PLASTICITY OF THE CERVICO-OCULAR REFLEX IN HEALTH AND DISEASE

PLASTICITEIT VAN DE CERVICO-OCULAIRE REFLEX IN GEZONDHEID EN ZIEKTE

Willem Kelders

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CHAPTER 1

Introduction

This thesis is about the cervico-ocular reflex (COR) and its role in the diagnosis of the controversial disease entity called whiplash. In this chapter we describe the COR and the other eye stabilization reflexes, its reflex path and the technical aspects of COR measurement. Also, we have made an overview of the relevant objective data available on whiplash. In the next chapters we will elaborate further on the relation between the COR and the other eye stabilization reflexes, the effect of age on the COR and the aspects of the COR and other eye stabilization reflexes in the whiplash patient.

EYE STABILIZATION REFLEXES

The ocular stabilization reflexes serve to stabilize the visual image on the retina during head movements. Several sensory systems contribute to this process. The vestibulo-ocular reflex (VOR) consists of an input of vestibular information and results in a movement of the eyes opposite to the direction of head movement. It is mainly responsive to head movements with a high frequency (Tabak et al. 1997). The optokinetic reflex (OKR) consists of visual motion input and results in a movement of the eyes in the same direction as the visual slip on the retina (see also table 1.1).

The COR, which is the main object of investigation in this thesis, is a reflexive eye response that is elicited by rotation of the neck. The reflex gets its input from the proprioception of muscles and the facet joints of the cervical spine (Hikosaka & Maeda, 1973). In every day life the COR is mostly obscured by the other eye stabilization reflexes (the VOR and the OKR). Therefore we have measured it in a laboratory situation during which the head is stabilized in space so the VOR is cancelled out, and in total darkness so there is no influence of the OKR (see also figure 1.2). The COR has an optimal response to head motion at low velocities, whereas the OKR and VOR perform better at high velocities (Van Die & Collewijn, 1986; Mergner et al. 1998). In an ideal situation these stabilization reflexes work together at all head velocities so there is an optimal ocular response. The COR was first described by Bárány in 1906. Since then there has been controversy about the existence of the COR. Some have claimed it does not exist at all (De Kleyn & Stenvers, 1941) or that COR gain (response magnitude / stimulus magnitude) is so low that it will be lost in the normal measurement error (Sawyer et al. 1994). Others were able to elicit a clear COR with maximum gains between 0.25 at 0.1 Hz (Huygen et al. 1991) and 0.45 at 0.0125 Hz (Mergner et al. 1998).

The VOR and the OKR decrease with old age (Mulch & Petermann, 1979; Aust, 1991; Paige, 1994). The COR can compensate for a complete loss of VOR function (Bronstein & Hood, 1986; Bronstein et al. 1995) but there are no data on the relation between COR and the other eye stabilization reflexes in healthy humans. Paige (1994) investigated a group of 81

subjects aged between 18 and 89 years. He found that the VOR in elderly has a lower gain and larger phase lead in the low frequencies. OKR and Smooth Pursuit gain were also decreased in elderly, but there was an increasing phase lag. As subjects got older there was less VOR suppression in adaptation experiments, which was also true for the VOR enhancement, but only in the low frequency range.

