The Human Oculomotor System

A clinical, physiological and methodological study of voluntary eye movements

ELINA ISOTALO

HELSINKI 1999

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Academic dissertation

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CONTENTS

ABBREVIATIONS

ABR	= auditory brain stem response
AICA	= anterior inferior cerebellar artery
ANOVA	= analysis of variance
CNS	= central nervous system
CPA	= cerebello-pontine angle
CT	= computerized tomography
DLPN	= dorsolateral pontine nucleus
EEG	= electroencephalography
EMG	= electromyography
ENG	= electronystagmography (including caloric test, saccades, pursuit and different nystagmus tests)
EOG	= electro-oculography
FEF	= frontal eye field
GA	= gain by amplitude
Gd-DTPA	= the gadolinium product used in MRIs with gadolinium enhancement
GLM	= general linear model
HAB	= hemangioblastoma
IO	= inferior olive
IROG	= infra-red oculography
LED	= light emitting diode
MOG	= magneto-oculography, the electromagnetic search coil technique
MRI	= magnetic resonance imaging
NF2	= neurofibromatosis type 2
PICA	= posterior inferior cerebellar artery
PEM	= pursuit eye movement
PPRF	= paramedian pontine reticular formation
PRPEM	= pseudo-random pursuit eye movement
PTA	= pure tone average
riMLF	= rostral interstitial nucleus of medial longitudinal fasciculus
SA	= saccadic accuracy
SD	= standard deviation
SPV	= saccadic peak velocity
SRT	= saccadic reaction time
VOG	= video-oculography

1. INTRODUCTION

Vertigo, dizziness, disequilibrium and loss of balance are common complaints of vestibular system disorders. The vestibular system controls spatial orientation and upright stance. Its symptoms can be peripheral in origin, affecting the vestibular end organ or nerve, or it may be central in origin, affecting the pathways traversing in multiple locations of the central nervous system (CNS).

Saccades are fast eye movements that are used when gazing at different objects, scanning the horizon, or when bringing targets of interest onto the fovea. Their function is to move the eyes so that a new target of interest will be seen on the fovea. Pursuit eye movements (PEMs) are slow eye movements used to monitor a moving target constantly by utilizing a negative visual feedback (Robinson 1965; Robinson 1981; Pyykkö and Schalén 1982; Leigh and Zee 1983b). The velocity of PEMs matches the velocity of a target of interest. Vision remains clear throughout the movement, and the image of the moving object is attended and kept on the fovea. The trajectories of voluntary eye movements travel commonly through the same neural circuitries as those of the central vestibular system (Gilman et al. 1981; Ito 1984). Disorders of the vestibular system can also affect the oculomotor system.

Disorders causing vertigo can be vascular (Fisher 1967), inflammatory (Jackson and Nissen 1993), autoimmunologic (McCabe 1979), traumatic (Rubin et al. 1993), iatrogenic (Goodhill and Harris 1993; Rubin et al. 1993), metabolic (Rubin et al. 1993), or can be caused by neoplasms of the cerebello-pontine angle, or other parts of posterior fossa (Wennmo 1982; Nedzelski 1983; Constans et al. 1986; Selesnick and Jackler 1992; Selesnick et al. 1993; Resche et al. 1993; Jackler 1994). In many instances, the oculomotor tests can be used to reveal the site of the lesion.

This study focuses on the accuracy of voluntary eye movements to reveal certain diseases affecting the peripheral or central vestibular system and the central oculomotor system. Because voluntary eye movements are used to exclude central causes of vertigo, it is important to know the discriminatory power of voluntary eye movement deficits in certain lesions. Methodological and physiological aspects and the vulnerability of the oculomotor system are also studied. This work focuses only on the horizontal saccadic eye movements and PEMs.

2. REVIEW OF THE LITERATURE

2. A. *Anatomical and physiological aspects of voluntary eye movements in primates*

2. A. 1. Saccadic eye movements

The programming of the saccades consists of a pulse and a step (Robinson 1964; Optican and Robinson 1980; Optican et al. 1986; Robinson et al. 1990). To create the needed change in neural activity (determined by step) for the new eye position (Westheimer 1954a), a saccadic velocity and metric command (determined by pulse) is generated in the reticular formation (Luschei and Fuchs 1972; Keller 1974; Hoyt and Frisen 1975; Henn and Cohen 1976; Hepp and Henn 1983). The frequency and duration of the neural discharge (controlled by pulse) determine the velocity and duration of a saccade, and determine the amplitude of a saccade (Optican and Robinson 1980). Thus, the pulse command is used to move the eye to a new position (Robinson 1964; Robinson 1970; Optican and Robinson 1980; Robinson 1981; Fuchs et al. 1985), while the step command is responsible for maintaining the eyes at the new position (Robinson 1964; Robinson 1970; Fuchs and Luschei 1970; Schiller 1970; Optican and Robinson 1980; Robinson 1981; Fuchs et al. 1985). After the saccade, a new steady-state firing frequency is achieved (Robinson 1964; Robinson 1970; Fuchs and Luschei 1970; Schiller 1970; Optican and Robinson 1980; Robinson 1981; Fuchs et al. 1985). The pulse command is related to the number of spikes in burst neurons of paramedian pontine reticular formation (PPRF) (Henn and Cohen 1976; Hepp and Henn 1983). The step change command is related to the so-called tonic neurons in PPRF (Keller 1974). According to Becker and Fuchs (1969), saccadic eye movements, in general, exhibit highly reproducible trajectories.

A glissade is the final process where the eye finally slides to the predetermined position (Robinson 1964; Fuchs and Luschei 1970). It occurs when the pulse is too small or too large for the demanded amplitude change. This causes the saccade to be hypo- or hyper-metric and to glide (Weber and Daroff 1971; Weber and Daroff 1972; Optican and Robinson 1980). Bilateral ablations of the flocculi and portions of paraflocculi severely impair the mechanism that suppresses the glissade, and flocculectomized animals also fail to adapt to optically imposed post-saccadic slip (Optican et al. 1980; Optican et al. 1986). It seems that the flocculus and/or paraflocculus are necessary for the successful suppression of the glissade (Optican et al. 1986).

According to Zee et al. (1976a), normal saccades may be produced by a neural network that computes a position in the orbit to which the eye is driven, rather than a distance the eye is moved. The brain is known to be capable of making saccades to a head coordinate system when there is no retinal error (Zee et al. 1976a). Target position in space (i.e., target position with respect to the head) can be calculated by adding eye positions in the orbit to retinal error (Zee et al. 1976a). Normal saccades may not necessarily be ballistic or preprogrammed, but only seem to be such because of high velocities and brief durations (Zee et al. 1976a). It appears that the cerebellum, and particularly the vermis, participates in the modulation of the amplitude of saccades (Zee et al. 1976b). In order to make accurate saccades, the brain must compute the position of the target of interest with respect to the position of the head in space (Zee et al. 1976a). The degree and magnitude of saccade dysmetria may depend upon the initial position of the eye in the orbit (Zee et al. 1976b). It seems that the miscalculation causing dysmetria operates on both retinal error and its visual recall, which is why dysmetria probably occurs in lesions of immediate pre-motor circuits of the CNS (Zee et al. 1976b).

A visual position error signal is used to elicit the oculomotor response, and this signal can be stored for about 350 ms (Becker and Fuchs 1969). The estimation of visual error is concluded about 75-100 ms before the execution of a saccade (Wheeless et al. 1966; Becker and Fuchs 1969). According to Wheeless et al. (1966), the eye has a 32% chance of altering its response if the target change occurs 85 ms before a saccade. If the target change occurs 185 ms before the saccade, the eye has a 75-80% chance to alter its response (Wheeless et al. 1966). In some instances, the saccades can be interrupted or can be generated with short saccadic reaction times (SRTs) (Fischer and Boch 1983). The distribution of SRT in monkeys has been found to have a first peak at about 70 ms and a second peak at about 140ms. The first peak was called "express saccades" and the second peak was thought to be "regular" saccades (Fischer and Boch 1983).

Express saccades have also been found in humans, with the SRT of about 100 ms (Fischer and Ramsperger 1984). According to Kalesnykas and Hallet (1987), the express saccades have an SRT of 110-160 ms and the anticipatory saccades have an SRT of <110 ms. In their studies, the combination of directional errors and amplitude errors provided a definition of what an anticipatory saccade and a visually-guided saccade is in any given subject (Kalesnykas and Hallet 1987).

Saccades larger than 15° are usually hypometric, consisting of a primary hypometric saccade and a corrective saccade addition (Becker and Fuchs 1969). In saccades, there is a presaccadic drift, typically attributed to expectation (Lemij and Collewijn 1989). The presaccadic drift varies from 0.4 to 1.5°, and it is in the direction of the next target position, prior to movement of the target (Lemij and Collewijn 1989).

Bahill et al. (1975b), demonstrated that about 70% of horizontal saccadic eye movements of 0 - 20º amplitude in normal control subjects have dynamic overshoot, and that 5% of these horizontal saccades have dynamic undershoot. The eye has

overshoot when it travels beyond its final position and then returns to the opposite direction, and the dynamic overshoot is the most common of the overshoot types (Bahill et al. 1975b). Dynamic overshoot occurs when a primary saccade is followed by a smaller rapid saccade in the opposite direction, with no delay (Bahill et al. 1975a). Dynamic overshoot is 0.15-0.5º on average (Bahill et al. 1975b; Kapoula et al. 1986). The saccadic commands to each eye must, to some extent, be different, because the dynamic overshoot in one eye is seen in normal subjects (Kapoula et al. 1986).

About models of saccadic eye movements

According to Westheimer (1954b), the saccadic system was ballistic. He found that the saccadic system could react to only one stimulus at a time, and there was a refractory period after the first, during which a second saccade could not be initiated.

According to Young and Stark (1963), the type of behavior seen in Westheimer's experiments could be considered as a sampled data system. The visual information (retinal error) is sampled, then the size, direction and duration of the upcoming saccade is calculated, and a decision to make a saccade is made (Young and Stark 1963). A preprogrammed saccadic command is then generated based upon the visual information that has been acquired during the initial visual sample (Young and Stark 1963). According to Young and Stark (1963), information about the visual world is again sampled, once the saccade is completed, in order to find if a correcting saccade is needed.

However, in later studies it has been discovered that visual information can be continuously acquired and used to modify the initial saccade until just about 70 ms before the movement begins (Wheeless et al. 1966; Becker and Jürgens 1979; Ottes et al. 1984). This has been found in experiments where the so-called double-step stimulus has been used. In the condition of double-step stimulus where there is no obligatory refractory period, two saccades can occur with virtually no intersaccadic interval. It has also been found that when there is a two-dimensional double-step stimulus, normal subjects can make a single curved saccade (van Gisbergen et al. 1987). This indicates that the saccade trajectory has been modified in flight with these cases (van Gisbergen et al. 1987).

According to present knowledge, saccadic eye movements are not ballistic in type. A local feedback system controls the saccadic size. An internal negative feedback loop controls the discharge of burst neurons, which intern determines the amplitude of the saccadic pulse (Robinson 1975; Zee et al. 1976a). This occurs by comparing continuously the desired eye position signal and the actual eye position. The neurons of saccadic pulse generator are driven until the eye reaches the target

(Robinson 1975; Zee et al. 1976a). At this point, the neurons stop discharging (Robinson 1975; Zee et al. 1976a). To this model, new concepts were later added (Carpenter 1988; Jürgens et al. 1981; McKenzie and Lisberger 1986; Scudder 1988).

The input and output of the final common integrator are summed to generate the pulse-step, and consequently, the motor neuron activity required to produce a saccade (Carpenter 1988). The output of the integrator which is also an internal representation of the position of the eye at any moment, is compared with a signal carrying the target position, i.e. the desired eye position (Carpenter 1988). The difference between these two constitutes a motor error signal (Carpenter 1988). In real saccades, however, the saccadic pulse is abruptly switched on and off, so the model could be called a bang-bang model of saccadic generation (Carpenter 1988).

Jürgens et al. (1981); McKenzie and Lisberger (1986); Scudder (1988) added to the local feed-back model a concept that the command signal is most likely the desired change in eye position. There seems to be two separate integrators, one common integrator for conversion of eye velocity signal to eye position commands (for all types of eye movements) and a separate neural network to integrate saccadic velocity commands for use in the feedback loop controlling the duration of the saccadic pulse command (Jürgens et al. 1981; Sparks et al. 1987; Sparks and Mays 1990).

Moreover, it seems clear that saccades are influenced by parallel cognitive processing in complicated ways right up to and possibly during the time of their execution (Robinson 1981). The different models are incomplete, and may require modifications, alterations and additions.

2. A. 2. Pursuit eye movements

Once the moving target is at the fovea, the image is stabilized on the retina by the PEM and vestibular system. According to Leigh and Zee (1983b), and Versino and Cosi (1990), the PEM system conducts three tasks: 1) continuous visualization of target moving in a stable visual environment, 2) suppression of vestibulo-ocular reflex during eye tracking, and 3) image stabilization during fixation. In different situations this involves vestibulo-ocular reflex system, and optokinetic system (Zee et al. 1974; Mack et al. 1982). Any impairment in PEM involves all three functions (Versino and Cosi 1990).

The PEM is triggered to movement of a target of interest by measuring the retinal error velocity (Rashbass 1961; Young and Stark 1963). Changes of target position can also trigger PEMs (Pola and Wyatt 1980). The reaction time of PEM system to random moving targets is approximately 100 ms in monkeys (Lisberger and Westbrook 1985), and 125 ms in humans (Becker and Fuchs 1985). Frontal eye field (FEF) seems to

play a role in predictive PEMs (Keating et al. 1985; Keating 1991). When humans track predictable targets, they quickly lock onto the target movement and are able to track it without any latency (Bahill et al. 1980). Humans appear to try to anticipate the future path of moving targets in PEMs (Kowler 1989). Their behavior suggests that they create an internal model of the target movement, and then track the output of this model, rather than the actual visual target (Bahill et al. 1980, Kowler 1989). Higher order CNS processes are presumably used in this internal model, to analyze the target movement and to predict future target positions (Bahill et al. 1980; Kowler 1989).

The neural reconstruction of the target velocity signal with respect to the environment requires information about target slip on the retina, eye velocity on the head, and in case of vestibulo-ocular reflex, head velocity with respect to the environment (Young 1977). In the control of PEM, the perception also influences by selecting the visual target (Mack et al. 1982).

About models of pursuit eye movements

PEM system uses continuous negative visual feedback to reduce the retinal error velocity during pursuit (Robinson 1965). The difference between target velocity and eye velocity is the error velocity signal in the model by Robinson (1965). The so-called open-loop (internal) gain/amplification factor determines the velocity of the resulting PEM (Leigh and Zee 1983b). The overall gain of the PEM system in this model is a closed-loop gain (Leigh and Zee 1983b).

In another model, the stimulus to the PEM system is not the retinal error velocity, but an internal representation of the motion of the target in space (Yasui and Young 1975). This representation is obtained by combining retinal error velocity with an eye velocity signal based on monitoring of efferent commands (= efference copy; corollary discharge) (Yasui and Young 1975).

Robinson (1981) considers that although the main stimulus for pursuit is the velocity of image slip on the retina, the PEM system also responds to the position of the target with respect to the fovea.

According to Carpenter (1988), PEM is primarily a function of retinal slip/error velocity. He considers that the closed-loop or open-loop models of PEM studies have defects, therefore, these models cannot explain PEMs in all different conditions.

Lisberger and Westbrook (1985) have studied the whole trajectory of PEMs. They found that by looking at the first 100ms of pursuit of a target that suddenly starts to move (which implies an effective open-loop response, since there is no time for visual feedback) shows that there are two components of response. In the first 20 ms, the acceleration of the eye is constant and unrelated to any aspect of the stimulus

(Lisberger and Westbrook 1985). Thereafter, the acceleration of the eye is strongly dependent on the position and velocity of the target, and on the background (Lisberger and Westbrook 1985). The models of PEM are defective, and subject to alterations and modifications.

2. A. 3. Supratentorial representation of voluntary eye movements

During PEM and visually evoked saccades, neurons in area 7 of the posterior parietal lobe are active (Lynch et al. 1977). The neurons are active during visual attention, and they contain neural circuits for focusing the object of interest (Lynch et al. 1977). It is likely that area 7 is not solely sensory or motor, but is involved in higher order aspects of sensory-motor integration (Andersen et al. 1987). The findings of Lynch et al. (1977) underlined that area 7 could be a mechanism for the selection of objects of interest. Both the eye position and eye movement signals of these neurons might be important in establishing or maintaining perceptual stability of space, and in providing the motor systems with the head-centered coordinates of targets that are necessary for calculating the correct trajectories of eye (Andersen et al. 1987). Robinson et al. (1978), reported that area 7 in primates is related to visual attention, and in this context is also related to movement.

According to Bruce and Goldberg (1985), FEF such as Broadman area 8, has an important role in generating voluntary eye movements. Visual activity of FEF may provide targets for visually guided saccades (Bruce and Goldberg 1985). FEF is involved in the processes of saccade generation (Bruce and Goldberg 1985; Deng et al. 1984). Goldberg and Robinson (1977) proposed that neurons in FEF and area 7 of the parietal lobe signal the presence of an important stimulus in the visual environment. According to Luria et al. (1966), in frontal lobe lesions the active control of eye movements is disturbed. Patients with a frontal lobe lesion have difficulties with attention span and their visual attention can be easily disturbed (Luria et al. 1966; Pyykkö et al. 1984). According to Pyykkö et al. (1984), FEF seems to govern the "preprogramming" of voluntary eye movements, therefore, a FEF lesion leads to difficulties in initiation of oculomotor tasks. In FEF, there are also neurons responding to fixation of foveal visual stimuli and to PEM (Bruce and Goldberg 1985; Bruce et al. 1985). Patients with frontal lobe lesions can have pursuit deficits (Luria et al. 1966; Henriksson et al. 1981). According to Keating (1991), FEF ablations or lesions with cooling, impair predictive pursuit and degrade visually guided foveal pursuit of all targets.

A small population of FEF cells encodes the current eye position in PEM (Bruce and Goldberg 1985). A FEF lesion transiently impairs predictive and visually guided PEM, and PEM appears to be more vulnerable to lesions than saccades (Keating 1991).

Saccadic eye movements have been found to be elicited by delicate, well-defined and restricted electrical stimulation of FEF (Robinson and Fuchs 1969), and FEFs have been found to have transcallosal connections (Künzle and Akert 1977; Bruce and Goldman-Rakic 1984). The callosal innervation is columnar, and the organization of saccade directions parallels the anatomical columns (Bruce and Goldman-Rakic 1984). Vertical saccades are thought to involve FEF bilaterally, whereas horizontal saccades are directed

into the contralateral field (Bruce and Goldman-Rakic 1984). Three types of presaccadic activity in neurons are observed; 1) activity linked to visual targeting, 2) activity related to movement of the eyes, and 3) anticipatory activity for target selection. A given neuron can have any or all three of these activities (Bruce and Goldberg 1985; Bruce et al. 1985). Cells of FEF associated with saccades are more or less topographically arranged (Bruce et al. 1985). Combined lesions of FEF and superior colliculus have a devastating effect on the saccadic eye movements, by reducing the frequency and range (Schiller et al. 1980). A lesion on either of these sites alone has a subtle affect (Schiller et al. 1980).

FEF does not appear to be involved in the generation of the express saccades of monkey (Schiller et al. 1987). However, according to Mayfrank et al. (1986), both FEF and area 7 seem to be necessary for the generation of express saccades in humans.

Hubel and Wiesel (1962; 1965) found that the visual cortex of cat has activity related to saccades and PEM. In the development of visual cortex, the visual experience in infancy plays an important role (Tychsen and Lisberger 1986). Humans who had treated or untreated strabismus early in life, have deficits in the perception of depth using binocular cues (Mohindra et al. 1985). The magnitude of the PEM deficits is correlated with the severity of strabismus in adults who have had monocular fixation since infancy due to strabismus (Tychsen and Lisberger 1986). The deficits are apparent in the perception of target motion (Tychsen and Lisberger 1986). These deficits may be due to the maldevelopment of visual motion processing in the visual cortex or its pathways. These pathways provide signals that are used for both the perception of motion and the initiation of PEMs (Tychsen and Lisberger 1986).

After removal of striatal cortex, the monkeys at first appear to be completely blind (Zee et al. 1987). But after a recovery time the monkeys regain their ability to make visually guided saccades and PEMs to small targets (Zee et al. 1987). However, this happens with increased saccadic or pursuit reaction times, increased variability of saccadic amplitudes, and more variable and erroneous trajectories of PEM (Zee et al. 1987). In these instances, the monkey uses extrastriate pathways to generate more volitional types of visual-ocular motor behavior, such as PEM and saccades (Zee et al. 1987).

It seems that superior temporal sulcus might contribute to the visual orientation system with posterior parietal and frontal cortical mechanisms (Luh et al. 1984). Middle temporal visual area is important for the initiation and maintenance of foveal pursuit (Newsome et al. 1985; Dürsteler et al. 1987). Pursuit deficit following a lesion to middle temporal visual area result from an inability to determine the speed of target motion (Newsome et al. 1985). Generation of pursuit by a position error seems to be mediated by areas other than middle temporal visual area (Newsome et al. 1985). Middle temporal visual area is selectively related to visual processing of motion information (Dürsteler et al. 1987).

Intracortical connections, and connections to cerebellum and brain stem

According to Goldberg and Robinson (1977), there are two different cortical mechanisms underlying gaze: 1) a qualitative analysis of the visual world provided by striate and prestriate cortex; and 2) signals of a significant object in the environment

provided by FEF and posterior parietal cortex. These two mechanisms are both visual because they describe the visual world to the oculomotor system (Goldberg and Robinson 1977).

Cortical areas associated with eye movements share many internal connections. The middle temporal visual area receives a direct projection from striate cortex (Newsome et al. 1985). Connections are found between area 7 and the temporal lobe (Petras 1971), between FEF and the middle and medial superior temporal area (Keating 1991), between FEF and area 7, FEF and the pretectal regions and the superior colliculus (Astruc 1971; Petras 1971; Künzle and Akert 1977; Stanton et al. 1982). The FEF participating in the PEM system connects the middle temporal visual area and the pontine nuclei (Newsome et al. 1985; Dürsteler and Wurtz 1988; Keating 1991). The pontine nuclei involved in the eye movements function as relay stations to the vestibulocerebellum (Brodal 1979). Apparently, FEF is not the sole pathway transmitting the selective command signals of the visual neurons of area 7 to the eye movement centers in the brain stem (Lynch et al. 1977).

Movement signal of FEF is largely mediated by the superior colliculus which can ignore the FEF signals and may trigger saccades in the absence of FEF signals (Bruce and Goldberg 1985). FEF also has projections to other nuclei in the brain stem related to eye movements (i.e. tegmental and basilar nuclei of the pons), but not to the extraocular motor nuclei, “accessory oculomotor” nuclei, or the PPRF (Astruc 1971; Künzle and Akert 1977; Stanton et al. 1982). The superior colliculus receives convergent projections from the retina and striate cortex (Wilson and Toyne 1970), and receives descending projections from frontal, temporal and parietal lobes (Kuypers and Lawrence 1967; Petras 1971; Künzle and Akert 1977). The superior colliculus is involved in the generation of saccade amplitude and direction (van Opstal and van Gisbergen 1989). According to Robinson (1972), the “collicular motor map” is organized in spatial (polar) coordinates (amplitude and direction).

Efferent projections from the superior colliculus reach the eye movement centers located in PPRF (Harting 1977; Lynch et al. 1977). The functional properties of the visual neurons in parietal lobe match completely with those of the premotor neural activity recorded in PPRF (Lynch et al. 1977), indicating a functional connection. Unlike the normal saccades, the express saccades cannot be generated without the superior colliculus (Schiller et al. 1987). The superior colliculus also plays a role in the generation of normal saccades, because a lesion of superior colliculus lengthens the SRTs of contralateral visual saccades (Schiller et al. 1987).

Middle temporal area, medial superior temporal area and some extrastriate areas have projections also to the dorsolateral pontine nucleus (DLPN) (Glickstein et al. 1980; Ungerleider et al. 1984; May and Andersen 1986). The DLPN and nucleus reticularis tegmenti pontis also receive inputs from the superior colliculus (Harting

1977). The DLPN has cells that discharge during PEMs (Suzuki and Keller 1984; Suzuki et al. 1984). The pontine nuclei (Langer et al. 1980) in turn seem to project to the contralateral or to the ipsi- and contralateral flocculus of the cerebellum (Langer et al. 1980; Brodal 1982; Langer et al. 1985a). According to Suzuki and Keller (1984), the DLPN could provide the PEM system with a retinal slip velocity component based an internal neural correlate of target velocity in space. Shinnar et al. (1973) and Brodal (1979) have found that DLPN also has connections to the vermal lobules VI and VII, and so it is also involved with the saccadic system.

2. A. 4. Cerebellum

The flocculus is a well-defined and relatively isolated part of the cerebellum (Alley 1977), and in primates it is intimately involved in visuomotor tasks (Takemori and Cohen 1974; Zee et al. 1976b; Alley 1977; Waespe et al. 1983; Keller 1988). The flocculus modulates the vestibular system via the visual system. Removal of the flocculus causes loss of visual suppression of vestibular responses (Takemori and Cohen 1974). The flocculus seems to inhibit the brain stem neurons responsible for transmitting vestibular information to the oculomotor system (Fukuda et al. 1972). The flocculus exerts a control of visual inputs for PEMs through a pathway coming from the brain stem (Langer et al. 1980; May et al. 1988; Brodal 1982; Langer et al. 1980).

In mammals, the flocculus receives input from variable brain stem parts mediating eye movements (Alley et al. 1975; Alley 1977; Lisberger and Fuchs 1978; Langer et al. 1980; Langer et al. 1985a). It receives afferents from the retina with directionally selective inputs (possibly via the inferior olive), (Maekawa and Simpson 1973; Simpson and Alley 1974). It also receives a direct projection from the vestibular nerve and secondary inputs from the specific vestibular nuclei, as well as projections from the perihypoglossal complex (Alley et al. 1975; Alley 1977; Winfield et al. 1978; Langer et al. 1980; Langer et al. 1985a). The perihypoglossal complex also includes prepositus hypoglossi nucleus (Alley et al. 1975; Langer et al. 1980; Langer et al. 1985a). Visual influx to flocculus is conveyed through the inferior olive from the striate cortex (Winfield et al. 1978; Langer et al. 1980; Langer et al. 1985a). There are afferents from the abducens nucleus, nucleus reticularis tegmenti pontis, PPRF, DLPN and ventrolateral nuclei of pons (Langer et al. 1980; Brodal 1982; Langer et al. 1985a; May et al. 1988).

There are three major efferent pathways, through which the flocculus influences or controls the extra-ocular motoneuron complex (Noda and Suzuki 1979; Zee et al. 1981). The flocculus projects to nuclei of extra-ocular motoneurons (Haines 1977; Alley 1977; Noda and Suzuki 1979; Langer et al. 1985b) through the ipsilateral vestibular nuclei (Carpenter and McMasters 1963; McMasters et al. 1966; Tarlov 1970; Langer et al. 1985b). Through this projection the flocculus seems to transmit vestibular information to the oculomotor

system (Fukuda et al. 1972), and this projection is also a part of the vestibulo-ocular reflex arc (Fukuda et al. 1972). The second pathway travels from the flocculus to the prepositus hypoglossi nucleus (Alley 1977; Noda and Suzuki 1979). The ipsilateral prepositus hypoglossi nucleus has a monosynaptic excitatory projection to trochlear nucleus (Baker et al. 1977). The ipsi- and contralateral prepositus hypoglossi nuclei have projections to the abducens nucleus (Maciewitz et al. 1977) and to the oculomotor nucleus (Graybiel and Hartwieg 1974). The third pathway (Noda and Suzuki 1979) conveys a projection from the flocculus to the ventral portions of dentate nucleus (Carpenter and Strominger 1965; Haines 1977) that projects to the oculomotor nucleus (Chan-Palay et al. 1976).

The activity of vestibular nuclei is not only coding the sensory inputs, (i.e., vestibular, proprioceptive and exteroceptive) but also a pattern of oculomotor activity. This indicates that the vestibular nuclei are also a premotor structure to the extra-ocular motoneuron complex (Büttner et al. 1981). Thus, visually induced oculomotor responses also depend upon the integrity of peripheral vestibular afferents (Büttner et al. 1981). The vestibular nuclei and flocculus interact in a complementary fashion, extending considerably the range of oculomotor functions (Büttner et al. 1981).

Flocculus functions to stabilize the images on the retina during head rotation and assists in the foveation of the target (Zee et al. 1981). The input to the flocculus (regarding eye position) is probably related to the proprioceptive impulses in the extraocular muscles, to impulses from the visual system (the retina), or impulses from brain stem (Noda and Warabi 1982). The output from flocculus is always related to the eye velocity with respect to the world (Lisberger 1982). Flocculus and paraflocculus also participate in the control of oculomotor reflexes that insure the visual acuity by preventing glissades (Zee et al. 1981).

The considerable deficits of PEMs in bilaterally flocculectomized monkeys imply that the flocculus plays a major role in the control of PEMs (Zee et al. 1981). PEMs can be elicited by electrical microstimulation of flocculus (Belknap and Noda 1987).

In saccades, the purpose of the neural activity of the flocculus is to adjust the pulse size to eliminate a glissade (Optican and Robinson 1980). It seems that the brain stem circuits that generate the amplitude of saccadic eye movements are slightly hypermetric, and in normal situations the amplitude is made correct by the flocculus (Optican and Robinson 1980). The flocculus seems to affect the fine adjustment of saccadic eye movements and the control of delicate positioning of the eyes for fixation (Noda and Suzuki 1979).

Oculomotor vermis of primates receives afferent projections from nucleus reticularis tegmenti pontis, pontine nuclei (involving paramedian pontine nucleus, pontine peduncular nucleus, DLPN), PPRF, vestibular nuclear complex, prepositus hypoglossi nucleus, and from inferior olivary nucleus (Shinnar et al. 1973; Brodal 1980; Keller and Crandall 1980; Yamada and Noda 1987). A lesion somewhere in these afferent pathways affects the function of oculomotor vermis. As there is ongoing

compensation and healing after the lesion of cerebellum, the oculomotor deficit may be difficult to interpret.

Adaptive control of the pulse command and the neural discharge controlled by it (which controls saccadic amplitude), is dependent upon the midline structures of the cerebellum (Optican and Robinson 1980). More recent studies (Noda and Fujikado 1987a; Noda and Fujikado 1987b; Noda et al. 1988) with microstimulation techniques have shown that the oculomotor vermis is situated in lobules VIc-VII of vermis in primates. Efferent Purkinje cell projections from oculomotor vermis project solely to fastigial nucleus (Yamada and Noda 1987); the oculomotor pathway first projects to the ipsilateral fastigial nucleus from where the pathways decussate to the contralateral fastigial nucleus (Noda and Fujikado 1987a; Noda and Fujikado 1987b; Noda et al. 1988). The synapses of the Purkinje cell efferents are situated in the contralateral fastigial nucleus (Noda et al. 1988). The direction of the saccade seems to be topographically organized in the oculomotor vermis (Noda and Fujikado 1987b). In microstimulation studies of oculomotor vermis, amplitude of the evoked saccade has been found to increase by the stimulus duration and frequency (Noda and Fujikado 1987b).

Vermal stimulation affects ipsilateral saccades and stimulation of neurons in the fastigial nucleus affects contralateral saccades (Noda et al. 1988). The neurons of fastigial nucleus are situated in the fastigial oculomotor region (Noda 1991). The primary function of the fastigial oculomotor region is related to the control of saccades, while regions related to vestibular and PEM functions are located rostral to the fastigial nucleus (Noda et al. 1990; Noda 1991).

The fibers of fastigial oculomotor region terminate primarily in the regions of the medial brain stem reticular formation (PPRF - horizontal preoculomotor neurons, rostral interstitial nucleus of medial longitudinal fasciculus - vertical preoculomotor neurons) that have direct projections to the extraocular motor nuclei (Noda et al. 1990; Noda 1991). The fastigial oculomotor region also projects to such brain stem regions that project to the cerebellum. For example, there are projections via the vestibular complex and the inferior olivary complex to the cerebellum (Noda et al. 1990; Noda 1991). The cerebellar output, through fastigial oculomotor region via the contralateral uncinate fasciculus (Noda and Ikeda 1989), independently influences the horizontal and vertical saccades (Fujikado and Noda 1987). It seems that a bulk of visual-oculomotor and cerebellar-oculomotor pathways projects to PPRF before reaching the extraocular motor nuclei (Cohen and Komatsuzaki 1972).

During PEMs, the discharge of posterior vermal cells is proportional to target velocity, while that of floccular cells depend upon eye velocity, retinal error velocity or eye acceleration (Lisberger and Fuchs 1978; Keller 1988; Pierrot-Deseilligny et al.

1990). The anatomical pathways from the flocculus and the posterior vermis are different. The posterior vermis projects via the fastigial nucleus to the neurons near the abducens nucleus, which are involved in PEMs (Yamada and Noda 1987). The vermis can partly compensate for the deficit in PEMs produced by limited floccular lesions or vice-versa (Keller 1988), but surgical ablation of the posterior vermis cannot be compensated for, as it causes saccadization of PEMs (Suzuki and Keller 1983). Lesions in vermal lobules VI and VII in monkeys cause a gain reduction of 30-50% in PEMs (Suzuki and Keller 1983), suggesting that vermal lobules VI and VII may also take part in generating PEMs. The flocculus is more involved in the motor aspects of maintaining ongoing pursuit, whereas vermal lobules VI and VII may influence the PEM system during rapid changes in target velocity (Keller and Heinen 1991). According to Suzuki and Keller (1983), the flocculus supplies a gaze velocity signal, whereas oculomotor vermis generates a target velocity signal. Paraflocculus participates in PEM generation as well (Zee et al. 1981). Both the flocculus and paraflocculus, as well as vermal lobules VI and VII, receive projections from visual nuclei of pons (Brodal 1979, Langer et al. 1985a).

It is possible that the flocculus, paraflocculus, nodulus and posterior vermis (lobules VI and VII) are all required for PEMs, and only the removal of large amounts of these structures can cause a profound deficit in PEMs (Zee et al. 1981; Suzuki and Keller 1983; Keller and Heinen 1991). It is also possible that lateral hemispheres of cerebellum and anterior superior vermis can participate in PEMs as well (Zee et al. 1981).

Cerebellum exerts control on PEMs through several pathways: the vestibular nuclei (Langer et. al 1985a), the neurons near the abducens nucleus (Yamada and Noda 1987), and the prepositus hypoglossi nucleus (Keller and Heinen 1991). The prepositus hypoglossi nucleus is anatomically connected to the extra-ocular motoneuron complex (Graybiel and Hartwieg 1974; Baker et al. 1977; Maciewitz et al. 1977).

Normally, each side of the cerebellum inhibits the vestibular nuclei ipsilaterally (Fukuda et al. 1972). As a consequence of hemicerebellectomy, this ipsilateral inhibition is absent (Westheimer and Blair 1974) and the imbalance in the steady-state output of the vestibular nuclei is generated producing a contralaterally directed drift in the darkness (Westheimer and Blair 1974).

Figure 1. a. Some neuroanatomical substrates for the oculomotor system.

