil properties: The center of the pupil is generally found by assuming that the pupil is circular or elliptical. While this assumption may lead to correct results, the shape of the human pupil is more complicated (Wyatt, 1995). Wyatt also showed that the center of the pupil changes by up to 1° when the pupil contracts or expands. In changing ambient lighting conditions, either constrictors or dilators may be used to keep the size of the pupil constant.

Visual – optical axis: The human eyeball is not a symmetrical structure, but has the fovea shifted medially. The shift between the visual axis and the optical axis of the eye varies between subjects, and is on average about 5° (Le Grand, 1980). The magnitude of this effect on 3D VOG recordings depends on the intersection of the visual axis with the pupil (Haslwanter and Moore, 1995). While some investigations indicate that this intersection may coincide with the center of the pupil (Wyatt, 1995), more data are needed to clarify this point.

Translation of eyeball: For large vergence angles the human eye also undergoes small translations within the orbit (Enright, 1980). For highly accurate VOG measurements this effect also has to be taken into consideration.

4.2.2 Scleral Search Coils

The standard way to record 3-dimensional eye movements is the scleral search coil technique (Fig. 4-5). The mathematical and technical foundations of the search coil technique have been described extensively (Robinson, 1963; Collewijn et al., 1975; Haslwanter, 1995; Haslwanter, 1997). Therefore I want to focus here on aspects of this technique that differ from VOG systems.

Calibration: While VOG systems require a calibration to determine anatomical parameters of the subject to be tested, search coils, used in systems with three orthogonal magnetic fields, don't require any such calibration. They only need one well defined eye position to determine the orientation of the coil on the eye (Bechert and Koenig, 1996; Kaspar and Hess, 1991). This explains the simple calibration procedures for search coil systems.

Slippage: In VOG systems the camera can slip with respect to the head, resulting in measurement errors of eye position and eye velocity. Similarly, in search coil systems the coil can slip with respect to the eye. The search coil is attached to the eye by suction, caused by a slightly smaller radius of the silicon annulus, in which the coils are embedded, compared to the cornea. Since search coils can't be adjusted individually to each subject, the suction holding the search coil to the eye is not always sufficient, especially in strongly myopic subjects. If the slippage occurs only once, the eye *positions* recorded by the system will be wrong. The eye *velocity*, however, will still be correct (except during the slippage itself), since the movement of the coil on the eye is still tracked correctly. In contrast, the errors induced by slippage of the camera with respect to the head affect eye position *and* eye velocity of the analyzed data.

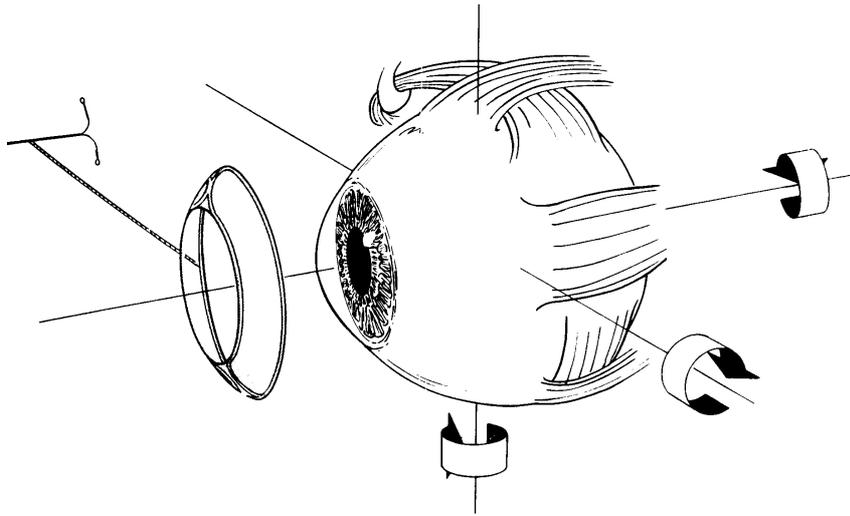


Fig. 4-5 Cartoon of a scleral search coil which is about to be mounted on the eye. With a „dual search coil“ or „combination search coil“ as shown here, horizontal, vertical and torsional eye movements can be recorded (Courtesy of Skalar Medical BV, Delft, The Netherlands).

Side effects: The trophic supply of the eye is mediated through the tear liquid. Since this is interrupted during search coil experiments, it can cause minor irritations of the eye. During the placement and removal of the search coil, there is also an – albeit minute – risk of corneal damage. VOG systems, which are non-invasive, don't suffer from these drawbacks.

Resolution and accuracy: In theory the spatial resolution of search coils is only limited by the electronic noise in the recording system. The real-life accuracy, however, is determined by a number of constraints that are difficult to assess: erroneous constant offsets in the recorded voltages, non-orthogonality of the magnetic fields, distortions of the magnetic fields by external influences, coil slippage, (uncompensated) non-orthogonality of the dual search coils, ...

Therefore most search coil systems have an accuracy of 5-10% of the measured eye position. Such accuracies are realistic also for VOG systems, despite the fact that the resolution is limited due to the pixelization of the image.

4.2.3 Discussion

Since VOG systems are affected by the anatomical characteristics of the subject to be tested, their development has proceeded much slower than the development of search coil systems. Also the high costs for the hardware and software involved has restricted the development and distribution of such systems. On the other hand, VOG development has profited enormously from the rapid progress in

video technology and computer science. This has enabled developers to reduce the number of system components, for example by eliminating the need for video recorders to store the data before the analysis. Other advances, such as cameras that allow the read-out of selected parts of the video image, have been critical in instrumental the sampling rate of video systems.

Also other trends in computer technology might help the development of video systems: some research groups have started to make the source code of their system available to other groups (“open software”).¹ This information allows the construction of a complete, binocular 3D VOG system at a total cost of only 30'000.- DM, and dramatically reduces the development time for newcomers in the field.

Nevertheless, VOG systems have not yet reached the threshold of general acceptance. This has seriously delayed the introduction of basic research findings, obtained with the search coil technique, into standard medical practice. Once the technological basis is firmly established, 3-dimensional eye movements could be very helpful in fields as diverse as otolaryngology, neurology, and ophthalmology. (Fetter and Sievering, 1995; Minor et al., 1999b).

Acknowledgements

A lot of the information presented in this section has been presented by the participants of a workshop on 3D VOG systems in Tübingen, from Nov 30 to Dec 2, 1999. I want to thank all the participants of the workshop for their contributions to the workshop as well as for the permission to publish this information.

¹ <http://www.nefo.med.uni-muenchen.de/~vog/>

5 EYE- AND HEAD-MOVEMENTS IN HEALTHY SUBJECTS

By analyzing the 3-dimensional eye movement responses to vestibular stimulation in healthy subjects we can address a number of interesting questions:

- What parts of the balance system get stimulated during different head movements?
- How do vestibular stimuli get transformed into eye movements?
- How is the information from the different sensory inputs combined to form an appropriate response to the head movements?
- Which control strategies do we use to execute eye- and head-movements?

The publications presented below provide answers to some of these questions.

5.1 Circular head shaking

Published as: T. Haslwanter and L. B. Minor. Nystagmus induced by circular head shaking in normal human subjects. Exp.Brain Res. 124 (1):25-32, 1999.

Eye movements elicited by vigorous head shaking are often used as a clinical test for the functional status of the semicircular canals and the brainstem structures that process vestibular signals. In a healthy subject the peripheral vestibular signals elicited during horizontal head shaking by moving the head to the right are cancelled by the signals from the subsequent head movement to the left, and upon termination of the head movement the eyes remain stable in space. If a patient has a unilateral vestibular deficit, e.g. no input from the left side, the head movements to the right won't be cancelled, and upon termination of the head shaking the remaining unbalanced stimulation of the right semicircular canals will elicit compensatory eye movements to the left. These signs are well understood, and provide valuable information for purely horizontal or vertical head movements. If the head is moved circularly (e.g. up – left – down – right), however, even healthy subjects develop a strong feeling of rotation and corresponding eye movements after abrupt termination of the head movement. This effect has been noticed previously, but has not been understood. We therefore recorded such head movements in healthy subjects, together with the ensuing eye movements. Using the analysis techniques established in chapter 3, we analyzed the head movements and calculated the resulting stimulation of the semicircular canals. Since the torsional head position is – like the torsional eye position – restricted to some kind of *Listing's Plane*, the semicircular canals experience during circular head shaking a stimulus that is very similar to a continuous rotation about the naso-occipital axis. This surprising result explains the strong feeling of rotation that is experienced as soon as the circular head movement is stopped, and nicely accounts for the observed eye movements.

5.2 Off-vertical Axis Rotations (OVAR)

Published as: *T. Haslwanter, R. Jaeger, S. Mayr, M. Fetter. Otolith-Canal Interaction During Off-Vertical Axis Rotations. (Exp. Brain Res, in press)*

Most vestibular-ocular tests are performed by either rotating subjects about an earth vertical axis, or by tilting them slowly to the left or right side. In the former case only the semicircular canals get stimulated, indicating rotatory movement, whereas the otolith input, indicating our orientation with respect to gravity, remains constant. In the latter case only the static otolith input changes, whereas the semicircular canals don't contribute to the oculomotor response. Not much is known about the effect of dynamic otolith input on our perception of orientation and movement in human subjects, and about the 3-dimensional eye movements elicited by such inputs.

To investigate the eye movement responses to dynamic otolith input and their interaction with signals from the semicircular canals, we rotated subjects about axes that were tilted by 15°, 30°, 60° or 90° with respect to the earth vertical. One of our main findings was that the 3-dimensional eye movements elicited by dynamic otolith input alone were much smaller than in either cats, monkeys, or rats, and did not adequately compensate for the body movement in space.

Since existing models of otolith-canal interaction could not account for our experimental findings at large angles of tilt, we tried to build a model that correctly predicts all our experimental results.

Thereby we started from a recent, successful model by Merfeld that is based on "optimal estimator theory" (Merfeld, 1995), and tries to incorporate all available vestibular information to re-construct our most likely orientation and movement in space. This model is based on the assumption that the CNS "knows" about the peripheral vestibular transfer functions. Thus the expected head velocity signal from the semicircular canals can be compared with an expected one, and the difference between the two can be used to adjust the estimated head velocity and thus the expected canal signal. Combining this model with changes that have been suggested for the otolith transfer function, we were able build a model that can reproduce all our experimental results.

5.3 Optimization

Published as: *D. Tweed, T. Haslwanter, and M. Fetter. Optimizing gaze control in three dimensions. Science 281 (5381):1363-1366, 1998.*

Many models about human movement control assume that the CNS tries to optimize certain parameters to determine the trajectory of the executed movement. Depending on the model, the optimized parameter can be the total energy, smoothness of the movement, distance in space etc. While no such model existed for the execution of combined eye-head-movements, another discussion arose in the oculomotor field on the underlying structure of the signals that control our eye movements: are they 2-dimensional, controlling only the direction of the line of sight? Or are they 3-dimensional, controlling the actual orientation of the eye? By studying the 3-dimensional trajectories of combined eye-head-movements, we were able to address both questions at the same time.

The answer to the question about the control structure of eye movement is relevant not only for oculomotor scientists who want to find out how the brain controls eye movements. It is also of interest for ophthalmologists, who have to correct for pathological defects of the orientation of the eye, and for psychologists who want to know how we use the retinal information from our two eyes to form a representation of the surrounding space.