In chapter 2 we describe the relation between COR gain and age, which to our knowledge was never studied before. There are two opposing hypotheses on this subject. One is that the COR may decline during aging similar to the other stabilization reflexes. The other hypothesis is that the COR increases to compensate for the loss of vestibular and optokinetic function. Reactions to vestibular function tests decrease with old age (Mulch & Petermann, 1979; Aust, 1991). With increasing age the number of nerve fibers of the ampullar nerve decreases with 40%, the number of macular nerve fibers a bit less (Engstrom et al. 1977). Schweigart et al. (2002) show an increase of the proprioceptive gain of the neck in older subjects, that appeared to have larger psychophysical responses to passive neck rotation. At the same time there is a decrease in the response to pure vestibular stimulation with age. They hypothesize that the larger cervical response compensates for the decreased vestibular function. In labyrinthine defective subjects there is a substantial increase in COR gain when compared to normal controls (Bronstein & Hood, 1986; Huygen et al. 1991; Heimbrand et al. 1996). So it seems that the COR has plasticity and can be increased with loss of vestibular input. In a case report Bronstein et al. (1995) demonstrated a patient with a temporary bilateral labyrinthine function loss. The COR gain increased to 0.51 and dropped again to 0.15 after labyrinthine function recovery. This implies a highly adaptive nature of the COR. An argument against the compensation hypothesis is that the COR is a low velocity reflex with maximum gains at frequencies below 0.1 Hz. The VOR on the other hand is a high velocity reflex with maximum gains of 0.9 at frequencies between 2.5 to 4 Hz in young adults (Paige, 1994). One would therefore expect that the low velocity COR could never take over the function of the high velocity VOR. Nonetheless, the COR gain is significantly increased in labyrinthine defective (LD) patients, even at frequencies that are normally not detected by the vestibular system (Bronstein & Hood, 1986). In chapter 3 we performed COR adaptation tests in a similar way to VOR adaptation tests.

Reflex	Input	Output
COR	Proprioception of the neck	Compensatory eye movement (i.e. in same direction of stimulus)
VOR	Vestibular information	Compensatory eye movement (i.e. in opposite direction of stimulus)
OKR	Visual slip on peripheral retina	Compensatory eye movement (i.e. in same direction as image motion)

Table 1.1 The eye stabilization reflexes

REFLEX PATHWAYS

The reflex pathway of the cervico-ocular reflex is not exactly known. Hikosaka & Maeda (1973) described cervical afferents ascending ipsilaterally in the spinal cord and crossing to the contra lateral side in the brain stem at the level of the inferior olive and from there projecting to the vestibular nuclei. Sato et al. (1997) found that impulses in neck muscle spindles produce excitation of neurons in the contra lateral vestibular nuclei by a disynaptic pathway relaying in the central cervical nucleus and crossing in the spinal cord.

In their paper on the COR in the squirrel monkey Gdowski et al. (2001) propose that the immediate premotor oculomotor pathways that produce the COR are the same neurons that produce the VOR. Secondary horizontal canal related vestibular neurons in the vestibular nucleus receive direct input from the vestibular nerve and are also sensitive to either static neck torsion information or neck motion information coming from the central cervical nucleus and area X in the vestibular nucleus. These neck signals can be modulated by inhibitory influence of Purkinje Cells in the flocculus. (See figure 1.1).

Maeda (1979) has shown that COR and VOR pathways converge upon common inhibitory or excitatory interneurons in the vestibular nuclei. There thus seems to be an important connection between COR and VOR in the vestibular nuclei. This is also true for the OKR, where direction selective retinal ganglion cells project to the accessory optic system, including the nucleus of the optic tract in the pretectum, which projects to the same medial vestibular nucleus that receives signals form vestibular afferents. Receiving neurons form this medial nucleus cannot distinguish between input from VOR or OKR and will respond in an identical manner (Kandel et al. 2000; Barmack, 2003).