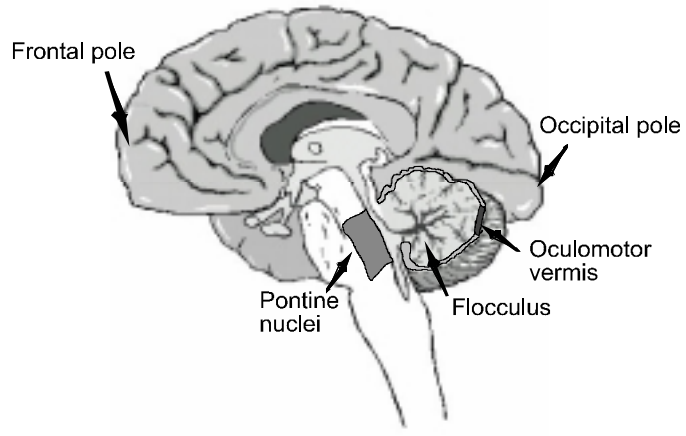
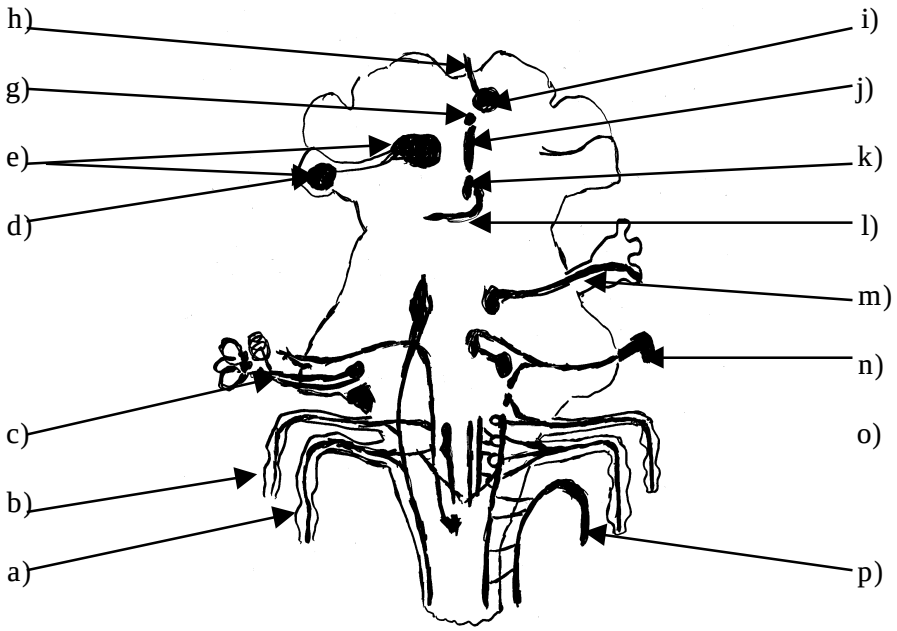


Figure 1. b. Posterior view of the brain stem . a) vagal nerve, b) glosopharyngeal nerve, c) vestibulo-cochlear nerve, d) lateral geniculate body, e) relay centers for fibers in optic tract, f) superior colliculus, g) oculomotor nucleus, h) oculomotor nerve, i) red nucleus, j) accessory oculomotor nucleus, k) trochlear nucleus, l) trochlear nerve, m) trigeminal nerve and ganglion and motor nucleus, n) abducens nucleus (between the loop of facial nerve), o) facial nerve, p) accessory nerve (modified from Netter 1991).



2. A. 5. Brain stem

The PPRF is situated in the pons, and it covers the medial portion of nucleus reticularis magnocellularis between 0.5 and 2.0 mm from the midline on either side of

the pons in the caudal half of the area between the trochlear and abducens nuclei (Ito 1984). PPRF is regarded to be a supranuclear structure responsible for conjugate horizontal eye movements (Cohen and Komatsuzaki 1972; Keller 1974; Henn and Cohen 1976; Hepp and Henn 1983). Frontal, temporal and parietal cortex have influence on PPRF through connections to the superior colliculus (Kuypers and Lawrence 1967; Petras 1971), and then to PPRF (Harting 1977; Lynch et al. 1977). PPRF circuits are involved in generating the innervation needed to produce a saccade (Cohen et al. 1968; Cohen and Henn 1972; Keller 1974; Henn and Cohen 1976) and can do so without the cerebellum (Optican and Robinson 1980).

According to Cohen et al. (1968) and Hepp and Henn (1983), the neural activity of PPRF is necessary for the generation of all horizontal saccades and for the coordination of all rapid eye movements. The main saccade-related populations of neurons are medium- and long-lead burst neurons. Burst neurons in the rostral PPRF have predominantly spatially-coded movement fields, while in the caudal PPRF, burst neurons demonstrate temporally coded driven activity dependent on the constriction direction of the extraocular eye muscles (i.e., almost horizontal or vertical) (Hepp and Henn 1983). Both the caudal and temporal PPRF neuronal populations contain long-lead and medium-lead burst neurons (Hepp and Henn 1983). The medium-lead burst neurons act as the predominant output for the saccadic pulse generator to the motoneurons (Hepp and Henn 1983). Spatio-temporal recoding of visually guided horizontal saccadic eye movements is also affected by the long-lead burst neurons in the PPRF (Hepp and Henn 1983). Pause units in PPRF have a continuous discharge rate that is stopped before and during eye movements, and the pauses appear either during all rapid eye movements or only when the movement is in a particular direction (Henn and Cohen 1976). At the level of PPRF, most burst units are silent or have irregular activity during periods of fixation or during slow eye movements (Henn and Cohen 1976). The tonic units of PPRF may provide additional drive to oculomotor neurons resulting in their increased discharge during pursuit or vestibular smooth eye movements (Robinson and Keller 1972; Keller 1974). Tonic units in PPRF discharge steadily during fixation at rates depending on eye position (Keller 1974). When the eye moves to a certain direction, the unit discharge rate increases, and that determines the eye velocity of PEM (Keller 1974).

Parameters of saccadic eye movements are represented in the activity of PPRF neurons (Henn and Cohen 1976). An eye movement can be predicted from the unit activity that precedes it (Henn and Cohen 1976). The intraburst discharge rate determines the saccadic velocity, but rarely determines the amplitude (Keller 1974). In cortical or collicular sites, the saccadic eye movements are coded on spatial coordinates (Robinson and Fuchs 1969; Robinson 1972). It seems that the translation from spatial information, coded by anatomical location, (Robinson and Fuchs 1969; Robinson 1972) to temporal information occurs in different neurons in PPRF (Keller

1974; Henn and Cohen 1976; Hepp and Henn 1983). The cerebellum (oculomotor vermis, fastigial nucleus, flocculus) affects the function of PPRF by adjusting the saccadic parameters (Zee et al. 1976a; Zee et al. 1976b; Noda and Suzuki 1979; Optican and Robinson 1980; Zee et al. 1981; Optican et al. 1986; Fujikado and Noda 1987; Noda and Fujikado 1987a; Noda and Fujikado 1987b; Noda et al. 1988; Noda et al. 1990; Noda 1991).

PPRF units project onto the extraocular motoneurons, either monosynaptically or disynaptically (Highstein et al. 1974; Büttner-Ennever and Henn 1976). The oculomotor nucleus receives a projection from contralateral PPRF via the contralateral abducens nucleus (Graybiel and Hartwieg 1974; Büttner-Ennever and Henn 1976). Finally, the information is transformed into a temporal discharge pattern of extra-ocular motoneurons to generate a saccadic eye movement (Hepp and Henn 1983).

PPRF also has projections to the contralateral PPRF, the pretectal area, the prepositus hypoglossi nucleus and medial vestibular nucleus (Büttner-Ennever and Henn 1976). According to Büttner-Ennever and Henn (1976), these connections could act in the precise co-ordination of all six pairs of extraocular muscles during eye movements.

Extraocular muscle proprioception participates in the control of eye movements in primates (ocular alignment and eye movement conjugacy), and contributes to the long-term adaptive mechanisms that regulate ocular alignment during fixation and saccades (Lewis et al. 1994). A mismatch between the efferent activity and proprioceptive afferent activity may act as an error signal needed in this process (Lewis et al. 1994). These findings confirm the assumptions of Fricker and Sanders (1975), that the main movements in the saccadic system are "preprogrammed" to a large extent, but the movements can be modified significantly by a rapid feedback system. They thought that the feedback system was too rapid to depend on visual information, and they suggested that the proprioceptors in the oculomotor muscles or tendons with feedback loops to the brain stem could be involved in that task (Fricker and Sanders 1975). Already Weber and Daroff (1972) had suggested that a feedback from proprioceptors in extraocular muscles might play a role in corrective saccadic eye movements rather than the visual feedback.

From the cerebral cortical pathways, the descending projections for PEMs appear to go through pontine nuclei (Keller and Heinen 1991). The pontine nuclei involved in PEMs are the inferior olive (Winfield et al. 1978; Langer et al. 1980; Langer et al. 1985a), nucleus reticularis tegmenti pontis (Suzuki et al. 1990), DLPN (May et al. 1988; Suzuki et al. 1990), lateral pontine nucleus (Nyby and Jansen 1951), and PPRF (Keller 1974; Raphan and Cohen 1978). These pontine sites have outputs to cerebellar structures of PEMs (Brodal 1979; Brodal 1980; Brodal 1982; Langer et al. 1985a; May et al. 1988).

As the eye velocity signals have to be transformed to eye position signals (Robinson 1975), there is a need for the so-called final common integrator (Robinson 1975). For all conjugate eye movements, the final common integrator (Robinson 1975) processes information between the cerebellum, brain stem and supratentorial areas

(Robinson 1975; Cannon and Robinson 1987). Fixation is impaired if nucleus prepositus hypoglossi and medial vestibular nucleus are lesioned unilaterally (Cannon and Robinson 1987). Neural integration for horizontal conjugate eye movements is severely impaired if nucleus prepositus hypoglossi and medial vestibular nucleus are destroyed bilaterally (Cannon and Robinson 1987). Nucleus prepositus hypoglossi and medial vestibular nucleus have reciprocal connections to the vestibulocerebellum (Alley 1977; Lisberger and Fuchs 1978). All three oculomotor subsystems (saccadic, PEM and vestibular systems) transmit a velocity signal to a final common integrator that produces the appropriate position information to make the eye move and to hold it in its new position (Zee et al. 1974). In the final common integrator, the eye-position signal is created from the velocity command signal by integration with respect to time, and is sent to the extraocular motoneurons in combination with the eye-velocity command signal (Cannon and Robinson 1987). In the vestibular nerve, the eye movement signal is coded in the time domain (i.e., firing frequency) (Wilson 1972; Robinson 1975; Robinson 1981).

Figure 2a. Some important parts and pathways of the saccadic system. riMLF = rostral interstitial nucleus of medial longitudinal fasciculus. Note the connection to the PEM system via DLPN and flocculus.

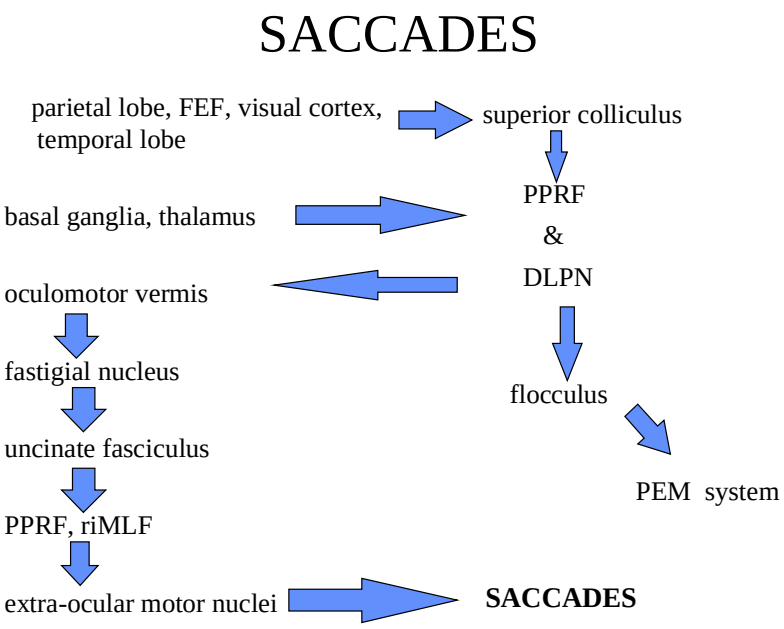
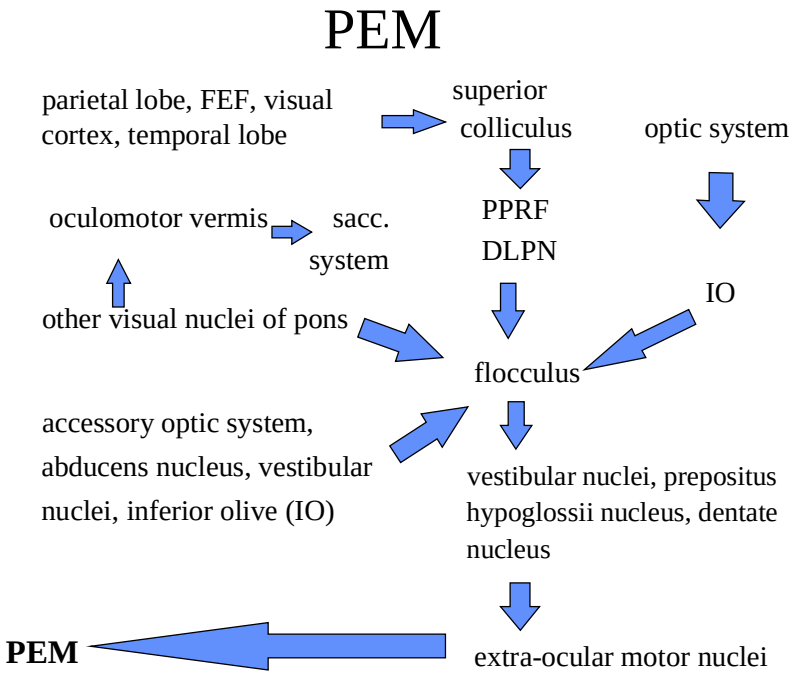


Figure 2b. Some important parts and pathways of the PEM system. Note the connection to the saccadic system via the visual nuclei of pons and oculomotor vermis.



Although there is a neurological segregation of the oculomotor system into saccadic, pursuit, vergence and vestibular portions, it has been demonstrated that the motoneuron represents a level of final common output in which these systems are presented (Keller 1974).

All extraocular motoneurons have some change in activity during eye movements, as well as all extraocular muscles have some activity change during every eye movement in the horizontal plane (Henn and Cohen 1976). For each eye movement a very specific ratio of innervation has to be established between motoneurons of every eye muscle (Henn and Cohen 1976). At the motoneuron level, there seems to be only one basic type of activity pattern (Fuchs and Luschei 1970; Robinson 1970). All voluntary eye movements (saccades, PEM and steady gaze) are reflected in the discharge characteristics of this single unit type (Fuchs and Luschei 1970). Abducens neurons demonstrate abrupt frequency changes during normal saccadic eye movements (phasic behavior), but the same neurons change their frequency gradually in association with PEMs, and with rolling eye movements of a drowsy animal (Fuchs and Luschei 1970). The firing frequency during such slow eye movements increases gradually as the eye moves laterally, or decreases as the eye moves medially (Fuchs and Luschei 1970). The firing frequency of abducens units demonstrates tonic behavior related to eye position (Fuchs and Luschei 1970).

2. B. *Aging and voluntary eye movements*

Voluntary eye movements change with aging (Miller 1969; Sharpe and Sylvester 1978; Spooner et al. 1980; Henriksson et al. 1980; Majima et al. 1981; Carter et al. 1983; Abel et al. 1983; Warabi et al. 1984; Whitaker et al. 1986; Hutton and Pallet 1986; Sharpe and Zackon 1987; Larsby et al. 1988; Tedeschi et al. 1989; Morrow and Sharpe 1993; Versino et al. 1993a; Paige 1994; Moschner and Baloh 1994; Kanayama et al. 1994).

Saccadic accuracy has been found to be poorer in elderly subjects than in middle-aged subjects (Sharpe and Zackon 1987; Tedeschi et al. 1989). Not all studies have been able to demonstrate this difference (Moschner and Baloh 1994).

In nonpredictive saccades (Spooner et al. 1980; Carter et al. 1983; Whitaker et al. 1986; Sharpe and Zackon 1987; Tedeschi et al. 1989; Moschner and Baloh 1994) and predictive saccades (Whitaker et al. 1986; Hutton and Pallet 1986; Sharpe and Zackon 1987), the SRTs are longer in elderly subjects than in middle-aged subjects. In children (Miller 1969), SRTs are also longer than in middle-aged subjects, both in nonpredictive and predictive saccades. According to Abel et al. (1983), the SRT is significantly increased in the elderly when compared to the SRTs of the young. According to Warabi et al. (1984), the most prominent change in saccades in healthy elderly subjects is the prolongation of time to catch a target. This results from an increase in SRTs and from a decrease in saccadic peak velocities (Warabi et al. 1984).

Saccadic peak velocity has been found to be lower in elderly subjects than in middle-aged subjects in the studies of Spooner et al. (1980) and Tedeschi et al. (1989). According to Majima et al. (1981), mean saccadic velocities are the highest at the age of 20-29 years, then gradually become lower and at the age 70-79 years suddenly decrease; the difference in velocity in their study was statistically significant in 10° saccades but not in 20° saccades. Sharpe and Zackon (1987) found that saccadic peak velocity is significantly reduced in the elderly compared to the young, for saccades predictable by target amplitude and direction, but that there is no difference between these groups in saccades that are nonpredictable by target amplitude and direction. Moschner and Baloh (1994) found that saccadic peak velocity was lower in the elderly than in the middle-aged only for a saccadic amplitude of ±30°. Abel et al. (1983) did not observe any significant differences in saccadic velocity and duration between the young and the elderly. The findings of these two studies are in line with those of Henriksson et al. (1980).

Tedeschi et al. (1989) demonstrated that the saccadic accuracy declined significantly and the SRT increased significantly in subjects older than 45 years. The saccadic peak velocity declined significantly in subjects older than 65 years.

In studies on PEMs, the following was observed: 1) pursuit velocity and pursuit velocity gain decreases in the elderly subjects when compared to middle-aged subjects, at least with higher stimulus velocities (Sharpe and Sylvester 1978) or even with all stimulus velocities (Larsby et al. 1988; Morrow and Sharpe 1993; Moschner and Baloh 1994; Paige 1994; Kanayama et al. 1994), 2) phase lag seems to lengthen in the elderly subjects when compared to middle-aged subjects (Sharpe and Sylvester 1978; Morrow and Sharpe 1993; Paige 1994), but, according to Larsby et al. (1988), phase shift values (phase leads and phase lags) are not affected by age, and 3) in children and teenagers the accuracy of PEMs is poorer than in the middle-aged (Larsby et al 1988).

2. C. *Measurement of voluntary eye movements*

2. C. 1. Recording techniques

Robinson (1963) introduced the magneto-oculography (MOG), a technique of measuring and recording eye movements using a scleral search coil in a magnetic field. The MOG recording method allows one to obtain a precise and continuous recording of eye movements. The coils placed on scleral annuli contain a flanking copper coil in which a voltage is induced as the eye moves in a magnetic field (Robinson 1963). The MOG method has been further developed by Collewijn et al. (1975), Collewijn (1977), and by Behrens (1989). The MOG recording method is used primarily in research, and is routinely used in some clinical laboratories (Yee et al. 1985). The semi-invasive placement of a search coil onto the eyeball restricts the application of MOG technique in clinical situations (Scherer et al. 1991). Moreover, the possibility of coil slippage, particularly during torsional movements, remains a potential source of error (Scherer et al. 1991).

In the electro-oculography (EOG) method, the position of natural dipole (the corneoretinal potential) is detected by electrodes placed on the canthi of the eyes (Henriksson 1956; Schlag et al. 1983). In neurotological practice, voluntary eye movements have been recorded by standard EOG methods for a long time, and it is still the most common method used for recording eye movements in neurotologic laboratories (Spooner et al. 1980; Carter et al. 1983; Larsby et al. 1988; Tedeschi et al. 1989; Chioran and Yee 1991; Moschner and Baloh 1994; Kanayama et al. 1994). One problem with the EOG method is a so-called spike artifact (obviously of muscle origin), however, that can be avoided if the electrodes are properly placed close enough to the outer canthi, and if the recording is properly low-pass filtered with digital filtering (Jäntti 1982a). If the spike artifact is not eliminated, it can affect and radically distort the measured peak velocity, duration, mean velocity and reaction time of horizontal

saccades (Jäntti 1982a). The most common disturbances in EOG recordings are; changes in the impedance of the skin (Jäntti 1982b), D.C. drift in corneoretinal potentials (Henriksson 1956; Schlag et al. 1983), electrical disturbances (Jäntti 1982b), and EEG (Baloh and Honrubia 1979; Jäntti 1982b) and EMG artifacts (Beaussart and Guieu 1977; Jäntti 1982a; Jäntti 1982b; Yee et al. 1985; Chioran and Yee 1991).

Infrared oculography (IROG) using infrared reflection device is used in some laboratories (e.g., Stark et al. 1962; Sharpe and Sylvester 1978; Hutton et al. 1983; Yee et al. 1985; Whitaker et al. 1986; Hutton and Palet 1986; Sharpe and Zackon 1987; Fischer et al. 1993). The IROG method utilizes photocells positioned over the limbus nasally and temporally to record horizontal eye movements. The photocells detect the amount of infrared light reflected from the surface of the eye (Smith and Warter 1960; Stark et al. 1962; Yee et al. 1985). According to Boghen et al. (1974), the saccadic peak velocities at horizontal saccades in certain saccade amplitudes are higher in normal subjects when recorded by the IROG method than when recorded by the EOG method.

The newest method for recording eye movements, video-oculography (VOG) was introduced by Clarke et al. (1991) and by Scherer et al. (1991). The VOG system can record eye movements in three dimensions: horizontal, vertical and torsional (Scherer et al 1991). The three components of ocular movements are video acquired and processed to provide position data, typically at 25 Hz (Guillemant et al. 1995). Through advanced image processing, VOG provides an estimate of the velocities, reaction times and accuracies of saccades, and on line computation of the slow velocity eye movements (Guillemant et al. 1995). The apparent position of the center of the pupil is calculated with an accuracy of 0.25°, with an algorithm that detects the shape of the pupil by analysis of its contours (Guillemant et al. 1995). The VOG system is non-invasive, the recordings are free of drift and electrophysiological artifact, and they remain stable in the presence of electromagnetic interference in the experimental environment (Scherer et al. 1991). However, it is less precise than the MOG technique (Scherer et al. 1991), because the sampling rate is too low to precisely define saccades (Juhola et al. 1985a; Juhola 1986; Guillemant et al. 1995).

Until recently, there have been few studies of voluntary eye movements in which both EOG and MOG recording methods have been used simultaneously (Chioran and Yee 1991; Yee et al. 1985; Schlag et al. 1983). Chioran and Yee (1991) studied vertical saccades with EOG and MOG recording methods in 5 normal subjects. The EOG measurements of vertical saccades were generally less accurate than those obtained by the search coil technique. The analysis of vertical saccades by EOG was, therefore, limited by the waveform artifacts that occurred with both upward and downward saccades (Chioran and Yee 1991). Peak velocity was especially affected by artifacts

(Chioran and Yee 1991). They concluded that there is evidence that the varying tissue resistance, eyelid blinks and electrical activity, originating probably from the frontalis and/or levator muscles, contribute to the production of EOG artifacts in vertical saccades. No data from the horizontal saccades was available.

Yee et al. (1985) studied the differences between EOG, MOG and IROG recording methods in vertical saccades. Differences between the peak velocities assessed with different recording methods were found. With the MOG method, upward and downward saccades had similar peak velocities in all fields of the orbit, and no artifacts were found in the MOG. But in two subjects, the superior fornix of the conjunctiva restricted the movement of contact lens in the 20-30° interval in the upper field. However, the MOG recording method was the most accurate of the recording methods studied. In EOG, artifacts from eyelid movements had major effects on trajectories and peak velocities of saccades. The EOG method overestimated the velocities of upward saccades. In most of the subjects, the IROG method could not accurately record eye movements greater than 10° in upgaze or 20° in downgaze. The peak velocities and amplitudes of upward saccades were underestimated in IROG. No data from the horizontal saccades was available.

Schlag et al. (1983) studied EOG and MOG recording methods with eye movements in cat and monkey. They studied both the horizontal and vertical eye movements (saccades and PEM). They concluded that the major drawback in EOG method is the slow D.C. drift which is still present, despite routine careful preparation of electrodes. The D.C. level varies with lighting conditions over long periods of time (Schlag et al. 1983). Consequently, frequent calibrations are an unavoidable necessity with the EOG technique (Schlag et al. 1983). When the conditions of calibration are adequate, however, the EOG technique is valuable (Schlag et al. 1983). Its advantages are simplicity of equipment and low cost. The discrepancies between EOG and the search coil technique seem to be less in horizontal eye movements than in vertical eye movements (Schlag et al. 1983). Saccades in recording signals of vestibulo-ocular reflex are detected at a 95% frequency, with both EOG and MOG techniques (Juhola et al. 1995).

According to Robinson (1964) and Boghen et al. (1974), the electronics of the recording system is very important, and systems using higher bandwidths have yielded faster and more accurate velocities.

2. C. 2. Stimulation techniques

According to a proposed standard of American National Standards Institute (ANSI S3.45-199X), red LEDs can be used as targets for saccade tests and pursuit tests. In

saccade tests, the LEDs must not subtend an angle greater than 1 degree of visual arc, and in pursuit test the target must not subtend a visual angle of greater than 3 degrees (see Blakley 1998).

Light emitting diodes (LEDs) have been widely used as targets for saccadic eye movements (e.g., Abel et al. 1979; Warabi et al. 1984) and for pursuit eye movements (Versino and Cosi 1990; Versino et al. 1993a). A laser dot projected on the screen or wall is also widely used (e.g., Bahill et al. 1980).

Constant and pseudo-randomized saccades (referring to the target displacement method) have been used in different eye movement studies (e.g., Spooner et al. 1980; Carter et al. 1983; Warabi et al. 1984; Takemori and Ida 1984; Sharpe and Zackon 1987; Tedeschi et al. 1989; Fischer 1993). In constant saccades, the target steps have varied between ±4º, and ±60º (Fischer 1993; Takemori and Ida 1984). Often the time delay between the predetermined target steps is pseudo-randomly presented in order to avoid anticipatory saccades (Fricker and Sanders 1975). In pseudo-randomized saccades, the range of target steps used has included: ±3º - ±36º, via ±5º - ±40º, to ±30º - ±40º (Spooner et al. 1980; Sharpe and Zackon 1987; Tedeschi et al. 1989). The target steps have jumped across the center from right to left or left to right (Takemori and Ida 1984; Sharpe and Zackon 1987), or the jump has been from the center to right or left (Spooner et al. 1980, Carter et al. 1983; Sharpe and Zackon 1987; Tedeschi et al. 1989; Fischer 1993).

In the study of PEMs, ramps (Versino and Cosi 1990; Versino et al. 1993a), sinusoidally moving targets (Stark et al. 1962), motion reflecting the vector sum of several sinusoids (Stark et al. 1962; Barnes et al. 1987) and random motion targets (Dallos and Jones 1963; Michael and Melvill Jones 1966; Barnes et al. 1987) all have been used as stimuli.

2. C. 3. Analysis techniques and computer systems, filtering, and sampling frequency

Analysis

The algorithm of the recording system is extremely important (Robinson 1964). Those studies utilizing higher bandwidths have yielded faster and more accurate velocities (Boghen et al. 1974). According to Boghen et al. (1974), laboratories conducting clinical oculographic recordings should establish their own normative baseline values with their own recording techniques and electronics for eye movement testing.

Until the 1980's, eye movements were acquired on paper recorders (Schalén 1981) and the parameters were assessed from the paper recordings (Henriksson 1956; Schalén 1981). Also, the storing of eye movements on electromagnetic tape for

computer analysis was used (Baloh et al. 1975a). During the 1980's, computer systems were developed for the analysis of eye movements, and on line analyzing of eye movement recordings could be done on computer files on hard disc (Juhola 1987; Barnes et al. 1987).

Measurement techniques

Filtering

Biological signals have to be filtered in order to eliminate the disturbances caused by contaminating biological and physical artifacts. The noise can increase the noise floor, thus reducing the sensitivity of the recording system or distort recorded signals, thus changing the results computed from them. Linear filters have been used for this purpose, but they often cannot preserve the sharp edges of signals (Nodes and Gallagher 1982). Nonlinear median filter has been found to smooth the data but preserve interesting phenomena (Heinonen and Neuvo 1987; Astola et al. 1987; Juhola 1991b).

Sampling Frequency

For saccades, the sampling frequencies have varied between 200 and 1000 Hz in previous studies (Baloh et al. 1975b; Bahill et al. 1981; Dick 1978). For PEMs, the sampling frequencies have also varied between 200 and 1000 Hz (Juhola 1990). Juhola et al. (1985b), Juhola (1986) and Juhola and Pyykkö (1987), observed that the lowest sampling frequency should be 400Hz to allow for saccade identification.

Parameters

Saccades

SRT, saccadic accuracy and saccadic peak velocity have often been assessed in saccade tests. The SRT can be assessed by computing the time from displacement of target or the appearance of target, to the beginning of the saccadic eye movement. Saccadic accuracy can be expressed in several ways: 1) assessing the amplitude of the initial saccade (Schalén 1981), 2) assessing the ratio of saccade amplitude to target amplitude, 3) expressing the above ratio as a percentage (Baloh et al. 1977), 4) assessing the difference between the saccadic amplitude and the target amplitude, and (5) expressing the difference as undershoot/overshoot (Weber and Daroff 1971). Saccadic peak velocity can, for example, be assessed by estimating the tangent of rapid eye movement (Schalén 1981), or by measuring the velocity over a 24ms period at the midpoint of the excursion of the eye (Mastaglia et al. 1979).

Pursuit eye movement

Velocity gain has been widely assessed in PEM tests. Velocity gain is the ratio of eye velocity: target velocity, usually computed to the point corresponding to the middle of

target trajectory or sometimes in some other points of the target ramp or sinusoid (Versino et al. 1993a). In the study of Versino et al. (1993a), velocity gain was replaced by pursuit index that is the ratio purified PEM: total target amplitude (correcting saccades were identified and removed from PEM to get the purified PEM). The benefit in using this index was that it enabled a global evaluation of smooth pursuit over the entire ramp. According to Versino et al. (1993a) pursuit index corresponds to the ratio of the integral of eye velocity signal (after catch-up saccades were removed from it) to the integral of target velocity signal.

2. C. 4. Consistency of voluntary eye movements

There are few studies on the reliability of voluntary eye movement results (Boghen et al. 1974; Schmidt et al. 1979; Tijssen et al. 1989; Brantberg 1992; Versino et al. 1993b). In these studies, the reliability of the tests has been evaluated by repeated measurements, and the voluntary eye movements have been found to be repeatable most often.

2. C. 5. Prediction of stimulus and voluntary eye movements

Takemori and Ida (1984) studied the influence of the prediction of saccades in 20 normal subjects, age ranging from 18 to 43 years. They found that the predictability versus nonpredictability of the target did not produce any significant differences in saccadic peak velocity or SRT.

According to Saslow (1967), neither the number of possible target positions (steps of 2º - 4º 6 º- 8º to right or left) nor the location of the target (overall range from -4º to +4)º affected the SRT. In the study of Saslow (1967), however, auditory guidance was involved in the saccadic task, which could affect the results. The stimulus paradigm did not fulfill conditions for pseudo-randomization of stimulus.

Findlay (1981) found that both spatial predictability and temporal predictability reduce SRTs for visually elicited saccades. The timing of a saccade is controlled by a separate mechanism from that which controls amplitude (Findlay 1981). For unpredictable movements the SRT is typically 170-350 ms; but in the case of a target making a predictable movement, the SRT can be reduced or even lost (Findlay 1981). He considered saccades with a SRT$\leq$ 100ms as anticipatory, and all saccades with a SRT>100ms as visually guided. The stimulus movements were only ±1.9º in a series of steps: (center) - (left/right) - (center) - (left/right) - (center), etc. The probability of the stimulus to move to the left or right was 0.5 for each, so the required saccadic amplitude was predictable. These experimental conditions may have affected his findings.

2. D. *Voluntary eye movements in normal subjects*

2. D. 1. Normal saccades

The accuracy of human saccades is significantly affected by the temporospatial arrangements of the targets and by their background illumination (Lemij and Collewijn 1989). The size of a saccade can vary considerably, from approximately 0.1º to 90º (Robinson 1981). Normal subjects often undershoot the target displacement by 5-20% and occasionally overshoot by 5-20% in saccadic performance (Weber and Daroff 1971). In the saccade test of Weber and Daroff (1971), the targets were continuously visible, and the saccades were made to and from midline position; the target displacement being the same in a given sequence. The majority of saccades were normometric at saccadic eye movements of 10º, whereas at 20º and 30º saccades, the frequency of normometric saccades was significantly decreased (Weber and Daroff 1971).

Visually controlled saccades to peripheral targets are slightly larger than the visually controlled saccades to the center, and the size appears as an increasing function of reaction time (Findlay 1981). Findlay's analysis supports the idea of a distinction in accuracy between the anticipatory and the visually guided saccades.

According to van Opstal and van Gisbergen (1989), the variability of saccadic position errors is attributed to the noise occurring at the level of the motor map of the superior colliculus. The computation of saccade amplitude and direction is subjected to noise (van Opstal and van Gisbergen 1989). The ratio of amplitude to direction scatter was approximately constant for all target positions tested in that study.

According to Warabi et al. (1984), SRT is dependent on the amplitude of the saccade. In their work, the size of target displacement/step and direction as well as the time interval of steps were randomized, and the steps were 10º, 20º, 30º or 40º to the right or left at a distance of ±10º or ±20º from the midline position. According to Saslow (1967), the lack of knowledge of the target trajectory does not necessarily affect the SRT in pseudo-randomized saccades. But predictive settings lead to anticipatory rather than "tracking" saccadic performance (Saslow 1967).

The lower limit of SRT for a "regular" saccade is 150ms (Stark et al. 1962). According to Fuchs (1967a) and Robinson (1981), when a target suddenly jumps to one side, a saccade follows in about 200-250 ms. SRT depends on the attention span, the luminance, size of target displacement, target disappearance and reappearance schedule (Robinson 1981). A typical SRT of 215 ms includes about 55 ms lost in the retina and about 25 ms lost in the premotor circuits and muscles, leaving about 135 ms for central processing (Robinson 1981).

Saccadic peak velocity and saccadic amplitude have a non-linear relationship (Zuber et al. 1965; Fuchs 1967a; Schmidt et al. 1979; Leigh and Zee 1983a); saccadic

peak velocity increases as saccadic amplitude increases. Anticipatory saccades possess the same saccadic amplitude and saccadic peak velocity relationship as visually controlled saccades (Findlay 1981). In EOG recordings, the mean of normal saccadic peak velocity values for 20º saccades has been approximately 320º/s (Wennmo et al. 1981; Schalén 1981), and for 60º saccades approximately 475º/s (Wennmo et al. 1981; Schalén 1981). With standard photoelectric recording techniques, the mean of normal peak velocity for 20º saccades is approximately 660º/s (Bahill et al. 1981). Sometimes, saccadic peak velocities may reach such values as 700º/s (Leigh and Zee 1983a). According to Bahill et al. (1981), the saccadic peak velocity is sensitive to the influence of the algorithms used to calculate the saccadic peak velocity.