Recent evidence had been in favor of the “2D-faction”. Single cell recordings in the superior colliculus, a midbrain structure immediately preceding the oculomotor neurons, indicated that at this stage the saccadic eye movement commands only contain information about the horizontal and vertical, but not about the torsional component (van Opstal et al., 1991). And recent findings about the anatomy of the extra-ocular muscles showed the existence of muscle-“pulleys”, structures that change the pulling directions of the extra-ocular muscles in such a way that a 2-dimensional eye movement command could explain all static eye positions (Demer et al., 1995; Raphan, 1998).

However, our experiments show unambiguously that the system has direct, active control about the torsional eye position. When we asked our subjects to perform combined torsional eye-head movements, the torsional eye-movement preceded the torsional head-movement on average by 40 ms. This confirms that the torsional eye position component is not a side-effect of the horizontal-vertical eye position command, but that it is actively controlled by the brain. This conclusion has since been confirmed by subsequent horizontal-torsional rotations of subjects, that proved that the vestibulo-ocular signal takes care of the non-commutativity of rotations (Tweed et al., 1999). The true answer to the “2D-3D”-question is therefore – as is often the case – somewhere in the middle: eye position control is inherently 3-dimensional, but in many cases a 2-dimensional control signal is sufficient to explain the observed eye position.

The results can be interpreted in terms of movement optimization: 3-dimensional eye positions can be explained for static and dynamic cases by assuming that eye position is optimized in the head for static head positions, while during the gaze shifts the path of the eye in space is optimized.

5.4 Rapid head impulses in healthy subjects

Published as: S. T. Aw, T. Haslwanter, G. M. Halmagyi, I. S. Curthoys, R. A. Yavor, and M. J. Todd. *Three-dimensional vector analysis of the human vestibuloocular reflex in response to high-acceleration head rotations I. Responses in normal subjects. J Neurophysiol 76:4009-4020, 1996.*

The standard clinical tests for the functional status of the vestibular system rely on the vestibulo-ocular responses to horizontal rotations on a turntable, and the eye movements elicited by caloric irrigation of the ear. Both these tests only investigate the low-frequency response, and only of the horizontal semicircular canals. On top of this structural selectivity, both tests have additional shortcomings: in the turntable test unilateral deficits can be masked by adapted responses from the other, healthy side. And weak responses to a caloric stimulus may be caused by bad thermal conductivity of the temporal bone, or by inaccurate irrigation of the tested ear.

All these shortcomings can be avoided by testing the balance system with short, rapid head movements. These *rapid head impulses* are quick (100 ms), high acceleration ($4000^\circ/s^2$) head movements that are elicited by passively turning the head of the subject.

We show that by executing not only horizontal head impulses, but also vertical and torsional ones it is possible to selectively stimulate each of the six semicircular canals. We also develop the analytical tools necessary to analyze the eye velocity responses elicited by 3-dimensional head movements.

Standard VOR tests only measure the horizontal movement component. If the spatial characteristics of the vestibulo-ocular responses are to be analyzed in three dimensions, it does not suffice to calculate only the magnitude of the elicited eye movement. Also the orientation of stimulus and response needs to be determined. Our data show that for horizontal, vertical, as well as for torsional head impulses the eye velocity response aligns well with the head velocity stimulus in healthy subjects. The gains are thereby close to ideal for the horizontal and vertical direction, but have a gain of only 0.7 for the torsional direction. We further show how the eye- and head-velocity traces can be used to determine the latency of the oculomotor responses. For all three directions the response latency lies about 10 ms.

6 APPLICATION OF 3-DIMENSIONAL ANALYSIS TECHNIQUES TO THE INVESTIGATION OF PATIENTS

The majority of vestibulo-ocular research is conducted in a clinical environment or surrounding, with the ultimate goal of applying the improved understanding of the physiology to a better diagnosis and treatment of patients. Pathologies of the central nervous system are sometimes hard to diagnose, since their effects on eye movements are often delicate and variable. But the direct and strong connections between the vestibular periphery and the oculomotor output facilitate the immediate diagnosis of peripheral vestibular deficits, since these deficits have distinct, observable consequences on eye movements elicited by vestibular stimulation. Therefore some of the tests presented below have already become standard tools in the diagnosis of dizzy patients.

6.1 Detecting functional deficits in a single semicircular canal

Published as: S. T. Aw, G. M. Halmagyi, T. Haslwanter, I. S. Curthoys, R. A. Yavor, and M. J. Todd. *Three-dimensional vector analysis of the human vestibuloocular reflex in response to high-acceleration head rotations II. Responses in subjects with unilateral vestibular loss and selective semicircular canal occlusion. J Neurophysiol 76:4021-4030, 1996.*

The peripheral vestibular system has an inherent asymmetry: while we are at rest, our peripheral vestibular nerves fire away with approximately 100 Hz. Stimulation of the peripheral vestibular nerves can increase the firing rate to several hundred Hz. Inhibition, however, can decrease the firing rate only down to zero. In this paper we describe how application of the *rapid head impulse test*, introduced in chapter 5.4, can use this asymmetry to localize functional deficits in single semicircular canals. For example, in a patient with a deficient *left* semicircular canal, a rapid head movement to the *right* drives up the firing rate of the right horizontal canal neurons, thereby eliciting an appropriate compensatory fast eye movement to the left. But a rotational head impulse to the left can only depress the firing rate of the left horizontal canal neurons down to zero, and the elicited eye movement won't even nearly compensate for the head movement. Thus the response to horizontal head impulses can be used to diagnose a functional deficit in the left or right horizontal semicircular canal. Similarly, vertical head impulses can reveal deficits in one of the vertical canals. To show this behavior for the horizontal,

anterior, and posterior canal, we measure the responses to head impulses in patients with a known unilateral vestibular deafferentation.

By testing patients with posterior canal occlusion we show that this test can localize a functional deficit even in a single semicircular canal. We also show that the eye movement responses lie in the plane of the stimulated canals, even if this elicits non-compensatory eye velocity components. For example, during a forward head movement both anterior canals get stimulated in a healthy subject. If the canal on one side is not responding, the magnitude of the eye velocity response is reduced. To find out if the side of the affected canal is on the right or left side, one needs to analyze the orientation of the eye velocity: since the eye velocity response lies in the plane of the remaining, working canal, the orientation of the 3-dimensional eye velocity clearly shows up the side of the pathology.

6.2 Detecting tumors on the cochleo-vestibular nerve

Published as: L. B. Minor, T. Haslwanter, D. Straumann, and D. S. Zee. Hyperventilation-induced nystagmus in patients with vestibular schwannoma. *Neurology* 53:2158-2167, 1999.

Even with modern imaging equipment small tumors on the cochleo-vestibular nerve can still be missed. Nevertheless, such tumors can cause dizziness or aural fullness, and can constitute a serious long-term threat to the patient. In this paper we show that small vestibulo-cochlear schwannoma can lead to distinct eye movement symptoms during *hyperventilation*. Hyperventilation is the repeated, rapid and deep inhalation and exhalation of air. It decreases CO₂ levels in the blood and the cerebro-spinal fluid, resulting in an increase in cerebro-spinal fluid pH and in a decrease in extracellular ionized Ca²⁺. If the tumor has caused partial demyelination of vestibular-nerve axons, thereby diminishing the spontaneous activity in these fibers, the spontaneous firing rate of these axons increases in the presence of diminished extracellular Ca²⁺, eliciting a sustained eye movement response.

Since such tumors typically only affect parts of the cochleo-vestibular nerve, the eye movements resulting from the nerve stimulation are directed predominantly along the orientations of the canals innervated by these nerve fibers. Projection of the eye velocity vector into the plane of the semicircular canals enabled us to predict the ampullary nerves that were excited as a result of hyperventilation. Therefore recording of 3-dimensional eye movements during hyperventilation can help to identify such tumors, and can be a valuable tool in the diagnosis of the dizzy patient.

6.3 Effects of cerebellar atrophy on multi-sensory integration

Published as: D. Anastasopoulos, T. Haslwanter, M. Fetter, and J. Dichgans. *Smooth pursuit eye movements and otolith-ocular responses are differently impaired in cerebellar ataxia. Brain 121 (Pt 8):1497-1505, 1998.*

The dominant projections of vestibular neurons go to oculomotor areas, down the spinal cord, and to the cerebellum. The functional role of the former two projections has been well investigated: the vestibular nuclei serve as the main relay center for the VOR, and the vestibulo-spinal pathways mediate postural responses which serve to keep us upright. Investigations of the role of the cerebellum in processing vestibular signals have concentrated on signals from the semicircular canals, and less is known about its importance for the processing of otolith signals. Recent studies in monkeys have shown that lesions in the vestibulocerebellum induce an increase in the horizontal velocity storage, while the horizontal velocity offset induced by *off-vertical axis rotation* (OVAR) is abolished (Angelaki and Hess, 1995). Since other studies have indicated significant differences in the processing of otolith signals between man and monkey (Angelaki and Hess, 1994a; Merfeld and Young, 1995; Fetter et al., 1996), we tested patients with cerebellar atrophy during smooth pursuit of a target and during rotations about off-vertical axis.

These experiments also allowed us to test another hypothesis: the responses of both the translational VOR, mediated by the otolith, and the pursuit system have been shown to be linearly dependent on the inverse of the viewing distance, so that a common central pathway for the two systems has been suggested, probably traveling through the cerebellum. Thus, the second aim of the study was to evaluate to what extent these reflexes are disturbed in cerebellar disease.

A small constant eye velocity component, which is directed opposite to the movement of the subject in space, is also missing in the patient group. This may reflect the fact that in patients the otolith signals cannot be utilized in computations thought to be important for spatial orientation mechanisms arising from the interaction of vestibular, visual and somatosensory signals. That finding corresponds to the findings in monkeys with cerebellar lesions (Angelaki and Hess, 1995).

As expected cerebellar patients also had a clearly degraded pursuit performance. At the same time, however, the response to linear accelerations during OVAR was enhanced. Since the amount of this enhancement did not correlate with the amount of pursuit impairment, degradation of smooth pursuit and pathological enhancement of otolith derived ocular responses seem to be independent effects of cerebellar degeneration. This indicates that the cerebellum may modulate the responses to otolith stimuli by direct inhibition.

7 VESTIBULAR STIMULATORS – AN OVERVIEW

The main function of the balance system is to indicate our movement and orientation in space, and to react accordingly. Therefore tests that investigate the balance system have to move the subject. Any movement can be decomposed into a linear and a rotatory movement component. As discussed above, these two types of movement are transduced by different areas of the vestibular system: the linear movements by the otoliths, and the rotatory movements by the semicircular canals.

A number of different devices have been constructed to move human subjects:

- a) Linear accelerators
- b) Centrifuges
- c) Postural platforms
- d) Rotators

Note that the vestibular system can also be stimulated selectively without moving the subject, for example by caloric stimulation (Fetter et al., 1998), by click-evoked stimulation of the otolith system (Colebatch et al., 1994), or by galvanic stimulation (Zink et al., 1998; Zink et al., 1997). While linear movements are by their nature restricted to relatively short periods of time, rotators and centrifuges can spin people for extended periods, and are therefore used more frequently. Since the majority of my work has involved rotators, I will discuss them in more detail below. For completeness, though, let me first give a short overview of a) - c).

7.1 Linear accelerators & Centrifuges

During a constant linear acceleration of a subject from a resting position with $acc \text{ } ^\circ/s^2$ for t seconds, the subject is translated by the distance $s = acc/2 * t^2$. Therefore linear accelerations can be delivered only for short durations, and most experiments on purely linear stimuli test the responses to linear oscillations (Baloh et al., 1988; Lathan et al., 1995). The eye movement responses to linear accelerations depend not only on the magnitude of the acceleration, but also on the viewing distance. For example, a translation by 10 cm requires a corrective eye movement of approximately 6° if the target is 1m away. If the target is at infinity (or just “very” far away), no eye movement at all is required to keep its image stable on the retina.