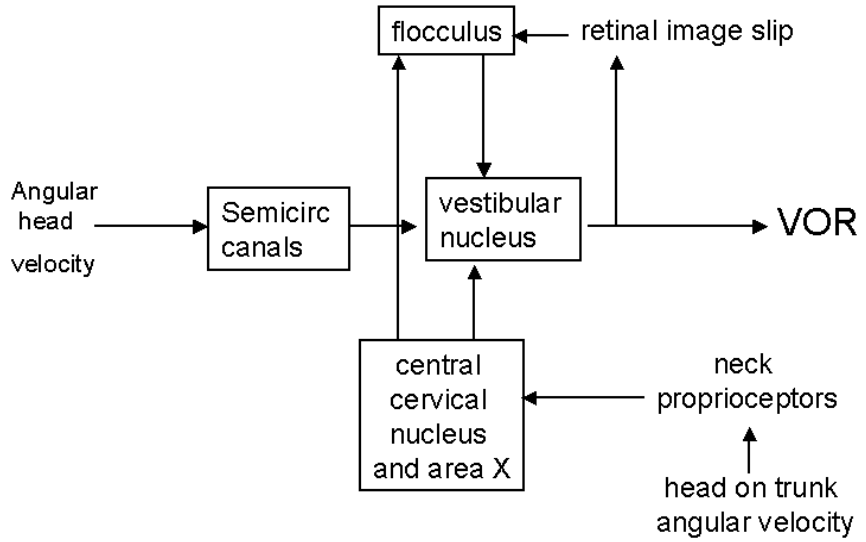


Figure 1.1 Schematic diagram of the hypothesized neural substrate that is used to produce and control the COR. Adapted from: Gdowski et al: Exp Brain Res. 2001 Oct;140(3):253-64.

TECHNICAL ASPECTS

In a laboratory situation the COR can be elicited in isolation in the absence of visual or vestibular input by fixating the head with a bite board in total darkness and by passive rotation of the body (trunk-to-head rotation). This situation is different from the situation in every day life where the body remains in the same position and the head rotates (head-to-trunk rotation).

COR research is complicated by various forms of measurement errors or noise. One of them is the smallness of the COR with typical response gains between 0 and 0.3. Another one is the strong variability of the gains between subjects. Noise can be minimized by using advanced eye movement registration equipment, testing relatively large groups and by identifying factors influencing the magnitude of COR gains such as age. In chapter 2 we report our results on a series of COR experiments on healthy subjects of different age groups. As we found a significantly increased COR gain in subjects over 60 years of age we matched all our groups for age.

We designed a special rotation chair that meets important criteria for safe and reliable COR testing. The most important criterion is safety. As the subject is fixated with the head in a bite board, we must be certain that the chair cannot overshoot the preset amplitude to prevent

rotation trauma of the neck. We achieved this by using a double axis system between the chair and the motor. (See figure 1.2)

Another important criterion is reliability. COR measurements can easily be influenced by other proprioceptive information, such as friction between the chair and the test subject or backlash on the point of turning in the cycle. This is prevented by using a chair that makes good contact with the test subject and using material on the chair that is resistant to friction (in our case rough fabric). We avoided backlash by the same double axis system so that the engine could simply keep on turning in one direction instead of making turning points. (See figures 1.2 to 1.4). We had to use a strong engine to be able to turn subjects at reproducible angular velocities.