Visual suppression occurs during saccades, and results from a central inhibitory process (Riggs et al. 1982), or from retinal smear (Volkmann 1962). Retinal smear is supposed to decrease the photochemical effect of visual stimulation (Volkmann 1962). According to Cambell and Wurtz (1978), in a contoured visual environment, a clear image before and/or after the saccade can mask the gray-out during eye movement. A gray-out would have been caused by a perception of a smeared visual scene during the eye movement (Cambell and Wurtz 1978).

2. D. 2. Normal pursuit eye movements

Tracking a target consists of two separate paths: a saccadic path for correction of position errors, to center the target image on the fovea; and a pursuit path for correction of velocity errors, to stabilize the target image on the retina (Rashbass 1961; Young and Stark 1963). The accuracy of eye tracking (i.e., PEM) depends upon cooperation between PEM and saccadic systems (Rashbash 1961; Fleming et al. 1969). Position errors less than approximately 0.5º are generally not corrected, since the image lies on the parafovea (Rashbass 1961; Young and Stark 1963). The reaction time and the refractory period of the PEM system is less than those of the saccadic system (Young and Stark 1963).

When target velocity increases, PEM becomes more saccadic and the relative share of pure PEM decreases (van den Berg and Collewijn 1986). When the velocity of pure PEMs is reduced, the number of superimposed saccades is increased, while the total amplitude of tracking may be normal or decreased (Pyykkö and Schalén 1984).

Velocity gain values of PEMs are influenced by target motion characteristics: target velocity, target acceleration, motion amplitude, and target frequency (Versino and Cosi 1990). The performance of the PEMs depends upon the spatio-temporal characteristics of the target movement (i.e., the amplitude, pattern and velocity) (Buizza and Schmid 1986).

The upper limit of human PEM velocity with a ramp stimulus is about 87 °/s and with a target velocity of 100 °/s (Meyer et al. 1985). At this value, eye velocity saturates (Meyer et al. 1985). According to Robinson (1981), the peak velocity of normal PEMs is not certain. Robinson (1981) has summarized the findings of different reports; the peak velocity of normal PEMs may range from 30°/s to 130°/s.

In velocity gain, there are no directional asymmetries according to van den Berg and Collewijn (1986). They found that directional preferences are absent when a subject pursues the target actively, and they showed that directional preferences are enhanced if foveal function is lowered. The stronger cortical guidance of the eye movements during pursuit decreases the variance of PEM with respect to the direction of the stimulus movement (van den Berg and Collewijn 1986).

In PEMs, the reaction time to a sudden change in velocity is about 130 ms (Robinson 1965). Of this time, 55 ms can be lost in the visual system and 25 ms in the motor system; the 50 ms left reflects central processing (Robinson 1981).

2. D. 3. Effect of environmental factors on voluntary eye movements

Saccadic performance is affected by alertness and fatigue (Becker and Fuchs 1969; Schmidt et al. 1979), alcohol (Franck and Kuhlo 1970; Wilkinson et al. 1974; Tedeschi et al. 1986), drugs (Aschoff 1968; Gentles and Thomas 1971; Tedeschi et al. 1986) among others.

With increasing fatigue, the PEM is increasingly replaced by saccades in the tracking task (Bahil et al. 1980). Also, the PEM system is influenced by alcohol, drugs, or by mental conditions (Rashbass 1961; Norris 1971; Wilkinson et al. 1974; Flom et al. 1976; Baloh et al. 1976; Bahill et al. 1980). It seems that the PEM system is more vulnerable than the saccadic system (Rashbass 1961).

In the study of Schmidt et al. (1979) fatigue of the extra-ocular muscles was not found to influence the saccadic peak velocity, but mental fatigue reduced the saccadic peak velocity. During normal use, the extra-ocular muscles never show symptoms of fatigue (Fuchs and Binder 1983).

Tedeschi et al. (1986) studied the effects of drugs and alcohol on saccadic eye movements. They found that: 1) amylobarbitone caused significant reduction of saccadic peak velocity, 2) amphetamine taken perorally did not affect saccadic eye movements; but when it was received in I.V. injections, it abolished a fatigue effect of repeated testing on saccadic eye movements, and 3) alcohol impaired the saccadic eye movements.

Alcohol reduces the peak and mean velocities of saccades (Franck and Kuhlo 1970; Lehtinen et al. 1979). Diazepam reduces mean saccadic velocity and disintegrates the usual one-step saccade into several short steps (Aschoff 1968).

In the study of Norris (1971), the effect of a benzodiazepine (nitrazepam) on PEMs was compared to that of a barbiturate (sodium phenobarbitone). Both caused saccadization of PEMs.

Psychological factors, such as motivation and attention (Becker and Fuchs 1969; Shagass et al. 1976; Schmidt et al. 1979; Robinson 1981; Siever et al. 1989; Versino and Cosi 1990), and cognitive expectation (Kowler and Steinman 1981; Kowler 1989), can affect the PEM and saccadic performance.

Saccades made in the dark are considerably slower than saccades made at clearly visible targets (Becker and Fuchs 1969). Saccades made with monocular viewing seem to be as accurate as those made with binocular viewing (Lemij and Collewijn 1989). According to Robinson (1964), in most normal subjects, temporal saccades are executed with a higher velocity and with more overshoot than nasal saccades. This asynchrony of action can result in an instantaneous image disparity between the two eyes of as much as 2.5º, as they make conjugate 15º saccades (Robinson 1964).

Boghen et al. (1974) studied the effect of the direction of stimulus movements in saccadic peak velocity. They tested temporal, nasal, centering, eccentric and across-the-center saccades in 15 normal subjects with 5º, 10º, 20º and 30º saccades. They found considerable intra- and intersubject variability, and they concluded that it is necessary to record a sufficient number of subjects and eye movements (of certain magnitude) to accurately define these responses. They found that there was no significant difference among various types of saccades, except for the peak velocity of nasal refixations that were significantly greater at the 30° amplitude than that of temporal saccades.

In the study of Abel et al. (1979) on the peak velocity-amplitude differences in extremes of lateral gaze (between targets at 30° and 40°), there was no significant difference between temporal and nasal saccades. There were no peak velocity differences between movements in the left and right fields of gaze or between the two eyes moving in the same direction (Abel et al. 1979).

2. E. *Voluntary eye movement and disease*

2. E. 1. Pathophysiological aspects of voluntary eye movements

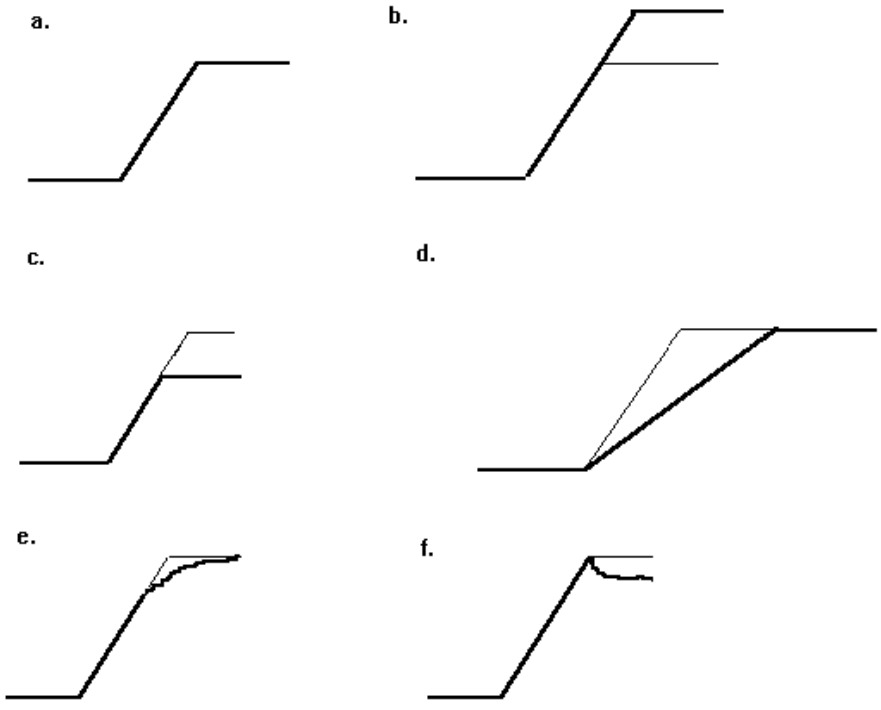
Lesions in the brain stem induce a reduction of saccadic peak velocity (Baloh et al. 1977). Because of the anatomical proximity of the brain stem and cerebellum most pathology in the posterior fossa yields combined disorders of cerebellum and brain stem (Pyykkö and Schalén 1984). In solitary cerebellar lesions, the saccadic peak velocity is not reduced (Baloh et al. 1977; Pyykkö and Schalén 1984) or is even enhanced (Pyykkö and Schalén 1984). In combined lesions, saccadic peak velocity is

usually decreased (Pyykkö and Schalén 1984).

Prolongation of SRT is seen in cases with degeneration or lesions of the cerebral cortex (Hoyt and Daroff 1971; Baloh et al. 1977; Pyykkö et al. 1984). The FEF lesions, unilaterally (Baloh et al. 1977) or bilaterally (Pyykkö and Schalén 1984), can cause the prolongation of SRT. Prolongated SRT, as well as dysmetria of saccades, saccadic slowing and impaired PEM, can be observed in degenerative processes that involve cortical and cerebellar trajectories (Solingen et al. 1977; Mastaglia et al. 1979).

Dysmetria of saccades is present in patients with a variety of lesions of the CNS (Baloh et al. 1977; Pyykkö and Schalén 1984; Watanabe et al. 1996). Hypometria of saccades may be found in lesions of the FEF and of the cerebellum (Zee et al. 1976b; Baloh et al. 1977), the basal ganglia (DeJong and Melvill Jones 1971), the superior colliculus (Heywood and Ratcliff 1975), and the brain stem (Zee et al. 1976a; Henriksson et al. 1981). Hypermetria of saccades is amplitude-dependent and may be found in cases of cerebellar lesions (Selhorst et al. 1976). In patients with cerebellar disorders, the percentage of overshoot is greater for smaller saccades; step stimuli greater than 20° usually evoke hypometric (undershooting) saccades, rather than hypermetric (overshooting) saccades (Selhorst et al. 1976). Pathological saccades are seen in **Figure 3**.

Figure 3. a. Normal saccade, b. Hypermetric saccade, c. Hypometric saccade, d. Slow saccade, f. Saccade with a glissade. A thin line shows the expected magnitude of the saccade.



Total cerebellectomy creates an enduring saccadic hypermetria and glissade (Optican and Robinson 1980). From these findings, it can be concluded that total cerebellectomy destroys both the pulse and step plasticity and the adaptive control of the saccadic system, (i.e., it abolishes all adaptive repair of the saccadic system) (Optican and Robinson 1980). Total cerebellectomy also severely impairs PEM and optokinetic nystagmus (Westheimer and Blair 1973; Westheimer and Blair 1974; Optican and Robinson 1980). When posterior vermis (lobules IV-IX) and paravermis are injured, PEM is preserved, but saccades become abnormally hypermetric (Optican and Robinson 1980). In these lesions, the glissade does not occur because the adaptive plasticity of the step is spared (Optican and Robinson 1980).

Bilateral flocculectomies cause the adaptive control of glissade to be severely injured (Optican et al. 1980; Optican et al. 1986), and it seems that the flocculus is involved in the adaptive control of the step (Optican and Robinson 1980).

Deficits following a middle temporal visual area lesion seem to result from disruption of visual processing, whereas the effects of lesions of higher cortical areas (i.e., striate cortex or parietal cortex) have motor components as well (Newsome et al. 1985). Visual cortex is crucial for saccades and PEM (Goldberg et al. 1982; Tychsen and Lisberger 1986; Zee et al. 1987). Damage to parieto-occipital areas of the cerebral cortex associated with vision causes deficits in PEM (Baloh et al. 1980; Leigh and Tusa 1985). Bilateral damage to lateral temporo-occipital areas of the cerebral cortex associated with vision causes disturbance in perception of movement in depth (Zihl et al. 1983). Both of these aforementioned cerebral lesions (Baloh et al. 1980; Leigh and Tusa 1985; Zihl et al. 1983) are extensive by nature, and explain why deficits in PEM are found. In monkeys, lesions in the primary visual cortex (Broadman's area 17, 18, 19) or the middle temporal visual area (Goldberg et al. 1982; Newsome et al. 1985; Zee et al. 1987) cause deficits in the initiation of pursuit. Duhamel et al. (1992) observed during saccadic performance in a patient with a fronto-parietal lesion, that the frontal and parietal lobes are critical for processing both retinal and eye movement informations.

The final common integrator for the conjugate eye movement systems is affected by lesions of the cerebellum, especially the flocculus and paraflocculus (Zee et al. 1981; Waespe et al. 1983).

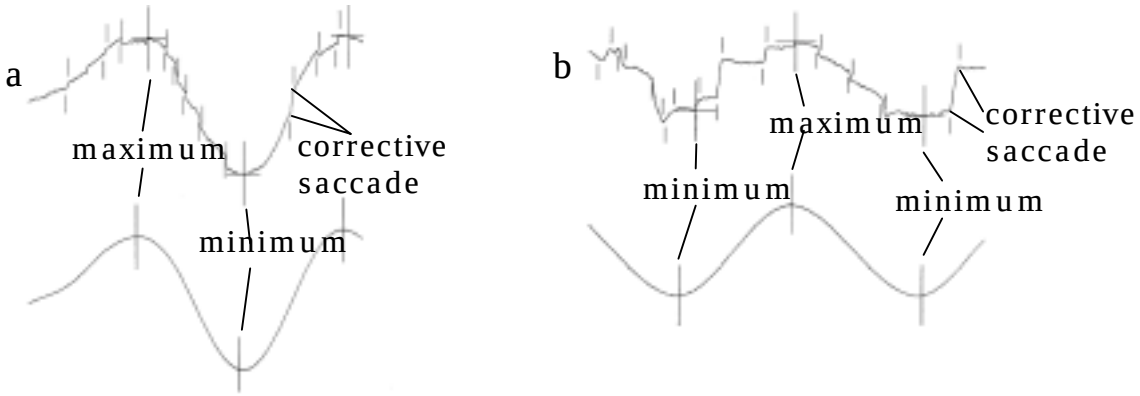
Flocculectomy in primates causes a gaze deviation nystagmus, saccadic PEMs, a downbeat nystagmus and a post-saccadic drift in saccades (Zee et al. 1981). Patients with hereditary cerebellar ataxia, cannot produce normal PEMs (Zee et al. 1976b). Pathological PEMs are seen in **Figure 4**.

2. E. 2. Voluntary eye movements in some specified disorders

a) *Menière's disease*

Menière's syndrome consists of fluctuating sensorineural hearing loss, episodic vertigo and tinnitus, and may result from several different pathological processes (Rauch et al. 1989; Pappas and Banyas 1991; Rauch et al. 1995; Kiang 1989). These may include obstruction of endolymphatic outflow, overproduction of endolymph, infection by viral or other infectious agents, trauma, vascular disease, autonomic instability, and immune-mediated injury (Rauch et al. 1995). The abundance of etiologic causes may reflect the heterogeneity of Menière's disease (Pappas and Banyas 1991).

Figure 4. A part of PEM recording. The movement of target and the PEM response.



Menière's disease is also characterized by attacks of rotatory vertigo and short lasting drop attacks, but in those cases with intractable Menière's disease, patients often complain of unsteadiness and gait disorders even during attack-free periods (Pyykkö et al. 1994b). They often complain about postural instability and dizziness when moving by themselves or when the visual surrounding is moving. When the duration of Menière's disease is long and vertigo attacks are frequent, unsteadiness persists between the attacks, which is a sign of irreversible damage to the vestibular sense organ (Schucknecht 1957). Otolithic crisis of Tumarkin may not be as rare a manifestation of Menière's disease as speculated (Black et al. 1982; Baloh 1990), and it is characterized by sudden drop attacks, called Tumarkin drop attacks. These attacks are probably due to rapid changes in vestibulospinal tone resulting from pathologic fluctuations in otolithic activity (Lewis 1996).

In cases of severe Menière's disease, it is very difficult to find any effective treatment for acute attacks. When Menière's disease is intractable and severe, intratympanically applied gentamicin is used as a treatment (streptomycin by Schucknecht 1957; gentamicin by Lange 1977; Beck and Schmidt 1978; Ödkvist et al. 1984; Ödkvist 1988). It is supposed to damage the secretory epithelium before affecting vestibular and cochlear function (Lange 1977; Beck and Schmidt 1978).

Bergenius (1985) studied 205 patients having unilateral hearing loss with audiovestibular tests. There were two patient groups: a cochlear group (117 patients; 6 of them with Menière's disease, others with sudden deafness, hereditary factors, head injuries, and unknown etiologies), and a retrocochlear group (88 patients, most of them tumorous, some with brain stem hemorrhages). Deranged saccadic pursuit and a significantly reduced peak velocity in voluntary saccades were considered pathological. Pathological results of at least one of the oculomotor tests, as well as the presence of gaze nystagmus, were denoted as oculomotor dysfunction. Bergenius (1985) found that patients with cochlear hearing loss seldom have oculomotor disturbance.

b) Cerebello-pontine angle tumors

The term cerebello-pontine angle (CPA) tumor is used in this study according to Lo (1994). He divides CPA tumors in extra-axial (located in the extra-axial compartment), extradural (extradural in origin but intrude into the CPA) and intra-axial (arising from the brain) tumors. CPA tumors consist of about 10% of all intracranial tumors (Zülch 1986; Russell and Rubinstein 1989). The differential diagnosis of a space-occupying lesion of the CPA consists primarily of vestibular schwannoma (from about 80 to 90%) and meningioma (from 3 to 12%) (Thomsen 1976; Brackmann and Bartels 1980; Berlinger et al. 1980; Nedzelski and Tator 1982; Eldridge and Parry 1992). The remaining masses include primary cholesteatoma (2%), facial nerve neuroma (1%), neuromas of other cranial nerves (0.2%) and other rare tumors (e.g., hemangioma, astrocytoma, medulloblastoma, glomus tumor) (Thomsen 1976; Brackmann and Bartels 1980; Berlinger et al. 1980).

Vestibular schwannoma

The largest and most common tumor in the CPA is vestibular schwannoma (Eldridge and Parry 1992). Vestibular schwannoma occurs in two forms: sporadic or neurofibromatosis type 2 (NF2). Sporadic tumors are unilateral and comprise almost 95% of the cases, while lesions associated with NF2 are typically bilateral and account for about 5% of vestibular schwannoma patients (Jackler 1994).

Vestibular schwannomas arise from the vestibular division of the eighth cranial nerve, and according to current opinion, originate from the superior or inferior divisions of the nerve equally (Clemis et al. 1986; Jackler 1994). Almost all vestibular schwannomas arise within the internal auditory canal (Jackler 1994; McKenna et al. 1993). Lanser et al. (1992) and Selesnick and Jackler (1992), suggest vestibular schwannomas originate within the internal auditory canal at the junction of peripheral and central myelin. In vestibular schwannoma (both sporadic and NF2), an aberration

in chromosome 22 has been found (a review by Jackler 1994). The majority of the vestibular schwannomas grow slowly (less than 0.7 mm/year according to Rosenberg et al. 1993), whereas about 10-15% have a significantly higher growth rate (exceeding 10 mm/year) (Jackler 1994).

There is no universally accepted method for measuring the size or volume of vestibular schwannoma. According to the literature, a single diameter is used most often. Jackler (1994) suggests that the single largest axial dimension (i.e., parallel to the posterior petrous wall as vestibular schwannoma enlarges) (Lo 1994) should be used to indicate schwannoma size. The intracanalicular part is not included in such a measurement.

While it is possible to describe a "typical" clinical presentation of vestibular schwannoma, it must be kept in mind that in the manifestations of vestibular schwannoma, there is a remarkable variability (Selesnick and Jackler 1992; Selesnick et al. 1993). The symptoms progress from slight (limited to the eighth nerve: hearing loss, tinnitus, vestibular dysfunction), to the intracanalicular stage, the brain stem compressive stage, and to the final stage where massive and life threatening symptoms of hydrocephalus occur (Jackler 1994).

The flocculus and nodulus are frequently compressed by large *vestibular schwannoma*, causing the flocculonodular syndrome of dysfunction (Selesnick and Jackler 1992). The syndrome is composed of disequilibrium and loss of successful equilibrium compensation strategies (Selesnick and Jackler 1992). Facial nerve motor dysfunction tends to occur gradually, in later stages of vestibular schwannoma (Selesnick and Jackler 1992). Symptoms arise from compression caused by vestibular schwannoma on the brain stem, cerebellum and cranial nerves (Selesnick and Jackler 1992).

Attacks of vertigo are not commonly associated with vestibular schwannoma (Jackler 1994), though they have been known to occur years before the discovery of the tumor (Selesnick et al 1993; Jackler 1994). It appears that vertigo, when present, is an early symptom during vestibular schwannoma growth, and may be caused by interference of the vestibular nerve or through interruption of the blood supply to the labyrinth (Jackler 1994). In contrast to vertigo that decreases with increasing tumor size, disequilibrium becomes more frequent with larger tumors (Selesnick et al. 1993). In tumors larger than 3 cm, the incidence rate of this disturbing syndrome exceeds 70% (Selesnick et al. 1993). The most likely mechanisms causing disequilibrium are uncompensated unilateral vestibular deafferentation, or persistent perverse input from the diseased vestibular nerve (Jackler 1994).

According to Selesnick and Jackler (1992) and Nedzelski (1983), in large vestibular schwannoma tumors there are ENG disorders, including saccadic PEMs and bilateral saccade overshoot. However, also according to Selesnick and Jackler (1992),

large vestibular schwannoma tumors often show normal ENG results - i.e. no spontaneous, positional or gaze nystagmus, normal saccades, PEMs, optokinetic nystagmus, normal caloric test, and normal fixation suppression of caloric response. Nedzelski (1983) found that abnormalities of PEMs, optokinetic nystagmus, gaze, and saccades in patients with large CPA tumors are caused by bilateral flocculus compression. He also reported that PEMs and optokinetic nystagmus were more sensitive than other oculomotor functions to the compressive effects of a CPA tumor.

Mrazek (1989) studied 47 vestibular schwannoma patients. In large or giant tumors, ocular dysmetria and lagging of the eyes during fixation on a moving target compensated by corrective saccades, provided evidence on the size of the tumor (Mrazek 1989). Symptoms were caused by compression of brain stem and the flocculonodular part of the cerebellum, which correlate with surgical and CT findings (Mrazek 1989).

Hulshof et al. (1989) examined 48 surgically confirmed vestibular schwannoma patients preoperatively with tests of fixation, optokinetic, spontaneous, and positional nystagmus, as well as caloric tests, saccades and PEMs. They found a significant correlation with the size of the tumor and the occurrence of abnormal saccades (dysmetria, flutter, opsoclonus), saccadic PEMs and the occurrence of gaze nystagmus, respectively. These tests were sensitive in tumors larger than 2 cm. In the study of Bergenius (1985), oculomotor disturbances were noted in nearly half of the retrocochlear group. The presence of oculomotor disturbance in patients with retrocochlear hearing loss strongly indicates brain stem and/or cerebellar involvement, because when only those patients with lesions of the brain stem or cerebellum were considered, all exhibited such disturbances (Bergenius 1985). According to Jackler (1994), abnormalities in PEMs are seen in a minority of large vestibular schwannoma.

Meningioma

Meningiomas originate from cell elements that form meninges and their derivatives in the meningeal spaces (Rubinstein 1972). The affinity of meningiomas for arachnoid villi accounts for the regularity with which meningiomas are attached to the dura (Rubinstein 1972). The preferential sites of origin of meningiomas correspond very closely to the points where the villi are most prevalent (Rubinstein 1972). Meningiomas account for about 13 to 18% of all primary intracranial tumors (Rubinstein 1972). In the posterior fossa, the CPA is the most common location; two thirds of the posterior fossa meningiomas arise at the porus acusticus or medial to it, near the superior petrosal sinus (Nager and Masica 1970; Nager et al. 1983). According to Brackmann and Bartels (1980) meningiomas account for 3.1% of the CPA tumors (glomus tumors were excluded from their study).

Meningiomas occur at any age, most commonly between 20 and 60 years of age, with the peak incidence rate at about 45 years (Nager et al. 1983). Incidence in females is greater than in males (Rubinstein 1972). Small symptomless meningiomas are often found in elderly, postmortem subjects (Rubinstein 1972). Symptoms of CPA meningiomas can be minimal and often vague, even with large tumors (Kumar et al. 1988). Initial symptoms can be otologic (Kumar et al. 1988). Meningiomas represent a serious form of neoplasm, characterized by frequent recurrences and metastases, which spread beyond the skull (Nager et al. 1983). The predominant symptoms of meningiomas involving the temporal bone are progressive hearing loss, headaches, vertigo, tinnitus, otorrhea, otalgia, facial weakness and/or loss of taste (Nager et al. 1983).

Kumar et al. (1988) studied 5 patients with CPA meningiomas. Saccadic tests were normal in all patients. The PEM test was saccadic in one patient and normal in the others. Three of the patients had subjective feelings of imbalance or dizziness.

According to Lalwani (1992), clinical manifestations of CPA meningiomas are similar to those of vestibular schwannoma (hearing loss and tinnitus) and are to some extent, more common in vestibular schwannoma, but trigeminal dysfunction occurs more often in CPA meningiomas. Lalwani (1992) reported that physical findings and audiovestibular test results are also similar in vestibular schwannoma patients and CPA meningioma patients.

Glomus jugulare tumor

Glomus jugulare tumors are benign but locally invasive neoplasms (Belal Jr. and Sanna 1982). They arise from elements that form part of the chemoreceptor system, and originate in the middle ear from the glomus jugulare (which consists of a group of cells situated in the adventitia of the jugular bulb), or along the ramus tympanicus of the glossopharyngeal nerve (Rubinstein 1972). The histologic picture is identical with that of a carotid body tumor; the diagnosis presents no difficulty in cases where the histologic picture is typical, but may be missed in those examples presenting clinically as a posterior fossa tumor (Rubinstein 1972). Glomus jugulare tumors often follow a consistent clinical pattern in their growth and extension (Rosenwasser 1968). According to Rosenwasser (1968), some glomus jugulare tumors originate or arise from glomus structures in the jugular bulb region, and then spread elsewhere, while other tumors remain confined to the middle ear.

The diagnosis of glomus jugulare tumors is based on both clinical and radiological studies (Belal Jr. and Sanna 1982). A history of unilateral progressive conductive hearing loss, pulsating tinnitus synchronous with the heartbeat, and episodes of acute bleeding from the ear are all symptoms of glomus jugulare tumors (Belal Jr. and Sanna 1982). Large glomus jugulare tumors easily affect the inner ear (Belal Jr. and Sanna 1982); sometimes patients with glomus jugulare tumors experience dizziness (Rosenwasser 1968). There appears to be no studies of saccade tests and pursuit tests in glomus jugulare patients.

Medulloblastoma

Tumors of neuronal and glial origin arising from the cerebellum and brain stem of adult patients may mimic an extra-axial CPA tumor (e.g., vestibular schwannoma, meningioma), and not present as an intra-axial tumor (House and Burt 1985). The site of origin and presumed tissue type may not be evident even after a complete neurotologic evaluation and computed tomography (CT) (House and Burt 1985). But they behave more aggressively than the more common extra-axial CPA tumors (House and Burt 1985). Medulloblastoma is a malignant tumor of glial origin, a primary brain tumor occurring in the cerebellum (Rubinstein 1972). Medulloblastoma cells are largely primitive or poorly differentiated. Most medulloblatomas show little or no evidence of differentiation (Rubinstein 1972). Medulloblastoma is a common mid-line posterior fossa tumor of childhood, but it may occur in adults when it is more laterally placed (Rubinstein 1972; House and Burt 1985). Approximately one-third of these cases will occur in adolescence and early adulthood, between the ages of 15 and 35 years; mainly situated in the lateral lobes (Rubinstein 1972). It may sometimes present in the CPA (House and Burt 1985; Brackmann and Bartels 1980).

The clinical picture of medulloblastoma is almost always that of a posterior fossa tumor (Rubinstein 1972). When present in the CPA, the symptoms of the tumor are produced by mass effect of tumor on adjacent structures in the CPA (Brackmann and Bartels 1980). The rapid development of audiovestibular symptoms in patients with symptoms of brain stem dysfunction and normal petrous pyramid x-rays should lead one to suspect an axial brain stem neoplasm (Brackmann and Bartels 1980; House and Burt 1985).

After a review of the literature, there appears to be no studies of saccade tests and pursuit tests in patients with CPA medulloblastoma.

c) Hemangioblastomas

Hemangioblastoma (HAB) is widely regarded as being vascular in origin (Rubinstein 1972), a cytologically benign vascular neoplasm of the CNS (Resche et al. 1993). Although grossly well defined, HABs have no capsule; the neoplasm is always found to reach the pia, and it often sprouts in a somewhat irregular fashion to the adjacent brain (Rubinstein 1972). Incomplete removal, therefore, leads to recurrence (Rubinstein 1972).

HABs have their own anatomical, pathological, clinical and epidemiological characteristics that separate them from other vascular tumors of the neuraxis (Resche et al. 1993). They usually present as cystic cerebellar tumors (Rubinstein 1972; House and Burt 1985). HABs are relatively uncommon, and their incidence ranges from 2 to 3% of all CNS tumors (Resche et al. 1993). HABs occur most often in posterior fossa, almost always in the cerebellum (Rubinstein 1972; Resche et al. 1993), occasionally in the spinal cord and rarely in supratentorial locations

(Rubinstein 1972; Constans et al. 1986). HABs comprise 8 - 12% of tumors within posterior fossa (Olivecrona 1952; Constans et al. 1986). All areas of the cerebellum may be involved, but the paramedian hemispheric area is especially vulnerable (Rubinstein 1972). According to Resche et al. (1993), cerebellar HABs are usually located in hemispheres, less frequently in the vermis and rarely in the tonsils. In some cases, the HAB has occurred as a CPA tumor (Brackmann and Bartels 1980; House and Burt 1985; Resche et al 1993). HAB may occur either as a single lesion or as a multicentric tumor (Resche et al. 1993). HABs may occur at any age (Rubinstein 1972), but the peak is between 20 and 40 years of age (Constans et al. 1986). Males are affected more frequently than females (Rubinstein 1972; Constans et al. 1986; Resche et al. 1993). Although familial cases and association with von Hippel-Lindau syndrome have been documented (Olivecrona 1952; Constans et al. 1986), most HABs arise sporadically (Olivecrona 1952). HABs may occur as a part (the retinal and neuraxial component) of the von Hippel-Lindau syndrome; an inherited autosomal dominant disorder characterized additionally by retinal angiomas, renal cysts or carcinoma, pheocromocytoma, and pancreatic cysts or carcinoma (Rubinstein 1972; Resche et al. 1993). According to the size of tumor and its site in the posterior fossa, clinical symptoms may vary.

Constans et al. (1986) made a study of 40 cases of posterior fossa HABs treated in their clinic. Most of their patients had a large cyst with or without a visible mural nodule. They didn't report the exact size of the cysts or tumors. In their series, 85% of the patients had symptoms due to intracranial hypertension (headache, vomiting), while dizziness and disturbances of equilibrium appeared as initial symptoms in about 40% of cases, and disturbance of gait was found in 25% of the cases.

According to Resche et al. (1993 - a review study), headache is the most common initial symptom present (> 90% of cases), but vomiting and gait disturbances are less frequent.

Büttner et al. (1994) studied eye movements in two patients with well-defined lesions (a-v malformation, HAB) of midline cerebellar structures including the fastigial nuclei on both sides. These patients did not have any lesions in the flocculus or in the brain stem, but both had bilateral lesions in the vermis. PEMs were well preserved, but saccades were severely dysmetric (hypermetric) symmetrically.

d) Infarction of cerebello-brain stem

The posterior fossa is supplied by branches of vertebral and basilar arteries, i.e. posterior and anterior inferior cerebellar arteries (PICA and AICA), superior cerebellar artery, anterior spinal artery and pontine branches of basilar artery. Depending on whether the artery thrombosed or ruptured, symptoms vary from slight to severe. Usually, the infarction affects both brain stem and cerebellum; infarctions that affect

only the cerebellum are comparatively rare (Büttner et al. 1981; Keller 1988; Magnusson and Norrving 1993).

Ischemia in the AICA distribution damages the central and peripheral vestibular system. It presents with isolated vertigo, vertigo associated with cochlear symptoms, or vertigo associated with dysfunction of the dorsal lateral pons and cerebellum (Oas and Baloh 1992). Diseases of posterior circulation (vertebrobasilar distribution, AICA and PICA distributions) may present with vertigo that is associated with central symptoms, with isolated vertigo, with vertigo and cochlear symptoms, or with a combination of central and peripheral abnormalities (Lewis 1996). Vertigo in these cases is usually monophasic (i.e. in stroke), but vascular disease affecting the vertebrobasilar circulation (transient ischemic attacks) present with recurrent episodes of vertigo (Lewis 1996). However, according to Amarenco et al. (1990), Pierrot-Deseilligny et al. (1990), and Magnusson and Norrving (1993), in cerebellar infarctions vertigo is the first and the most prominent, if not the sole, symptom. Infarction in the distribution area of distal PICA causes acute vertigo and nystagmus, which can simulate acute peripheral vestibular disorders (Rubenstein et al. 1980). The AICA and branches of PICA supply the flocculo-nodular lobe (Carpenter and Sutin 1983). Infarction in the territory of superior cerebellar artery, including the posterior inferior vermis, the oculomotor vermis (Noda and Fujikado 1987a; Noda and Fujikado 1987b; Noda et al. 1988), dentate and fastigial nucleus (Carpenter and Sutin 1983), causes ataxia of gait and seldom any vertigo (Kase et al. 1985).

Kato et al. (1986) studied positional nystagmus, optokinetic nystagmus, fixation suppression of caloric nystagmus and PEM tests in cerebellar lesions. They observed a patient with a large low-density area in the left cerebellum (indicating a cerebellar infarction), and the patient had no cerebellar signs and symptoms nor abnormal findings in the oculomotor tests. In bilateral cerebellar infarctions and hemorrhages, PEMs were always pathologic (saccadic) and in unilateral cases PEMs were mostly pathologic (in 12 to 14 cases) (Kato et al. 1986).

Yee (1989) made a study of findings in clinical examinations and results of eye movement recordings in 91 consecutive patients with downbeat nystagmus. PEMs, saccades, VOR and visual-vestibular interactions and optokinetic nystagmus were tested in addition to different nystagmus tests. Of these patients, 22 patients had a cerebellar or cerebello-brain stem infarction. Diagnosis of the cause of downbeat nystagmus was obtained by neurologic examinations; CT scans were made, but could not be used in obtaining the diagnosis (e.g., in most patients with infarctions CT scans were not sensitive enough to demonstrate the lesions). The majority of downbeat nystagmus patients (72 out of 91) were tested with eye movement tests, and almost all (99%) had abnormal horizontal eye movements of cerebellar pattern (including impaired PEMs, impaired OKN, inability to suppress VOR) (Yee 1989). When their

results were compared to control subjects (19) and cerebellar atrophy patients (11), control subjects differed from both patient groups, but the patient groups didn't differ from each other. In 87% of the patients with downbeat nystagmus, the localizations of lesions made by eye movement recordings were restricted to the cerebellum alone. According to Yee (1989), it seems that downbeat nystagmus is usually produced by lesions in the cerebellum which also damage pathways that control the horizontal PEM system and the visual-vestibulo-ocular interactions.