Centrifuges are an alternative way of delivering linear accelerations. While they have the disadvantage that the linear acceleration is combined with a simultaneous rotatory acceleration, they have the big advantage that they allow the delivery of linear stimuli for extended periods of time.

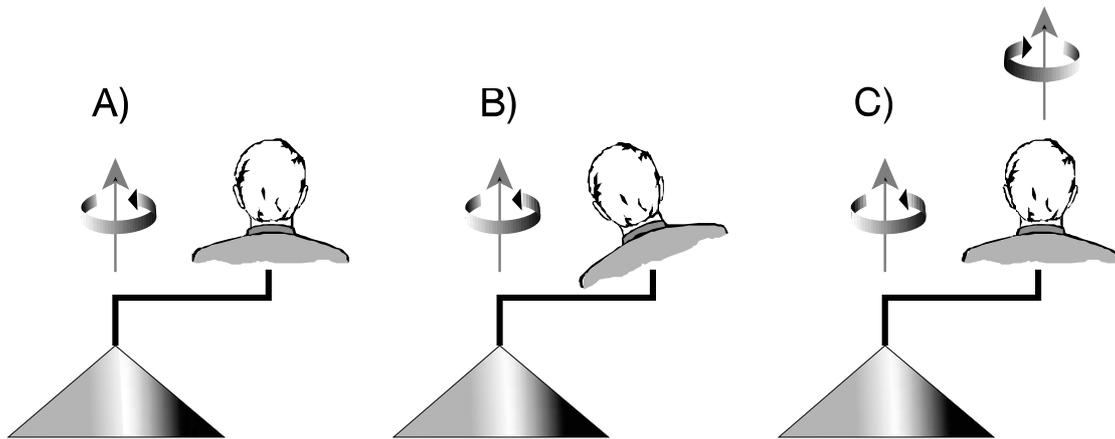


Figure 7-1 A) Fixed orientation centrifuge. B) Swinging centrifuge: the subject tilts such that the gravito-inertial force always points downward. C) Counter-rotation: the orientation of the subject stays constant with respect to space.

There are three types of centrifuges (Fig. 7-1):

- A) Fixed orientation: The orientation of the seat of the subject is fixed with respect to the arm of the centrifuge. This is the most common type of centrifuges.
- B) Swinging: The orientation of the seat always follows the gravito-inertial force, so that the combination of gravity and the centrifugal force always points “downward” as seen by the subject.
- C) Counter-rotation: A few experimental setups have a rotator out on the arm of the centrifuge. This allows, for example, to keep the orientation of the subject stable in space during the centrifugation, by spinning the eccentric rotator with the same speed but in the opposite direction as the centrifuge.

7.2 Postural Platforms

One function of the balance system is to keep us upright. This requires adequate postural responses when our center-of-mass is shifted as during translations. Such postural responses are mediated by the vestibulo-spinal pathways. *Posturography platforms* allow to translate or swivel the base on which the subject is standing. The response can be quantified in different ways:

Pressure platforms: The subject is standing on the posturography platform such that the center of gravity is exactly in the middle, and coincides with the intersection point of four equal *pressure pads*. From the pressure on each of those four pads, the forward/backward sway as well as the lateral sway of the subject can be determined.

Electro-myculogram (EMG): Muscle activity can be measured by recording the electrical activity of the nerve cells innervating the muscles. This gives accurate information on the activity of the muscles involved in the postural response. From the latency of these patterns important information can be obtained about clinically relevant parameters like nerve conduction velocity.

Video-based systems: Another way to quantify the response is to record the movement of the individual elements of the body of the subject with video-based systems. Currently the most advanced system is *Optotrak* (Northern Digital Inc., Waterloo, Ontario). It is based on active infrared markers that can be attached to the body, and can be tracked with a precision of 0.1 mm.

Advanced postural platforms allow small linear translations of the subject in all spatial directions, as well as rotations of the platform. Such a platform was recently installed at the Department of Neurology at the University Hospital in Freiburg. While the use of such platforms for medical diagnoses has decreased in importance, they are very valuable for investigations aiming for a better understanding of the perception of movement and on the elicited postural responses (Mergner and Rosemeier, 1998).

7.3 Rotators / Turntables

The most common devices to test the functional status of the vestibular system are rotators or “turntables”. Turntables that rotate a subject about an earth-vertical axis require less space than centrifuges or linear accelerators, and are regularly used for standard clinical tests.

The responses to rotations can be quantified by measuring:

- Eye movements
- Perceived orientation and movement in space
- Postural responses

Eye movements: In contrast to linear accelerators, an ideal response to a rotational movement is - to a first approximation - a rotation by the same amount in the opposite direction.² So if the head rotates by 10° to the right, the subject must rotate the eyes 10° to the left to keep the image of the target stable on the retina. This simple response pattern, together with the direct connections between the vestibular system and the oculomotor system, make eye movement responses by rotatory stimuli an ideal system to test for functional deficits of the balance system.

Perceived orientation & movement in space: Another measure to quantify responses to a rotation in space is to ask the subject to indicate the perceived orientation. This can involve

² If one takes the distance between the eyes into consideration, and the fact that the rotation axis cannot go exactly through the center of the two eyes, small corrections have to be applied (Crane et al., 1997).

- the orientation with respect to the starting position (“Indicate when you face in the opposite direction from your starting position”, (Stangl, 1997)).
- the orientation with respect to gravity, for rotations about axes that are *not* earth-vertical (“Indicate when you are oriented exactly horizontally”, (Anastasopoulos et al., 1997; Anastasopoulos et al., 1999)).

Postural responses: For safety reasons it is usually necessary to fixate subjects to the rotating device. Therefore only limited postural changes are possible, such as the movement on the head during rotations accelerations or decelerations.

7.3.1 One-dimensional

Most turntables are constructed such that they have one fixed, earth vertical axis of rotation. These turntables allow the investigation of the horizontal vestibulo-ocular responses. Since many pathologies, like vestibular neuritis or vestibular neuroma, affect the horizontal semicircular canals (Fetter and Dichgans, 1996; Minor et al., 1999b), such turntables have become a frequently used diagnostic tool.

7.3.2 Three-dimensional

Rotations about an earth-vertical axis, with the subject in the upright position, only test the responses of the horizontal semicircular canals, and the orientation of the subject with respect to gravity stays unchanged. To overcome these limitations, a few laboratories have built multi-axis turntables. The easiest way to obtain rotations about tilted axes is by putting a standard turntable on a platform that can be tilted.



Figure 7-2 Centrifuge / Turntable, Dept. of Psychology, Zürich

Due to mechanical limitations, such devices are limited typically to tilt angles up to 30° (Denise et al., 1988; Darlot et al., 1988; Furman et al., 1992). Other laboratories have built setups that allow to bring the subject in arbitrary static positions with respect to gravity (Mast and Jarchow, 1996). By restricting the movements to very low accelerations and velocities, it is possible to simplify the engineering tasks involved in constructing such a multi-axis centrifuge. For example, the turntable in Fig. 7-2, which is mounted out on the arm of a centrifuge, can rotate the subject about all three axes, but only at velocities up to $6.4^\circ/\text{s}$.

Only two laboratories, one in Tübingen (Germany), and one in Zürich (Switzerland) have constructed multi-axes turntables with motors that are strong enough to elicit significant dynamic vestibular responses. While at first sight a 3D turntable might appear to be a simple mechanical extension of a 1d turntable, the engineering requirements are daunting. Consider some of the construction requirements:

- The structure should contain a minimum amount of metal, since current eye movement recording systems are typically using magnetic field setups which can be influenced by larger amounts of metal in their vicinity.
- The signals from the turntable, sometimes only in the mV range, have to be transmitted through slip-rings. They must not be influenced by the signals and currents of the engines driving the turntable motors.
- The setup, which can weigh up to a few thousand kg, should be stable under the large centrifugal forces that occur during high-velocity rotations.

In the following I will concentrate on these two multi-axes turntables and describe them in more detail.

7.3.2.1 3D Turntable – Tübingen

The first fully three-dimensional rotator ever built for vestibular research is located at the Department of Neurology at the University Hospital in Tübingen (Koenig et al., 1996). It consists of two nested, fully motorized axes (see Fig. 7-3).

The outer axis is always earth-horizontal, and can accelerate with $205^\circ/\text{s}^2$ to velocities of up to $200^\circ/\text{s}$. The inner axis has a smaller dynamic load, and can perform accelerations of $395^\circ/\text{s}^2$ up to velocities of $500^\circ/\text{s}$.

Two non-motorized axes and an opaque sphere surrounding the seat to which the subject is fixated are nested inside the inner motorized axis. The outer of these two axes allows changing the orientation of sphere and subject manually in steps of 22.5° up to 90° . In the starting position this axis is oriented earth-horizontally. The second non-motorized axis allows swiveling the seat to which the subject is attached by up to 180° .

3-dimensional eye movements can be recorded with the dual search-coil technique. The magnetic field is generated by large magnetic field coils with a diameter of 1.4 m that are attached to the outside of the sphere. These large field coils have the advantage that the magnetic field has a large homogeneous area, which allows the recording not only of eye movements but also of large head movements.

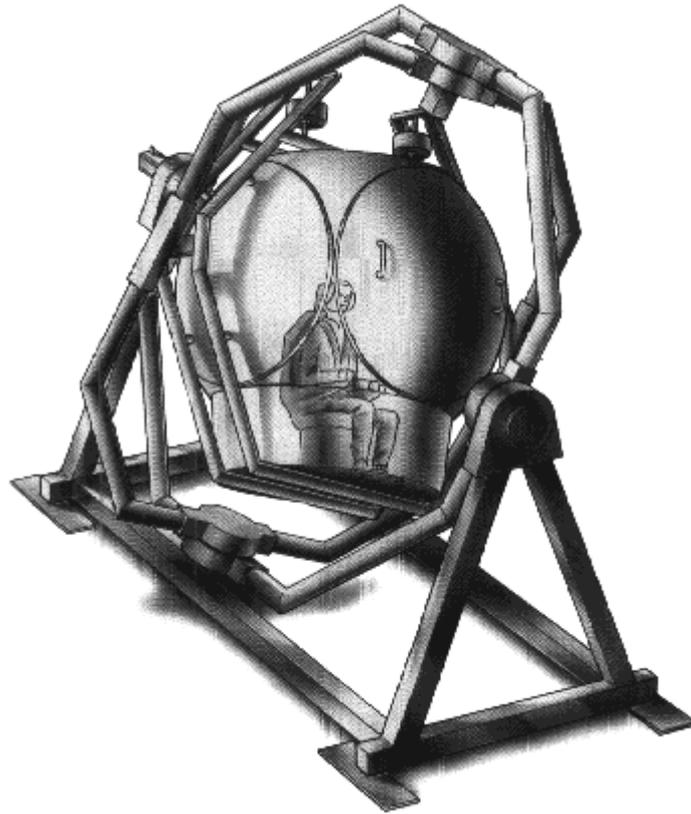


Figure 7-3 Turntable Tübingen

The sphere surrounding the subject eliminates any visual input during rotations of the subject, and also allows the projection of visual and optokinetic stimuli. The visual stimuli are generated by deflection of a laser beam, and the optokinetic stimulus by a small, planetarium-like device. Both setups are mounted just above the head of the subject. While the visual stimulus can be used very effectively, the effectiveness of the optokinetic stimulus is limited by the weak optokinetic responses in humans (Fetter et al., 1992). The uniform shape of the sphere also lends itself to experiments testing space perception, in healthy subjects as well as in patients with neurological (Anastasopoulos et al., 1997) or psychological (Karnath, 1994; Karnath and Fetter, 1995; Karnath et al., 1996) pathologies.