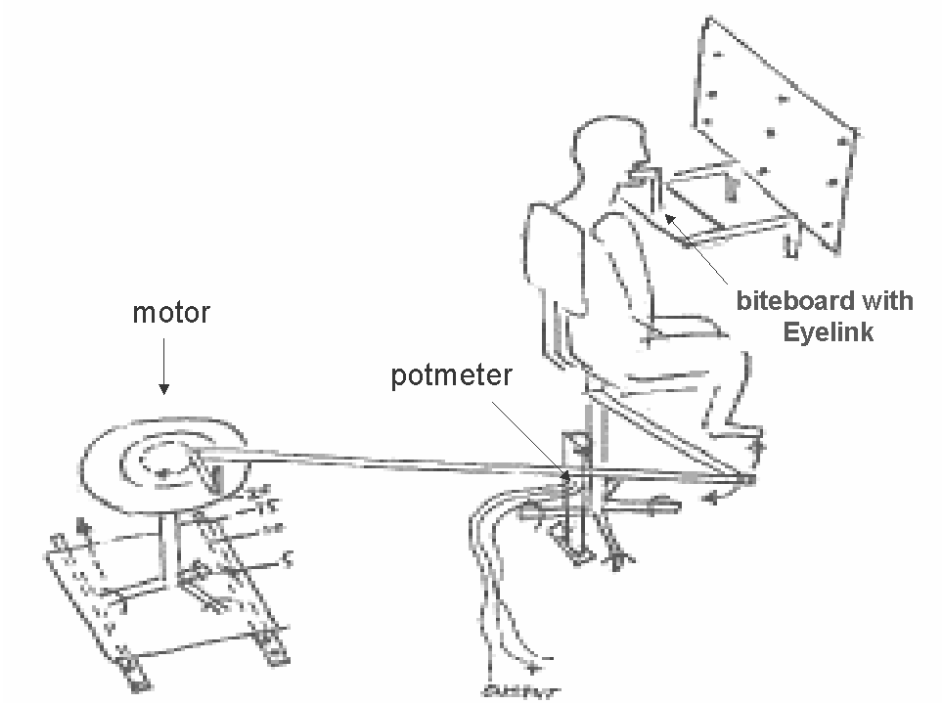


Figure 1.2 Schematic drawing of COR setup.

Figure 1.3 The COR setup with the double axis system and the bite board fixation.

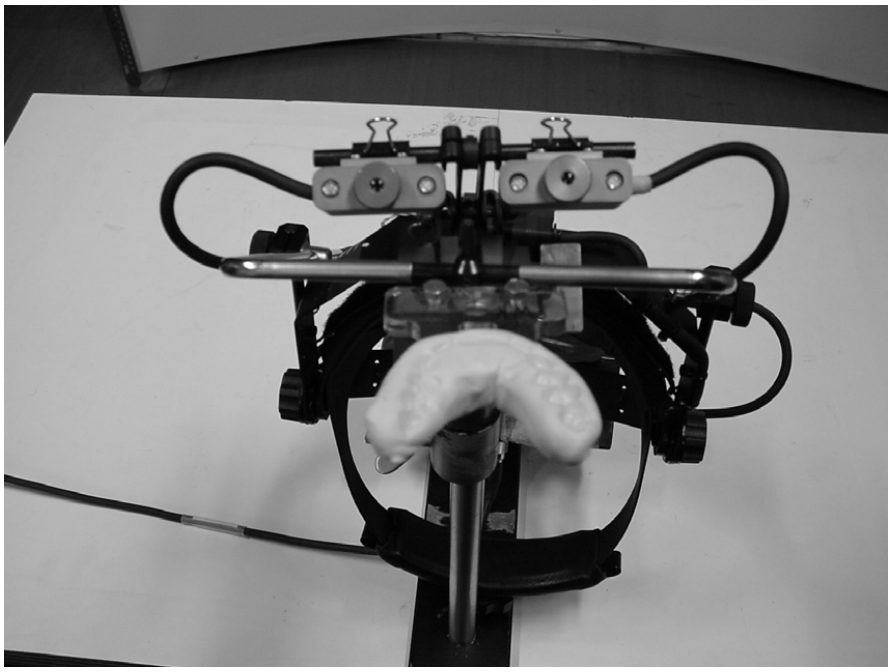


Figure 1.4 The bite board with the Eyelink® infrared video optic eye tracking system attached.

WHIPLASH

Definition and epidemiology

Whiplash can be defined as a mechanism of energy transfer to the neck due to rapid acceleration and deceleration of the head relative to the neck. It is mostly caused by rear end or side impact motor vehicle collisions or analogous traumata. Important in the definition is the absence of direct trauma to the head. Crowe coined the term whiplash in 1928 (Crowe, 1928). Nowadays whiplash injury and its clinical entities are usually referred to as whiplash associated disorders (WAD), the term introduced by the Quebec Task Force (Spitzer et al. 1995). Annual incidence is estimated at 3.8 per 1000 population (Barnsley et al. 1994) and is still rising. There has been a more then fivefold increase in incidence since seatbelts in cars became compulsory (Minton et al. 2000).

WAD is mostly characterized by a combination of neck pain, headache and attention deficits. However signs and symptoms are various and often include stiffness of the neck, vertigo, tinnitus, visual disturbances and fatigue (Eck et al. 2001). The annual costs of WAD are estimated at 300 million dollars in the Netherlands and 29 billion dollars in the United States (Freeman et al. 1999).