In a study of Magnusson and Norrving (1993), 24 consecutive patients with sudden onset of vertigo but without cochlear or neurological symptoms, were examined with neuro-imaging techniques and with saccades, PEMs, caloric nystagmus, spontaneous nystagmus, gaze nystagmus and optokinetic nystagmus. MRIs or CTs were imaged on all patients, and Doppler sonography of the vertebral and carotid arteries were investigated. Six of these 24 patients diagnosed as having a vestibular neuritis had a verified cerebellar infarction in MRI or CT. Vertebral artery occlusion without a demonstrated infarction was found in two subjects. All of the subjects with cerebellar infarctions had severely reduced PEM. In other subjects, PEM was not considered pathological.

Allum et al. (1991) studied normal subjects, patients with peripheral vestibular disorders, vestibular schwannoma, central vestibular disorder (pontine infarction) and tested them with optokinetic nystagmus, PEM test, VOR and caloric responses. Of these tests, contralateral slow-phase velocity to the 15°/s stimulus in the PEM test and gain asymmetry to a 30°/s optokinetic stimulus were the best measures to differentiate patients with central vestibular disorder from those with peripheral vestibular disorder and from normal subjects. However, PEM measures could not significantly differentiate patients with central vestibular disorder from patients with vestibular schwannoma. This may be due to the frequent correcting saccades demonstrated by patients with vestibular schwannoma in the eye tracking test (Allum et al. 1991).

Pierrot-Deseilligny et al. (1990) observed an infarction in the region of the left PICA (mainly its medial branch) in a patient that was 80 years old. The patient had experienced sudden vertigo with unsteadiness, vomiting, and posterior headache, but she had no auditory symptoms. Her ipsilateral upper limb was ataxic, she had ipsilateral conjugate gaze deviation, and concomitantly the head deviated towards the lesion. Otherwise, she did not have any neurologic deficits. Her MRI showed damages in the inferior part of the vermis (from VI to X lobules), and the lesions extended to the inferior part of the ipsilateral cerebellar hemisphere. The flocculus, cerebellar peduncles and brain stem were spared. Horizontal saccades were totally normal; foveal PEM tested with a sinusoidally moving small target was saccadic bilaterally. The velocity gain of PEM was bilaterally low. The case study of Pierrot-Deseilligny et

al. (1990) is in line with the findings of Suzuki and Keller (1983), Keller (1988) and Keller and Heinen (1991), showing that the posterior vermis is involved in PEMs.

2. F. Diagnostic aspects

Audiometry and auditory brain stem response

Pure tone audiometry and speech discrimination are used to evaluate the hearing of the subject. The discrimination between cochlear and retrocochlear hearing loss can be assessed with pure tone audiometry and speech discrimination to some extent. Auditory brain stem response (ABR) is used to detect the site of lesion in the auditory pathways.

Previously, ABR was used to detect a vestibular schwannoma or other CPA tumors. In early ABR studies, the detection rate was about 70 to 80% (Dauman et al. 1988; Hashimoto et al. 1991; Ruckenstein et al. 1996) and the most profound problems have been found to concern detection of intracanalicular schwannomas (Wilson et al. 1992; Godey et al. 1998). The detection rate of ABR, however, has been above 95% according to 36 studies reviewed by Brackmann and Kwartler (1990). In a study by Selesnick et al. (1993) of 126 vestibular schwannoma patients, the ABR was entirely normal in 6% of those patients for whom ABR was studied before the referral. These patients had tumors that measured less than 10 mm in diameter. In the same study, 4% of the cases had a totally normal audiologic screening profile (speech reception threshold < 20 dB, speech discrimination score > 80%, high frequency hearing, i.e. in 4 kHz, < 20 dB). Unfortunately, ABR misses a significant number of CPA tumors (8%), especially those of nonvestibular schwannomas (one-third are false-negatives) (Welling et al. 1990).

According to Brackmann and Forquer (1983), 25% of posterior fossa lesions have normal ABR.

Hearing thresholds may be normal in pure tone audiometry in patients with vestibular schwannoma. In the study of Shaan et al. (1993), 6 % of 100 consecutive patients with vestibular schwannoma had normal pure tone audiometry and a normal speech discrimination score. In the study of Selesnick et al. (1993), 26% of the patients with vestibular schwannoma experienced a sudden hearing loss. In addition, some of the vestibular schwannoma patients manifested a cochlear type of hearing loss rather than a retrocochlear type (Flood and Brightwell 1984).

Saccade tests and pursuit eye movement tests

In the study of Bergenius et al. (1983), there were three false-negative results with caloric, eye tracking and gaze nystagmus tests in 21 vestibular schwannoma patients

(tumor size ranged from 6-40 mm). In patients with tumors larger than 15-20 mm, tests for eye movement, ABRs and stapedius reflex were pathologic.

Hulshof et al. (1989) observed that in most of the vestibular schwannoma patients studied, the peripheral part of the vestibular system was severely disturbed. This could cause abnormal saccades (in 19% of cases), pathologic PEMs (42%) and pathologic caloric tests (73%).

Patients with large CPA-tumors (>30 mm) frequently elicit pathologies in saccadic eye movements (47% pre- and postoperatively) and PEMs (66% preoperatively, 53% postoperatively) (Nedzelski 1983). According to Nedzelski (1983), the oculomotor system is seldom affected by small or medium sized tumors (<30 mm). For large tumors, the PEM defects are most commonly bilateral; in saccadic eye movements, the saccadic accuracy is impaired (saccades are hypermetric), but saccadic peak velocity is normal (Nedzelski 1983).

Patients with peripheral labyrinthine lesions can have initial deficits (in less than 25% of patients) in PEM, but they are rapidly compensated for after the acute lesion (Baloh et al. 1977). Patients with chronic peripheral vestibular disorders usually have normal PEM and optokinetic nystagmus (Baloh et al. 1977).

Saccadic eye movements are usually unaffected by CPA tumors, although sometimes ipsilateral saccadic dysmetria (in less than 25% of patients) is found (Baloh et al. 1977). According to Baloh et al. (1977), patients with large CPA tumors (producing brain stem compression) often have deficits in PEM (reduced velocity gain in more than 75% of patients) and optokinetic nystagmus, whereas patients with small CPA tumors (without brain stem compression) have normal PEM and optokinetic nystagmus.

Patients with cerebellar atrophy have bilateral and consistent saccade dysmetria, as well as impaired PEMs (in more than 75% of cases) (Baloh et al. 1975a; Baloh et al. 1977). Because of anatomical proximity of oculomotor trajectories and gaze centers in the brain stem, brain stem disease usually cause impairment of saccades and PEMs (Baloh et al. 1977).

In fronto-parietal cortical lesions (tumors), the SRT is bilaterally increased in more than 75% of the patients; PEM is ipsilaterally pathological, and as well, the saccades are hypometric contralaterally in 25-75% of patients. Saccadic peak velocity is bilaterally slowed in less than 25% of patients (Baloh et al. 1977).

Imaging

First generation CT scanners detected vestibular schwannoma tumors larger than 20 mm (Welling et al. 1990). High resolution CT with air contrast then followed, and with them tumors from 10 mm could be imaged (Welling et al. 1990). The MRI has replaced the CT in screening work-ups for vestibular schwannoma. MRI is the most

effective with gadolinium enhancement, permitting tumors as small as 3 mm, or possibly smaller to be diagnosed (Welling et al. 1990; Telischi et al. 1993).

According to Zbar et al. (1997), intralabyrinthine vestibular schwannomas can sometimes be missed even with gadolinium-enhanced MRI. They reported that a small population of patients diagnosed with Menière's disease might actually have an isolated intralabyrinthine vestibular schwannoma as a cause of their symptoms.

According to Constans et al. (1986), small HABs can escape detection with CT scanning. According to Resche et al. (1993), in infratentorial HABs the CT demonstrates hydrocephalus (if it exists) and the neoplasm, but the sensitivity and accuracy of CTs are limited by beam-hardening artifacts induced by the petrous bone. They believe that MRIs are the best imaging modality for most intracranial tumors, particularly in the evaluation of brain stem tumors. They draw the conclusion that the MRI, especially the Gd-DTPA enhanced MRI, appears more sensitive than the CT in detecting lesions and delineating their exact nature.

2. G. Knowledge-based systems, decision tree analysis and oculomotor deficits

Knowledge-based systems have recently been applied in medicine to assess laboratory tests, to improve diagnostic work-ups and to enhance resolution in imaging examinations. Knowledge-based systems can store, retrieve and analyze vast amounts of knowledge and data (Hedberg 1993). Knowledge-based systems can be combined with other technologies, such as neural networks (adaptive, where it learns and trains itself), case-based reasoning (the ability to store, analyze and process previous experiences) and genetic algorithms (search an entire domain for a solution, breeding on successive success paths) (Hedberg 1993). In the vestibular field, three expert programs have been developed (Gavillan et al. 1990; Mira et al. 1990; Kentala et al. 1996a; Kentala et al. 1996b). So far, in only one of these programs have the voluntary eye movements been included (Kentala et al. 1996a; Kentala et al. 1996b).

There are various knowledge-based systems that are capable of inferring and providing solutions from the data that is available. These knowledge-based systems are adaptive, and most can operate with incomplete data. One of these systems is called the decision tree induction (Quinlan 1990). It employs a top-down, divide-and-conquer strategy that partitions off the given set of objects into smaller and smaller subsets in step with the growth of the tree (Quinlan 1990). The analysis starts with a sample of objects that belong to one of the possible classes. The properties of objects are known only through the values of attributes. Two objects can be distinguished only if they have different values for some attribute or attributes. Attributes can be nominal or continuous variables. The decision tree data set is trained with learning.

A training set (a collection of objects whose classes are known) is always used. The training set must be a representative sample of the population studied (Quinlan 1990).

The assumption underlying all inductive learning is that if patterns can be identified that account for the class membership of known objects, these patterns (rules) can be used to predict classes of new unseen objects. A training classification task provides the classification rule that works well on the objects in a given training set (Quinlan 1990). A decision tree is a recursive structure for expressing the classification rules, and it comprises of nodes and leaves. The tree may consist of a test that has a set of different possible outcomes. There will be a subsidiary decision tree for each outcome. The nodes represent tests based on features of example cases, and leaves represent classes (i.e. decisions). In classification, the algorithm starts at the root of the tree. If it is a leaf at the root of the tree, the object is assigned to the class associated with that leaf. If the root of the decision tree is a test, the outcome of this test for a given object is determined and the process continues using the subsidiary decision tree associated with that outcome. An object is thus classified by tracing out a path from the root of the decision tree to one of its leaves. The root attribute is thought to be the most important one in the classification (Quinlan 1990).

The decision tree analysis can be used to evaluate the correct classification of objects or to predict a possible class of a new object. The validity of this analysis increases with increase in the number of cases (objects) in the analysis (Quinlan 1990, Kentala et al., in press).

3. PURPOSE OF THE STUDY

1. To study the effect of age and gender on voluntary eye movements.

2. To study the laterality of voluntary saccades and the repeatability of voluntary eye movements with special reference to PRPEM.

3. To compare the EOG and MOG technique in recording the voluntary eye movements.

4. To study the effect of certain peripheral or central lesions on voluntary eye movements.

5. To evaluate with the decision tree algorithm, the validity of voluntary eye movements in discriminating the site of lesion.

6. To study the relationship between the signs, symptoms and findings, and voluntary eye movements in patients with peripheral or central lesions.

4. SUBJECTS AND METHODS

4. A. *Subjects*

4. A. 1. Control subjects

a. Normative data

Normative data of voluntary eye movements was collected from 45 healthy subjects. In the constant and pseudo-random saccades, mean age of control subjects was 48 years (18-88 years); 30 were females and 15 were males. In the PRPEMs, the mean age of control subjects was 45 years (18-86 years); 30 were females and 15 were males.

b. Aging

For studying the effect of aging on voluntary eye movements, 119 normal subjects were tested. Included among the 119 subjects, 45 subjects were from the above normative data group. The mean age of the subjects was 37 years (range 6.5 to 88 years). There were 40 children under 16 years (22 girls, 18 boys), 38 adults from 18 to 49 years (24 females, 14 males) and 41 elderly from 50 to 88 years (26 females, 15 males).

c. Gender

Differences between the genders were studied in age-matched female and male subjects selected from the subject pool. In all, 25 females and 25 males were studied. The mean age of the subjects was 50 years (range 15.5 to 87 years).

d. Side difference

The laterality of saccades was studied on the 45 subjects of the normative data group.

e. Repeatability

The PRPEM tests were done in two different days to 17 normal subjects who were tested for analyzing the repeatability of PRPEM. Their mean age was 34 years (18 to 48 years); 10 were females and 7 were males. The interval between these two measurement times averaged 6 days (range from 1 to 14 days).

f. EOG and MOG measurement

Ten normal subjects were tested to the study differences of voluntary eye movements recorded by EOG and MOG methods. The mean age of the subjects was 38 years (29 to 51 years); 2 were females and 8 were males. Constant and pseudo-random saccades were recorded in 9 subjects; PRPEMs were recorded in 10 subjects.

All the normal subjects were healthy without any neurotologic or ophthalmologic disorders. The refraction disorders in control subjects and patients were corrected with eyeglasses or contact lenses. The visual acuity was least 0.8 to 1.0. Some of the subjects had (latent) squint (under 7º) but those did not call for any action.

All tested subjects participating in the studies (normal subjects and patients) were volunteers and informed consents according to the Helsinki Declaration were provided. The study protocol was reviewed and approved by a local ethical committee at the Helsinki University Central Hospital (HUCH).

4. A. 2. Patients

a) Menière's disease

Sixty-two patients with moderately severe to severe Menière's disease were examined. Eye movements were tested before (49 patients) and after (13 patients) the intratympanic gentamicin treatment. Mean age was 49.5 years (range 19.5 to 73.5 years). Forty-two were females and 20 were males. Diagnosis of Menière's disease was made on the basis of neuro-otological exams. A CT scan of the inner ear and posterior fossa, as well as MRIs were done as needed. Of the 13 patients who were examined after the gentamicin treatment, 11 had few, if any, symptoms of Menière's disease. Two patients had difficult symptoms; one required a retreatment with gentamicin later, the other developed symptoms in the other, previously healthy ear. Menière's disease was bilateral in 13 out of 62 patients.

Data of symptoms, signs and findings at the time of eye movement testing was collected. The pure-tone average (PTA) of hearing thresholds of 0.5, 1, 2, 3 (= mean of 2 and 4 kHz) kHz (according to Committee on Hearing and Equilibrium of the American Academy of Otolaryngology-Head and Neck Surgery, AAO-HNSF, 1995) was evaluated from the affected and treated ear. The mean of the PTA was 58 dB, ranging from 8 to 120 dB. The working capacity was assessed according to Total Handicap Score of AAO-HNSF in 1985 (AAO-HNS 1985; Pearson and Brackmann 1985), in which the working capacity is expressed on a four-point scale. Working capacity ranged from 2 to 4 and the mean was 3.8. Other signs and symptoms were also classified on a four point scale (1=none, 2=slight, 3=moderate, 4=severe). Mean *tinnitus* was 3.0; the mean severity of the *Tumarkin* drop attacks was 2.1; the mean

unsteadiness was 2.3; and the mean *severity of rotatory vertigo* was 3.3 **(Tables 1a. and 1b.)**. Mean duration of symptoms of Menière's disease before the gentamicin treatment was about 9 years, ranging from 0 to 30 years.

Table 1a. Symptoms, signs and findings of Menière patients evaluated on a four-point scale, and their distribution. It includes tinnitus, the severity of Tumarkin drop attacks, the amount of unsteadiness in attack-free periods, the severity of vertigo and the working capacity.

scale

	1	**2**	**3**	**4**	**Total number**
Tinnitus	2	13	31	16	62
Tumarkin	32	3	15	12	62
Unsteadiness	14	18	25	5	62
Rotatory vertigo	5	7	12	38	62
Working capacity	0	0	12	50	62

number of patients in different classes of the scale

Table 1b. The mean PTA of hearing thresholds at 0.5, 1, 2 and 3 kHz in Menière patients (3 kHz = mean of 2 and 4 kHz), and its distribution.

PTA	*<20*	*20-39*	*40-59*	*60-79*	*80-99*	*100-119*	*>120 dB*	*in total*
Number of patients	4	10	21	16	8	1	2	62

b) Operated cerebello-pontine angle tumors

Altogether, 35 patients with operated CPA tumors were randomly selected from about 350 CPA tumor patients treated between 1979 and 1992. All were examined with voluntary eye movement tests. From this group, 31 patients had vestibular schwannomas, four had meningiomas, one had a glomus jugulare tumor and one had a medulloblastoma. Two patients had a bilateral vestibular schwannoma. Out of the 35 patients with operated CPA tumors, 20 had been on the left side and 17 on the right (two patients had bilateral vestibular schwannomas). Mean age of the operated CPA tumor patients was 50.5 years (range from 18 to 67 years). There were 21 females and 14 males. The largest axial diameter (according to Jackler 1994; Lo 1994) of the CPA tumors had ranged from 7 to 60 mm (mean 32.4 mm), and patients were post-operative from 1.5 months to 12 years (mean 4 years) before voluntary eye

movement tests were taken. The operation had been radical in 26 patients, and in 9 cases it had been a resection.

Table 2a. Data about the operated CPA tumor patients and their operations.

	mean	*minimum*	*maximum*
age; (y)	50.5	18	67
diameter; (mm)	32.4	7	60
duration of operation; (h)	7.5	3.75	14
interval*	4y	1.5mo	12y

*y=years, mo=months ; time interval between the operation and eye movement tests

The status of the facial nerve one year after the operation was expressed with a measure evaluating the function of facial muscles according to the House & Brackmann classification *(*House and Brackmann 1985*)* (**Table 2b**). Pure-tone threshold of the affected ear at 1000 Hz before the operation and 3 months after the operation ranged from 0 to 120 dB (mean 57 dB) and from 0 to 120 dB (mean 112 dB), respectively (**Table 2c**)**.** CPA tumors had been cystic in 5 patients. Duration of the operation procedure lasted from 3 hours 45 minutes to 14 hours (mean 7.5 hours).

Table 2b. The function of the facial nerve assessed by the function of muscles in face, and its distribution among operated CPA tumor patients.

House & Brackmann classification (the function of the muscles of face)							
	House & Brackmann scale						
	1	***2***	***3***	***4***	***5***	***6***	
number of patients	11	3	4	5	6	6	(total 35)
			(mean 3.3)				

Table 2c. Pure tone thresholds (dB) of the affected ear in 1000 Hz assessed before operation and 3 months after operation.

pure tone threshold of 1.0 kHz dB scale	*before operation, number of patients*	*3 months after operation, number of patients*
0-20 dB	7	1
21-40 dB	7	1
41-80 dB	12	1
80-120 dB	9	32

The clinical data of operated CPA-tumor patients was used for examining the factors that determine PRPEM and saccade deficits in operated CPA-tumor patients.

c) Operated hemangioblastoma

Twenty patients with HAB of the cerebellum were examined. They were randomly chosen from patients who had been operated for HAB of the cerebellum in the Department of Neurosurgery at HUCH during the years of 1966-1992. Their mean age was 51 years (range 35 to 74 years). Fourteen were females and 6 were males. The interval between the latest operation and voluntary eye movement tests ranged from 10 months to 26 years, and the mean interval was 11.5 years. In 4 subjects, 2 to 5 operations were necessary for each. One patient had a cyst near the HAB. In this patient only was the cyst operated on the first time; in the second surgery the tumor itself was removed with a new cyst**.** The second patient had 5 operations because of HAB recurrence due to von Hippel-Lindau syndrome (Rubinstein 1972; Resche et al. 1993). The third patient had 3 resections of cerebellar HAB, and the fourth patient had 2 operations because of HAB recurrence due to von Hippel-Lindau syndrome. MRIs taken of the head were done to all operated HAB patients with high-field MRI (1.0T and/or 1.5 T), as well as gadolinium (Gd-DTPA) enhancement. The MRIs were further analyzed in the study to reveal the anatomic site of the lesion.

An ophthalmologist made neuro-ophthalmologic examinations of all patients with HAB. None of the patients demonstrated ophthalmologic lesions that could essentially affect the results of the eye movement tests.

d) Infarctions of cerebello-brain stem

Twenty patients with infarctions of cerebellum, cerebello-brain stem or brain stem were examined. Their mean age was 53 years (range from 39 to 64 years). Six were females and 14 were males. The infarctions had been from 2 weeks to 10.5 years (mean 3.5 years) before the eye movement tests were done. These patients were referred from the Departments of Neurology and Neurosurgery at HUCH, and were

chosen from among patients treated in those departments from 1981 to the beginning of 1993. Those patients who had an infarction more than a year before the eye movement tests, were imaged with low-field (0.1T) or high-field (1.0 T and/or 1.5 T) MRIs of the head. From the other patients, MRIs were re-evaluated that had been taken at the time infarctions.

c. and d. The MRI findings were analyzed in operated HAB patients and patients with infarction of cerebello-brain stem with special reference in the cerebellum to the *flocculus*, *fastigial nucleus*, *oculomotor vermis*, and in the *brain stem* to PPRF, vestibular nuclei, prepositus hypoglossi nucleus, inferior olivary nucleus and oculomotor nuclei. (Kretschmann and Weinrich 1992). Irrespective of whether the finding was unilateral or bilateral, it was classified as one. When it did not exist, it was classified as zero. In some cases, there were no MRI findings in the brain stem, but there were large lesions just beside it impinging on the brain stem. Also, the symptomatology (patients with infarction) or operation data (patients with HAB) showed that the brain stem was indeed damaged. In these cases, the finding of brain stem was classified as one (**Table 3**.).

Table 3. Patients with infarction of cerebello-brain stem and operated HAB patients and their MRI findings.

Operated *HAB patients*, n = 20				
	Flocculus	*fastigial nucleus*	*oculomotor vermis*	*brain stem*
n	10 (0)	8 (3)	9 (5)	4 (1)
ratio	10/20	11/20	14/20	5/20
Patients with infarction of cerebello-brain stem, n = 20				
	Flocculus	*fastigial nucleus*	*oculomotor vermis*	*brain stem*
n	6 (0)	7 (1)	10 (2)	12 (1)
ratio	6/20	8/20	12/20	13/20

Patients with unilateral lesions; numbers in parenthesis ( ) = the number of patients with bilateral lesions.
n=number of patients
ratio = the number of uni- and bilateral lesions / the total number of patients

4. B. *Equipment and program*

4. B. 1. Recording methods

EOG recording was done binocularly by placing active Ag - Ag-Cl electrodes lateral to

the outer canthi of the eyes and the reference electrode on the forehead. Careful test preparations were done. Horizontal eye movements were measured. The resolution of the EOG recording system was about 1º (Juhola 1991a).

The device for recording MOG consisted of 2 vertical and 2 horizontal induction coils 0.73 and 1.10 m in diameter respectively, the verticals were at a distance of 0.38m from each other and the horizontals were at a distance of 0.57m from each other. The system was custom-made. The resolution of the MOG method was about 0.1º. The subject was seated on a chair at the center of the induction coils. The search coil (Skalar Medical, The Netherlands) was placed on the right eye in all subjects. Before application of the search coil, the eye was anesthetized with a topical anesthetic, (0.4% oxybuprocaine HCl, Oftan Obucain®). The wearing time of the scleral annulus on the eye was restricted to about 30 minutes.

An ophthalmologist examined the status of the cornea after the study of recording methods. Some subjects had significant endothelial edema caused by hypoxia under the thick scleral annulus; corneal epithelial erosions were also noticed in some subjects.

4. B. 2. Stimulus

A visual stimulator with a laser spot was used to guide saccades and PRPEM. The stimulator reflected a laser beam to the black wall in a darkened room in front of the subject who was told to follow with the gaze a dot caused by the beam. A head support was used to restrict movement. The stimulator was controlled by an HP71B microcomputer (Juhola et al. 1989). The main microcomputer (HP9000 series 300) controlled the HP71B by giving commands at the onset and end of the stimulator function. (Juhola et al. 1989).

To stimulate saccades at a constant amplitude of 60°, the stimulator was programmed to move the laser beam between two fixed locations (+ 30° <=> - 30°) on a time basis. The constant saccades were predictable with reference to the magnitude of target steps, but unpredictable with reference to the time interval of target steps, ranging from 0.9 to 1.7s.

In the pseudo-random stimulation of saccades, the laser beam jumped 20°, 40° and 60° to the right and the left pseudo-randomly (+ 10° <=> - 10°; + 20° <=> - 20°; + 30° <=> - 30°). The time interval of target steps was unpredictable, ranging from 0.9 to 1.7s (Aalto et al. 1989).

Figure 5A. Stimulation of constant saccades

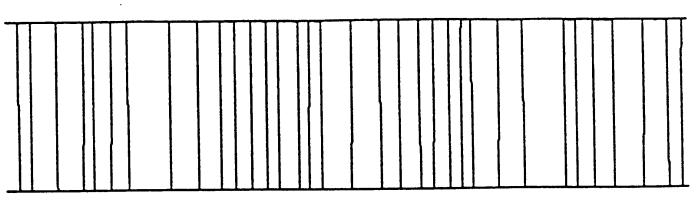
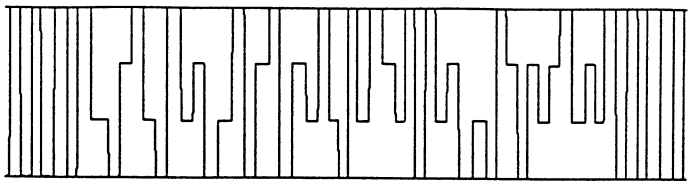
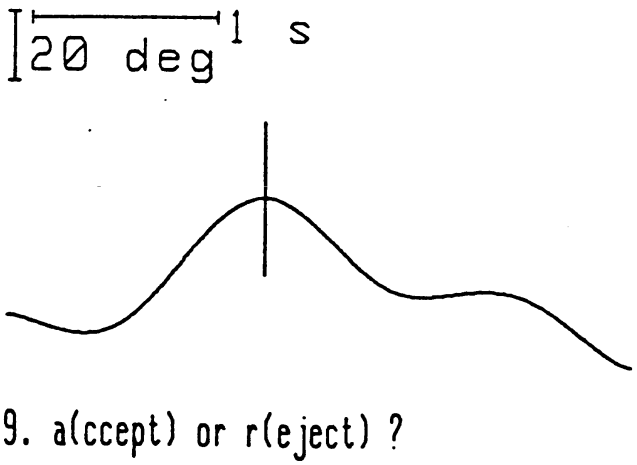


Figure 5B. Stimulation of pseudo-random saccades.



To stimulate PRPEMs, two sinusoids of different frequencies were programmed. A primary frequency of 40° amplitude was mixed with a secondary lower-frequency signal of 20° amplitude. The frequencies were not allowed to be one another's multipliers (Aalto et al. 1989).

Figure 5C. A part of the stimulation of PRPEMs



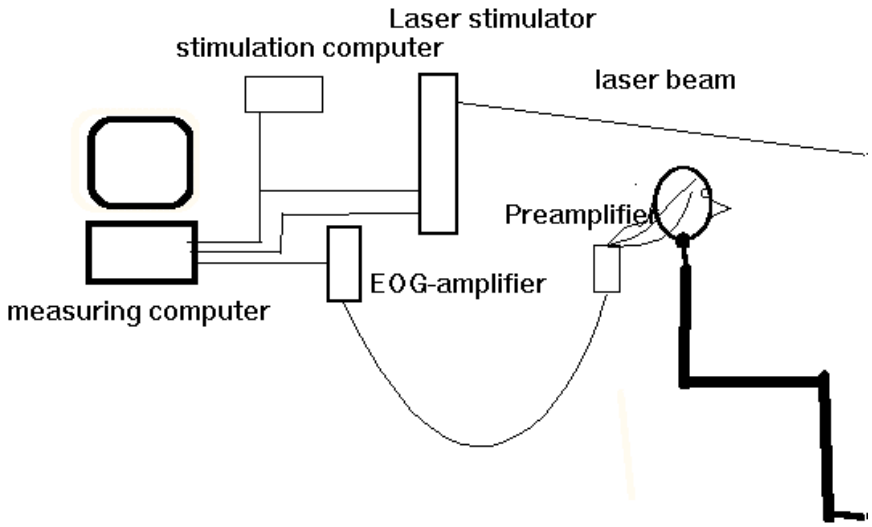
4. B. 3. Equipment and signal analysis

The computer performed analysis from the eye movement signals and computed the results (Juhola et al. 1989). The computer was furnished with an analog-digital

converter (HP98640A) with a 13-bit resolution (Juhola et al. 1989). The sampling frequency was 400Hz (Juhola et al. 1989) which was high enough to include the details of the saccades (Juhola and Pyykkö 1987; Juhola et al. 1985b). The analog signals of the eye movements were amplified and low-pass filtered by using an analog filter with a cut-off frequency of 100 Hz (Juhola et al. 1989). After the analog-to-digital conversion, the signals were digitally filtered with a nonlinear hybrid median filter (Juhola 1991b) at a cutoff frequency of 70 Hz (Juhola 1990) with a filtering window of nine samples (Juhola 1991b).

After filtering, the calibration of signals was made (Juhola 1990). This was performed by using a saccade of a constant amplitude (±10° of amplitude and 10s of duration) for PRPEM tests, and it was done at the beginning of each test. In the case of saccade tests, the calibration (à 9s) was done at the beginning and end of each saccade test with saccades of ±30º amplitude. In the study for testing differences in EOG and MOG recording methods, a horizontal calibration of ±10º by amplitude and 15s by duration was done before each voluntary eye movement test.

Figure 6. A figure of the computer system used.



Syntactic Pattern Recognition Method of Eye Movement: The recognition and analysis programs of eye movements were implemented in Pascal programming language (Juhola et al. 1989).

The computer used a syntactic method for the recognition and analysis of eye movements. The syntactic pattern recognition method was based on formal languages and grammars and on a parser algorithm which analyzed digital eye movement signals

as strings (sequences of grammatical symbols) of the formal languages (Juhola 1990). Both the stimulus signal and the response signal were processed and analyzed.

a. Saccades

In saccades, the angular velocity during a 20 ms segment of signal was computed by linear regression that gave a mean velocity value for the segment (Juhola 1988a; Juhola 1990). Thereafter, the velocity value of every segment was assessed by comparing the velocity value of the segment to given limits (Juhola 1990). When the magnitude of the angular velocity exceeded a certain threshold found experimentally, the beginning of a saccade was found (Juhola 1986). The end of a saccade was found when the magnitude of velocity fell back below the threshold (Juhola 1986). The value of ±40°/s was used as the limit of the velocity for saccades (Juhola 1986; Juhola 1988a). If the absolute velocity of a segment was larger than +40°/s or below -40°/s, that segment could be assumed to be within a saccade. The eye movement segments were expressed in terminals of the formal language according to how they were situated in, above or below the limits (Juhola 1986; Juhola 1988a).

The advantage of the syntactic pattern recognition method is that it reveals the structure of the saccade (syntactic elements) as terminals of the formal language (Juhola 1988b). It can distinguish small artifacts and deviations in signals from eye movements (Juhola 1988b).

b. Pseudo-random pursuit eye movement

The signal was smoothed with a nonlinear median filter in order to dampen noise generated from various biological and physical sources (Juhola 1991c). The angular velocity was calculated segment-wise from the positional signals of the stimulus and its response, as in saccades (Juhola 1991c). Both signals were divided into consecutive segments. The length of the segment was chosen to be 0.040s (Juhola 1991c). Using linear regression, a slope for each segment was computed that was equal to the mean velocity with regard to that segment (Juhola 1991c). Using four different symbol types, exceptionally fast parts in otherwise slow pursuit eye movement signals, were marked to correspond possible saccades, artifacts and noise peaks in them (Juhola 1991c). The idea was to determine those segments of the response that were slow and close to stimulus velocity, and those segments that significantly differed from the stimulus velocity having considerably larger values (Juhola 1991c). The threshold of ± 15°/s above or below the stimulus velocity was applied in the classification of segments (Juhola 1991c). This threshold was found experimentally. Its purpose was to separate saccades as well as other rapid eye movements, e.g., blinks from the slow PEMs (Juhola 1991c).

The syntactic pattern recognition method classified PRPEMs into rising and falling flanks of sine waves as well as corrective saccades (Juhola et al. 1991). The syntactic forms of the signal were analyzed by using a so-called formal language and grammar (Juhola et al. 1991). From the segments, the syntactic pattern recognition method got strings of terminals that the program analyzed (Juhola et al. 1991). After this syntactic pattern recognition process, correction saccades were eliminated from the response signal (Juhola et al. 1991). The program also recognized maxims and minims of the sine waves (Juhola et al. 1991).

4. C. Parameters analyzed in the eye movement tests

4. C. 1. Saccades

The saccade program first recognized the saccades from the signal and then computed the saccadic accuracy (defined in the present work as the difference between stimulus amplitude and response amplitude of the subject), SRT and the saccadic peak velocity (SPV) for each saccade (Juhola et al. 1989). It then computed the mean values and the standard deviations of these parameters in 60º saccades to the left and right (Juhola et al. 1989) in constant and in pseudo-random saccades. In the analysis of saccadic eye movements, only the primary saccades were studied and analyzed in this work.

For statistical analysis of patient data, rightward and leftward parameters were shifted to ipsi- and contralateral parameters according to the site of lesion. In control subjects, the mean of the leftward and the rightward parameter was used as both the ipsi- and contralateral parameter.

4. C. 2. Pseudo-random pursuit eye movement

After the recognition process, the saccades were removed from the response signal (Juhola et al. 1991). Gain was given as a ratio of response and stimulus. For gain determination in this study, the mean ratio of the response and stimulus amplitudes of sine waves (*GA=gain by amplitude*) was used (Juhola 1991c). The *phase* difference (expressed in seconds) was obtained by computing the time difference between maxims (or minims) of the response and the stimulus (Juhola 1991c). Mean phase values were used.

4. D. Test conditions

In PRPEM, tests were done with four frequency combinations to normal subjects and to patients, except to the Menière's patient group and except to the normal subjects in the study of EOG and MOG recording methods. The four frequency combinations

were: 0.15 and 0.35 Hz, 0.25 and 0.425 Hz, 0.3 and 0.7 Hz, and 0.45 and 0.7 Hz. Results of eye movement tests in patients were compared to the results in control subjects. In this comparison, the frequency combinations 0.25 and 0.425 Hz as well as 0.45 and 0.7 Hz were used. These combinations were also used in assessing the correlation between eye movement results and clinical data. The frequency combination of 0.25 and 0.425 Hz was chosen for further analysis in order to reduce the testing time in examining patients with Menière's disease. In preliminary tests, this frequency combination seemed to be effective in differentiating patients from control subjects. In the study for testing EOG and MOG recording methods, two frequency combinations were used in order to reduce the time that the subjects had to wear the search coil on the eye. With these normal subjects, the frequency combinations of 0.25 and 0.425 Hz, and 0.45 and 0.7 Hz were used.