7.3.2.2 3D Turntable – Zürich

The second 3-dimensional turntable for vestibular tests has been installed at the Department of Neurology at the University Hospital in Zürich (Fig. 7-4). It has been constructed with the financial support of the Koetsier Foundation, the Swiss Department of Education, as well as the Department of Neurology of the University Hospital in Zürich.

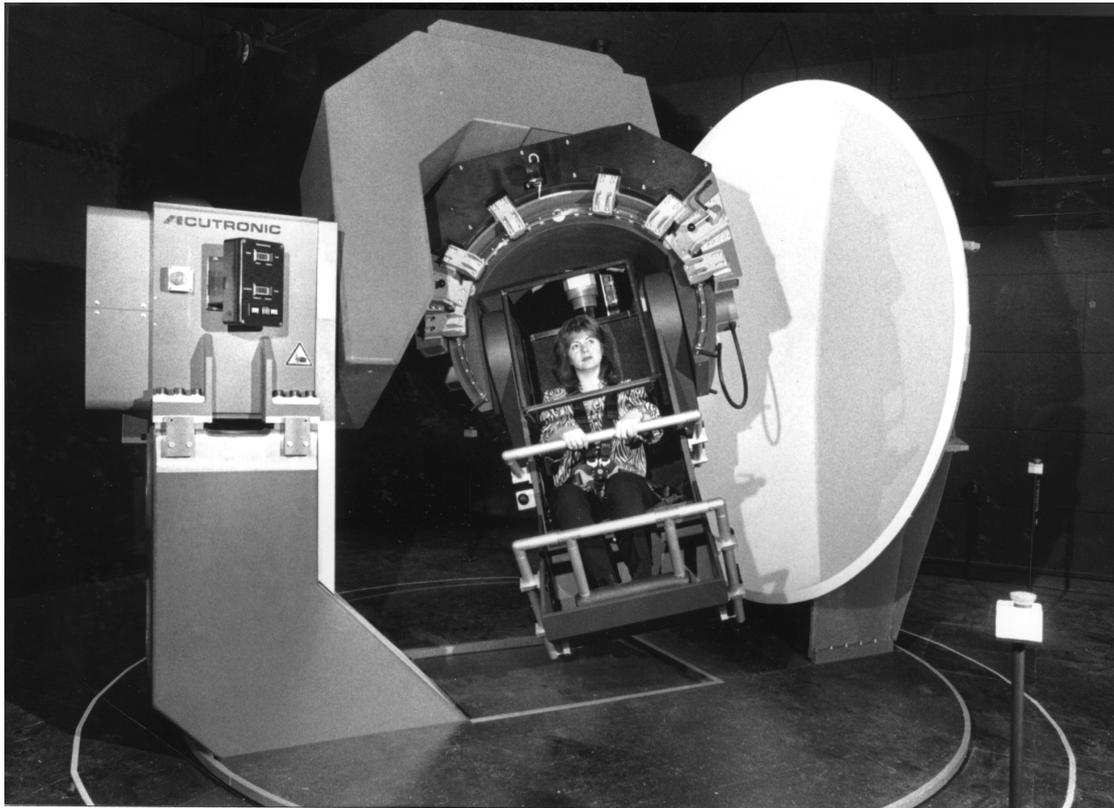


Figure 7-4 Turntable Zürich

In contrast to the turntable in Tübingen, this device has *three* servo-driven axes. The outer axis is earth vertical (shown by the round platform in Fig. 7-4), and the inner two axes are arranged like the ones on the Tübingen turntable. In addition the chair, which is mounted to the inner axis, can be brought in roll and pitch offset positions up to $\pm 30^\circ$. Despite the large weight of the rotating part (4'500 kg), the turntable in Zürich has a unique dynamic range (Table 7-1), and the additional motorized axes leads to more flexibility in the design of experiments. Despite the fact that the maximum velocities and accelerations do not significantly exceed the specifications of the Tübingen turntable, the use of a more advanced control system (*Acutrol*, by Acutronic, Switzerland) leads to a clear improvement in the performance.

	Inner Axis	Middle Axis	Outer Axis
Max. Velocity [°/s]	400	200	200
Max. Acceleration [°/s ²]	460	190	90

Table 7-1 Dynamic characteristics of the 3D turntable in Zürich

These accelerations allow high frequency oscillations of the subject. Figure 7-5 gives the maximum amplitudes for each axis as a function of the oscillation frequency.

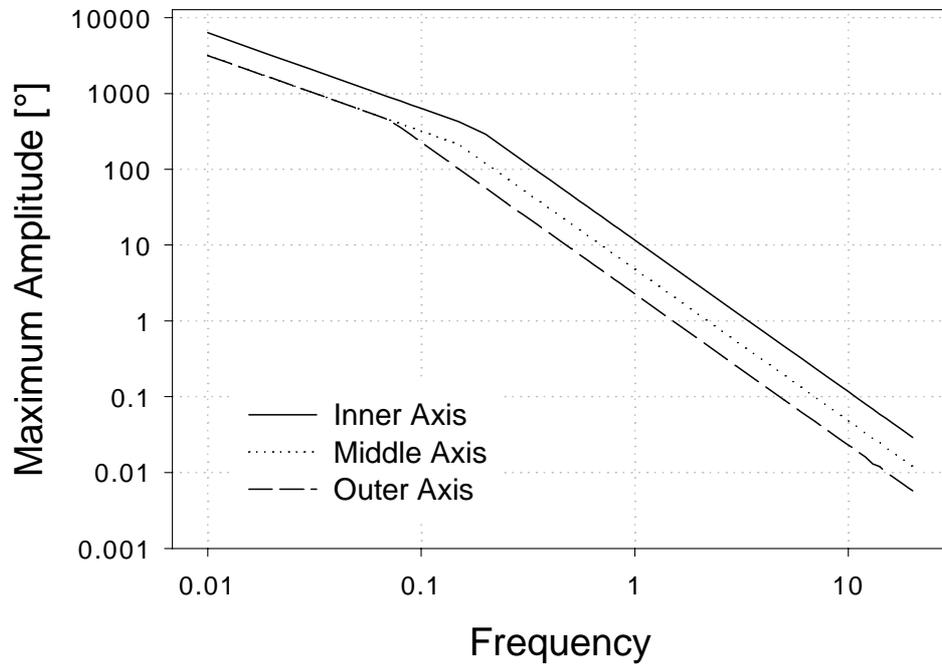


Figure 7-5 Dependence on oscillation frequency and amplitude on the 3D turntable in Zürich

To ensure that the head is not moving during the experiments, it is fixated by thermoplastic sheets that can be molded individually to the head of the subject (Fig. 7-6).



Figure 7-6 Head fixation

This technique for fixating the head has originally been devised to localize the head during radiation therapy, and has turned out to provide a comfortable and accurate head fixation during the experiments. Eye movements can be recorded with the dual search coil technique. The magnetic field is thereby generated by a square frame with a side length of 40 cm, that is aligned with the rotational center of the turntable. Eye movements can be generated by vestibular stimulation, or by projecting a visual stimulus on a spherical screen 1.5 m in front of the subject, with a diameter of 2.3 m. The laser and deflection mirrors for the visual stimulus display will be mounted on the inner axis of the turntable, just above the head of the subject.

The machine offers the option to mount an additional chair on the outer axis at a radius of 1.5 m (in place of the opto-kinetic screen). The maximum radial acceleration with that setup is 18.3 m/s^2 ($= 1.86 * g$).

7.4 Experiments on 3D turntables

7.4.1 Canal responses

Ideally, a turntable should permit to deliver two different types of stimuli:

- Stimuli that resemble naturally occurring movements as closely as possible.
- Selected, controlled stimulations of individual parts of the balance system, that lead to a better understandings of the workings of the system.

7.4.1.1 Naturally occurring movements

3D VOR WITH A HIGHER FREQUENCIES

Natural head movements have surprisingly large dynamics. During walking or running, for example, the head bobs up and down with a frequency of up to 2.7 Hz (peak frequency), which provides a high frequency stimulus to the otolith system (Viirre et al., 1997). And natural head turns are executed with rotatory accelerations up to $3000^\circ/\text{s}^2$ and velocities up to $400^\circ/\text{s}$ (Thurtell et al., 1999), strong stimuli for the semicircular canals. Due to technical limitations, however, investigations have concentrated on low frequencies, focusing on the function of the horizontal semicircular canals. The only set of experiments that tested the VOR in all three dimensions was restricted to accelerations of $70^\circ/\text{s}^2$, and to oscillations of 0.3 Hz (Tweed et al., 1994a; Tweed et al., 1994b). The *Zürich Turntable* (ZTT) constitutes the ideal device to test the horizontal, vertical, and torsional VOR closer to its natural working range. Interesting results can be expected, since the three components of eye movements (horizontal, vertical, and torsional) are not equivalent: horizontal movements (left/right) are symmetrical. Vertical movements show a natural up/down asymmetry. And while horizontal and vertical eye movements shift the gaze direction (i.e. the line of sight), torsional eye movements

(clockwise / counterclockwise) do not change the location of the target point. Therefore an extension of sinusoidal oscillations to higher frequencies can be expected to give us a better understanding of the extent and dynamic behavior of these asymmetries.

EYE-HEAD MOVEMENTS

Almost all tests of the VOR are conducted with the head fixed. This situation is not encountered in everyday life, where our head is free to compensate for movements of the body in space. Because of negligible inertia of the eye and the considerable inertia of the head, it can be expected that in real life the head contributes significantly to the compensation of slow movements, but only little to fast head movements. If that is the case, the control system underlying combined eye-head responses has to take this fact into considerations. Using the ZTT, it is possible to investigate this effect, not only for horizontal, but also for vertical and torsional movements.

7.4.1.2 Selected stimulation of the balance system

PHARMACOLOGICAL DIFFERENCES OF THE SCCS

The horizontal, anterior, and posterior SCCs differ not only in their orientation. They also use different neuro-transmitters to deliver their signals to the EOMs. This is the underlying reason for the up-beat nystagmus elicited by large doses of nicotine (Sibony et al., 1987): the anterior canals, which cause slow downward eye movements when stimulated, are affected differently than the posterior canals, which cause downward eye movements. Also the intake of larger quantities of alcohol induces a centrally generated up-beat nystagmus (Fetter et al., 1999).

The ZTT can be used to measure the gain of eye movements elicited by pitching subjects forward or backward, i.e. movements that stimulate the anterior and posterior canals separately. This allows a selective testing of the pharmacological effect of substances on the central nervous system.

RESPONSES TO CALORIC STIMULATION

The diagnosis of the functional status of the SCCs often relies on the results of *caloric testing*. This test induces a unilateral stimulation of the semicircular canals by generating a temperature gradient in the temporal bone (Gentine et al., 1991; Gentine et al., 1990). Despite the widespread use of this test, the underlying physiological mechanisms of this stimulus are still only poorly understood.

Using a 3D turntable it is possible to bring the subject in any orientation with respect to gravity during the caloric stimulation of the balance system. As Aw et al. have shown, this can be used to achieve a better understanding of this important medical test (Aw et al., 1998). The research by Aw has been looking at the unilateral contribution of the individual canals. It is not yet understood how the canals on the stimulated and non-stimulated side interact. A better understanding would put the caloric test on solid scientific ground.