The Quebec task force developed a classification for whiplash associated disorders (WAD) (Spitzer et al. 1995). WAD Grade 0 indicates no complaints or physical signs, patients with WAD Grade 1 suffer from neck complaints (such as pain, tenderness and stiffness) but no physical signs, WAD Grade 2 indicates neck complaints and musculoskeletal signs (e.g. decreased range of motion). WAD Grade 3 comprises those patients with neck complaints and neurological signs (such as sensory deficit) and WAD Grade 4 are patients with fracture or dislocation of the cervical spine (see table 1.2).

Grade 0	No complaints or physical signs
Grade 1	Neck complaints such as pain, tenderness and stiffness without physical signs
Grade 2	Neck complaints and physical signs
Grade 3	Neck complaints and neurological signs
Grade 4	Neck complaints and fracture or dislocation of the cervical spine

Table 1.2 WAD grades according to the Quebec Task Force

A review by Lovell and Galasko (2002) showed that most studies report a percentage of patients with permanent disability between 6 and 18%.
A review by Fischer et al. (1997) showed that most patients recover fully within 3 months. 86% of patients who had complaints after 3 months still had them after 2 years. Recovery rate was 52% after one and 38% after 2 years. After 2 years, 30% of patients experienced persistent neck pain, 10 % experienced persistent headaches.
Patients with pre existent head trauma or headaches were at risk for delayed recovery.

Theories on the cause of WAD
There is no clear cause for chronicity of WAD. An abnormal psychological response to pain or other psychiatric disturbances have been found, also zygoapophyseal joint pain as the reason for chronic neck pain after a whiplash injury has been suggested (Lovell & Galasko, 2002).
It is thought that a disturbance of proprioception in the facet joints of the cervical spine and deep muscles of the neck plays an important role in the pathogenesis of WAD. Gimse et al. (1996) performed caloric, neurophysiologic and clinical tests on 26 whiplash patients. No other injury to the vestibular system or the central nervous system was demonstrated. All WAD subjects performed significantly worse than their healthy controls in smooth pursuit and saccade movements during reading and during neck torsion (smooth pursuit neck torsion test). According to the authors these findings are most probably due to damage to the posture control system by disorganisation of neck proprioceptive information.

In their extensive review of neurotologic literature on whiplash, Fischer et al. (1997) proved that neurotologic testing fails to demonstrate clearly defined abnormalities. Some studies they looked at showed a positional nystagmus, unilateral caloric weakness or directional preponderance. However, no control groups or clearly defined normal values were used. They also mentioned that other oculomotor disturbances have been described: disturbance of convergence and/or accommodation, temporary paresis of the abducens nerve and superior oblique muscles, fixation instability, saccadic smooth pursuit responses, hypo metric horizontal saccades, reduction in mean saccadic peak velocity and smooth pursuit gain. Spontaneous nystagmus in the literature varied from none to 63%. An average of 4% of uni- or bilateral canal paresis was seen.

Fisher et al. (1995) showed vestibular hyper reactivity (i.e. an increase in VOR gain) in 53% of patients, similar to patients with spasmodic torticollis, who also experience a limited active range of motion of the neck (Huygen et al. 1989). No abnormality in COR or a cervical nystagmus were described. The vestibular hyper reactivity (enhanced VOR) was attributed to adaptation in order to compensate for limited active range of motion of the neck. They also found a hyperventilation syndrome in 38% of whiplash patients, suggesting involvement of the reticular formation, which influences both the VOR and the respiratory centre. Stabilometry showed significantly increased body sway in 67-75 % of patients, depending on stimulus frequency, probably because of increased reliance upon visual clues. BERA showed no abnormalities in most studies. Some authors found EEG abnormalities, others could not find any.

Neuropsychological tests showed attention deficits, loss of concentration and memory and increased risk of depression and anxiety, especially with a long history of pain.