4. E. The site of lesion and voluntary eye movement deficits

To study how the eye movement tests correlate with the site of lesions, the normative and patient data was rearranged. The operated CPA tumor patients were placed in the *brain stem lesion* group, if the diameter of the tumor was above 30 mm, and in the *peripheral lesion* group if the diameter was $\leq$ 20 mm. The operated CPA tumor patients whose diameter of tumor was larger than 20 mm but under or equal to 30 mm were placed in the undefined group. Operated HAB patients and patients with cerebello-brain stem infarction were grouped according to the MRI findings to the groups of *brain stem lesion*, *cerebellar lesion* or *cerebello-brain stem lesions*. Menière patients were placed in the *peripheral* lesion group.

4. F. Decision tree analysis

The decision tree analysis was used to classify the cases according to voluntary eye movements. The data of the site of lesion was used. Decision tree analysis was also done to study the effect of classification with respect to control subjects by changing the classification of lesions to a degree. Patients with peripheral lesions were grouped to the peripheral lesion group; whereas cerebellar, brain stem and cerebello-brain stem lesion groups were placed in the central lesion group.

With the data of three groups (control, peripheral and central groups), the constant and pseudo-random saccade tests were used, together with PRPEM tests with the four frequency combinations, and with GA and mean phase.

Data from the five groups (control subjects, peripheral, cerebellar, cerebello-brain stem and brain stem patients), plus constant and pseudo-random saccade tests were used, together with the PRPEM tests with four frequency combinations and with GA and mean phase values.

4G. Statistical analysis

In studies of control subjects and patients, the order of frequency combinations of PRPEM throughout these studies were randomized according to the Latin square method. Transformations of the parameters were made when needed to normalize the distribution of the parameters (Norusis 1993).

To evaluate the effect of aging on voluntary eye movements, a regression analysis with curve estimation procedure (Norusis 1993) was used. In the curve estimation procedure, the linear, quadratic and cubic functions were applied. One-way analysis of variance (ANOVA; Scheffe's test) (Norusis 1993) was used to study the possible differences in voluntary eye movements between different age groups. The subjects were divided into three groups: young (n = 40 subjects from 6 to 16 years old), middle-age (n = 38 subjects from 18 to 49 years old) and elderly (n = 41 subjects from 50 to above 80 years old). In these studies, the means of rightward and leftward saccade parameters were studied.

In studying the gender differences in voluntary eye movements, the statistical analysis was done with Student's t-test in two independent samples (Norusis 1993). The means of rightward and leftward saccades were used in the analysis. Saccades test and PRPEMs were studied.

To identify individual differences in: 1) the laterality of saccades, 2) between EOG and MOG recording methods 3) between constant and pseudo-random saccade tests, and 4) between 20º and 60º saccades in pseudo-random saccades, the paired samples t-test was used (Norusis 1993).

Repeated measures ANOVA was used to reflect the differences at the level of individual in evaluating the differences between the different frequency combinations in PRPEM (Norusis 1994a). One-way ANOVA (Scheffe test) was used to study the differences at the level of the whole group (Norusis 1993).

In studying the repeatability of the PRPEM results, the repeated measures ANOVA (Norusis 1994a) was used for statistical analysis. The two variables analyzed for possible differences and possible interactions were stimulus = different frequency combinations (with four factor levels) and measurement time (with two factor levels).

Student's t-test in two independent samples was used to evaluate whether the differences between the group of control subjects and a certain patient group were statistically significant (Norusis 1993).

The general linear model (GLM) (SAS Institute Inc. 1989) was used to: 1) evaluate the correlation of clinical findings and voluntary eye movement deficits in patients with Menière's disease, 2) evaluate the importance of clinical and operative factors on voluntary eye movement deficits in operated CPA-tumor patients, 3) correlate MRI findings, age and the voluntary eye movement deficits in operated hemangioblastoma

patients, and 4) correlate MRI findings, age and the voluntary eye movement deficits in patients with infarction of cerebello brain stem. Before the GLM procedures, R-Square tests (SAS Institute Inc. 1989) were analyzed.

The discriminant analysis (Norusis 1994b) was made to: 1) classify patients (with moderately severe to severe Menière's disease as peripheral patients; operated CPA tumor patients, operated HAB patients and patients with infarction of cerebello-brain stem as central patients) and control subjects into correct groups by means of the voluntary eye movement performance, and 2) classify the subjects into correct groups with reference to the localization of lesion by means of the voluntary eye movement performance. With localization data, the frequency combination 0.25 and 0.425 Hz was only used in PRPEM.

In the decision tree analysis, artificial intelligence was used, and the analysis was done using Quinlan See5 (Quinlan 1998) classifier generator, a descendant of C4.5 (Quinlan 1993).

When p was < 0.01, it was considered a statistically significant difference. When p was <0.05, it was considered as a tendency of difference.

In statistical analysis, the *SPSS 6.1 for Windows*, *SPSS 7.5 for Windows* and *SAS for Windows* were used.

5. RESULTS

5. A. Control subjects

5.A.1. Normative data

Means and SDs of SA, SRT and SPV in *constant saccades*, are seen in **Table 8**; 4.5% of the saccades were hypometric.

Means and SDs in *pseudo-random saccades* of SA20° and SA60°, SRT20º and SRT60º, SPV20º and SPV60º , are seen in **Tables 9a** and **9b**. In 20º saccades, 11% were hypometric, and in 60º saccades, 6.8% were hypometric.

In *PRPEM*, GA and mean phase varied with different frequency combinations (**Figures 12a and 12b,** mean + SD). The GA value for the *0.15 and 0.35Hz* frequency combination was 0.86, and at the *0.45 and 0.7Hz* frequency combination GA was 0.68. The range of individual results was about the same (i.e. 0.36) in different frequency combinations. Mean phase steadily shortened by the following increasing frequency combinations: 0.129s at *0.15 and 0.35Hz*, 0.107s at *0.25 and 0.425Hz*, 0.93s at *0.3 and 0.7Hz*, and 0.82s at *0.45 and 0.7Hz*. The range of individual mean phase values with different frequency combinations diminished with the shortening of the mean normative value.

5. A. 2. Aging and voluntary eye movements

When testing differences between age groups *in constant saccades*, SA was larger ($p<0.01$) in the young group than in the middle-aged group (**Table 4a**). None of the tested curve estimations adequately described the connection between age and SA, SRT or SPV.

In pseudo-random saccades, SA20° and SA60° were larger ($p<0.01$) in the elderly group than in the middle-aged group. In SRTs and SPVs of 20° and 60° saccades, there were no significant differences between the age groups. (**Table 4b**). The quadratic function could be used to describe the connection between age and SA20° ($p<0.001$, $r=0.412$), between age and SA60° ($p<0.001$, $r=0.368$), and SRT20° ($p<0.001$, $r=0.367$). The middle-aged had the lowest SA20° and SA60°, and the shortest SRT20°. None of the tested functions described the connection between age and SRT60º, SPV20°, or SPV60°.

Table 4a. SA (°), SRT (s) and SPV (°/s) of constant saccades (CS) and pseudo-random saccades (PRS) (60°) in young (n=40), middle-aged (n=38) and elderly (n=41) subjects. Mean and standard deviations (SD) are given. Results of Scheffe test.

	SA CS / PRS	SRT CS / PRS	SPV CS / PRS
Young	4.4±1.9 / 6.2±2.7	0.22±0.04 / 0.19±0.04	641±97 / 674±90
vs. middle-age	* / *	NS / NS	NS / NS
Middle-age	2.9±1.6 / 4.1±1.9	0.22±0.04 / 0.19±0.03	615±98 / 630±92
vs. elderly	NS / NS	NS / NS	NS / NS
Elderly	3.6±1.9 / 5.5±2.6	0.22±0.04 / 0.19±0.04	613±97 / 639±9
vs. young	NS / NS	NS / NS	NS / NS

* = p<0.01, NS = non-significant

Table 4b. SA (°), SRT (s) and SPV (°/s) of pseudo-random (PRS) 20° and 60° saccades in young (n=40), middle-aged (n=38) and elderly (n=41) subjects. Mean and standard deviations (SD) are given. Results of Scheffe test.

	SA 20°/ 60°	SRT 20°/ 60°	SPV 20°/ 60°
Young	2.3±0.9 / 6.2±2.7	0.19±0.04 / 0.19±0.04	548±78 / 674±90
vs. middle-age	NS / *	NS / NS	NS / NS
Middle-age	1.9±0.6 / 4.1±1.9	0.18±0.03 / 0.19±0.03	520±77 / 630±92
vs. elderly	* / NS	NS / NS	NS / NS
elderly	2.8±1.1 / 5.5±2.6	0.20±0.04 / 0.19±0.04	525±82 / 639±95
vs. young	NS / NS	NS / NS	NS / NS

* = p<0.01, NS = non-significant.

When *PRPEM* was tested for differences between the age groups with respect to GA in different frequency combinations, no statistically significant differences between age groups were observed. For the mean phase in all frequency combinations, the middle-aged had a shorter mean phase (p<0.01) than the elderly. For frequency combinations of *0.25 and 0.425Hz* and *0.3 and 0.7Hz*, a significant difference (p<0.01) in the performance between the young and the elderly groups was observed. (**Table 5a-b**). The quadratic function could be used to describe the connection between age and GA with frequency combinations of 0.15 and 0.35Hz (p<0.01, r=0.430), 0.25 and 0.425Hz (p<0.01, r=0.415), 0.3 and 0.7Hz (p<0.01, r=0.324), and 0.45 and 0.7Hz

(p<0.01, r=0.288). The middle-aged had the highest GAs. To analyze the mean phase, the quadratic function could be used to describe connections between age and mean phase with frequency combinations of 0.25 and 0.425Hz (p<0.01, r=0.492), 0.3 and 0.7Hz (p<0.01, r=0.424), and 0.45 and 0.7Hz (p<0.01, r=0.382). The middle-aged had the shortest mean phases.

Table 5a. - b. Mean + SD results of **a.** GA and **b.** (mean) phase (in s) in frequency combinations of 0.15 and 0.35Hz (1), 0.25 and 0.425Hz (2), 0.3 and 0.7Hz (3), 0.45 and 0.7Hz (4) in young (n=40), middle-aged (n=38) and elderly (n=41) subjects. Results of Scheffe test.

a.

	GA 1	*GA 2*	*GA 3*	*GA 4*
Young	0.79±0.10	0.72±0.11	0.62±0.10	0.61±0.11
vs. middle-age	NS	NS	NS	NS
Middle-age	0.86±0.10	0.80±0.09	0.65±0.10	0.65±0.11
Vs. elderly	NS	NS	NS	NS
Elderly	0.79±0.14	0.74±0.13	0.62±0.10	0.61±0.11
vs. young	NS	NS	NS	NS

* = p<0.01, NS = non-significant.

b.

	phase 1	*phase 2*	*phase 3*	*phase 4*
Young	0.136±0.045	0.107±0.027	0.090±0.029	0.093±0.028
vs. middle-age	NS	NS	NS	NS
Middle-age	0.117±0.038	0.092±0.026	0.086±0.019	0.080±0.019
vs. elderly	*	*	*	*
Elderly	0.149±0.041	0.130±0.032	0.111±0.032	0.101±0.026
vs. young	NS	*	*	NS

* = p<0.01, NS = non-significant.

5. A. 3. Gender and voluntary eye movements

In the *constant saccade*s, no significant differences were found in SA60º, SRT60º and SPV60º across gender lines. In *pseudo-random saccades*, the SPV20° tended to differ (p=0.015) between the genders (e.g., SPV20° was 493°/s in females and 548°/s in males). When *PRPEM* was tested at the four frequency combinations, no statistically significant differences in GA and mean phase between males and females were observed.

5. A. 4. Side difference and saccades

In *constant saccade*s, the SPV60º tended to differ significantly (p=0.015) between rightward (SPV60°=606º/s) and leftward (SPV60°=620º/s) saccades at the individual

level in paired samples t-test. Where the whole group of 45 subjects was concerned (Student's t-test), none of the saccade parameters differed significantly between rightward and leftward saccades. In *pseudo-random saccades*, the SPV60º differences were significant ($p<0.01$) between rightward (SPV60°=615º/s) and leftward (SPV60°=632º/s) saccades at the individual level. There were no significant differences between the rightward and leftward parameters by the group as a whole (45 subjects of normative data group / Student's t-test).

5. A. 5. Repeatability of pseudo-random pursuit eye movements

The frequency combination used demonstrated a significant correlation ($p<0.001$, power = 1.000) with GA and mean phase. "Power" describes the influence of the factor, where the value 0.000 indicates that the factor analyzed has no influence on the measured variables and 1.000 indicates that the factor analyzed exclusively affects the variables measured. Measurement time tended to cause a difference in mean phase ($p<0.05$, $p=0.028$, power = 0.621). During mean phase, the phase lag was shorter at every frequency combination at the second measurement time, whereas the GA did not differ systematically or significantly at different measurement times (**Table 6.**).

Table 6. Mean + SEM results in the repeatability test with different frequency combinations.

Stimulus	***0.15+0.35Hz***		***0.25+0.425Hz***		***0.3+07Hz***		***0.45+0.7Hz***	
The test	***1st***	***2nd***	***1st***	***2nd***	***1st***	***2nd***	***1st***	***2nd***
The parameter								
GA	0.88±0.03	0.86±0.03	0.82±0.03	0.83±0.02	0.69±0.03	0.72±0.02	0.69±0.03	0.71±0.03
Phase	0.13±0.01	0.12±0.01	0.10±0.01	0.09±0.01	0.09±0.01	0.08±0.00	0.09±0.01	0.07±0.00

phase= mean phase (s)

5. A. 6. Voluntary eye movements recorded by EOG and MOG methods

Figure 7a. This is an example of MOG and EOG recordings and of the stimulus of pseudo-random saccades in a 30-year old control subject.

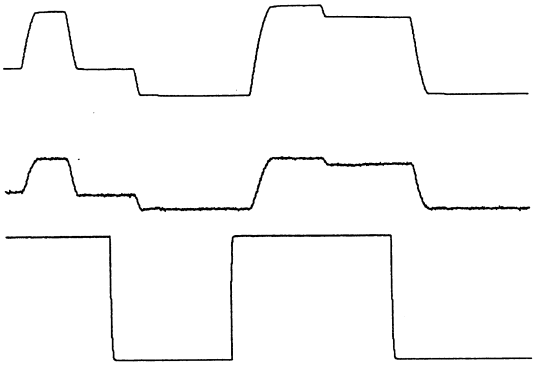
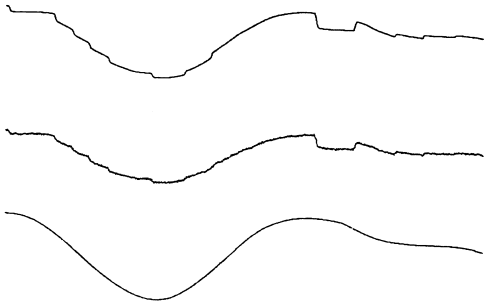


Figure 7b. A short part of a MOG and EOG recording and of a stimulus of PRPEM in the same control subject as in **Figure 7a**.



In *constant saccades*, the SA was better ($p<0.005$) and the SPV tended to be lower ($p=0.013$) in MOG recordings than in EOG recordings (**Table 7a**). The individual results in SA varied between 2.3 - 8.4° in EOG and between 0.5 - 7.9° in MOG; in SRT between 0.145 - 0.255s in EOG and between 0.149 - 0.256s in MOG; in SPV between 377 - 707°/s in EOG and between 308 - 677°/s in MOG.

Table 7a. SA, SRT and **SPV** of **60°** constant saccades, with **EOG** and **MOG** recording methods. Mean + SD results. Results of paired samples t-test.

Parameter	***in EOG***	***in MOG***	***Paired samples t-test***
SA (°)	4.0±2.0	2.9±2.2	**
SRT (s)	0.192±0.039	0.191±0.039	NS
SPV (°/s)	541±103	515±108	*

NS= a non-significant difference, * = $p<0.05$, ** = $p<0.01$

In *pseudo-random saccades*, the SPV60° was lower ($p<0.005$) and the SA tended to be better ($p=0.041$) in MOG than in EOG (**Table 7b**). The individual results in

SA60º varied as follows: from 2.7 - 19.5° in EOG and 0.5 - 16.1° in MOG, from 0.145 - 0.230s in EOG and 0.141 - 0.214s in MOG, and from 449 - 756°/s in EOG and 345 - 718°/s in MOG.

Table 7b. SA, SRT and **SPV** of **60º** saccades in **pseudo-random saccades** with **EOG** and **MOG** recording methods. Mean + SD results. Results of paired samples t-test.

Parameter	***in EOG***	***in MOG***	***Paired samples t-test***
SA (º)	6.9±5.3	5.7±4.9	*
SRT (s)	0.170±0.023	0.165±0.023	NS
SPV (º/s)	601±84	558±105	**

NS= non-significant difference, * = p<0.05, ** = p<0.01.

The recording method for PRPEM did not cause any significant effect on GA and mean phase (**Table 7c**). At a frequency combination of *0.25 and 0.425 Hz*, the individual results in GA varied between 0.592 - 0.872 in EOG recording, and between 0.604 - 0.880 in MOG recording. For the mean phase they varied between 0.067 - 0.0158s in EOG and between 0.051 - 0.158s in MOG. For a frequency combination of *0.45 and 0.7 Hz*, GA varied between 0.445 - 0.750 in EOG and between 0.471 - 745 in MOG; mean phase varied between 0.065 - 0.116s in EOG and between 0.054 - 0.114s in MOG.

Table 7c. Results of **GA** and **mean phase** in **PRPEM** tests with **EOG** and **MOG** recording methods. Assessed frequency combinations of **0.25 and 0.425 Hz** and **0.45 and 0.7 Hz**. Mean + SD results. No significant differences in paired samples t-test.

Stimulus	***0.25+0.425Hz***		***0.45+0.7Hz***	
Parameter	*in **EOG***	*in **MOG***	*in **EOG***	*in **MOG***
GA	0.727±0.094	0.763±0.088	0.629±0.107	0.605±0.098
Mean phase (s)	0.106±0.030	0.103±0.036	0.085±0.016	0.079±0.017

5. B. *Patients*

5. B. 1. Menière's disease

In moderate to severe Menière's disease, patients' deficits in voluntary eye movements were correlated with certain clinical findings, which are associated with the severity of the disease.

With regard to ***constant saccades***, the ipsilateral SRT was significantly lengthened ($p<0.01$, $r^2=0.364$) in patients with high PTA. There was an interaction of PTA and Tumarkin attacks, indicating that patients with hearing loss and severe Tumarkin attacks had a prolonged ipsilateral SRT (Ipsilateral SRT = 0.02 x PTA + 2.86 x PTA & Tumarkin attacks). A lengthened contralateral SRT ($p=0.027$, $r^2=0.290$) was observed in patients with high PTA and with those demonstrating an interaction of poor hearing and severe Tumarkin attacks (Contralateral SRT = 0.50 x PTA + 1.70 x PTA & Tumarkin attacks). Contralateral SPV ($p=0.042$, $r^2=0.174$) tended to be lower in patients with high PTA than those with a low PTA. There was a correlation between PTA and advanced age, indicating that patients who had a high PTA and advanced age had a lower ipsilateral SPV (Contralateral SPV = -0.41 x PTA - 0.74 x PTA & age).

With regard to ***pseudo-random saccades*** (at 20° and 60°), the contralateral SRT20º was significantly lengthened ($p<0.01$, $r^2=0.673$) in patients with severe tinnitus. There was also a correlation between rotatory vertigo attack and working capacity, indicating that these patients had a lengthened contralateral SRT20º (Contralateral SRT20º = 0.91 x tinnitus + 0.42 x rotatory vertigo & working capacity). Contralateral SRT60º tended to be lengthened ($p=0.011$, $r^2=0.517$) in patients with severe tinnitus. There was a correlation between tinnitus and working capacity, indicating that they had a lengthened contralateral SRT60º (contralateral SRT60º = 0.06 x tinnitus + 1.65 x tinnitus & working capacity). Ipsilateral SPV20º tended to be lower ($p=0.037$, $r^2=0.539$) in patients with advanced age or severe Tumarkin drop attacks. There was a correlation between advanced age and rotatory vertigo attack, indicating a lower ipsilateral SPV20º than in other patients (Ipsilateral SPV20º = -2.96 x age - 1.21 x Tumarkin attacks -1.96 x age & rotatory vertigo).

In evaluating **PRPEM** at the frequency combination of 0.25 and 0.425Hz, GA was significantly lower ($p<0.005$, $r^2=0.642$) in patients with severe tinnitus and unsteadiness during attack-free periods, than in other patients. There was a correlation between unsteadiness during attack-free periods and advanced age, indicating that patients with severe unsteadiness during attack-free periods and advanced age had a lower GA. There was also a correlation between severe tinnitus and advanced age, indicating that this combination produced a lower GA than the other patients (GA = - 0.30 x tinnitus - 0.34 x unsteadiness - 0.23 x unsteadiness & age - 0.34 x tinnitus & age).

5. B. 2. Operated cerebello-pontine angle tumor

Deficits in voluntary eye movements were related to the tumor size, the radical nature of the operation, adherence of tumor, and age of the patient.

In regard to ***constant saccades***, the contralateral SRT was significantly lengthened ($p<0.005$, $r^2=0.666$) in patients with poor facial nerve function after surgery. Patients with advanced age and with a cystic tumor had a lengthened contralateral SRT (contralateral SRT = 1.94 x facial nerve function after surgery + 1.35 x age & cysticity). Ipsilateral SPV tended to be lower ($p=0.030$, $r^2=0.274$) if the tumor had been cystic than in other cases. Patients observed with a large tumor and advanced age had a lower ipsilateral SPV than the others (ipsilateral SPV = - 2.24 x cysticity - 2.27 x size of tumor & age).

In regard to ***pseudo-random saccades*** **(20° and 60° saccades)**, the ipsilateral SRT20º tended to be lengthened ($p=0.036$, $r^2=0.472$) in patients with poor facial nerve function after surgery and in post-operative cystic tumor patients. Patients who previously had a radical operation and a long operation time were observed to have a lengthened ipsilateral SRT20º (ipsilateral SRT20º = 2.20 x facial nerve function after surgery +1.38 x cysticity + 0.62 x radicality of operation & operation time). Ipsilateral SPV60º tended to be lower ($p=0.040$, $r^2=0.253$) in patients of radical operations. Patients with advanced age, cystic tumor and a long operation time were observed to have a lower ipsilateral SPV60º than the other patients (ipsilateral SPV60º = - 0.53 x radicality of operation - 1.26 x age & cysticity & operation time).

Regarding ***PRPEM*** at a frequency combination of *0.25-0.425Hz*, the GA tended to be lower ($p=0.031$, $r^2=0.291$) in patients who previously had a large diameter tumor. Patients with radical operations and a cystic tumor had a lower GA than the others (GA = - 1.79 x size of tumor - 1.60 x radicality of operation & cysticity of tumor).

In the ***PRPEM*** with the frequency combination of *0.45-0.7Hz*, the mean phase was significantly lengthened ($p<0.01$, $r^2=0.311$) in patients with radical operations of cystic tumors, or a large diameter tumor (Mean phase = 1.98 x size of tumor + 2.39 x radicality of operation + 1.40 x cysticity of tumor).

5. B. 3. Operated hemangioblastoma

Deficits in voluntary eye movements of operated HAB patients correlated with certain MRI findings.

In regard to ***constant saccades***, the ipsilateral SRT was significantly lengthened ($p<0.005$, $r^2=0.543$) in patients with an oculomotor vermis lesion. Patients with a brain stem lesion and advanced age were observed to have a lengthened ipsilateral SRT (ipsilateral SRT = 0.25 x oculomotor vermis lesion + 1.25 x brain stem lesion & age). Ipsilateral SPV tended to be lower ($p=0.026$, $r^2=0.430$) in patients with a fastigial nucleus lesion. It was also observed that patients with fastigial nucleus lesions and

advanced age had a lower ipsilateral SPV (ipsilateral SPV = - 0.20 x fastigial nucleus lesion - 0.68x fastigial nucleus lesion & age).

For **pseudo-random saccades** (at 20° and 60°), ipsilateral SRT20º was significantly lengthened ($p<0.01$, $r^2=0.509$) in patients with brain stem lesions. Patients with oculomotor vermis lesion and advanced age had a lengthened ipsilateral SRT20º (Ipsilateral SRT20º = 2.65 x brain stem lesion + 0.91 x oculomotor vermis lesion & age). Contralateral SA20º tended to be poor ($p=0.016$, $r^2=0.466$) in patients with brain stem lesions. Patients with oculomotor vermis lesion together with advanced age were shown to have an inaccurate contralateral SA20º (contralateral SA20º = 2.55 x brain stem lesion + 1.66 x oculomotor vermis lesion & age). Ipsilateral SPV60º tended to be lower ($p=0.031$, $r^2=0.418$) in patients with fastigial nucleus lesions. Patients with brain stem lesions and advanced age had a lower SPV60º than those without these findings (ipsilateral SPV60º = - 2.12 x fastigial nucleus lesion - 1.25 x brain stem lesion & age).

In ***PRPEM*** at a frequency combination of *0.25 and 0.425Hz*, the GA tended to be lower ($p=0.015$, $r^2=0.472$) in patients with flocculus lesions; patients with brain stem lesions and advanced age had a lower GA (GA = - 0.68 x flocculus lesion - 3.02 x brain stem lesion & age of the patient).

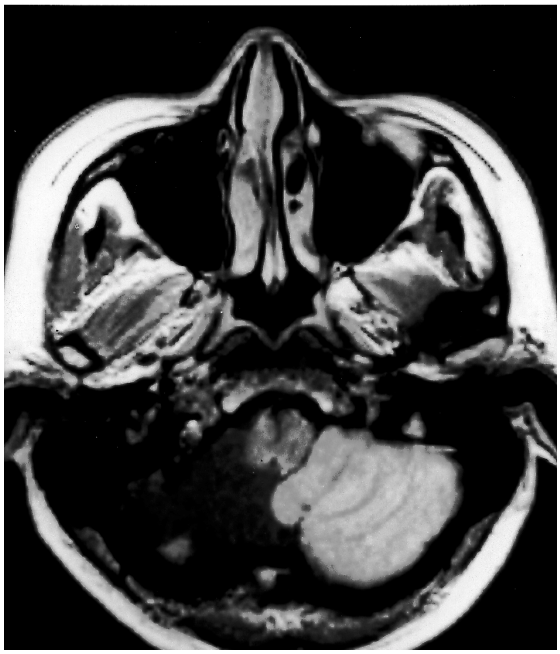
In ***PRPEM*** at a frequency combination of *0.45 and 0.7Hz*, brain stem lesions tended to correlate ($p=0.010$, $r^2=0.416$) with a lengthened mean phase and a reduced GA (Brain stem lesion = -2.88 x GA + 0.05 x mean phase.).

5. B. 4. Infarction of cerebello-brain stem:

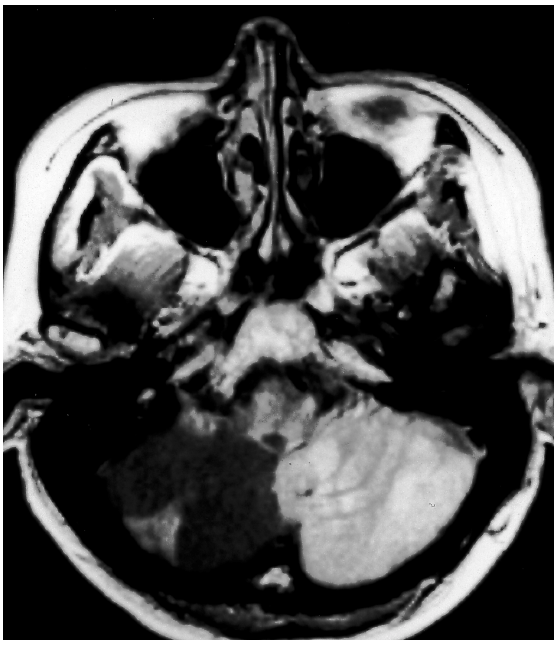
Figure 8a-c demonstrates the MRI findings from a 48 year-old female patient (subject 1) with a right-sided cerebello-brain stem infarction due to thrombosis of arteria cerebelli superior, which occurred at the age of 36. She demonstrated a reduced SPV and lengthened SRT of the saccades, and SA was normal. She had normal PRPEMs. **Figure 9a-b** shows her recordings of pseudo-random saccade tests and a part of one PRPEM recording.

Figure 8a-c. MRI findings from the subject 1. Three successive axial segments of high-field MRIs (1.5 T) of the posterior fossa. An old and accurately limited infarction is observed in the right cerebellar hemisphere, and it also extends to the posterior part of the brain stem. Only the cranial part of the right cerebellar hemisphere is intact.

a)



b)



c)

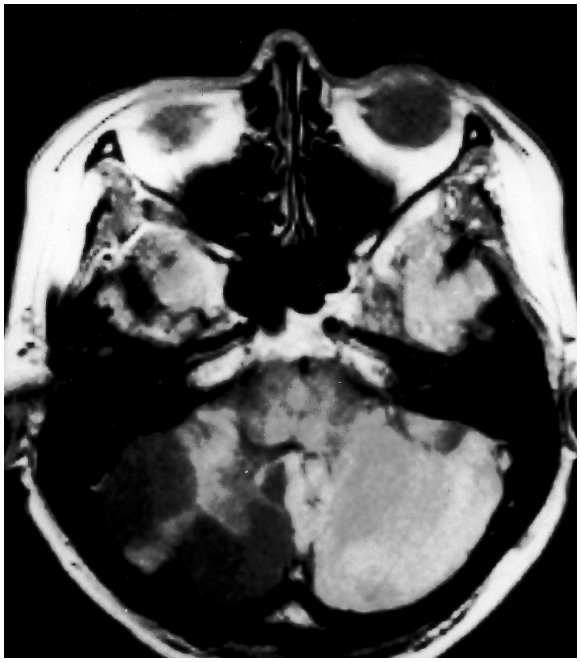


Figure 9a-b. The pseudo-random saccades recording (a) and a part of one PRPEM recording (b) in subject 1.

a)

b)

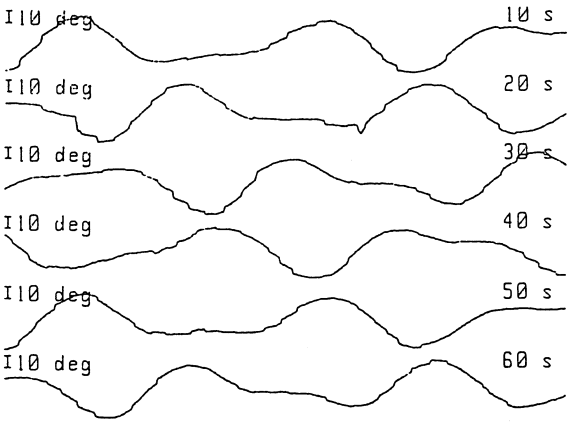
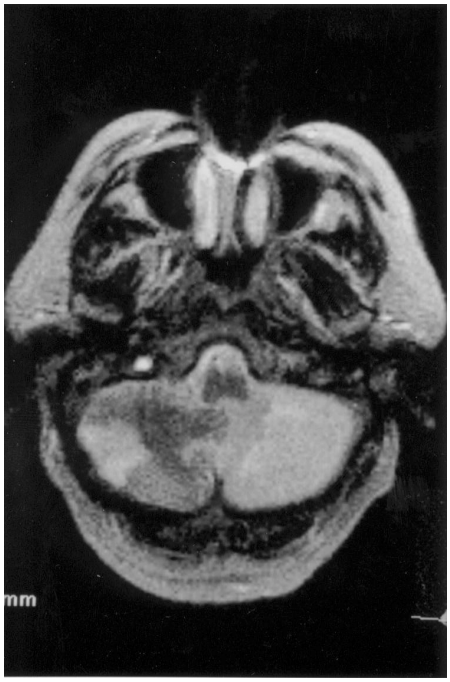


Figure 10a-b. Two low-field MRIs of subject 2, (right) is of the coronal segment at the level of tentorium, (Left) is of the axial segment at the level of posterior fossa. There were vast lesions in the posterior fossa, both in the cerebellum and brain stem. The lesions are more prominent on the right side, but they extend to the left side. Flocculus is unilaterally injured but brain stem, fastigial nucleus and oculomotor vermis are bilaterally injured.



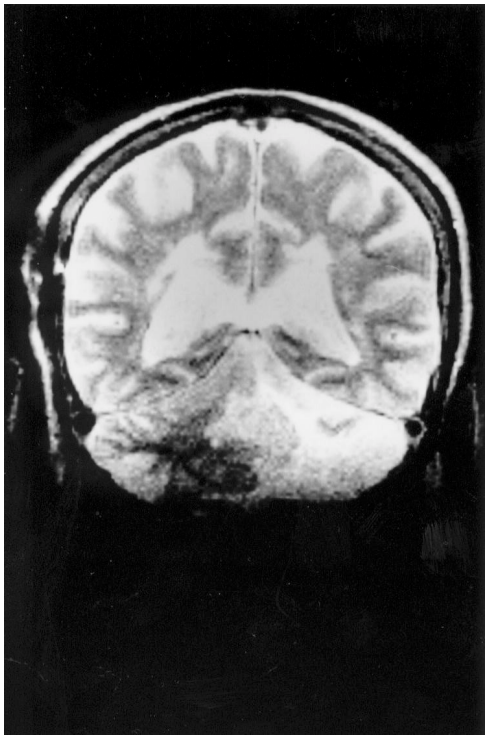
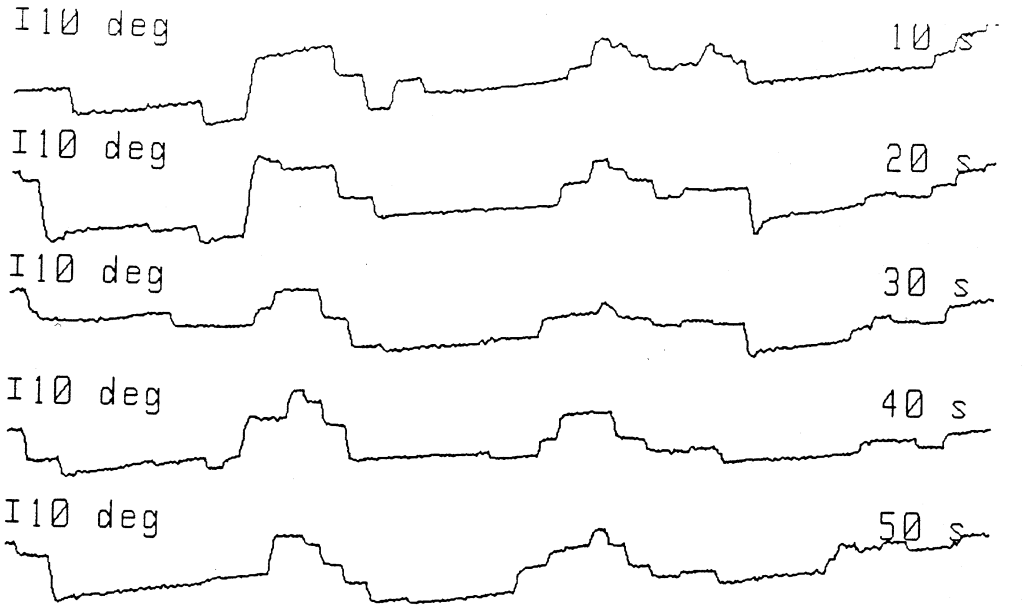


Figure 11. This demonstrates the PRPEM recording of a 59 year-old man with infarction and secondary hydrocephalus, which occurred at the age of 50 (subject 2). He suffered from meningitis after the infarction. An MRI was done during this study, nine years after the infarction. His MRI's revealed a vast infarction of the right cerebellar hemisphere extending to the left hemisphere (**Figure 10**). In the tests, he had impaired PRPEMs. He showed increased corrective saccades during PRPEMs, and the velocity of the saccades was very low. He had increased phase lag and severely reduced GAs even with the lower frequency combinations. He could not perform the saccadic tests because of calibration difficulties.