CARDINAL AXES OF THE VOR

The VOR does not respond symmetrically to rotations about different axes. While horizontal and vertical head movements – which result in a displacement of the line-of-sight - have a gain of up to one, the gain of torsional rotations is significantly smaller (Tweed et al., 1994b). Until recently it has been assumed that the torsional direction is parallel to the primary position. But recent experiments on the ZTT have revealed that this is not the case. By extending this study to find the directions of maximum and minimum gain, it would be possible to determine accurately the geometric properties of vestibular elicited eye movement responses in three dimensions.

7.4.1.3 Pathologies

PATHOLOGIES WHICH AFFECT ONLY PART OF THE BALANCE SYSTEM

Some diseases target only a small, specific part of the balance system. In chapter 6.2, for example, I have shown how tumors can affect dominantly the horizontal and anterior semicircular canals. Another example is *benign paroxysmal positional vertigo*, or BPPV. Fetter et al. have used their 3D turntable to find out about the characteristics of posterior SCC BPPV, the most common form of BPPV (Fetter and Sievering, 1995). More interesting is horizontal canal BPPV, which occurs much more rarely (Nuti et al., 1996): the SCCs are not exactly orthogonal, and it is currently not understood how CNS resolves this non-orthogonality. Two alternatives are possible: a stimulation of one single canal could elicit eye movements that lie exactly in the plane of that canal. In that case the non-orthogonality of the canals would have to be compensated by interactions of the left and right vestibular system. Or stimulation of a single canal could elicit eye movements that do *not* lie in the plane of that canal, but have a slightly different orientation to compensate for the non-orthogonality of the canals. While this deviation is only small for the posterior canal (8 °), it is much more prominent for the horizontal canal (21 °), and recordings in patients affected by this horizontal canal BPPV could answer that question.

CANALS AFFECTED BY MENIERE'S DISEASE

Meniere's disease is one of the most frequent otological problems. But a lack of understanding of its exact origin and effects has hampered the development of efficient treatments. Neither surgical approaches nor treatment with medication have a high success rate. To understand the origin of Meniere's disease, researchers have been working with animal models in Guinea pigs (Kimura, 1967). Such studies should be complemented by an investigation of the exact effects of this disease. Using a 3D turntable, Fetter et al have shown that BPPV affects only one of the six semicircular canals (Fetter and Sievering, 1995). Similar techniques could be applied to test if all parts of the balance system are affected equally, or if the disease is more disturbing to some canals than to others.

EFFECTS OF CEREBELLAR ATROPHY ON CANAL RESPONSES

It is well known that the cerebellum has a strong influence on the processing of vestibular responses. For example, removal of the cerebellar nodulus and uvula makes it impossible for the subject to use dynamic otolith cues to determine the movement in space. This has been demonstrated with controlled cerebellar lesions in monkeys (Angelaki and Hess, 1994b; Angelaki and Hess, 1995), as well as with tests of human subjects with cerebellar atrophy (Anastasopoulos et al., 1998). It is also known that cerebellar atrophy leads to an instability of the vertical eye movements (Boehmer and Straumann, 1998). However, nothing is known about the VOR deficits of patients with cerebellar atrophy in 3 dimensions. A better understanding of these deficits might allow a more focused physiotherapy of such patients, and enable them to make better use of their remaining vestibular function.

7.4.2 Otolith-canal interactions

The ZTT permits two types of combined otolith-canal stimulation. In the standard configuration with the subject sitting at the center of the rotations, the otoliths are stimulated by their changing orientation with respect to gravity. This setup permits the investigation of a number of interesting paradigms. As described above (7.3.2.2), it is also possible to use the ZTT as a fixed-orientation centrifuge. That setup allows to investigate the interaction of otolith responses with stimulation of the semicircular canals.

7.4.2.1 Off-vertical axis rotation

Off-vertical axis rotation (OVAR) stimulates canals and otoliths simultaneously during the initial phase of the rotation. In the steady state a purely dynamic otolith stimulus remains. Surprisingly, the responses of humans and monkeys to such a stimulus show dramatic differences in their gain: while monkeys are able to use the dynamic otolith input to reconstruct their movement in space, humans are not able to do so. This conclusion is not yet accepted by the scientific community and often challenged. In chapter 5.2 we have developed a model that suggests an explanation for this discrepancy. One prediction of this model is a dependence of the horizontal eye velocity modulation on the target distance, while the vertical and torsional eye movement components should stay unaffected. Using the ZTT it will be possible to test this prediction.

7.4.2.2 Pitch-while-rotating

While natural head movements combine otolith and canal input, little is known about the dynamics of this interaction. The ZTT is the only existing device that allows to pitch a subject about the earth-horizontal inter-aural axis, while at the same time rotating the whole setup about an earth-vertical axis. This stimulus, called *pitch-while-rotating* (PWR), combines a dynamic stimulation of the SCCs with a dynamic stimulation of the otoliths. Due to the geometry of this stimulation, the relative stimulation of

each of the three canals (horizontal / anterior / posterior) strongly depends on the experimental parameters, such as speed of rotation, amplitude, and frequency of pitching. This allows a comprehensive investigation of otolith-canal interaction.

7.4.2.3 Pharmacology of nausea suppressants

PWR offers one of those stimulus combinations where the signals from the otoliths and the individual canals do not agree with each other. Such *conflict stimuli* are highly nauseogenic in nature, and can be used to induce *motion sickness* in a controlled way. Outside vestibular laboratories motion sickness effects can appear under different conditions:

- Car-sickness
- Sea-sickness
- Space-motion syndrome (about 50% of all astronauts feel violently ill during the first few days in space)

The ability to generate motion sickness in a controlled way opens the door to aimed investigations of pharmaceutical substances that suppress nausea. The combination of such tests with eye movement recordings also allows an objective quantification of the effects of those substances on brainstem reflexes mediating vestibulo-ocular responses. Such tests might allow us to measure the effects of the pharmaceutical substances on the alertness of the subject.

7.4.2.4 Multi-axis rotations

The three motorized axes of the ZTT permit paradigms in which many SCCs are stimulated simultaneously. When a subject is rotated about an earth-vertical axis for more than one minute, the feeling of rotation vanishes and the subject feels stationary in space. Pitching or rolling the subject, while the rotation continues, stimulates the SCCs in a complex way such that they do not indicate the pitching movement alone, but a complicated “tumbling” movement in space. With conventional one-axis turntables it has not been possible to investigate such complicated stimuli, and it is not known how the CNS interprets the resulting activation pattern of canals and otoliths.

7.4.2.5 Centrifugation

The ZTT can act as a centrifuge when a chair is positioned 1.5 m from the center of the outer rotation axis. Thereby the large power of the motors allows accelerations of up to $90^\circ/s^2$. To test the dynamics of otoliths-canal interactions, subjects can be oscillated in different orientations. From investigations to velocity steps on centrifuges, it is known that the responses to velocity steps depend strongly and non-linearly on the orientation of the subject on the centrifuge (Curthoys et al., 1999; Curthoys et al., 1998). Understanding the dynamics of this otolith-canal interaction might elucidate the underlying physiological processes.

7.4.3 Purely otolith responses

The ZTT also allows to bring subjects into different positions with respect to gravity and keep him there. This elementary function permits the test of the effects of gravity on *Listing's Plane*. Listing's Plane is an organizational principle that reduces the number of degrees of freedom of spontaneous eye movements from three to two (Haslwanter, 1992). It has been shown in monkeys that the orientation and location of this plane is not stationary, but depends on the orientation of the monkey in space: a roll tilt of the monkey shifts the plane forward or backward, whereas a pitch tilt of the monkey leads to a "counter-pitching" of that plane (Haslwanter et al., 1990). So far the response has been assumed to be similar in human subjects. In light of the different reactions between humans and monkeys to combined otolith-canal simulations, this hypothesis needs to be tested. Investigations by other groups that have looked at the effect of tilt onto the properties of 3-dimensional eye positions have been restricted to smaller tilt angles (Klier and Crawford, 1998). The ZTT with its setup to record 3-dimensional eye movements is an ideal device for such a test.

7.4.4 Psychophysical experiments

One of the tasks of the vestibular system is to keep us from falling over. This requires that we have a good perception of our orientation with respect to gravity. By incorporating a setup option that allows subjects to actively control their movement with the chair, the ZTT can be used to investigate the space perception. One current project by T. Jarchow, D. Straumann and myself uses the ZTT to measure the contribution of extra-vestibular information to the perception of the subjective horizontal. Thereby healthy subjects, as well as paraplegic subjects with the spinal cord dissection at different locations, are asked to position themselves horizontally, once while the turntable is stationary and once while the turntable is rotating with 100°/s. Since the head is in the center of the rotation, the rotation should affect only extra-vestibular somatosensory inputs, and different responses between the subject groups would indicate the role of extra-vestibular information for our space perception.

Similar tests can be performed with subjects who suffer from bilateral vestibular loss due to ototoxic medication. By testing the contribution of non-vestibular inputs we can determine how well other sensory inputs can replace a complete loss of vestibular function.

Another interesting subject group is patients who have suffered from a stroke. Currently the functional contribution of the different cortical areas involved in the processing of vestibular signals is unclear (Brandt and Dieterich, 1999). By asking stroke subjects to orient themselves upright and/or horizontal on the ZTT, we can investigate the effect of an insult in the regions affected by the stroke on our perception of space.

7.4.5 Visual-vestibular interaction

The vestibular system is not a “stand-alone” part of the central nervous system, but strongly interacts with information coming from other sensory inputs. Especially the visual input is tightly integrated with the vestibular input: Waespe and Henn have shown that optokinetic stimulation directly excites cells in the vestibular nucleus (Waespe and Henn, 1979). This effect explains the strong feeling of movement when looking from a stationary train onto another train close by that starts to move.

The ZTT is not optimized for large field visual input. This can be circumvented, however, by asking subjects to wear magnifying glasses or inverting prisms for some time before the experiment. Changing the visual input that corresponds to head movements changes the VOR gain (Bloomberg et al., 1991; Melvill et al., 1988). If the subjects are then tested in complete darkness, several interesting questions can be addressed:

- Do horizontal inverting prisms change the gain of the vertical VOR?
- How does the gain change in the left and right eye in subjects with unilateral vestibular deficits?
- How does a combination of visual and vestibular inputs alter the perception of movement?

Alternatively, a large field visual input could perhaps be obtained by virtual reality displays.

BILATERAL VESTIBULAR LOSS

Diseases of the auto-immune system, like Cogan’s syndrome, can lead to a bilateral loss of the vestibular function. Nevertheless, such patients still show a VOR gain between 0.1 and 0.2 (Bohndorf et al., 1996). Using the ZTT it would be possible to test if the VOR gain of such patients can be increased. This could perhaps be achieved by exposing them to sinusoidal oscillations about different axes while the light is turned on. This “learning” of a simple paradigm could conceivably lead to a more efficient use of the remaining vestibular input, resulting in an increase of the VOR gain in everyday life.

VISUAL-VESTIBULAR DOUBLE STEP EXPERIMENTS

In a static situation, fast eye movements or *saccades* are performed very stereotypically. An eye movement to a flashed target is always executed by a rotation about a fixed axis, with predictable dynamic characteristics (“saccadic main sequence”, (Becker, 1988)). In everyday life, however, the head is rarely static, and targets have to be visually acquired while the head is moving. With the ZTT this situation could be investigated experimentally, by abruptly decelerating a subject from a continuous rotation with a constant velocity, and presenting visual targets as soon as the subject has come to a stop.