As for the methodology of the reviewed studies, Fisher et al. (1997) found poor definition of type of injury and type of accident. Usually, age and gender were not mentioned, no distinction between symptomatic and asymptomatic patients was made and control groups were hardly used.

Treatment

For the Cochrane Collaboration, Verhagen et al. (2004) reviewed the literature on conservative treatments for whiplash, with the question in mind if patients with WAD grade I and II benefited from active conservative treatments such as traction, massage and exercises, in comparison to passive treatments like electrotherapy, electromagnetic field therapy and soft collars, or no treatment at all. For patients with acute whiplash, they found a trend suggesting that those who received active treatments may have less pain and stiffness in due course and may be able to perform everyday activities better than those who received passive treatments; however, the evidence was conflicting. There were insufficient data to

draw any conclusions on treatment for patients with whiplash related problems that lasted longer than six months.

Tests

Unfortunately, there is no objective and reliable test available to diagnose WAD. Nederhand et al. (2000, 2002) investigated acute whiplash patients with EMG studies and found a decrease in EMG activity when patients had more complaints. Radiology (CT and MRI scans) of the brain and the cervical spine almost never show abnormalities (Ronnen et al. 1996; Borchgrevink et al. 1997).

Jonsson et al. (1991) performed plain cervical X-rays on 22 cervical spine specimens from traffic accident victims with fatal head injuries. A total of 245 lesions to the cervical spine were discovered on precision cryosection of the specimens. These lesions were missed on the plain X-ray. They consisted mostly of facet joint and ligamentum flavum injuries, uncovertebral injuries and disc lesions. A second look of the X-rays demonstrated only 4 of the 245 missed lesions. This shows that a negative plain radiograph does not preclude fracture, dislocation or hematoma of the cervical spine.

A quantifiable and objective measure that is used routinely in the Otorhinolaryngology practice for the evaluation of vestibular function is the recording of eye stabilization reflexes (electronystagmography). As the proprioception of the cervical spine is a known source of input for one of these reflexes (COR), we tried to find a reliable test for WAD based on equilibrium testing procedures, as described in chapters 4 and 5.

PROPRIOCEPTION (COR) AND WHIPLASH

We are not the first to investigate the COR in whiplash patients. Several other authors did this already more than a decade ago. Fischer et al. (1995) performed sinusoidal COR stimulation with a peak-to-peak amplitude of 60º in 32 whiplash patients (age range 21-66 years), and compared the gains to a group of healthy subjects measured by Huygen et al. (1991). They found a significant raise in COR gain in only one whiplash patient.

Oosterveld et al. (1991) were able to elicit a proprioceptive cervical nystagmus in 168 out of 262 whiplash patients by manually rotating the patients head bilaterally over an angle of 60º and fixating it for 30 seconds in that position. These results were significantly different from normal controls.

Heikkila & Wenngren (1998) found a restricted cervical range of motion, proprioceptive disturbances and failure of oculomotor functions in 27 whiplash patients by comparing their kinesthetic sensibility and oculomotor function with that of healthy controls. They concluded

that the dysfunction of the proprioceptive system in whiplash patients may affect oculomotor function.

OVERALL AIM

The overall aim of this thesis is to establish whether the COR is a suitable tool for the diagnosis of whiplash injury. In order to answer this question we need to answer other questions about the specific characteristics of the COR:
Are there circumstances, such as age, that can influence the COR?
Is there a synergistic function between COR and the other eye stabilization reflexes, i.e. the VOR and the OKR?
Is it possible to induce a rapid adaptation of the COR?
Is there a difference in the magnitude of the COR between whiplash patients and healthy controls?
Is there a synergy between the COR and the OKR and VOR in whiplash patients?