Figure 11. A part of one recording of PRPEMs in subject 2.



In patients with infarction of cerebello-brain stem, deficits in voluntary eye movements correlated with certain MRI findings.

For ***constant saccades***, the ipsilateral SPV was significantly lower ($p<0.01$, $r^2=0.560$) in patients with brain stem lesions. Young patients with brain stem lesions were observed to have a lower ipsilateral SPV than other patients (ipsilateral SPV = - 2.87 x brain stem lesion - 2.35 x [-age] & brain stem lesion). Ipsilateral SPV tended to be lower ($p=0.049$, $r^2=0.315$) in patients with brain stem lesions and in patients with flocculus lesions (ipsilateral SPV = - 2.50 x brain stem lesion - 1.14 x flocculus lesion). Ipsilateral SA tended to be deteriorated ($p=0.048$, $r^2=0.400$) in patients with oculomotor vermis lesions. Patients with fastigial nucleus lesions and advanced age exhibited an inaccurate SA (ipsilateral SA = 2.90 x oculomotor vermis lesion + 2.03 x age & fastigial nucleus lesion).

When studying the role of the anatomical site of lesion to voluntary eye movement deficits, the brain stem lesion was found to be significantly related ($p<0.005$, $r^2=0.580$) to reduced bilateral SPVs. It was also related to an interaction of reduced contralateral SPV and advanced age (brain stem lesion = - 2.03 x ipsilateral SPV - 2.51 x contralateral SPV - 0.32 x age & contralateral SPV). Flocculus lesion tended to be related ($p=0.049$, $r^2=0.315$) with bilaterally lengthened SRTs (flocculus lesion = 0.90 x ipsilateral SRT + 0.43 x contralateral SRT).

For ***pseudo-random saccades*** **(with 20° and 60° saccades)**, the contralateral SPV60º was significantly lower ($p<0.01$, $r^2=0.527$) in patients with brain stem lesions. It was observed that patients with brain stem and a fastigial nucleus lesion had a lower contralateral SPV60º than other patients (Contralateral SPV60º = - 1.81 x brain stem lesion - 0.33 x fastigial nucleus lesion & brain stem lesion). Ipsilateral SPV60º tended to be lower ($p=0.049$, $r^2=0.398$) in patients with flocculus lesions. Patients with brain stem lesions and advanced age were observed to have a lower ipsilateral SPV60º (ipsilateral SPV60º = - 0.71 x flocculus lesion - 1.63 x age & brain stem lesion).

For ***PRPEM*** at the frequency combination ***0.25 and 0.425Hz***, there were no correlations between MRI findings and deficits of PRPEM (with GA and mean phase analyzed). At the frequency combination ***0.45 and 0.7Hz***, mean phase was significantly lengthened ($p<0.001$, $r^2=0.555$) in patients with oculomotor vermis lesions and flocculus lesions (mean phase = 3.42 x oculomotor vermis lesion + 1.88 x flocculus lesion).

When analyzing the role of anatomical site of lesion to voluntary eye movement deficits, PRPEM, at a frequency combination of 0.45 and 0.7 Hz, demonstrated a significant correlation between lesions of the oculomotor vermis ($p<0.005$, $r^2=0.490$), and lengthened mean phase and reduced GA (oculomotor vermis lesion = 3.44 x mean phase - 0.96 x GA). A lesion in the flocculus tended to correlate ($p=0.015$, $r^2=0.389$) with lengthened mean phase and a reduced GA (flocculus lesion = 3.25 x mean phase - 1.96 x GA).

5. C. *Control subjects and patient groups*

5. C. 1. Differences in voluntary eye movements between control subjects and patients

a. Saccades

In ***constant saccades*** of control subjects, the SAs, SRTs and SPVs were the best, and the variance was the smallest in control subjects. Patients with infarction of cerebello-brain stem had the longest SRTs and the lowest contralateral SPV, whereas

the operated CPA tumor patients had the lowest ipsilateral SPV (**Table 8**). The SAs were the least affected of the constant saccade parameters, whereas the SRTs were the most deteriorated and were significantly lengthened in every patient group.

Table 8. Results of constant saccades (at 60º) in control subjects and different patient groups (mean + SD). Statistically significant differences between control subjects and patients of a patient group were assessed by Student's t-test.

Class	contral. (º)	SA contral. (s)	SRT contral. (º/s)	SPV ipsil. (º)	SA ipsil. (s)	SRT ipsil. (º/s)	SPV
Cont.	2.7±1.3	0.213±0.033	613±74	2.7±1.3	0.213±0.033	613±74	
Men.	3.3±2.6	0.250±0.063 **	564±81 **	3.3±2.2	0.257±0.074 **	554±78 **	
CPA	4.5±2.9 **	0.267±0.054 **	564±86 *	4.4±2.6 **	0.268±0.058 **	530±92 **	
HAB	4.7±3.9 *	0.261±0.039 **	561±94 *	4.5±4.1	0.273±0.052 **	569±121	
Inf.	3.7±1.8 *	0.280±0.068 **	547±87 **	3.9±2.3 *	0.276±0.071 **	538±90 **	

* = $p<0.05$, ** = $p<0.01$, Cont. = control subjects, Men. = patients with Menière's disease, Inf. = patients with cerebello-brain stem infarction, contral. = contralateral; ipsil. = ipsilateral

In ***pseudo-random saccades*** of control subjects, the SAs, SRTs and SPVs were the best in the control subjects. Patients with infarction of cerebello-brain stem had the longest SRTs and the lowest SPVs in 20º saccades, whereas in 60º saccades, the Menière's patients had the longest SRTs, and patients with the infarction of cerebello-brain stem had the lowest SPVs (**Table 9a-b**). The SAs were not significantly affected in any of the groups, whereas the SRTs and SPVs were deteriorated in most cases. The saccades of 60º were more deteriorated than the saccades of 20º.

Table 9. Results of pseudo-random saccades of: a) 20°, and b) 60° in control subjects and different patient groups (mean + SD). Statistically significant differences between control subjects and patients of a patient group were assessed by Student's t-test.

a) 20º saccades

Class	contral. SA (º)	contral. SRT (s)	contral. SPV (º/s)	ipsil. SA (º)	ipsil. SRT (s)	ipsil. SPV (º/s)
Cont.	2.2±0.9	0.182±0.025	512±68	2.2±0.9	0.182±0.025	512±68
Men.	2.8±2.1	0.205±0.039	479±55 *	2.6±2.1	0.209±0.048	471±51 **
CPA	2.4±1.1	0.209±0.035 **	494±69	2.8±1.8	0.204±0.031 **	501±71
HAB	3.0±1.9	0.203±0.032 *	475±78	2.9±1.8	0.210±0.033 **	488±71
Inf.	2.4±1.1	0.225±0.037 **	464±57 **	2.4±1.6	0.211±0.039 **	459±52 **

b) 60º saccades

Class	contral. SA (º)	contral. SRT (s)	contral. SPV (º/s)	ipsil. SA (º)	ipsil. SRT (s)	ipsil. SPV (º/s)
Cont.	4.1±1.8	0.182±0.026	624±80	4.1±1.8	0.182±0.026	624±80
Men.	6.0±4.7	0.241±0.056	563±66 **	5.0±3.1	0.243±0.062	555±76 **
CPA	5.6±4.0	0.234±0.043 **	593±77	5.6±3.4	0.240±0.059 **	571±88 *
HAB	5.9±4.2	0.229±0.038 **	553±77 **	6.1±4.9	0.233±0.035 **	572±119 *
Inf.	5.6±4.2	0.238±0.044 **	536±83 **	6.4±5.0	0.238±0.051 **	536±97 **

* = p<0.05, ** = p<0.01, Cont. = control subjects, Men. = patients with Menière's, disease, Inf. = patients with cerebello-brain stem infarction, contral. = contralateral; ipsil. = ipsilateral

Differences between constant and pseudo-random saccades (in each group)

When comparing constant and pseudo-random saccades of 60º in *control subjects*, the mean SAs and SRTs differed significantly (p<0.01) between constant and pseudo-random saccades, as tended the mean SPVs (p=0.020). The mean SA was more accurate, the mean SRT longer, and the mean SPV was lower in constant saccades than in pseudo-random saccades.

For patients with *Menière's disease*, no significant (p<0.01) differences in ipsilateral and contralateral SAs, SRTs and SPVs were found between constant and pseudo-random saccades.

In *operated CPA tumor* patients, the ipsilateral and contralateral SRTs and contralateral SPV differed significantly (p<0.01) between constant and pseudo-random saccades. SRTs were longer and contralateral SPV lower in constant saccades than in pseudo-random saccades. The ipsilateral SA tended to be more accurate (p<0.05) and

ipsilateral SPV tended to be lower ($p<0.05$) in constant saccades than in pseudo-random saccades.

In *operated HAB* patients and patients *with infarction of cerebello-brain stem*, the ipsilateral and contralateral SRTs differed significantly ($p<0.01$) between constant and pseudo-random saccades. For infarction of cerebello-brain stem, the ipsilateral SA tended to differ between constant and pseudo-random saccades ($p<0.05$). SRTs were longer and ipsilateral SA more accurate in constant saccades than in pseudo-random saccades.

b. pseudo-random pursuit eye movement

In **PRPEM**, GA was the highest in control subjects at every frequency combination and the lowest in operated CPA tumor patients, although not all of the differences between the control group and a certain patient group were statistically significant. Mean phase behaved differently. Only with the highest frequency combination did the control and CPA operated subjects demonstrate a difference; control subjects had the shortest mean phase and the operated CPA tumor patients had the longest one. Statistically significant differences between control subjects at any given patient group are shown in **Table 10.**

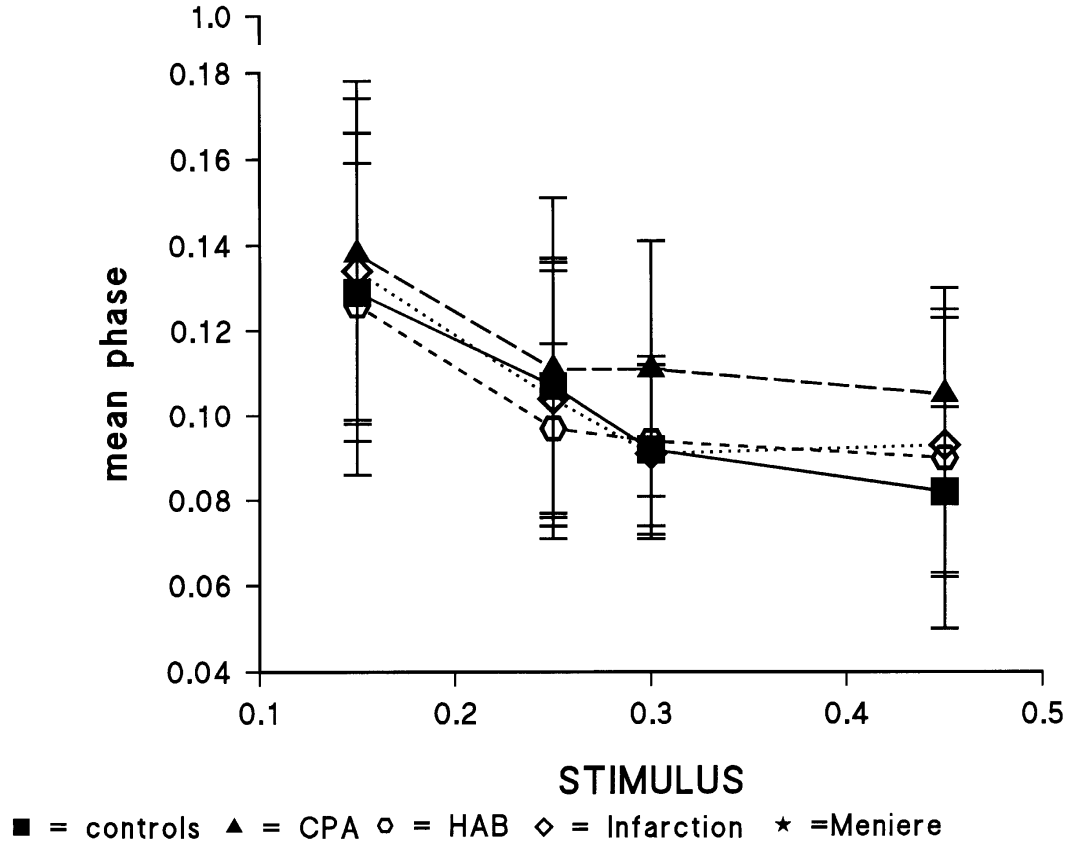
Table 10. Results of Student's t-test in PRPEM with different frequency combinations. The differences between control subjects and patients of a patient group. 2 = 0.25 and 0.425 Hz, 4 = 0.45 and 0.7 Hz.

	GA 2	**GA 4**	**Phase 2**	**phase 4**
Cont. vs. Men.	**	missing	NS	missing
Cont. vs. CPA	**	**	NS	**
Cont. vs. HAB	**	**	NS	NS
Cont. vs. Inf.	*	**	NS	NS

NS= a non-significant difference, * = $p<0.05$, ** = $p<0.01$, Cont. = control subjects, Men. = patients with Menière's disease, Inf. = patients with cerebello-brain stem infarction

Figures 12a. & b. GA (**a**) and phase (**b**) of PRPEM in different groups of patients and in the group of control subjects with different frequency combinations.

a.



b.

Frequency combinations and pseudo-random pursuit eye movements (in different groups)

In *control subjects*, GA had the greatest and mean phase had the longest values for the lowest frequency combination, and these parameters differed significantly between different frequency combinations ($p<0.01$, repeated measures ANOVA). With rising frequency combinations, values of GA were reduced and the values of mean phase shortened. In one-way ANOVA (Scheffe's test), several significant differences were found **(Table 11).**

Table 11. Control subjects. Results of one-way ANOVA; the statistically significant differences between different frequency combinations in GA and (mean) phase. a = 0.15 and 0.35 Hz, b = 0.25 and 0.425 Hz, c = 0.3 and 0.7 Hz, d = 0.45 and 0.7 Hz.

	a vs. b	**a vs. c**	**a vs. d**	**b vs. c**	**b vs. d**	**c vs. d**
GA	*	**	**	**	**	NS
Phase	**	**	**	NS	**	NS

NS= a non-significant difference, * = $p<0.05$, ** = $p<0.01$.

In *operated CPA tumor* patients and in patients *with cerebello-brain stem infarction*, GA and mean phase differed significantly ($p<0.01$) between different frequency combinations (repeated measures ANOVA). In *operated HAB* patients, GA differed significantly ($p<0.01$) between different frequency combinations (repeated measures ANOVA) and mean phase tended to differ ($p<0.05$) between different frequency combinations. GA had the greatest and the mean phase had the longest values in the lowest frequency combination. With rising frequency combinations, GA values were reduced and mean phase shortened. In one-way ANOVA (Scheffe's test), several statistically significant differences were found (**Table 12a-b**).

Table 12a. Operated CPA patients and operated HAB patients. Results of one-way ANOVA; the statistically significant differences between different frequency combinations in GA and (mean) phase. a = 0.15 and 0.35 Hz, b = 0.25 and 0.425 Hz, c = 0.3 and 0.7 Hz, d = 0.45 and 0.7 Hz.

	a vs. b	**a vs. c**	**a vs. d**	**b vs. c**	**b vs. d**	**c vs. d**
GA	NS	**	**	**	**	NS
Phase	*	*	**	NS	NS	NS

NS= a non-significant difference, * = $p<0.05$, ** = $p<0.01$.

Table 12b. Patients with infarction of cerebello-brain stem. Results of one-way ANOVA; the statistically significant differences between different frequency combinations in GA and (mean) phase. a = 0.15 and 0.35 Hz, b = 0.25 and 0.425 Hz, c = 0.3 and 0.7 Hz, d = 0.45 and 0.7 Hz.

	a vs. b	**a vs. c**	**a vs. d**	**b vs. c**	**b vs. d**	**c vs. d**
GA	NS	**	**	*	*	NS
Phase	*	**	**	NS	NS	NS

NS= a non-significant difference, * = $p<0.05$, ** = $p<0.01$.

5. C. 2. *Discriminatory power of voluntary eye movements of patients and control subjects*

Operated-CPAs, operated-HABs and cerebello-brain stem infarction patients were combined to form a "central" group, and Menière's patients formed the "peripheral" group, and control subjects were "controls".

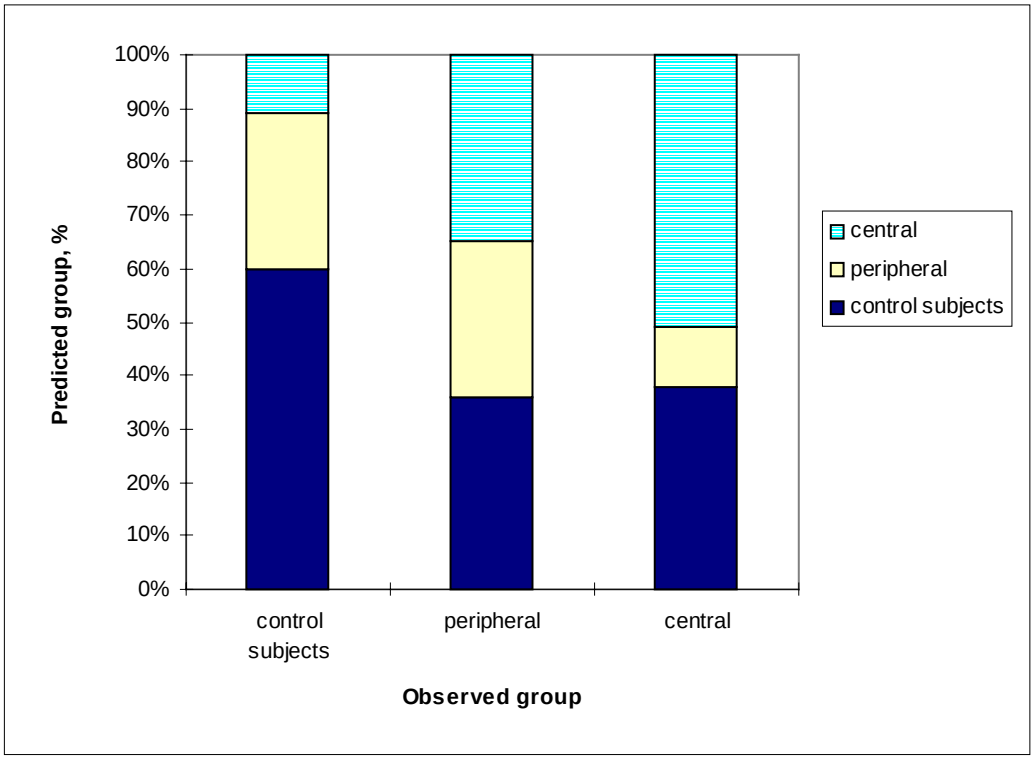
In ***constant saccades***, the overall classification was correct in 55% of the cases. In control subjects, 76% of the cases were correctly classified, and 22% placed incorrectly as peripheral patients. In central patients, 56% were correctly classified, and 22% incorrectly classified as peripheral patients or control subjects. Twenty-seven percent of the peripheral patients were correctly classified, 38% incorrectly placed as control subjects. Overall correct classification in ***pseudo-random saccades*** was achieved in 56% of all cases. Seventy-eight percent of the control subjects were correctly classified, 15% were incorrectly classified as peripheral patients. For central patients, 45% were correctly classified, and 37% of cases were incorrectly classified as peripheral patients. In peripheral patients, 48% were correctly classified, 22% of the cases were incorrectly classified as control subjects.

Based on discriminant analysis and saccade tests, control subjects in 76 to 78% of the cases were correctly classified, but some were incorrectly classified as peripheral patients. Peripheral patients were most often classified as peripheral patients or control subjects. Central patients were most often classified as central or peripheral patients. Problems occur when differentiating central patients from peripheral patients.

In ***PRPEM*** with a frequency combination of *0.15 and 0.35Hz* with a GA and mean phase, the overall correct classification was achieved in 70% of all cases in discriminant analysis. Classification of control subjects were correct 78% of the time,

and central patients 65%. With a frequency combination of *0.25 and 0.425Hz*, the overall correct classification was achieved in 48% of all cases in discriminant analysis. This was the only frequency combination where the peripheral group was included. In control subjects, 60% were correctly classified, 29% were incorrectly classified into the peripheral group, and 11% incorrectly into the central group. In central patients, 51% were correctly classified, while 38% went incorrectly into control subjects and 11% incorrectly into peripheral patients. In peripheral patients, 27% were correctly classified, while misclassifications were almost equally distributed into the other groups. With a frequency combination of *0.3 and 0.7Hz*, correct classification was achieved in 69% of all cases in discriminant analysis. In control subjects, 78% were correctly classified, and in central cases it was 64%. With a frequency combination of *0.45 and 0.7Hz*, correct classification was achieved in 74% of all cases of discriminant analysis (**Figure 13**). In control subjects, 82% were correctly classified, and in central cases, it was 69%.

Figure 13. Classification of cases into control subjects, peripheral or central patients by means of PRPEM at 0.25 and 0.425Hz frequency combination. Observed group is the real group.



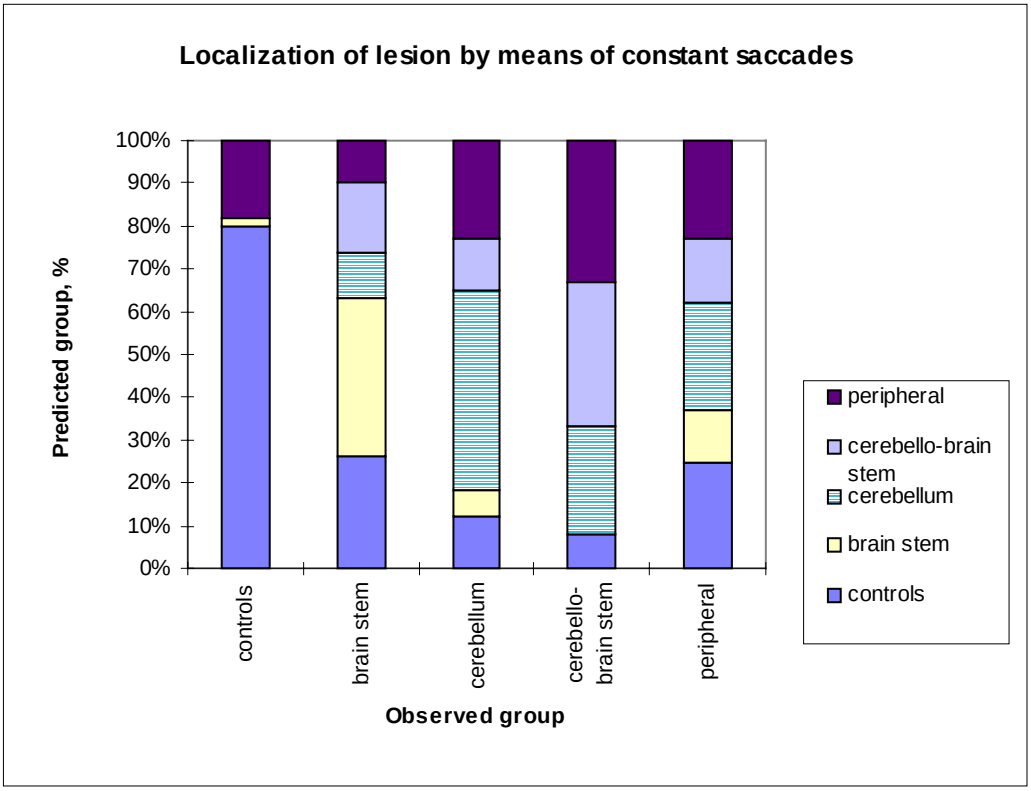
Based on discriminant analysis with PRPEM tests, control subjects were correctly classified in 60-82% of the cases. By means of the frequency combination 0.25 and 0.425 Hz, it was most difficult to discriminate control subjects from other groups.

Patients with central lesions were correctly classified in 51-69% of the cases. However, the frequency combination of 0.25 and 0.425 Hz was again, the most difficult to evaluate. Patients with peripheral lesions were the most difficult to discriminate from other groups.

5. C. 3. *The site of lesion and voluntary eye movement deficits*

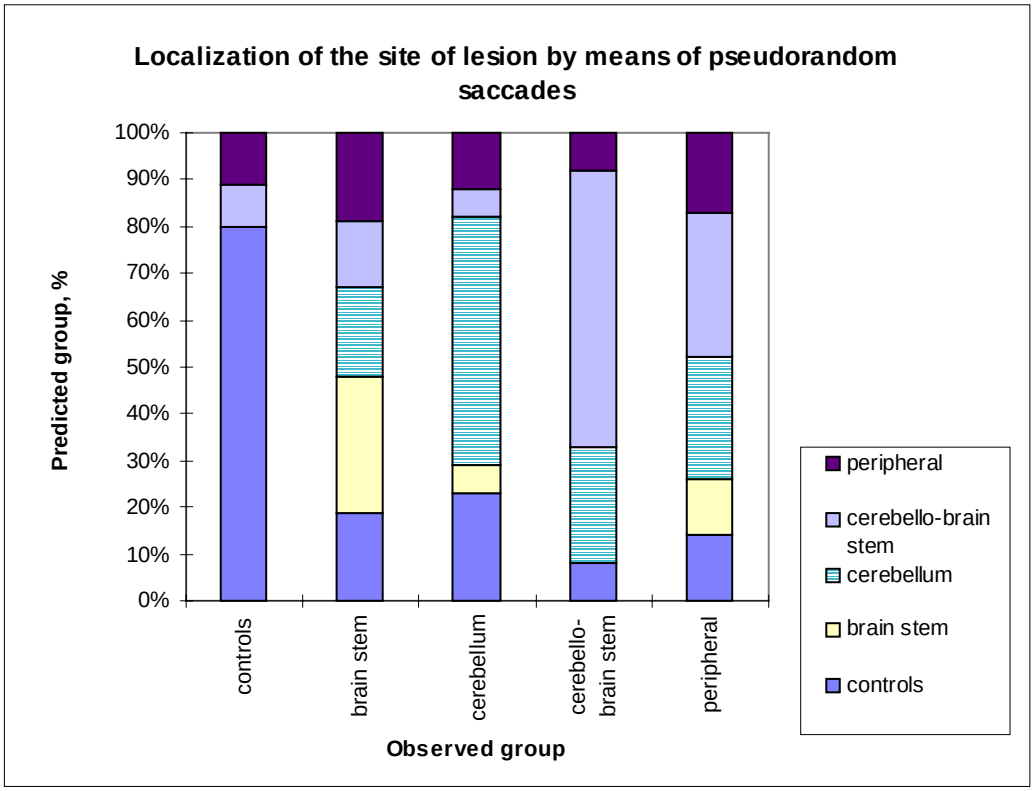
With ***constant saccades***, the site of lesion could be discriminated correctly in 48% of all cases. Control subjects were correctly classified in 80% of the cases. Patients with brain stem lesions were correctly classified in 37%, cerebellar lesions in 47%, cerebello-brain stem lesions in 33%, and peripheral lesions in 23% of all cases. (**Figure 14a**).

Figure 14a. Here is shown how the controls subjects and patients having lesions in different sites were classified according to the performance in constant saccades. Observed group is the real group.



With ***pseudo-random saccades*** (60° saccades), the site of lesion could be discriminated correctly in 49% of all cases. Control subjects were correctly classified in 80% of the cases. Patients with brain stem lesions were correctly classified in 29%, cerebellar lesions in 53%, cerebello-brain stem lesions in 58% and peripheral lesions in 17% of all cases (**Figure 14b**).

Figure 14b. Here is how the controls subjects and patients having lesions in different sites were classified according to the performance in pseudo-random saccades. Observed group is the real group.



With **PRPEM** at a frequency combination **0.25 and 0.425Hz**, the site of lesion could be discriminated correctly in 33% of all cases. Control subjects were correctly classified in 51% of the cases. Patients with brain stem lesions were correctly classified in 20%, cerebellar lesions in 29%, cerebello-brain stem lesions in 61%, and peripheral lesions in 14% of all cases (**Figure 14c &d**).

Figure 14c. Scatterplot of the discrimination analysis with PRPEM and the frequency combination of 0.25 and 0.425 Hz. Group 1 = control subjects, group 2 = patients with brain stem lesions, group 3 = patients with cerebellar lesions, group 4 = patients with cerebello-brain stem lesions, group 5 = patients with peripheral lesions.

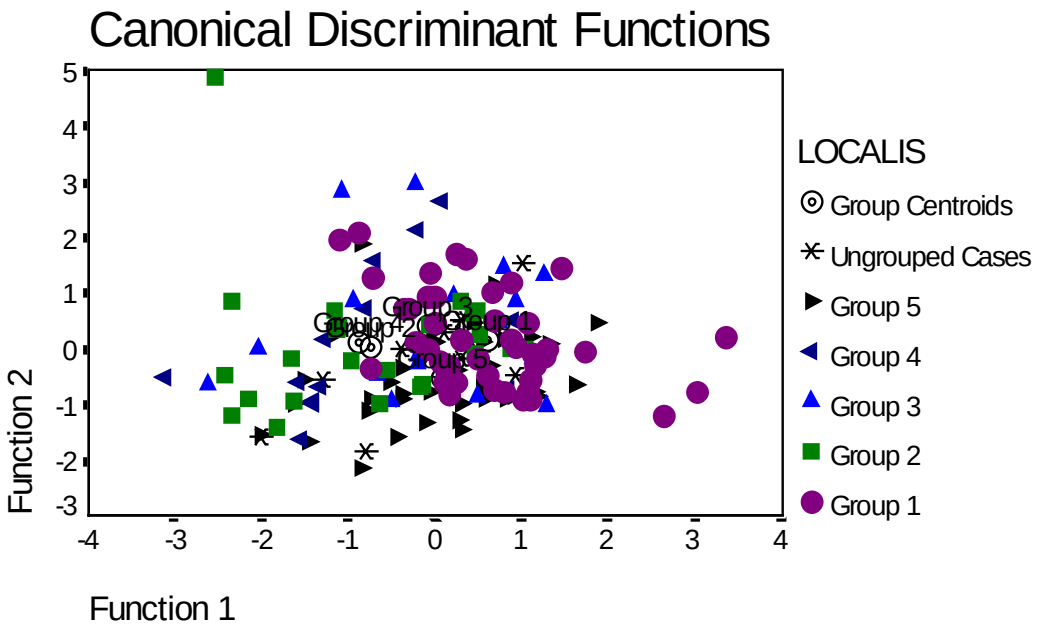
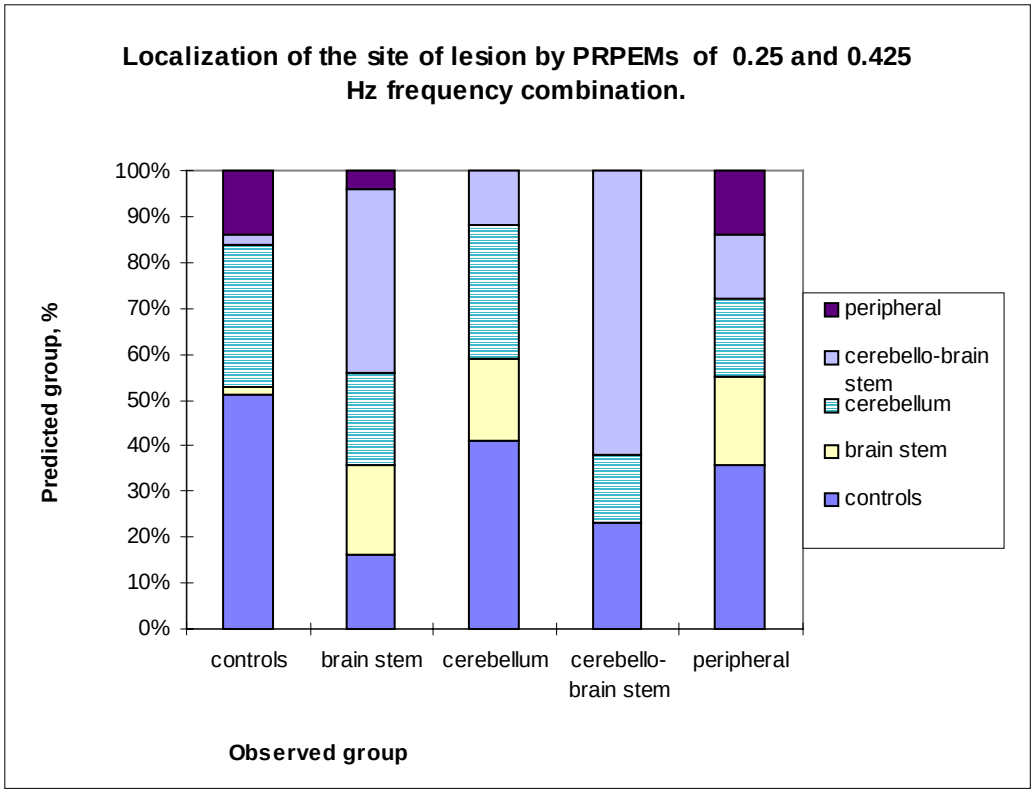
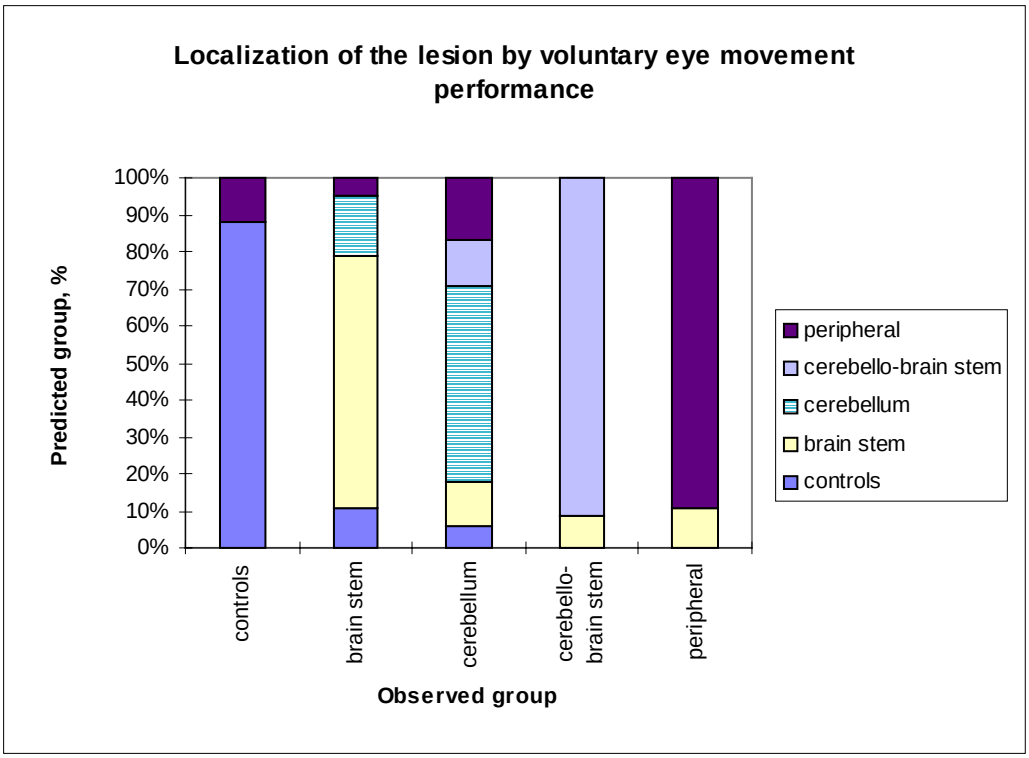


Figure 14d. Here is how the controls subjects and patients having lesions in different sites were classified according to the performance in PRPEM with the frequency combination of 0.25 and 0.425 Hz. Observed group is the real group.