7.4.6 Studies without vestibular input

The recording system for 3-dimensional eye movements can also be used for interesting studies that do *not* require any vestibular stimulation.

SPONTANEOUS NYSTAGMUS AFTER VESTIBULAR NEURITIS

In the acute stage of vestibular neuritis, the function of the horizontal and anterior canals on the affected side is abruptly abolished. Over the course of a few weeks or months, the patient adjusts to this new situation and learns to use the remaining vestibular input to determine his movement in space. By studying the time development of the recovery, we could gain an insight into the learning processes that occur in the central nervous system during that period of adaptation. The learning process could be studied by observing the spontaneous nystagmus that patients show immediately after the onset of the vestibular neuritis. The asymmetry between horizontal/vertical eye movements on the one side and torsional eye movements on the other side should be reflected in the recovery of the patients: while horizontal and vertical nystagmus components affect the gaze direction and therefore lead to a shift of the target on the retina, the torsional components to not change our line of sight. It would be interesting to observe how this asymmetry affects the recovery after the acute stage of the neuritis.

By repositioning the subject during the acute stage of the neuritis, it would also be possible to test the effect of the neuritis on otolith-canal interactions.

8 CONCLUSIONS

Over the last ten years recording and analysis techniques for the investigation of 3D eye- and head-movements have come of age, and are now widely applied in research. This development has considerably improved our understanding of vestibular stimulation, oculomotor control, and how we orient ourselves in space. We also have been able to use this understanding to significantly improve the diagnosis of dizzy patients, sometimes with very simple and easily understandable tests. But the standard technology for recording 3-dimensional eye movements, the scleral search coil technique, is still only suitable for research-oriented environments. To bring the full benefit of our improved understanding of the vestibulo-ocular system to the patient, the development of video-based systems has to go one step further to achieve the necessary accuracy and reliability. In many closely related areas of research, like ophthalmology, the measurement and analysis techniques for 3D recordings are only beginning to get used. I hope that the developments described in this manuscript can establish a solid basis on which this new research can build to improve our understanding of movements in space, in healthy subjects and in patients.

Acknowledgements

I want to thank Dr. K. Hepp, who initially lured me into this exciting field, and later who has given me the opportunity to come back to Zürich as a post-doctoral researcher. He knows when to put me under pressure - without him this “Habilitation” would have been in the writing for much longer. Dr. K. Hess, for organizing research funds and providing a supportive environment for multi-disciplinary research. Dr. D. Straumann, for his comments on early draft of the manuscript – I am lucky to be able to work with such a competent and congenial researcher and doctor. The Koetser Foundation, who provides generous funding to the Dept. of Neurology, and also contributed significantly to the construction of the *Human 3D turntable* here in Zürich. My wife Jean – nobody else would have been willing to move with me all over the globe, just to get back to where we started. Finally to the late Dr. Volker Henn, who built up the laboratory, also masterminding the *Human 3D turntable*, and who gave me a wonderful introduction and start into the field.

Conclusions

9 REFERENCES

- Anastasio TJ (1992) Simulating vestibular compensation using recurrent back-propagation. *Biol Cybern* 66: 389-397
- Anastasio TJ, Bower (1992) Recurrent backpropagation models of vestibulo-ocular reflex provide experimentally testable predictions. In: Eeckman (ed) *Computation and Neural Systems*.
- Anastasopoulos D, Bronstein A, Haslwanter T, Fetter M, and Dichgans J (1999) The role of somatosensory input for the perception of verticality. *Ann N Y Acad Sci* 871: 379-383
- Anastasopoulos D, Haslwanter T, Bronstein A, Fetter M, and Dichgans J (1997) Dissociation between the perception of body verticality and the visual vertical in acute peripheral vestibular disorder in humans. *Neurosci Lett* 233: 151-153
- Anastasopoulos D, Haslwanter T, Fetter M, and Dichgans J (1998) Smooth pursuit eye movements and otolith-ocular responses are differently impaired in cerebellar ataxia. *Brain* 121 (Pt 8): 1497-1505
- Angelaki DE (1992) Spatio-temporal convergence (STC) in otolith neurons. *Biol Cybern* 67: 83-96
- Angelaki DE, Bush GA, and Perachio AA (1993) Two-dimensional spatiotemporal coding of linear acceleration in vestibular nuclei neurons. *J Neurosci* 13: 1403-1417
- Angelaki DE, and Hess BJ (1994a) Inertial representation of angular motion in the vestibular system of rhesus monkeys. I. Vestibuloocular reflex. *Neurophysiology* 71: 1222-1249
- Angelaki DE, and Hess BJ (1994b) The cerebellar nodulus and ventral uvula control the torsional vestibulo-ocular reflex. *J Neurophysiol* 72: 1443-1447
- Angelaki DE, and Hess BJ (1995) Lesion of the nodulus and ventral uvula abolish steady-state off-vertical axis otolith response. *J Neurophysiol* 73: 1716-1720
- Angelaki DE, and Hess BJ (1996) Three-dimensional organization of otolith-ocular reflexes in rhesus monkeys. I. Linear acceleration responses during off-vertical axis rotation. *J Neurophysiol* 75: 2405-2424
- Aw ST, Haslwanter T, Fetter M, Heimberger J, and Todd MJ (1998) Contribution of the vertical semicircular canals to the caloric nystagmus. *Acta Otolaryngol (Stockh)* 118: 618-627
- Baloh RW, Beykirch K, Honrubia V, and Yee RD (1988) Eye Movements Induced by Linear Acceleration on a Parallel Swing. *J Neurophysiol* 60: 2000-2013
- Bartl K, Siebold C, Glasauer S, Helmchen C, and Buettner U (1996) A simplified calibration method for three dimensional eye movement recordings using search coils. *Vision Res* 36: 997-1006
- Bechert K, and Koenig E (1996) A search coil system with automatic field stabilization, calibration, and geometric processing for eye movement recording in humans. *Neuro-ophthalmology* 16: 163-170
- Becker W (1988) Metrics. In: Wurtz, Goldberg J (eds) *The neurobiology of saccadic eye movements*. Elsevier Science Publishers BV, pp 13-67
- Bloomberg J, Melvill JG, and Segal B (1991) Adaptive plasticity in the gaze stabilizing synergy of slow and saccadic eye movements. *Exp Brain Res* 84: 35-46
- Boehmer A, and Straumann D (1998) Pathomechanism of mammalian downbeat nystagmus due to cerebellar lesion: a simple hypothesis. *Neurosci Lett* 250: 127-130
- Bohndorf M, Baykal HE, Plinkert PK, and Pleyer U (1996) Acoustic, vestibular and ophthalmologic findings and treatments in six patients with cogan's syndrome. *HNO* 44: 302-306
- Brandt T, and Dieterich M (1999) The vestibular cortex. Its locations, functions, and disorders. *Ann.N.Y.Acad.Sci.* 871: 293-312

References

- Bush GA, Perachio AA, and Angelaki DE (1993) Encoding of head acceleration in vestibular neurons I. Spatiotemporal response properties to linear acceleration. *J Neurophysiol* 69: 2039-2055
- Carpenter RS (1988) *Movements of the Eyes*. Pion Ltd, London,
- Cartwright AD, and Curthoys IS (1996) A neural network simulation of the vestibular system: implications on the role of intervestibular nuclear coupling during vestibular compensation. *Biol Cybern* 75: 485-493
- Clarke AH, and Krzok W (1996) Using smart sensor technology for high-speed, high-resolution eye movement measurements. *Suppl J Vest Res* 6:
- Colebatch JG, Halmagyi GM, and Skuse NF (1994) Myogenic potentials generated by a click-evoked vestibulocollic reflex. *J Neurol Neurosurg Psychiat* 57: 190-197
- Collewijn H, van der Mark F, and Jansen TC (1975) Precise recording of human eye movements. *Vision Res* 15: 447-450
- Collewijn H, Van der Steen J, Ferman L, and Jansen TC (1985) Human ocular counterroll: assessment of static and dynamic properties from electromagnetic scleral coil recordings. *Exp Brain Res* 59: 185-196
- Crane BT, Viirre ES, and Demer JL (1997) The human horizontal vestibulo-ocular reflex during combined linear and angular acceleration. *Exp Brain Res* 114: 304-320
- Curthoys IS, Halmagyi GM, Haslwanter T, Burgess AM, Black RA, and Topple A (1999) Human three dimensional eye movements in response to interaural linear acceleration during off center yaw rotation on a centrifuge. *Archives Italiennes de Biologie* 137: 44-45
- Curthoys IS, Haslwanter T, Black RA, Burgess AM, Halmagyi GM, Topple AN, and Todd MJ (1998) Off-center yaw rotation: effect of naso-occipital linear acceleration on the nystagmus response of normal human subjects and patients after unilateral vestibular loss. *Exp Brain Res* 123: 425-438
- Darlot C, Denise P, Droulez J, Cohen B, and Berthoz A (1988) Eye movements induced by off-vertical axis rotation (OVAR) at small angles of tilt. *Exp Brain Res* 73: 91-105
- Demer JL, Miller JM, Poukens V, Vinters HV, and Glasgow BJ (1995) Evidence for fibromuscular pulleys of the recti extraocular muscles. *Invest Ophthalmol Vis Sci* 36: 1125-1136
- Denise P, Darlot C, Droulez J, Cohen B, and Berthoz A (1988) Motion perception induced by off-vertical axis rotation (OVAR) at small angles of tilt. *Exp Brain Res* 73: 106-114
- Diamond SG, Markham CH, Simpson NE, and Curthoys IS (1979) Binocular counterrolling in humans during dynamic rotation. *Acta Otolaryngol* 87: 490-498
- Donders FC (1848) Beitrag zur Lehre von den Bewegungen des menschlichen Auges. *Hollaend Beitr Annal Physiol Wiss* 1: 104-145
- Eccles JC (1976) From electrical to chemical transmission in the central nervous system. *Notes Rec.R.Soc.Lond.* 30: 219-230
- Enright JT (1980) Ocular translation and cyclotorsion due to changes in fixation distance. *Vision Res* 20: 595-601
- Enright JT (1998) Estimating peak velocity of rapid eye movements from video recordings. *Behavior Res Meth & Instr* 30: 349-353
- Fernandez C, and Goldberg JM (1971) Physiology of Peripheral Neurons Innervating Semicircular Canals of the Squirrel Monkey. II. Response to Sinusoidal Stimulation and Dynamics of Peripheral Vestibular System. *J Neurophysiol* 34: 661-675
- Fetter M, Aw ST, Haslwanter T, Heimberger J, and Dichgans J (1998) Three-dimensional eye movement analysis during caloric stimulation used to test vertical semicircular canal function. *The American Journal of Otology* 19: 180-187
- Fetter M, and Dichgans J (1996) Vestibular neuritis spares the inferior division of the vestibular nerve. *Brain* 119: 755-763