When the discrimination analysis was done with evaluating the voluntary eye movement performance (both saccade tests and PRPEM with 0.25 and 0.425Hz frequency combination), a more accurate classification was achieved (**Figure 15)**. The site of lesion could be discriminated correctly in 75.5% of all cases.

Figure 15. Here is how the controls subjects and patients having lesions in different sites were classified according to the voluntary eye movement performance (constant and pseudo-random saccades, PRPEMs with the frequency combination of 0.25 and 0.425 Hz). Observed group is the real group.

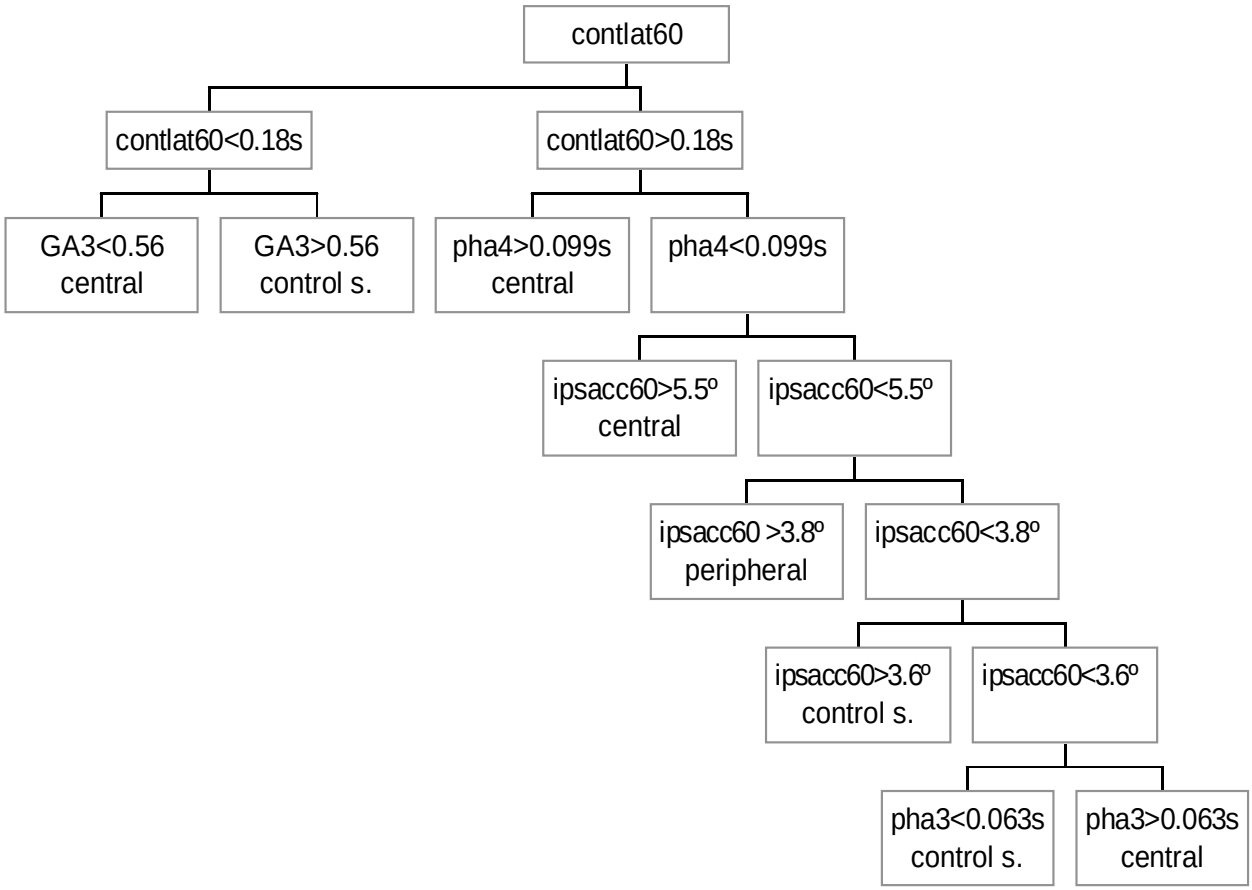


5. C. 4. Decision tree analysis and oculomotor deficits

Two different evaluations with decision tree analysis were done.

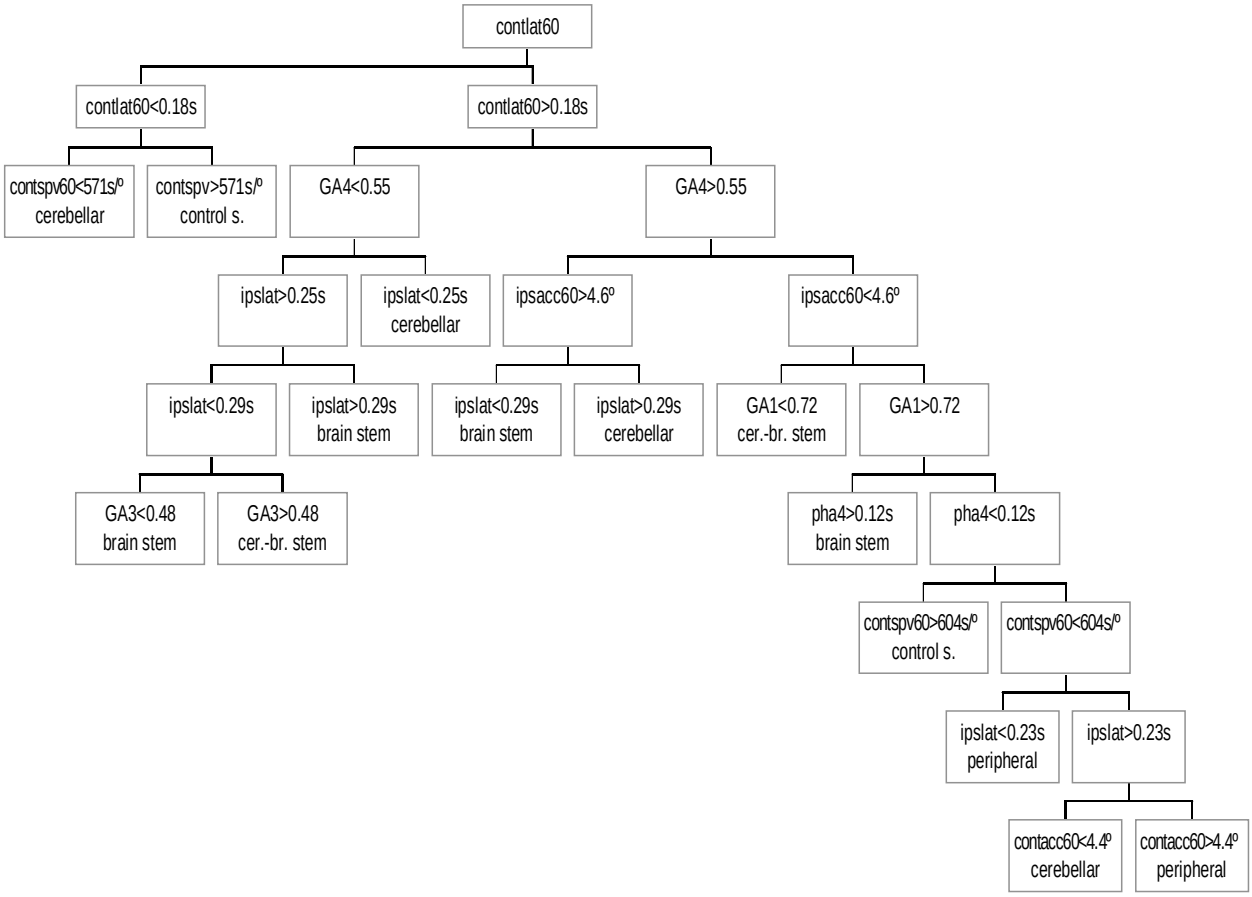
With the localization data and the classification of cases into three groups (control subjects, peripheral and central patients), the correct classification of cases by means of a decision tree was achieved in 97.1% of all cases. All of the control subjects were correctly classified. Of the peripheral patients, 17% were incorrectly classified into the control group. For central patients, 2% were incorrectly classified into the peripheral group. The attributes used and the decision tree are presented in **Figure 16.** The parameters were as follows: contralateral SRT of 60º pseudo-random saccades (contlat60), GA of the frequency combination 0.3 and 0.7 Hz (GA3), mean phase of the frequency combination 0.45 and 0.7 Hz (pha4), ipsilateral SA of 60º pseudo-random saccades (ipsacc60), and mean phase of the frequency combination 0.3 and 0.7 Hz (pha3).

Figure 16. The decision tree with the localization data and cases classified into three groups (control subjects, peripheral and central patients).



With the localization data and the classification of cases into five groups (control subjects, peripheral, cerebellar, cerebello-brain stem, and brain stem patients), the correct classification of cases by means of a decision tree was achieved in 91.4% of all cases. In control subjects, 94% were correctly classified. For patients with brain stem lesions, 5% were incorrectly classified to cerebellar lesions. For patients with cerebellar lesions, 6% were incorrectly classified to brain stem lesions. In cerebello-brain stem lesions, 16% were incorrectly classified with brain stem lesions. For patients of peripheral lesions, 16% were incorrectly classified to brain stem lesions **(Figure 17)**. The parameters were as follows: ipsilateral SRT of constant saccades (ipslat), contralateral SPV of 60º pseudo-random saccades (contspv60), ipsi- and contralateral SAs of 60º pseudo-random saccades (ipsacc60, contacc60), contralateral SRT of 60º pseudo-random saccades (contlat60), GAs at frequency combinations of 0.3 and 0.7 Hz (GA3), 0.45 and 0.7 Hz (GA4), and 0.15 and 0.35 Hz (GA1), and a mean phase at a frequency combination of 0.45 and 0.7 Hz (pha4).

Figure 17. The decision tree with localization data and cases classified into five groups (control subjects, peripheral, cerebellar, cerebello-brain stem, and brain stem patients).



6. DISCUSSION

6. 1. General comments

In line with other researchers, the present study demonstrates that maturation followed by degeneration of voluntary eye movements appears to be a continuous process, taking place throughout life. Gender has only a small effect on voluntary eye movement performance. In patients with Menière's disease, the lesion is peripheral, but in severe Menière's disease the CNS (Löchen 1977; Sörensen et al. 1977) and central vestibular control systems may be compromised, so the voluntary eye movement system might also be impaired.

The literature indicates that single voluntary eye movement tests have been demonstrated to be effective in diagnosing the disease causing vertigo and in evaluating the site of lesion causing vertigo (Allum et al. 1991; Wennmo 1983; Schalén et al. 1982; Henriksson et al: 1981). In the present study, voluntary eye movement performance was effective in diagnosing lesion site if used in conjunction with a decision tree analysis. However, there is a contributing factor to the difference between the findings of this study and previous studies regarding the utility of single voluntary eye movement tests. Patients in the present study had chronic and large lesions, rather than acute and restricted lesions (Wennmo 1983; Schalén et al. 1982; Henriksson et al 1981).

The oculomotor dysfunction in the present study can best be interpreted as a timing error of the voluntary eye movements found in patients with different diseases and different lesions. This timing error correlated with the severity of disease, as has been documented previously in faulty nystagmus among patients with central lesions (Dahlen 1983)

6. 2. *Voluntary eye movements in normal subjects*

The amount of hypometry in saccades in this study was similar to findings of Becker and Fuchs (1969) and Weber and Daroff (1971). The SRTs of this study are consistent with the previous findings of Stark et al. (1962), and Robinson (1981).

The values of SPV with constant saccades of 60º amplitude and pseudo-random saccades of 20º and 60º amplitude were somewhat higher than the SPV values of Wennmo et al. (1981) and Schalén (1981). These differences reflect the algorithms used to calculate SPV, and thus confirm the findings of Bahill et al. (1981).

In the present work, SA and the SPV were significantly affected by the amplitude of the saccade, confirming the results of Zuber et al. (1965), Weber and Daroff (1971), Schmidt et al. (1979), Warabi et al. (1984) and Lemij and Collewijn (1989).

In control subjects and some patient groups, the PRPEMs with different frequency combinations demonstrated a similar pattern. The GA and the mean phase reduced with rising frequency combinations.

When the target motion consists of a small number of sinusoids (4 or less), the spectrum of tracking eye movements contains only those frequencies present in the stimulus (St-Cyr and Fender 1969). But as the spectral content of the target motion increases (e.g., 7 or 13 frequencies), the response of the pursuit system demonstrates greater errors, including reduced gain and increased phase lag (St-Cyr and Fender 1969). St-Cyr and Fender (1969) also found that when target motion consists of a small number of sinusoids, the pursuit system responds preferentially to the highest frequency present. Therefore, if a subject attempts to follow a target whose motion may be described as a sum of two components which are close in frequency, the subjects respond preferentially to the higher one, at the expense of the lower one (St-Cyr and Fender 1969). These findings are in line with the results of Barnes et al. (1987) and Isotalo et al. (1992). The findings of the present study confirm previous works. In this work, there were no significant differences in GA and mean phase between the frequency combinations of 0.3 and 0.7 Hz and 0.45 and 0.7 Hz. The higher frequency combination seemed to be preferentially affected.

The amount of phase lead and phase lag in PEMs varies according to the extent of predictability of the stimulus (Stark et al 1962; Young and Stark 1963; Michael and Melvill Jones 1966). However, according to the study by Kowler and Steinman (1981), even when target motion cannot be predicted at all, human subjects will produce some anticipatory PEMs. Predictable stimuli usually cause phase leads. The amount of phase lead diminishes, and the size of phase lag increases with increasing unpredictability (Fuchs 1967b; Stark et al 1962; Michael and Melvill Jones 1966). In addition, the increasing stimulus frequency increases the size of phase lag (º) (Michael and Melvill Jones 1966). In this work, mean phase (s) was shortened significantly with increasing frequency combination.

The gain of the oculomotor tracking system decreases with increasing frequency (St-Cyr and Fender 1969). There is a general trend towards diminishing gain as the complexity of target motion increases from simple sinusoidal movements via sums of sinusoids (Stark et al. 1962) to band-limited white/Gaussian noise (Dallos and Jones 1963; Michael and Melvill Jones 1966). The more predictable the target motion is, the more accurately it can be traced (Michael and Melvill Jones 1966; Larsby et al. 1988). The ability of the visual tracking system to maintain fixation is a function of the predictability of the stimulus, as well as a function of its frequency and amplitude (Michael and Melvill Jones 1966). The GA was significantly affected by frequency combination, reducing with increasing frequency combination, which coincides with previous studies (Michael and Melvill Jones 1966; St-Cyr and Fender 1969).

6. 3. Age and the oculomotor system

The accuracy of saccadic function continually improves through maturity to middle age. In the present work, it was observed that SA60°s in constant and pseudo-random saccades and SA20° in pseudo-random saccades were the best in the middle-age group. These findings are in line with those of Sharpe and Zackon (1987) and Tedeschi et al. (1989), but contradictory to those of Moschner and Baloh (1994). However, Moschner and Baloh (1994) found a tendency towards hypometric saccades in some older subjects when compared to younger subjects, and the older subjects had greater intrasubject variability in accuracy measurements than the younger subjects. Age distribution was different in their study when compared to the present study.

SRTs have also been found to be the shortest in middle-aged subjects when compared with elderly or younger subjects (Miller 1969; Spooner et al. 1980; Carter et al. 1983; Abel et al. 1983; Warabi et al. 1984; Whitaker et al. 1986; Hutton and Pallet 1986; Sharpe and Zackon 1987; Tedeschi et al. 1989; Moschner and Baloh 1994). In this work, none of the SRTs in constant or pseudo-random saccades showed any statistically significant differences between the various age groups. However, in pseudo-random saccades with SRT20°, the best performance was found in the middle-age group, which warrants further study. In the studies of Whitaker et al. (1986), Carter et al. (1983), Spooner et al. (1980) and Abel et al. (1983), there were few older subjects tested. In a study by Miller (1969), there was a small amount of children and teenagers tested, and Warabi et al. (1984) had only a small amount of young adults (19-26 years) participating in their study. In the study by Moschner and Baloh (1994), only a small amount of middle-aged adults were tested. The total amount of tested subjects was small in studies by Hutton and Palet (1986) and Sharpe and Zackon (1987). Most of the above mentioned studies regarding age-related changes in saccadic performance center on middle-aged and elderly subjects, or children, teenagers and middle-aged subjects.

Age factors can explain the difference between results of this work and previous studies. However, conclusions are hampered in these studies because of a narrow sample of subjects. As in the study of Tedeschi et al. (1989), where the age range was 15-75 years, children were not included. In their study, the number of subjects tested was large, but the target displacements in saccades were different between this and previous studies mentioned above. Additionally, in none of these studies was saccadic amplitude of 60° included, and in some studies the largest amplitudes were 40° (Tedeschi et al. 1989; Sharpe and Zackon 1987; Warabi et al. 1984). That may affect the results of these works in SRTs.

The SPV has been found to be lower in elderly subjects than in middle-aged

subjects (Spooner et al. 1980; Tedeschi et al. 1989) and lower than in young subjects (Majima et al. 1981; Warabi et al. 1984). This contradicts the studies of Abel et al. (1983) and Henriksson et al. (1980) who did not observe any consistent correlation of SPV with age. However, in the present study there were no SPVs in constant or pseudo-random saccades that showed any statistically significant differences between age groups. These findings coincide with the findings of Abel et al. (1983) and Henriksson et al. (1980). As there is large inter-subject variability in the saccadic peak velocity values in the elderly and the young, there is a considerable overlapping in SPVs of different age groups (Warabi et al. 1984). Abel et al. (1983) did not observe any significant differences in SPV between the young (18-37 years) and the elderly (59-87 years). As well, Henriksson et al. (1980) found no consistent variation of saccadic peak velocity with age. In both studies, there were elderly subjects who made faster saccades than the younger ones (Abel et al. 1983; Henriksson et al. 1980). In this work, the youngest group seemed to have the highest SPVs, even though the differences between the age groups were not statistically significant. These findings are also in line with the findings of Majima et al. (1981).

Care must be taken when comparing the results of studies that have used different stimulus paradigms in the saccadic tests. The type of stimulus paradigm may affect the results, such as Takemori and Ida (1984) versus Sharpe and Zackon (1987) versus the present study, in our conclusions regarding prediction of stimulus.

Pursuit velocity decreases in elderly subjects when compared to middle-aged subjects (Sharpe and Sylvester 1978; Larsby et al. 1988; Morrow and Sharpe 1993; Moschner and Baloh 1994; Paige 1994; Kanayama 1994). Reduced velocity is reflected as a deteriorated PEM accuracy (in this work, the GA). The findings of the present study are in line with the findings of Sharpe and Sylvester (1978), Larsby et al. (1988), Morrow and Sharpe (1993), Moschner and Baloh (1994), Paige (1994), and Kanayama (1994). The present study also confirms the findings of Larsby et al. (1988), showing that the accuracy of eye movements in children and teenagers is not matured when compared to the middle-aged. The findings of this work coincide with those previously mentioned studies referencing the best pursuit performance in the middle-age group. This study also confirms the findings of Versino et al. (1993a) regarding the correlation of pursuit index (resembles GA of this study) with age. The effect of age on the accuracy of PEMs was best when observed in the curve estimation procedure by nonlinear regression: the quadratic function was the best fit, and the best performance in age scale was found in the middle-aged group.

The reason why significant differences between age groups in GA were not found in this work with one-way ANOVA, could be explained by the pseudo-randomization influencing PEM performance in all subjects to such a degree that the differences between the age groups were not significant. The predictability of the stimulus

movement can affect the variability of the PEM accuracy (gain of PEM), which means the more unpredictable the stimulus movement is, the larger the variability of the gain of PEM. The type of target movement used in different studies has varied. These have included totally predictable oscillating movements (Paige 1994), constant velocity ramp movements (Sharpe and Sylvester 1978; Spooner et al. 1980), predictable sinusoidal movements (Hutton et al. 1983; Larsby et al. 1988; Moschner and Baloh 1994; Kanayama et al. 1994), and pseudo-randomized movements (Larsby et al. 1988). In the present study, large intra-group variability could hide the differences, however, trends were observed. The GA was lower in the young and elderly than in the middle-aged subjects with different frequency combinations. Corrective saccades seem to increase in the elderly when compared to the middle-aged (Larsby et al. 1988; Hutton et al. 1993), or at least a trend of increased saccadization in the elderly can be found (Sharpe and Sylvester 1978). In this work the increased saccadization in the elderly was observed as the reduced GA.

Phase lag has been found to lengthen with advancing age, as cited by Sharpe and Sylvester (1978), where latency was assessed from the onset of target motion to the beginning of PEM. In studies by Morrow and Sharpe (1993) where latency was similarly assessed, they found diminished initial pursuit acceleration in the elderly. In studies by Paige (1994), phase shift was assessed by computer, and for all age groups, phase lead was found in the lowest stimulus frequency, and whereas phase lag increased with increasing stimulus frequency. Larsby et al. (1988) did not find the phase shift to be affected by age. In their study the phase lead was found only at the very lowest frequencies and velocities of the stimulus with sinusoidal sweep or with pseudo-randomization. In the present work, the best PEM performance with reference to mean phase was found in the middle-aged group. The mean phase was at its shortest in the middle-aged group (one-way ANOVA). As well, the phase lag in age-scale (curve estimation procedure by nonlinear regression) showed the same results. These findings of phase differences in different age groups are in line with the findings of Sharpe and Sylvester (1978) (constant velocity ramp movement), Morrow and Sharpe (1993) (step-ramp stimuli), and Paige (1994) (predictive oscillating movement). These results confirm that PEM ability is a function of target predictability as well as target frequency and age of the tested subjects (Larsby et al. 1988). In the latest mentioned study there were different kinds of stimuli forms, and the pseudo-randomized stimulus consisted of a sum of sinusoids in the frequency range of 0.2 - 2.0 Hz.

The age distribution in these PEM studies is not similar. Separate age groups were used by Sharpe and Sylvester (1978), Hutton et al. (1983), Larsby et al. (1988), Morrow and Sharpe (1993), Moschner and Baloh (1994) and Kanayama et al. (1994). Overlapping age groups were used by Spooner et al. (1980), and continuous age

distribution was used by Paige (1994). The amount of tested subjects is often insufficient (Sharpe and Sylvester 1978; Spooner et al. 1980; Hutton et al. 1983; Larsby et al. 1988; Morrow and Sharpe 1993; Moschner and Baloh 1994; Kanayama et al. 1994). The advantage to the study by Larsby et al. (1988) is including children and teenagers, ranging from 7 to **(**85**??)** years, but only a few subjects were tested.

POSSIBLE CAUSES FOR THE DEGENERATION OF VOLUNTARY EYE MOVEMENTS:

According to Robinson (1981), a signal representing motor error (the difference between desired eye position in the orbit and actual eye position) drives brain stem burst neurons. Hypometric saccades could be explained by a deficient motor error signal (Sharpe and Zackon 1987). Atrophy of the frontal lobe neurons could contribute to the saccadic hypometria of aging (Sharpe and Zackon 1987), or it could be caused by degeneration of the centers involved in programming the correct execution of saccadic eye movements, such as the cerebellum (Tedeschi et al. 1989).

Aging entails a progressive quantifiable deterioration in the ability to control eye movements driven by vestibular and visual inputs (Paige 1994). Visual and vestibular systems are important in maintaining a gaze on visual targets and maintaining retinal image stability during natural behavior (Paige 1994). Failure of visual and vestibular control of gaze presumably results in disintegration of visual stability and orientation in space (Paige 1994).

Reduced oculomotor capacity in elderly subjects might be due to: 1) degenerative processes (Sharpe and Sylvester 1978; Larsby et al. 1988), such as loss of neurons and dendritic synapses in various areas of the CNS (Kemper 1984), 2) reduction of Purkinje cells in the cerebellum (Hall et al. 1975), 3) modifications in specific neurotransmitter systems (Selkoe and Kosik 1984), 4) degeneration of the extraocular muscles (Miller 1975), or 5) vascular problems (Linville and Arneric 1991) caused by increasing age. PEM is driven by visual motion information, and impaired pursuit initiation in elderly subjects compared to young and middle-aged subjects could be caused by senescent degradation of afferent visual motion inputs (Morrow and Sharpe 1993). This could also lengthen the phase lag in elderly subjects. Degraded conversion of visual sensory inputs to motor commands might also explain the decline in gain of PEM to moving stimuli and the impairment of saccadic accuracy in the elderly subjects (Morrow and Sharpe, 1993). To some extent reduced attention span belongs to normal aging, and it can affect PEM performance in the elderly (Versino et al. 1993a). This was also seen in the present study with respect to PRPEMs in elderly subjects. According to Spooner et al. (1980), symmetrical impairment of any of the oculomotor subsystems in an elderly person should be interpreted with caution.

6. 4. Gender and voluntary eye movements

Gender differences in voluntary eye movements has been studied by Becker and Fuchs (1969), Sharpe and Sylvester (1978), Hutton et al. (1983), and Whitaker et al. (1986).

No important differences between genders could be found in any of the eye movement tests in the present study. These results coincide with the results by Sharpe and Sylvester (1978) and Whitaker et al. (1986). There seems to be no difference in voluntary eye movements across genders.

There were some tendencies found in pseudo-random saccades; SPV20º tended to be lower in females than in males ($p<0.05$). In SPVs of 60º saccades in pseudo-random and constant saccades, females had lower values than males. In these cases, the differences were not statistically or mildly significant. These findings could be the result of early emphasis on childhood males to exercise tasks requiring rapidity and fast reaction times. On the other hand, physical facts might play a role. These results also coincide with the results of Hutton et al. (1983) who did not find any gender effect in tracking eye movements. They did observe that tracking in elderly women was somewhat poorer than in elderly men. They studied the PEMs, but it is reasonable that these findings can also be observed in saccades.

According to Becker and Fuchs (1969), saccades in female subjects appear to be faster than in males, which contradicts the findings of the present study. One needs to take into account the possible inadequacy of their study design when explaining these differences.

6. 5. Laterality and saccades

Differences between rightward and leftward saccades or PEMs have been analyzed by Baloh et al. (1976), Carter et al. (1983), Meyer et al. (1985), Hutton and Pallet (1986), van den Berg and Collewijn (1986), Versino and Cosi (1990), and Versino et al. (1993a). In studying the diagnostic and localization value of voluntary eye movements, the means of rightward and leftward SA, SRT and SPV were used as the ipsilateral and contralateral parameters for control subjects.

Some studies have found differences between eye movements (right and left) in saccades (Hutton and Pallet 1986) and in PEMs (Meyer et al. 1985); whereas many others have not found any differences, either in saccades (Carter et al. 1983), or in PEMs (Baloh et al. 1976; van den Berg and Collewijn 1986; Versino and Cosi 1990; Versino et al. 1993a).

Hutton and Pallet (1986) found an asymmetry in SRTs for unpredictable horizontal saccades in right-handers. Right-handers had shorter SRTs for rightward than for leftward saccades, the directional differences for SRTs relating to motor or central integrative processes. However, Carter et al. (1983) found no differences

between rightward and leftward SRTs. In this present work, no significant differences in the laterality of SRTs were found. In this study and in the study of Carter et al. (1983), the tested subjects' left- or right-handedness was not taken into consideration.

There seems to be a left-right asymmetry in peak velocity of human PEMs (Meyer et al. 1985). In saturation velocity (= the highest velocity) of human PEM, leftward ones often seem to be higher than rightward ones with the tested subjects (Meyer et al. 1985). According to Meyer et al. (1985), a directional preponderance of 24% in saturation velocity is not abnormal. The findings of this study agree with findings by Meyer et al. (1985). In pseudo-random saccades, the rightward SPV60° was significantly lower than the leftward SPV60°. This trend was also found in SPV20°s of pseudo-random saccades and in SPV60°s of constant saccades, but the differences were not significant. The trend that rightward SPVs were lower than leftward SPVs was without any exceptions. In other parameters, such a constant trend was not found. However, Meyer et al. (1985) studied PEMs, and in this work only the saccades could be studied, though it seems logical that the effect of laterality is equally found in both saccades and PEMs.

In velocity gain, there were no directional asymmetries according to van den Berg and Collewijn (1986). In the study by Baloh et al. (1976), there were no significant differences found in the velocity parameters of leftward and rightward PEMs in normal subjects. In the study of Versino et al. (1993a) and Versino and Cosi (1990), pursuit index and pursuit gain were not influenced by the direction. Unfortunately, in the present work, the side differences of PRPEM could not be analyzed.

In the present work, a tendency for rightward saccades to be slower than leftward saccades (in paired samples t-test) was observed. Though possible technical errors were controlled by changing the polarity, it did not change the differences between rightward and leftward saccades. The saccade tests of the control subjects were done in two different test labs. The testing systems in both labs were identical. The differences between rightward and leftward saccades were found in control subjects tested in both laboratories. So far, there is no evidence of a systematic fault in the testing system, program or equipment. As such, they should still be further evaluated, to totally exclude other systematic faults. It seems possible that the dominating hemisphere may affect the voluntary eye movement system too. Further evidence and study on dominant hand and eye responses is warranted.

Others have not found statistically significant differences in saccadic peak velocity between rightward and leftward saccades. The reason may be due to large variability and/or using the Student's t-test in the statistical analysis. And in this work, the Student's t-test didn't show any statistically significant differences in SPVs, SAs or SRTs between rightward and leftward saccades.

The results show that the mean values of parameters (SA, SRT, SPV) for

rightward and leftward saccades at a level of a group (i.e. control subjects) do not differ significantly from each other. Therefore, in the analysis of the differences between the results of patients and control subjects, the mean of a rightward and a leftward saccade parameter can be used as the contralateral and ipsilateral saccade parameters for control subjects.

When the results of individuals are statistically analyzed, there is a tendency for the leftward SPVs to be quicker than the rightward ones.

6. 6. Methodological aspects

a. Repeatability of pseudo-random pursuit eye movement tests

Assessing of the reliability of eye movement tests has been done in a few previous studies, though most of them were not systematic. The most thorough studies were done by Tijssen et al. (1989), Brantberg (1992) and Versino et al. (1993b). The repeatability has usually been tested by assessing the tests twice (Boghen et al. 1974; Schmidt et al. 1979; Versino et al. 1993b). Schmidt et al. (1979) tested many of their patients twice, several years apart, with the same tests. Boghen et al. (1974) measured saccadic peak velocity characteristics of normal subjects, and also explored repeatability by testing a few of their subjects on two occasions several months apart. Tijssen et al. (1989) tested optokinetic after-nystagmus three times with four trials (12 samples) in 30 subjects; Brantberg (1992) tested optokinetic after-nystagmus I (OKAN I) four times with four trials in 16 subjects; Versino et al. (1993b) tested directionally unpredictable saccades and PEM of triangular ramps two to three times with five trials (in 20 subjects twice, in 12 subjects three times).

Different statistical methods have been used (Boghen et al. 1974; Tijssen et al. 1989; Brantberg 1992; Versino et al. 1993b). Tijssen et al. (1989) studied the intrasubject variability with assessing the coefficient of variation, and Brantberg (1992) used one-way analysis of variance with covariance and two-way analysis of variance. Versino et al. (1993b) used the repeated measures analysis of variance. Boghen et al (1974) used paired sample's t-test. Schmidt et al. (1979) did not use any statistical analysis, but evaluated the findings of eye movement recordings.

Tijssen et al. (1989) discovered that at least eight measurements were necessary to obtain a precise estimate of the initial slow-phase velocity of optokinetic after-nystagmus or of the directional asymmetry and preponderance of optokinetic after-nystagmus. This was caused by large intrasubject variability. Brantberg (1992) found considerable intrasubject variability of values for directional asymmetry in OKAN I in healthy subjects, which is why the clinical meaning of OKAN I is less than that of optokinetic after-nystagmus II, with the latter found as repeatable. Schmidt et al. (1979) also found the findings of eye movements repeatable. Versino et al. (1993b)

found the saccade and PEM tests repeatable, and only in saccadic amplitude/peak velocity relationship coefficients was there some difference in the results of different measurement times; even so, they still considered it reliable. Boghen et al (1974) found that with small saccades ($\leq 10^{o}$) there seemed to be significant differences between the saccadic peak velocity results at different measurement times, but that happened rarely with bigger saccades.

The results of this work coincide with previously cited studies pointing to the fact that eye movement tests are repeatable. The differences in statistical methods or in the number of measurement times between these different studies did not cause contradictory results.

However, measurement time showed a tendency for effect on mean phase. In the case of mean phase, there seemed to be a possible learning effect, as the phase lag was systematically shorter on the second time in each frequency combination. The variability of PRPEM results did not appear to be large in this work. In previous studies, some exceptions in the repeatability of eye movement tests have also been found. Some parameters in eye movement tests seem to be more susceptible to the learning effect or to large variability.

b. Differences of voluntary eye movements recorded by EOG and MOG methods

In EOG recordings, high frequency noise contaminates the signal, causing a large variation in the results (Beaussart and Guieu 1977; Jäntti 1982a; Jäntti 1982b; Yee et al. 1985; Chioran and Yee 1991). In MOG, the noise contamination is much less, which reduces the variability, and increases the reliability of this measure (Schlag et al. 1983; Yee et al. 1985). The findings of this study of saccades agrees with this view. The SA in saccade tests was better (smaller) in MOG recordings than in EOG recordings. This may be due to the fact that the EOG recording technique is contaminated by EMG and noise, which could increase the SA in EOG recordings. The recording techniques did not affect SRT in either saccade tests. High frequency noise minimally affects the time parameters. Because the search-coil glides on the eye in the MOG recordings and because of EMG artifact, high frequency noise (Chioran and Yee 1983; Yee et al. 1985) and slow d.c. drift (Schlag et al. 1983) might have been present in EOG recordings, the SPV was lower in MOG than in EOG. Careful preparations at the beginning of the test were done to reduce the EOG artifacts. According to Robinson (1964), coil slippage is only a contaminating factor if the slippage is greater than 0.5° in eye movement tests. The cable of the search coil (all 10 subjects had a search coil on the right eye) could also have had some influence on eye movements.

In PRPEM, the recording method didn't influence GA or mean phase in paired

samples t-test.

In PEMs, the recording method doesn't have a significant effect on parameters (GA, mean phase), but in saccades the effect on the parameters (SA and SPV) is significant. It seems that PEMs are not as susceptible to high frequency noise as saccades.

In the study of Schlag et al. (1983) the EOG recording method seemed to be less accurate than the MOG method. However, they decided that with careful test preparations, the EOG method could still be used in audiovestibular testing, especially when testing horizontal eye movements.

The findings of the present study coincide with the findings of Schlag et al. (1983) regarding horizontal saccades. Interestingly, it was discovered that PEMs are resistant to the effect of the recording method.

The disadvantage of the MOG method (i.e., the inconvenience it causes to the subject) restricts its use in routine tests. Some subjects had significant endothelial edema caused by hypoxia under the thick scleral annulus, and some corneal epithelial erosion was also noticed. No long standing changes could be seen. The MOG recordings are not totally free from artifacts (Schlag et al. 1983). Scleral coils can often obstruct the visual field of tested subjects (Schlag et al. 1983), and using scleral coils in recording eye movements requires more cooperation from the tested subjects than does the EOG method (Yee et al., 1985).

The EOG method in recording voluntary eye movements is more convenient than the MOG method, and the EOG method is accurate enough in assessing eye movements on a horizontal plane in clinical practice (Schlag et al. 1983). The advantages of EOG over the MOG method are its simplicity, convenience and lower costs. The EOG recording method is also preferable in assessing voluntary eye movements in clinical work.

6. 7. Physiological aspects

a. Prediction of stimulus and saccadic eye movements

Takemori and Ida (1984) found that the ability to predict movement of the target has minor effects on saccade parameters. Still, the saccadic peak velocity tended to be faster and the SRT longer in predictive saccades than in non-predictive saccades. In the study of Takemori and Ida (1984), the saccadic amplitudes and stimulus frequency were much smaller than in the present study. That could explain why they didn't find any differences between the predictive and non-predictive saccades.

In the study by Miller (1969), the ability to predict target movement had a slight tendency to affect the SRT. In his study, only saccades with small amplitudes were studied.

In the study by Whitaker et al. (1986), the ability to predict target movement (predictable vs. non-predictable saccades) did not affect SRTs. But in their study, the stimulus movements were only ± 2.8º, and in non-predictable saccades only the side of stimulus movement was non-predictable. In predictable saccades, prior knowledge of the target's side was also given. These facts could have affected their results so that the predictability vs. nonpredictability of stimulus did not affect the SRTs in their study.

Sharpe and Zackon (1987) have studied the differences between non-predictable and predictable saccades, and their findings were confirmed by the findings of the present work concerning its healthy subjects. In the study by Sharpe and Zackon (1987), SRTs were affected to some degree; the non-predictable saccades had shorter SRTs than the totally predictable saccades. In this work, the SRT was shorter in pseudo-random saccades when compared to the constant saccades. Neither in this work nor the work of Sharpe and Zackon (1987) were the SPVs significantly affected by the predictability. Still, in both studies, the saccadic peak velocity was higher in non-predictable than predictable saccades. According to Sharpe and Zackon (1987), saccadic accuracy was affected by predictability, the accuracy being worse in non-predictable saccades. In this work, the SA was more inaccurate in pseudo-random saccades when compared to constant saccades.

These studies show that one must be careful when comparing the results of different studies with different kinds of saccade stimuli. In general, the prediction of saccadic stimulus seems to have some effect on saccadic parameters.

With the present study, in other patient groups except those with Menière's disease, the ability to predict saccades was about the same as in control subjects. The reason for a shortage of prediction of voluntary eye movements may be linked to enhanced visual motion perception in Menière patients (Pyykkö et al 1994a).

The eye movement defects that are caused by several diseases and disorders can best be seen in movements of larger amplitudes (Pyykkö and Schalén 1982). For this reason as constant and pseudo-random saccades of 60° amplitudes were used in the current investigation. It is not clear whether it is necessary to assess saccades of 20º or 60º. The overall performance of saccades is more important for providing useful information.

b. Effect of different frequency combinations on pseudo-random pursuit eye movements

In this work, the GA decreased and the mean phase shortened with the increasing frequency combination of PRPEM. This is in line with the findings of Michael and Melvill Jones (1966) and St-Cyr and Fender (1969).

Control subjects and patients of the operated CPA and HAB tumors, and those with infarction of cerebello-brain stem, had the same profile where the effect of increasing frequency combinations on GA and mean phase (i.e., the accuracy and timing of the PRPEM) was concerned. This profile is therefore, preserved in many diseases causing vertigo.

The different frequency combinations can best be evaluated with profile analysis of frequency combinations.

6. 8. Voluntary eye movements and the severity of the disease in patients with:

a. Menière's disease

According to Schalén et al. (1982), the saccadic system is normal in patients with peripheral vestibular disorders despite the presence of spontaneous nystagmus. In PEMs, the frequency and amplitude of superimposed saccades show a small but distinct increase in the direction of fast phase of nystagmus (Schalén et al. 1982; Pyykkö and Schalén 1984). In this study, patients with moderately severe or severe Menière's disease had distinctly increased SRTs of constant and pseudo-random saccades, decreased SPVs of constant and pseudo-random saccades, and reduced GA of PRPEM, when compared to control subjects.

Differences may be due to the severity of disease. Since oculomotor activities may vary due to the stage and activity of Menière's disease, patients with advanced severity were chosen to participate in the study. Results of this work reflect findings typical of patients with severe Menière's disease, including: deficits of voluntary eye movements, correlation of clinical symptoms and oculomotor pathology, and the discrimination analysis among the different groups.

According to this work, a pure vestibular lesion (with advanced severity) can cause disorders of voluntary eye movements. This work shows that the vestibular system can affect the voluntary eye movement system, at least in some cases, and naturally, central lesions cause more advanced disorders of voluntary eye movements.

In this study, both PEMs and saccades were affected. The inadequacy of the PEM and saccadic systems reflected an error in the time process (= timing) for patients with severe Menière's disease. This was reflected in the lengthened SRT and the decreased SPV of constant and pseudo-random saccades. In PRPEM, this error in timing was reflected in reduced GA. The error in timing caused an increased saccadization of PRPEM, and that caused the reduction of GA, confirming previous observations by Pyykkö and Schalén (1984). It seems that corrective saccades are increased greatly in patients with severe and active disease, and that increased saccadization is reflected in the GA results. All neural processes are controlled by time.

In this work, the error of timing with reference to mean phase was not observed in patients with Menière's disease. Saccades compensated the total eye tracking. As this saccadic compensation of PEM operated in a proper timeframe, no lengthening of phase lag was observed. Still, there might be lengthening in the pre-motor processing of information required for the programming of eye movements. The misleading information derived from the lesioned vestibular system would cause the lengthening in the premotor processing, and that could also affect the oculomotor system. The lengthening in the premotor processing of information would cause saccadization of PEMs.

Visual information, although good for recalibrating the faulty vestibular system, may be misleading if the vestibular loss is fluctuant and causes repeatable attacks (Pyykkö et al. 1994a). According to Pyykkö et al. (1994a), the dominance of the visual system may lead to dysfunctions where movements of the visual frame can cause postural illusions. Clinically, patients with Menière's disease have complaints in their ability to watch TV, drive a car, etc. This visual "overruling" in moving visual surrounding causes "postural vection" and indicates a distrust of the central postural system on vestibular detectors of the inner ear (Pyykkö et al. 1994a). If there is a mismatch between the visual information and the information coming from the affected vestibular system as in Menière's disease, it could result in the timing error found in this work.

As far as the author can ascertain, there are no previous studies about voluntary eye movements and clinical symptoms in Menière's disease.

In this work, lengthened SRTs and lowered SPV as well as reduced GA of PRPEM were associated with symptoms and findings reflecting the severity and intractability of Menière's disease (poor hearing level, severe Tumarkin attacks, severe tinnitus, poor working capacity, severe rotatory vertigo attacks or severe unsteadiness during attack-free periods), and with aging.

b. Operated cerebello-pontine angle tumor

In large vestibular schwannomas, saccadic dysmetria (Nedzelski 1983; Mrazek 1989; Hulshof et al. 1989) can be found. But according to Selesnick and Jackler (1992), large vestibular schwannoma tumors don't always manifest any oculomotor abnormalities. Saccadic eye movements are usually unaffected by CPA tumors (Baloh et al. 1977). Saccadic peak velocity has been found to be normal, according to Baloh et al. (1977) and Nedzelski (1983). In this work, operated CPA tumor patients had poorer performance in saccades than control subjects, especially in SRTs and often in SPVs. Sometimes, the SA was also disturbed in operated CPA tumor patients.

In large vestibular schwannomas, saccadization of PEM (Nedzelski 1983; Hulshof

et al. 1989; Selesnick and Jackler 1992) and deficits in PEM (Baloh et al. 1977) can be found. Patients with brain stem compression by CPA tumors have significant slowing of eye velocity of PEM (Baloh et al. 1976). Patients with peripheral vestibular lesions and patients with small vestibular schwannomas have normal velocity parameters of PEM (Baloh et al. 1976). In this work, the operated CPA tumor patients had poorer performance in GA and mean phase than control subjects.

The results of this work confirm the results of previous studies about saccade and PEM deficits. In this study, however, the deficits in saccades were not restricted to dysmetria; the oculomotor pathology in operated CPA tumor patients was the most profound in SRTs and could be found in some SPV results. The timing of saccades in operated CPA tumor patients is deteriorated. And the pathology found in some SPV results may refer to cases where the compression of brain stem by a large tumor has affected the SPV performance. This is in line with the findings of Baloh et al. (1976). The error in timing also deteriorates the SPV. The saccadization of PEMs found in previous studies is reflected in the reduced GAs of PRPEM in this work. Slowing of eye velocity of PEMs in large CPA tumors found by Baloh et al. (1976) is reflected via the saccadization of PEMs to the reduced GAs. The disorders of timing are also found in PRPEM phase performance; the mean phase is lengthened in operated CPA tumor patients.

Both the saccades and PEMs have errors of timing in operated CPA tumor patients. The error of timing is more profound in operated CPA tumor patients than of patients with Menière's disease. In this work, the diameter of CPA tumors had ranged from 7 to 60 mm (mean 32.4 mm), so tumors had been relatively large and compression of brain stem had occurred in many cases. Therefore, the compression by the CPA tumor itself, not just the tumor surgery, has resulted in lesions to the oculomotor system in the brain stem of many of these patients. Further studies are needed to confirm which of these two factors is more important; the compression caused by the CPA tumor or the tumor surgery.

Based on saccade tests, no side differences of pathological process could be made. An injury in the brain stem during surgery of CPA tumors may lead to a deteriorated ipsilateral saccadic performance. According to Rosenberg et al. (1993) and Selesnick et al. (1993), the compression of brain stem and cerebellum begins if the diameter of CPA tumor exceeds 20 mm. In large CPA tumors, the flocculus and the nodulus can be compressed by the tumor (Selesnick and Jackler 1992). Compression of these structures can cause oculomotor pathology. According to Selesnick and Jackler (1992), CPA tumors compressing the brain stem cause ipsilateral lesions first, but when the tumor is very large, lesions in the contralateral side can be found, too (Selesnick and Jackler 1992). This could explain why the oculomotor pathology was not restricted only to the ipsilateral parameters. In

contralateral parameters, deficits were also found. Another explanation for this might be the fact that the side of a CPA tumor cannot be consistently identified by the abnormality of PEMs or saccades; the abnormality can be ipsilateral, contralateral or even bilateral (Baloh et al. 1976; Baloh et al. 1977). This may reflect the fact that the parapontine horizontal gaze centers are very close together and brain stem distortion from the tumor might result in bilateral or contralateral parapontine damage (Baloh et al. 1976). Coelho and Prasher (1990) reported of a patient with vestibular schwannoma who had normal ABR ipsilaterally but abnormal ABR contralaterally. According to these particular studies, the lateralization of lesion in CPA is difficult by the means of these tests.

Since in this particular study the time interval between tumor surgery and the voluntary eye movement tests was long, it must be noted that the central compensation mechanisms have also affected oculomotor performance.

So far there have not been any published studies about the correlation of the clinical character of CPA tumors and the deficits of the voluntary eye movements.

It was observed that constant and pseudo-random saccades and PRPEM could be influenced by the clinical behavior of the CPA tumor. The SRT, the SPV and the GA were affected.

Facial nerve function after surgery, the cysticity of tumor and duration of operation correlate to the adherence of the CPA tumor. The more adherent the CPA tumor is, the more severe damage that can result during the operation. The tumor size, the radicality of the operation, the factors correlated to the adherence of tumor and the aging of the patient, all influence the recovery of eye motor functions in CPA tumor patients. The amount of eye motor function recovery correlates with the subjective handicap of the oculomotor functions in these patients.

c. Operated hemangioblastoma and subsequent oculomotor deficits

The author knows of no studies about voluntary eye movements, in which the tests have been done solely on HAB or operated HAB patients.

In differentiating operated HAB from control subjects with saccades, SRTs were the best parameters; the differences were significant in SRTs of 60° saccades. Additionally, some of the SPVs were distinctly lowered in operated HAB patients when compared with normal subjects.

In *PRPEM* with a 0.25 and 0.425 Hz frequency and a 0.45 and 0.7 Hz frequency combination, operated HAB patients had distinctly lower GAs than control subjects. The mean phase was not distinctly lengthened in these patients.

One must bear in mind that these patients were tested a considerable time after the operation. Results of this study are restricted to operated HAB patients, where

central compensation mechanisms (i.e., central plasticity) (Robinson 1976; Optican and Robinson 1980; Optican et al. 1980; Robinson 1982 - a review) have also affected their oculomotor performance. In unoperated HAB patients, the oculomotor performance may be quite different. In this study, the effects of the HAB tumor itself, plus the effects of surgery and central compensation mechanisms on voluntary eye movement performance cannot be differentiated from each other.

d. Infarction of cerebello-brain stem and subsequent oculomotor deficits

In this study, in constant and pseudo-random saccades SRTs were lengthened and SPVs lowered in patients with infarction of cerebello-brain stem when compared to control subjects. The SAs were not so profoundly impaired in patients with infarction of cerebello-brain stem than the SRTs and SPVs. These results coincide with the findings of Baloh et al. (1977). According to Baloh et al. (1977), saccadic peak velocity and SRT are often impaired in patients with brain stem lesions, whereas saccadic dysmetria is seldom found. According to (Watanabe et al. 1996), the saccades can be hypometric in cerebello-brain stem infarction. The findings of the present work confirm this.

In *PRPEM* with both frequency combinations used, patients with infarction of cerebello-brain stem had distinctly lower GAs than control subjects. The differences between patients with infarction of cerebello-brain stem and control subjects became more significant with the higher frequency combination. The reduction of GA in patients with infarction of cerebello-brain stem reflects the saccadization of PRPEM. These results coincide with the findings of previous studies about PEMs in patients with infarction of cerebellum, and cerebello-brain stem (Kato et al. 1986; Yee 1989; Pierrot-Deseilligny et al. 1990; Magnusson and Norrving 1993; Watanabe et al. 1996) and with previous studies of lesions in brain stem (Baloh et al. 1977).

Kato et al. (1986), Pierrot-Deseilligny et al. (1990) and Magnusson and Norrving (1993) discovered that PEMs in cerebellar infarctions are severely impaired, largely replaced by saccades. According to Yee (1989), PEMs can also be saccadic in cerebello-brain stem infarctions.

Because several of these patients with infarction of cerebello-brain stem did have the infarction a considerable time ago before the eye movement tests, the central compensation mechanisms are inclined to have affected the voluntary eye movement performance in these patients as well.

e. MRI findings and oculomotor deficits in operated hemangioblastomas, and infarction of cerebello-brain stem

It was observed that a solitary lesion may not cause a distinct pattern of disturbance

in voluntary eye movement. No specific eye movement disturbance may be linked to a specific anatomic site in cerebellum or brain stem in clinical studies of patients, or chronic patients. Contrastingly, it was also observed that a distinct disturbance in voluntary eye movements may be the result of several (solitary or non-solitary) lesions. Therefore, in patients with diffuse lesions, a distinct oculomotor disturbance was difficult to identify. These findings pertain to both groups studied.

According to Keller (1988), the exact pattern of saccadic dysmetria, the direction and metrics, cannot be precisely predicted from the site of cerebellar lesion. The inconsistent effects of cerebellar lesions might be due to variations in the exact location of lesions (Keller 1988). The findings of the present work are similar to the concept by Keller (1988).

Several brain stem structures are included in the pathways of voluntary eye movements (Alley et al. 1975; Alley 1977; Lisberger and Fuchs 1978; Winfield et al. 1978; Langer et al. 1980; Brodal 1982; May et al. 1988; Langer et al. 1985a; Cannon and Robinson 1987). In the present work, brain stem lesions seem to have the most profound effect on PRPEMs and constant and pseudo-random saccades, which confirms the findings of Baloh et al. (1977). This is in accordance with the above mentioned fact that several brain stem sites affect oculomotor function.

In the present work, the most reduced SPV results were seen in cases with cerebello-brain stem lesions which confirms the findings of Baloh et al. (1977) and Pyykkö and Schalén (1984). In the present work, increased SRT, reduced SPV, and impaired PRPEMs were found in cerebellar and brain stem lesions. This is also in line with the findings of Solingen et al. (1977) and Mastaglia et al. (1979). Dysmetria of saccades is related to a variety of lesions of the CNS (Baloh et al. 1977; Pyykkö and Schalén 1984; Watanabe et al. 1996), but in this study the dysmetria of saccades was seldom seen.

In the study of Takagi et al. (1998), the lesions of dorsal vermis in monkeys seem to affect saccadic eye movements profoundly. Lesions were centered on lobules VI and VII. In horizontal saccades, they caused lengthening of the SRT, worsening of saccadic accuracy and a reduction of the saccadic peak velocity and saccadic acceleration. The findings of this work agree with those of Takagi et al. (1998). In the present work, oculomotor vermis lesions with some other posterior fossa lesions did affect the SA, the SRT and the SPV. According to Büttner et al. (1994), the fastigial nuclei lesions and oculomotor vermis lesions cause hypermetric saccades, but PEM is preserved in those lesions. In the present work, fastigial nucleus and oculomotor vermis lesions caused inaccurate SA in patients with infarction. But, in the same patients the oculomotor vermis lesion was associated with PRPEM deficits. The reason for this discrepancy might be that in this study many patients had multiple lesions in the pathways of oculomotor function, so the effects of the lesions on the oculomotor

function were compromised. In clinical work, natural lesions in patients are most often not distinct. The study of Büttner et al. (1994) was restricted to the oculomotor findings of two patients with distinct lesions of both oculomotor vermis and fastigial nuclei.

In the present study, brain stem lesions correlated with reduced SPV in infarction patients. In operated HAB patients, fastigial nucleus and brain stem lesions were associated with reduced SPV; the fastigial nucleus lesions and brain stem lesions were often seen in the same patients. This might be explained by the fact that fastigial nucleus and brain stem are anatomically adjacent structures (Noda and Fujikado 1987b), and so both can be injured at the same time.

The PEM system is vulnerable to external processes, environmental factors and various disease processes (Versino and Cosi 1990). Therefore, a variety of CNS diseases may affect PEMs, and PEM disturbance can be an early indicator of a pathological process (Zee et al. 1976a; Troost and Daroff 1977). In this study, brain stem, oculomotor vermis and flocculus lesions seem to impair PRPEMs. Both the GA and mean phase were deteriorated.

In this study, flocculus lesions impaired the PRPEM but did not affect the SA of saccades. The finding that impaired PRPEMs and flocculus lesions correlate with each other coincide with other studies (Zee et al. 1976b; Zee et al. 1981; Waespe et al. 1983). A new finding was made in that the flocculus lesions were associated with lengthened SRTs in patients with infarction of cerebello-brain stem.

As the vestibular and visual system affect the actions of each other at the level of flocculus, it might be concluded that lengthening of the eye movement responses might be due to the lengthened procession of mismatched vestibular and eye movement signals at the level of the flocculus. However, as the neural pathways of voluntary eye movements are complicated, this needs further study.

The findings by Suzuki and Keller (1983) which suggest that oculomotor vermis might also take part in generating PEM, were confirmed by the present study. PRPEM deficits were found in patients with infarction of cerebello-brain stem having oculomotor vermis and flocculus lesions.

The saccade-related eye movement system and the PEM system both have plasticity (Robinson 1976; Optican and Robinson 1980; Optican et al. 1980; Robinson 1982 - a review) for different kinds of lesions. The cerebellum plays a vital role in the control of long-term, plastic and adaptive oculomotor changes that allow the nervous system to adjust its performance (Robinson 1976; Optican and Robinson 1980; Optican et al. 1980). This may raise a problem for interpreting clinical material, as the onset of a selectively cerebellar lesion can unmask a previously occurred brain stem lesion compensated by that part of the cerebellum (Keller 1988). Then, an oculomotor deficit may be produced which would not have been present with either

lesion alone (Keller 1988). That can complicate the interpretation of the findings of voluntary eye movements, which also happened in the present work.

6. 9. Site of lesion and voluntary eye movement deficits

In the present study, control subjects could be differentiated from patients by means of saccade tests and the PRPEMs. Many patients (regardless of diagnosis or site of lesion) had poorer eye movement performance than control subjects. Some patients had normal eye movement performance, and therefore, in both central and peripheral patient groups, some of the cases were incorrectly classified into control subjects. The most difficult aspect was to identify the peripheral patients from central patients or control subjects with a single saccade test or PRPEM test.

When the site of lesion was defined by means of clinical data, the correct classification of all subjects by means of a single voluntary eye movement test did not improve from the previous study (a). Still, based on saccade tests, healthy subjects were easily differentiated (80%) from patients with peripheral lesions and from patients with brain stem, cerebellar and cerebello-brain stem lesions, whereas PRPEM was poor in this task (51%). Shortage of PEM was caused by a large variability in the results of PRPEM in even healthy control subjects (possibly caused by vigilance, interest, etc.). The discriminatory power of voluntary eye movements have been studied in only a few cases. For example, Wennmo (1983) found better accuracy in the discriminatory power of voluntary eye movements than what could be seen in the present work. But his findings may be biased by a small number of examined subjects with acute lesions.

When the whole voluntary eye movement performance was used to localize the lesion, the localization was more accurate than by any of the single eye movement tests.

It is difficult to find the laterality of lesions to be consistent with the voluntary eye movement deficits of patients. This is well typified by the above-mentioned studies concerning the clinical correlation of voluntary eye movement deficits of this work. One reason for this could be the fact that there are decussations along the pathways of voluntary eye movements; saccadic pathways, as well as PEM pathways, decussate in the cerebellum in a very limited area (Yamada and Noda 1987; Noda et al. 1988; Noda et al. 1990; Noda 1991). Likewise is the case with DLPN that discharges during PEM (Suzuki et al. 1984) and projects to the contralateral flocculus of the cerebellum (Brodal 1982; Langer et al. 1985a). This might be the reason why lesions in certain areas can affect either ipsilateral or contralateral functions or even functions on both sides.

The findings of the present work about the accuracy of a single eye movement

test to correctly classify the patients according to the level/site of lesion differ from the results of Henriksson et al (1981), Schalén et al. (1982), Wennmo et al. (1983) and Allum et al. (1991).

Henriksson et al. (1981) studied voluntary saccades in seven patients with FEF lesions, eight patients with pontine disorders, five with acute encephalitis (cortical and/or cerebellar dysfunction with pontine involvement) and six with various vestibular diseases. The group sizes were small, and many patients had acute lesions. In *pontine* disorders, they found that peak velocity was greatly reduced, but the saccadic accuracy varied from normal to a pronounced deterioration (Henriksson et al. 1981). For *encephalitis*, the saccadic peak velocity was increased but saccadic accuracy was deteriorated (Henriksson et al. 1981). With encephalitis, the cerebellum and cortex are injured, and therefore, the disturbances found may be due to the loss of inhibition normally exerted by these structures (Henriksson et al. 1981). The saccades are broken off too early, making the saccadic peak velocity profile an exceptional one. In the present study, patients with disease-causing *central* lesions (in cerebellum, brain stem, cerebello-brain stem or cerebello-pontine angle) had reduced or normal, but not increased SPV. In *peripheral vestibular* disorders, there were some differences found between control subjects and the patients in saccadic peak velocity and accuracy, but the differences were not statistically significant (Henriksson et al. 1981). Contrastingly, patients with peripheral lesions (Menière patients) had distinctly reduced SPVs when compared to control subjects. Unfortunately in the study of Henriksson et al. (1981), the number of subjects tested was limited and the Student's t-test was used only in the statistical analysis; only the differences between a certain patient group and the control group were tested. Another reason for the differences between these two studies might be that in the present work, the variety of diagnoses was more restricted.

Schalén et al. (1982) studied PEMs in six patients with peripheral disorders (i.e., vestibular neuritis), six with FEF lesions, six with cerebellar disorders (tumor, degenerative cerebellar disease, acute encephalitis, vascular infarction), and six patients with brain stem disorders (vascular infarction, progressive supranuclear palsy). As controls, 20 healthy subjects were tested. In their work, the Student's t-test was used; only the differences between a certain patient group and the control group were tested. Many patients had acute lesions, but some patients with frontal cortical or cerebellar disorders had chronic lesions and group sizes were small (Schalén et al. 1982). In *peripheral* disorders, the only defect of PEMs was a significantly increased saccadization of PEM (Schalén et al. 1982). In the present study, that was also found as a reflection in the reduced GA. But the difference between these studies is that in the present study, the amplitude of pursuit was also significantly reduced. In *cerebellar* and especially *brain stem* disorders, the amplitude

of pursuit was significantly reduced and the saccadization of PEM was significantly increased (Schalén et al. 1982). Findings of the present study agree with their PEM findings in patients with central disorders.

Wennmo (1983) found that in *cerebellar* disorders, the saccadic peak velocity was normal, increased or decreased. Dysmetria of saccades was found in 50% of these patients and saccadization of PEM was found in one-third of the patients (Wennmo et al. 1983). According to the present work, the cerebellar lesion affected the peak velocity and timing of saccades. In *cerebello-brain stem* disorders, seen in the study of Wennmo et al. (1983), the dysmetria of saccades was found in all patients, saccadic peak velocity was reduced, and saccadization of PEM was increased in 80% of the patients. Whereas, in the present study the SAs in patients with cerebello-brain stem lesions were not significantly deteriorated. However, as in patients with cerebellar lesions, the velocity and timing of saccades were significantly deteriorated in patients with cerebello-brain stem lesions. The GA was significantly reduced in these patients, reflecting the increased saccadization of PRPEM. The reason why SA was not significantly altered in patients of the present study's analysis, might also depend on the wide variability of SA.

Allum et al. (1991) observed that the performance in PEM could differentiate control subjects and patients with peripheral vestibular disorder, from patients with central vestibular disorders. The limiting factor of this study was the small number of different patients (especially the four patients with central vestibular deficit) and control subjects. Patients with a central vestibular disorder were bound to have oculomotor disturbance in their work. According to the present work, it seems that the efficiency of single voluntary eye movement tests in the diagnosis is poorer than what the study of Allum et al. (1991) suggested.

If one wants to evaluate the merits of voluntary eye movement tests in localizing the site of lesion, the tests should be done to patients with acute lesions. The importance of a single saccade or PRPEM test in predicting the site of lesion in the nervous system in a vertigo patient is questionable, because a certain patient can have a deteriorated performance in one test with some parameters, and normal performance in others. More accurate localization of the level/site of lesion can be achieved by evaluating the whole voluntary eye movement performance, as it was seen when this procedure was done in the discriminant analysis.

6. 10. *Decision tree analysis and oculomotor deficits*

The database of a neurotologic expert system with attributes concerning symptoms, medical history, clinical tests and examinations (Kentala et al. 1996a; Kentala et al. 1996b) has been analyzed by applying the decision tree analysis (Kentala et al., in

press). Relevant parameters for classification of patient cases were extracted from the database. Their findings suggest that oculomotor tests and other neurotologic tests are of minor value in the classification of patients with benign positional vertigo, Menière's disease, sudden deafness, traumatic vertigo, vestibular neuritis, and vestibular schwannoma (Kentala et al. 1996b; Kentala et al., in press).

To my knowledge, there are no studies as yet, concerning where the site of lesion has been assayed by applying artificial intelligence in voluntary eye movements. In this work, analysis was assayed by making the decision tree analysis. In this assay, the overall performance of the saccadic and PRPEM system proved to be the most effective. The performance ability in different voluntary eye movements (constant and pseudo-random saccades, PRPEM with different frequency combinations) could accurately classify control subjects and patients with lesions at different sites of the neural system into correct groups. It almost always correctly classified those subjects that had divergent results from the mean performance of their group in some of the voluntary eye movement tests, or in some parameters of these tests. By combining the parameters of saccades and of PRPEM in the decision tree analysis, the model of voluntary eye movement lesion was linked to the site of lesion. The most important attributes (i.e., parameters) in the classification task were the SRT, GA, and mean phase. This confirms the findings of earlier parts of this work regarding the meaning of oculomotor tests in diagnosis and localization of lesions. Timing errors are the most relevant in differentiating patients from control subjects.

In chronic lesions, if the lesion affects the oculomotor centers, the site of lesion can be verified by means of voluntary eye movement performance. In other cases, improvement with time is often outstanding. However, if the lesions are at important sites in the oculomotor pathways, the improvement is not so remarkable. Another oculomotor center cannot totally compensate for the function of the affected center. In such cases, the defects in voluntary eye movement are more or less permanent.

The use of a single voluntary eye movement test is not effective in evaluating the site of the lesion, or the diagnosis. This was formerly seen in both the analysis of the discriminatory power of voluntary eye movements in patients and control subjects, and in the analysis of localizing the site of lesion in the nervous system.

7. CONCLUSIONS

1. Age affects the saccadic and PRPEM performance to a degree. The middle-aged had the best overall performance in voluntary eye movements. For children and teenagers, the voluntary eye movements were maturing, and in the elderly the performance seemed to degenerate with age. There were no significant differences between genders in eye movement performance, even though males showed a tendency for more rapid saccadic eye movements than females.

2. The SPV showed a tendency to be higher in leftward saccades than in rightward saccades within the individual level in healthy subjects. This might be affected by the hemispheric dominance. Within the level of a group, the direction of a saccade does not affect the saccadic parameters in healthy subjects. A single PRPEM test result was found to be repeatable and reliable enough, with the exception of mean phase shift that tended to be systematically shorter in repeated measurements.

3. In PRPEMs, the recording method did not have a significant affect on parameters, but in saccades, accuracy was better and velocity was lower in MOG than in EOG. The EOG recording method is still preferable in assessing voluntary eye movements in clinical praxis.

4. Voluntary eye movement tests bring new information to the diagnostics of vertigo patients, but the meaning of a single voluntary eye movement test as the only test in making the diagnosis, is inadequate. Each of the voluntary eye movement tests should be used with other diagnostic procedures and the results of different procedures should be given equal consideration. The timing of saccades (reaction time) is the most susceptible to disturbances in patients with lesions at different sites of the neural system. In PRPEM, the timing disorder of these patients is reflected on saccadization of PRPEM that reduces the GA.

   The plasticity of the brain, even though abundant, is not completely effective. The disorders of voluntary eye movements in patients with chronic lesions at different sites of the neural system have reduced with reference to patients of acute lesions. But years after a lesion, there are still disorders to be found in the voluntary eye movements.

5. The whole performance ability of the voluntary eye movement system was crucial in evaluating the site of lesion in these kind of chronic vertigo patients. The performance ability can be evaluated accurately with artificial intelligence.

6. Voluntary eye movements tested with this system provide necessary information about the function of the brain that is reflected by functional symptoms and disorders.

This work indicates that in patients with peripheral or central lesions along the pathways for voluntary eye movements, there were timing errors (lengthened SRT, lengthened phase lag or saccadization of PEM) in voluntary eye movements. This could have been caused by disturbance in the premotor processing of voluntary eye movements. Depending on the site of lesion, different indices of neural processing time were disturbed.

It is recommended that in the future, testing the whole voluntary eye movement performance in patients with vertigo and evaluating the correlation of voluntary eye movement performance to the subjective symptoms of the patient, be included in the diagnostic procedures. The use of artificial intelligence is recommended in this analysis, since it can “learn” from previous analysis and so improve the accuracy of localizing the lesions.

8. SUMMARY

Purpose: The aim of the present work was to evaluate physiological, methodological and clinical aspects of voluntary eye movement tests.

Subjects and Methods: Constant and pseudo-random saccades and PRPEMs were assessed in control subjects and patients with computer based equipment. In control subjects, the effect of age and gender on voluntary eye movements, as well as the laterality of saccades and repeatability of PRPEM tests were tested. Also, the effect of the EOG and MOG recording methods on voluntary eye movement results was tested in healthy subjects. Different kind of patients, most of whom had chronic lesions (moderately severe or severe Menière's disease, operated CPA tumor, operated HAB of cerebellum, infarction of cerebello-brain stem), were tested and their voluntary eye movement performance was compared to that of healthy subjects. The correlation of voluntary eye movement deficits to subjective symptoms and clinical data of patients was also analyzed. The accuracy of a single voluntary eye movement test, the whole voluntary eye movement performance to localize the level/site of lesion was analyzed with discrimination analysis. The accuracy of the whole voluntary eye movement performance to localize the site of lesion was also analyzed with a decision tree analysis.

Results: SA and pursuit gain (GA) and phase (mean phase) were deteriorated with advancing age in elderly subjects. In children and teenagers, the oculomotor system was maturing. In middle-aged subjects, voluntary eye movement performance was at its best. No significant differences between the genders in voluntary eye movement performance were observed. The direction of saccades did not affect the saccadic parameters in healthy subjects. The PRPEM test was found to be repeatable with the exception of mean phase, where a tendency of learning effect seemed to affect to some degree. When compared to the MOG recording method, the EOG recording method was found to be reliable enough in the assessment of horizontal voluntary eye movements. In each patient group, the subjective symptoms and clinical findings correlated with the voluntary eye movement deficits. A single voluntary eye movement test was not effective in localizing the level/site of lesion (with a single saccade test a correct localization was achieved in 48-56% of all cases, and with a single PRPEM test a correct localization was achieved in 33-48% of all cases). When using the whole voluntary eye movement performance, however, the accuracy improved and the correct localization was achieved in 75.5% of all cases with discrimination analysis. When artificial intelligence that "learns from previous experience" was used with the whole voluntary eye movement performance data in the localization task, the accuracy was further improved (correct localization in 91.4 - 97.1% of all cases).

Discussion and Conclusions: In clinical praxis, the age of the subject tested has to be taken into account when evaluating the results of voluntary eye movement tests. In clinical praxis, the gender of the subjects tested or the laterality of, at least saccades, do not have to be taken into account. According to the methodological studies (the repeatability of PRPEM tests, the effect of EOG and MOG recording method), this system for assessing voluntary eye movements can be used in clinical and research work. Voluntary eye movements provide necessary information about the function of the brain that is reflected by functional symptoms and disorders. With reference to testing patients, especially with chronic lesions, the whole voluntary eye movement performance should be evaluated and analyzed with artificial intelligence in order to localize the level/site of lesion.

In the future, the correlation of subjective symptoms of a patient with vertigo and their whole voluntary eye movement performance should be evaluated in order to aid diagnosing.

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