References

- Fetter M, and Haslwanter T (1999) 3D eye movements--basics and clinical applications. *J Vestib Res* 9: 181-187
- Fetter M, Haslwanter T, Bork M, and Dichgans J (1999) New insights into positional alcohol nystagmus using three-dimensional eye-movement analysis. *Ann Neurol* 45: 216-223
- Fetter M, Heimberger J, Black RA, Hermann W, Sievering F, and Dichgans J (1996) Otolith-semicircular canal interaction during postrotatory nystagmus in humans. *Exp Brain Res* 108: 463-472
- Fetter M, and Sievering F (1995) Three-dimensional eye movement analysis in benign paroxysmal positioning vertigo and nystagmus. *Acta Otolaryngol* 115: 353-357
- Fetter M, Tweed D, Misslisch H, Fischer D, Koenig E (1992) Multidimensional descriptions of the optokinetic and vestibulo-ocular reflexes. In: Anonymous *Annals New York Academy of Sciences*. pp 841-842
- Fry GA, and Hill WW (1962) The center of rotation of the eye. *Am J of Optom and Arch Am Acad Optom* 390: 581-595
- Fuchs AF, Scudder CA, and Kaneko CR (1988) Discharge patterns and recruitment order of identified motoneurons and internuclear neurons in the monkey abducens nucleus. *J Neurophysiol* 60: 1874-1895
- Furman JM, Schor RH, and Schumann TL (1992) Off-vertical axis rotation: a test of the otolith-ocular reflex. *Ann ORL* 101: 643-650
- Gentine A, Eichhorn JL, Kopp C, and Conraux C (1990) Modelling the action of caloric stimulation of the vestibule I. The hydrostatic model. *Acta Otolaryngol* 110: 328-333
- Gentine A, Eichhorn JL, Kopp C, and Conraux C (1991) Modelling the action of caloric stimulation of the vestibule II. The mechanical model of the semi-circular canal considered as an inflatable structure. *Acta Otolaryngol* 111: -10
- Golgi C (1906) The neuron doctrine - Theory and facts. In: Anonymous *Nobel Lectures: Physiology or Medicine, 1901-1921*. Elsevier, 1967, Amsterdam, pp 189-217
- Groen E, Bos JE, Nacken PF, and de GB (1996) Determination of ocular torsion by means of automatic pattern recognition. *IEEE Trans Biomed Eng* 43: 471-479
- Grossman GE, Leigh RJ, Abel LA, Lanska DJ, and Thurston SE (1988) Frequency and velocity of rotational head perturbations during locomotion. *Exp Brain Res* 70: 470-476
- Guillemant P, Ulmer E, and Freyss G (1995) 3-D eye movement measurements on four Comex's divers using video CCD cameras, during high pressure diving. *Acta Otolaryngol. Suppl (Stockh)* 520 Pt 2: 288-292
- Guldin WO, and Gruesser OJ (1998) Is there a vestibular cortex? *Trends Neurosci* 21: 254-259
- Günther M (1997) Computersimulationen zur Synthetisierung des muskulär erzeugten menschlichen Gehens unter Verwendung eines biomechanischen Mehrkörpermodells. (PhD Thesis, Natural Sciences, Physik, Eberhard-Karls-Universität Tübingen)
- Hamilton WR (1899) *Elements of Quaternions*. Cambridge University Press, Cambridge,
- Hardy M (1934) Observations on the innervation of the macula sacculi in man. *Anatomical Record* 59: 403-418
- Haslwanter T (1992) Listing's law as an organizational principle for eye-, head-, and arm-movements. (Dr. rer. nat. Thesis, Physics, ETH Zurich, Switzerland)
- Haslwanter T (1995) Mathematics of Three-Dimensional Eye Rotations. *Vision Res* 35: 1727-1739
- Haslwanter T (1997) Measurement and analysis techniques for 3d eye-movements. In: Fetter M, Haslwanter T, Misslisch H, Tweed D (eds) *Three-dimensional kinematic principles of eye-, head-, and limb movements*. Harwood Academic Publishers,
- Haslwanter T, Curthoys IS, Halmagyi GM, Black RA, Topple AN, and Todd MJ (1995) Torsional Eye Velocity Components During Yaw Angular Acceleration Identify the Side of Unilateral Vestibular Deafferentation. *Acta Otolaryngol Suppl* 520: 62-64

References

- Haslwanter T, and Moore ST (1995) A Theoretical Analysis of Three-Dimensional Eye Position Measurement Using Polar Cross-Correlation. *IEEE Trans Biomed Eng* 42: 1053-1061
- Haslwanter T, Straumann D, Henn V, Hess BJ (1990) Effects of static torsion on Listing's plane in the monkey. In: AnonymousEurop J Neurosci. pp 163
- Hatamian M, and Anderson DJ (1983) Design considerations for a real-time ocular counterroll instrument. *IEEE Trans Biomed Eng* 30: 278-288
- Haustein W (1989) Considerations on Listing's Law and the primary position by means of a matrix description of eye position control. *Biol Cybern* 60: 411-420
- Helmholtz H (1867) *Handbuch der physiologischen Optik*. Voss, Leipzig,
- Hess BJ, and Angelaki DE (1993) Lesion of the cerebellar nodulus and the ventral uvula modify three-dimensional vestibulo-ocular and optokinetic reflexes. *Soc.Neurosci.Abstr.* 1593
- Karnath HO (1994) Subjective body orientation in neglect and the interactive contribution of neck muscle proprioception and vestibular stimulation. *Brain* 117: 1001-1012
- Karnath HO, and Fetter M (1995) Ocular space exploration in the dark and its relation to subjective and objective body orientation in neglect patients with parietal lesions. *Neuropsychologia* 33: 371-377
- Karnath HO, Fetter M, and Dichgans J (1996) Ocular exploration of space as a function of neck proprioceptive and vestibular input - observations in normal subjects and patients with spatial neglect after parietal lesions. *Exp Brain Res* 109: 333-342
- Kaspar H, and Hess BJ (1991) Magnetic Search Coil System for Linear Detection of three-dimensional angular movements. *IEEE Trans Biomed Eng Electron*: 466-475
- Katz E, Vianney de Jong JM, Buettner-Ennever JA, and Cohen B (1991) Effects of midline section on the velocity storage and the vestibulo-ocular reflex. *Exp Brain Res* 87: 505-529
- Kimura RS (1967) Experimental blockage of the endolymphatic duct and sac and its effect on the inner ear of the guinea pig. A study on endolymphatic hydrops. *Ann.Otol.Rhinol.Laryngol.* 76: 664-687
- Klier EM, and Crawford DJ (1998) The human oculomotor system accounts for 3-d eye orientation in the visual-motor transformation for saccades. *J Neurophysiol*
- Koenig E, Westermann H, Jaeger K, Sell G, Bechert K, Fetter M, and Dichgans J (1996) A new multi-axis rotating chair for oculomotor and vestibular function testing in humans. *Neuro-ophthalmology* 16: 157-162
- Kopula J (1996) Modeling eye rotations using eccentric rotation axes for calibration of video-based eye movement measurement. (Diploma Thesis, TU Berlin)
- Lathan CE, Wall II, and Harris LR (1995) Human eye movement response to z-axis linear acceleration: the effect of varying the phase relationships between visual and vestibular inputs. *Exp Brain Res* 103: 256-266
- Le Grand Y (1980) *Physiological optics*. Springer, Berlin,
- Leigh RJ, Robinson DA, and Zee DS (1981) A hypothetical explanation for periodic alternating nystagmus: Instability in the optokinetic-vestibular system. *Ann NY Acad Sci* 619-635
- Lewis RF, and Zee DS (1993) Ocular motor disorders associated with cerebellar lesions: Pathophysiology and topical localization. *Rev Neurol (Paris)* 149: 665-677
- Mach E (1875) *Grundlinien der Lehre von den Bewegungsempfindungen*. Engelmann, Leipzig,
- Maier M (1987) *Anatomische Rekonstruktion der Macula-Epithel*.
- Mast F, and Jarchow T (1996) Perceived body position and the visual horizontal. *Brain Res.Bulletin* 40: 393-398
- Melvill JG, Guitton D, and Berthoz A (1988) Changing patterns of eye-head coordination during 6 h of optically reversed vision. *Exp.Brain Res* 69: 531-544

References

- Merfeld D (1995) Modeling human vestibular responses during eccentric rotation and off vertical axis rotation. *Acta Otolaryngol* 520: 354-359
- Merfeld DM, and Young LR (1995) The vestibulo-ocular reflex of the squirrel monkey during eccentric rotation and roll tilt. *Exp Brain Res* 106: 111-122
- Mergner T, and Rosemeier T (1998) Interaction of vestibular, somatosensory and visual signals for postural control and motion perception under terrestrial and microgravity conditions--a conceptual model. *Brain Res Brain Res Rev* 28: 118-135
- Mhoon EE, Bernstein LP, and Towle VL (1997) Saccular influence on the otolith-spinal reflex and posture during sudden falls of the cat. *Am.J Otol.* 18: 86-92
- Minor LB (2000) Superior canal dehiscence syndrome. *Am.J Otol.* 21: 9-19
- Minor LB, Haslwanter T, Straumann D, and Zee DS (1999b) Hyperventilation-induced nystagmus in patients with vestibular schwannoma. *Neurology* 53: 2158-2167
- Minor LB, Lasker DM, Backous DD, and Hullar TE (1999a) Horizontal vestibuloocular reflex evoked by high-acceleration rotations in the squirrel monkey. I. Normal responses. *J.Neurophysiol.* 82: 1254-1270
- Mittelstaedt H (1995) Evidence of somatic graviception from new and classical investigations. *Acta Otolaryngol Suppl* 520 Pt 1: 186-187
- Moore ST, Haslwanter T, Curthoys IS, and Smith ST (1996) A geometric basis for measurement of three-dimensional eye position using image processing. *Vision Res* 36: 445-459
- Nakayama K (1974) Photographic determination of the rotational state of the eye using matrices. *Am J Optom & Physiol Optics* 51: 736-742
- Naufal PM, and Schuknecht HF (1970) Vestibular, facial, and oculomotor neuropathy in diabetes mellitus. *Arch Otolaryngol* 96: 468-474
- Nuti D, Vannucchi P, and Pagnini P (1996) Benign paroxysmal positional vertigo of the horizontal canal: a form of canalolithiasis with variable clinical features. *J Vestib Res* 6: 173-184
- Ohm J (1928) Die Hebelnystagmographie. *Gradfies Arch Ophthal* 120: 235-252
- Peterka RJ, and Merfeld DM (1996) Calibration techniques for video-oculography. *J Vestib Res* 6: S75
- Probst-Mueller E, Straumann D, Scherberger H, Henn V (1996) Primary eye position and the orientation of Listing's Plane is independent from stereotaxic head coordinates. In: Anonymous Soc Neurosci Abstr. pp 2033
- Rambold H, Churchland A, Selig Y, Jasmin L, and Lisberger SG (1999) Partial Ablation of Floccular Complex Causes Linked Deficits in Motor Learning in the VOR and Smooth Pursuit Eye Movements. (Conference Proceeding)
- Ramon y Cajal S (1892) A new concept of the histology of the central nervous system. In: Anonymous Hafner, 1977, New York, pp 7-29
- Raphan T (1998) Modeling control of eye orientation in three dimensions. I. Role of muscle pulleys in determining saccadic trajectory. *J.Neurophysiol.* 79: 2653-2667
- Raphan T, Matsuo V, and Cohen B (1979) Velocity storage in the vestibulo-ocular reflex arc (VOR). *Exp Brain Res* 35: 229-248
- Robinson DA (1963) A method of measuring eye movement using a scleral search coil in a magnetic field. *IEEE Trans Biomed Eng* 10: 137-145
- Robinson DA (1964) The mechanics of human saccadic eye movement. *J Physiol* 174: 245-264
- Robinson DA (1965) The Mechanics of Human Smooth Pursuit Eye Movement. *J Physiol* 180: 569-591
- Rodrigues O (1840) Des lois géométriques qui régissent les déplacements d'un système solide dans l'espace, et de la variation des coordonnées provenant de ses déplacements considérés indépendamment des causes qui peuvent les produire. *J de Mathématiques Pures et Appliquées* 5: 380-440

References

- Schreiber K (1999) Erstellung und Optimierung von Algorithmen zur Messung von Augenbewegungen mittels Vido-Okulographie-Methoden. (Diploma Thesis, Physics, Eberhard-karls-Universität Tübingen)
- Sibony PA, Evinger C, and Manning KA (1987) Tobacco-induced primary-position upbeat nystagmus. *Ann.Neurol.* 21: 53-58
- Spoendlin H, and Schrott A (1990) Quantitative evaluation of the human coclear nerve. *Acta Otolaryngol (Stockh)* 470: 61-70
- Stangl W (1997) Räumlich-dynamische Präzision des vestibulo-okulären Reflexes und der Raum-Zeit-Wahrnehmung bei sportartspezifischen Gruppen. (Dr. phil. Thesis, Univ. Stuttgart)
- Straumann D, Haslwanter T, Hepp-Reymond MC, and Hepp K (1991) Listing's law for eye, head and arm movements and their synergistic control. *Exp Brain Res* 86: 209-216
- Sung, K. and Reschke, M. F. A model-based approach for the measurement of eye movements using image processing. NASA. 97. NASA Technical Paper 3680.
- Tabak S, Collewijn H, Boumans LJ, and Van der Steen FA (1997) Gain and delay of human vestibulo-ocular reflexes to oscillation and steps of the head by reactive torque helmet I. Normal subjects. *Acta Otolaryngol* 117: 785-795
- Thalmeier T (1999) Weiterentwicklung einer Vorrichtung zur Messung von Augenbewegungen in der Medizin. (Dipl.Ing. Thesis, Fachhochschule München, Fachbereich 06, Feinwerktechnik und Mikrotechnik / Physikalische Technik)
- Thurtell MJ, Black RA, Halmagyi GM, Curthoys IS, and Aw ST (1999) Vertical eye position-dependence of the human vestibuloocular reflex during passive and active yaw head rotations. *J.Neurophysiol.* 81: 2415-2428
- Tweed D, Fetter M, Sievering D, Misslisch H, and Koenig E (1994a) Rotational kinematics of the human vestibuloocular reflex II. Velocity steps. *J Neurophysiol* 72: 2480-2489
- Tweed D, Haslwanter T, and Fetter M (1998) Optimizing gaze control in three dimensions. *Science* 281: 1363-1366
- Tweed D, Sievering D, Misslisch H, Fetter M, Zee D, and Koenig E (1994b) Rotational kinematics of the human vestibuloocular reflex I. Gain matrices. *J Neurophysiol* 72: 2467-2479
- Tweed D, and Vilis T (1987) Implications of rotational kinematics for the oculomotor system in three dimensions. *J Neurophysiol* 58: 832-849
- Tweed DB, Haslwanter TP, Happe V, and Fetter M (1999) Non-commutativity in the brain. *Nature* 399: 261-263
- Van der Glas M, Bosman J, de Jong I, Bovendeerd PHM, van Campen DH, and Kingma H (1999) Real time data processing with the video eyetracker. (Conference Proceeding)
- van Opstal AJ, Hepp K, Hess BJ, Straumann D, and Henn V (1991) Two- rather than three-dimensional representation of saccades in monkey superior colliculus. *Science* 252: 1313-1315
- Viirre E, Demer JL, Haslwanter T, Misslisch H, Tweed D (1997) Head and eye in three dimensions during standing, walking and running. In: Fetter M (ed) Three-dimensional kinematics of eye, head and limb movements. Harwood Academic Publishers, Amsterdam, pp 217-223
- Waespe W, Cohen B, and Raphan T (1985) Dynamic modification of the vestibulo-ocular reflex by the nodulus and uvula. *Science* 228: 199-202
- Waespe W, and Henn V (1977) Neuronal activity in the vestibular nuclei of the alert monkey during vestibular and optokinetic stimulation. *Exp Brain Res* 27: 523-538
- Waespe W, and Henn V (1979) The Velocity Response of Vestibular Nucleus Neurons During Vestibular, Visual, and Combined Angular Acceleration. *Exp Brain Res* 37: 337-347
- Wyatt HJ (1995) The form of the human pupil. *Vision Res* 35: 2021-2036
- Yardley L (1990) Contribution of somatosensory information to perception of the visual vertical with body tilt and rotating visual field. *Perception & Psychophysics* 48: 131-134

References

- Young LR, Collins CC, Hyde JE (1971) Pursuit eye tracking movements. In: Bach (ed) Control of eye movements. Academic Press, New York, pp 429-513
- Young LR, and Oman CM (1969) Model for vestibular adaptation to horizontal rotation. *Aerosp Med* 40: 1076-1080
- Young LR, and Sheena D (1975) Methods & Designs: Survey of eye movement recording methods. *Behavior Res Meth & Instr* 7: 397-429
- Zee DS, Yamazaki A, Butler PH, and Gucer G (1981) Effects of Ablation of Flocculus and Paraflocculus on Eye Movements in Primate. *J Neurophysiol* 46: 878-899
- Zhu D (1997) Video-Based Approach For Tracking Eye Orientation In Three Dimensions. (PhD Thesis, Graduate School of The City University of New York)
- Zhu D, Moore ST, and Raphan T (1999) Robust pupil center detection using a curvature algorithm. *Comput.Methods Programs Biomed.* 59: 145-157
- Zink R, Bucher SF, Weiss A, Brandt T, and Dieterich M (1998) Effects of galvanic vestibular stimulation on otolithic and semicircular canal eye movements and perceived vertical. *Electroencephalogr.Clin Neurophysiol.* 107: 200-205
- Zink R, Steddin S, Weiss A, Brandt T, and Dieterich M (1997) Galvanic vestibular stimulation in humans: effects on otolith function in roll. *Neurosci.Lett.* 232: 171-174

References

10 APPENDIX

10.1 Curriculum Vitae

Date of Birth: May 2, 1964
Nationality: Austrian

Education

ETH (Swiss Federal Institute of Technology), Inst. for Theoretical Physics. Zürich, Switzerland.
Doctoral Degree in Physics („Doctor rerum naturarum”) with thesis entitled *Listing's law as an organizational principle for eye-, head-, and arm-movements*.
Graduated February 1992.

University of Innsbruck, Dept. of Theoretical Physics. Innsbruck, Austria.
Undergraduate Degree in Physics („Magister rerum naturarum”) with thesis entitled *Two-photon excitation of Rydberg-states close to the ionization threshold*.
Graduated with honors, March 1988.

Humanistic Gymnasium. Hall / Tirol, Austria.
Graduated with honors, June 1982.

Work experience

ETH, Inst. for Theoretical Physics & Univ. of Zürich, Dept. of Neurology. Zürich, Switzerland.
Senior postdoctoral fellow. Tutorials for physics lectures. Experimental investigation and theoretical modeling of the vestibular system.
February 1999 – present.

DLR (Deutsche Weltraumagentur). Munich, Germany.
Scientific adviser for the development of a video-based eye-tracking device for the *ISS* (International Space Station).
1998 – present.

University Hospital Tübingen, Dept. of Neurology. Tübingen, Germany.
Scientific Investigator. Introduction of new diagnostic procedures for testing of vestibular patients. Investigation of interaction of otolith system and semicircular canals in the generation of compensatory eye movements. Supervision of doctoral theses in physics and medicine.
August 1995 – December 1998.

University of Sydney, Dept. of Psychology. Sydney, Australia.
NH&MRC Research Officer. Design and implementation of the first accurate video-system for the recording of 3-dimensional eye movements. Investigation of the effects of vestibular deafferentation on oculomotor control during combined angular and linear accelerations (in collaboration with the Neuro-otology Department, Royal Prince Alfred Hospital).
October 1992 - April 1995.

University of Zürich, Dept. of Neurology. Zürich, Switzerland.
Research assistant. Investigation of the effects of vestibular stimulation on the control of 3-dimensional eye movements in monkeys. Application of control principles of eye-movements to head- and arm-movements in humans.
January 1990 - August 1992.

ETH Zürich, Inst. of Quantum Optics. Zürich, Switzerland.
Teaching and research assistant. Tutorials for physics lectures. Development of Monte Carlo simulation program to evaluate laser-atom interaction. Electronic stabilization of diode laser systems.
October 1988 - December 1989.

Appendix

10.2 List of Publications Included

1. T. Haslwanter. *Mathematics of Three-Dimensional Eye Rotations*. Vision Res 35:1727-1739, 1995.
2. T. Haslwanter and S. T. Moore. *A Theoretical Analysis of Three-Dimensional Eye Position Measurement Using Polar Cross-Correlation*. IEEE Trans Biomed Eng 42:1053-1061, 1995
3. T. Haslwanter and L. B. Minor. *Nystagmus induced by circular head shaking in normal human subjects*. Exp.Brain Res. 124 (1):25-32, 1999.
4. T. Haslwanter, R. Jaeger, S. Mayr, M. Fetter. *Otolith-Canal Interaction During Off-Vertical Axis Rotations*. (Exp. Brain Res, in press)
5. D. Tweed, T. Haslwanter, and M. Fetter. *Optimizing gaze control in three dimensions*. Science 281 (5381):1363-1366, 1998.
6. S. T. Aw, T. Haslwanter, G. M. Halmagyi, I. S. Curthoys, R. A. Yavor, and M. J. Todd. *Three-dimensional vector analysis of the human vestibuloocular reflex in response to high-acceleration head rotations I. Responses in normal subjects*. J Neurophysiol 76:4009-4020, 1996.
7. S. T. Aw, G. M. Halmagyi, T. Haslwanter, I. S. Curthoys, R. A. Yavor, and M. J. Todd. *Three-dimensional vector analysis of the human vestibuloocular reflex in response to high-acceleration head rotations II. Responses in subjects with unilateral vestibular loss and selective semicircular canal occlusion*. J Neurophysiol 76:4021-4030, 1996.
8. L. B. Minor, T. Haslwanter, D. Straumann, and D. S. Zee. *Hyperventilation-induced nystagmus in patients with vestibular schwannoma*. Neurology 53:2158-2167, 1999.
9. D. Anastasopoulos, T. Haslwanter, M. Fetter, and J. Dichgans. *Smooth pursuit eye movements and otolith-ocular responses are differently impaired in cerebellar ataxia*. Brain 121 (Pt 8):1497-1505, 1998.

Appendix

10.3 Abbreviations

3D	3-Dimensional
BPPV	Benign Paroxysmal Positional Vertigo
CCD	Charge Coupled Device
CMOS	Complementary Metal Oxide Semiconductor
CNS	Central Nervous System
CT	Computer Tomography
DOF	Degrees Of Freedom
EMG	Electro-Musculogram
EOG	Electro-Oculography
EOM	ExtraOcular Muscle
FOV	Field Of View
FPGA	Field Programmable Gate Array
Hz	Hertz
IR	Infrared
LED	Light Emitting Diode
MRI	Magnetic Resonance Imaging
NTSC	National Television Standards Committee (American format for television)
OVAR	Off-Vertical Axis Rotation
PAL	Phase Alternation Line-rate (European format for television)
PC	Personal Computer
PET	Positron Emission Tomography
PWR	Pitch-While-Rotating
SCC	SemiCircular Canal
VCR	VideoCassette Recorder
VOG	Video-OculoGraphy
VOR	Vestibulo-Ocular Reflex
ZTT	Zürich TurnTable

Appendix