SCOPE OF THIS THESIS

The above questions are answered in the next chapters:
Chapter 2 describes two characteristics of the COR, i.e. the rise of COR gain with increasing age and the synergy between the COR and the VOR, meaning that the COR increases when the VOR decreases and vice versa.
Chapter 3 addresses the ability of the COR to rapidly adapt by inducing a visual-proprioceptive mismatch during ten minutes.
In chapter 4 the elevated COR gains in whiplash patients are discussed, while in chapter 5 the lack of synergy between the eye stabilization reflexes in whiplash patients is described.
The results of this thesis are discussed in chapter 6.

REFERENCES

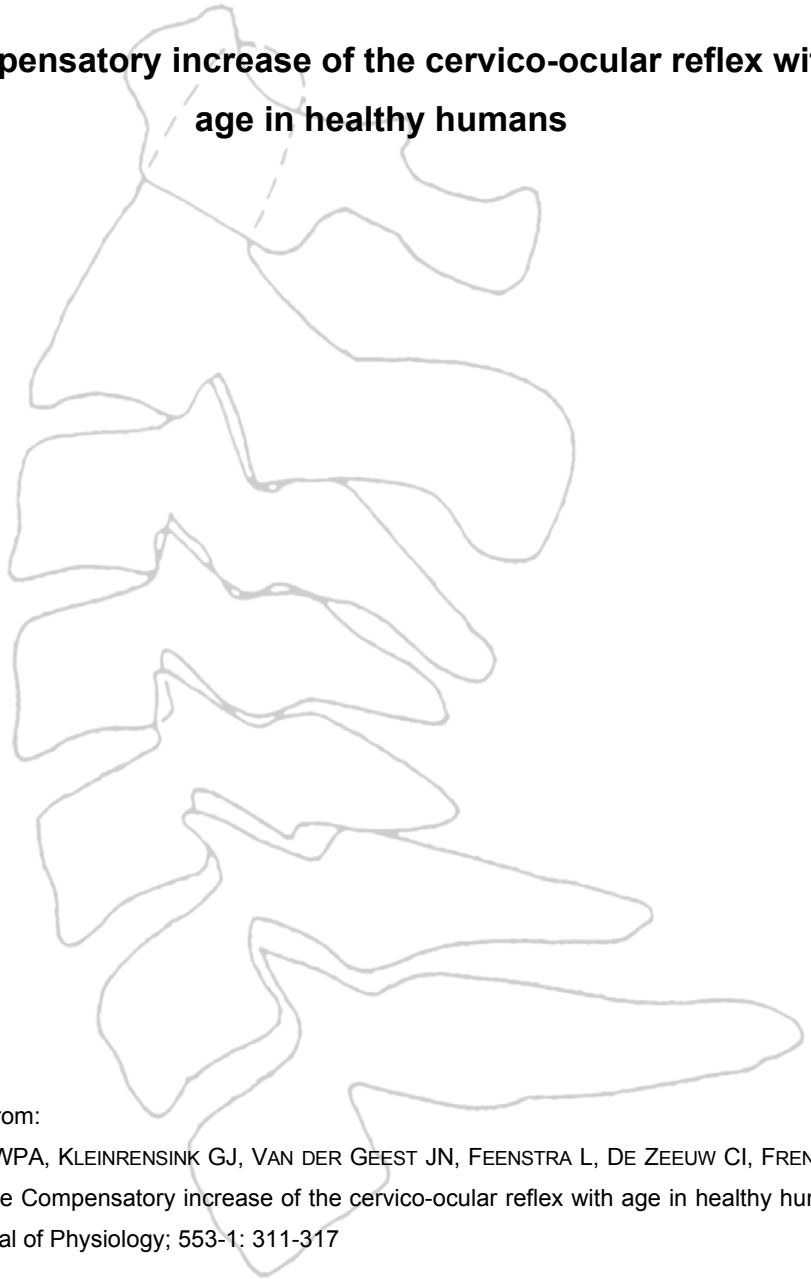
- AUST G (1991): [The effect of age on vestibulo-ocular reactions] Der Einfluss des Lebensalters auf vestibulo-okulare Reaktionen. Laryngorhinootologie 70, 132-137.
- BÁRÁNY R (1906): Augenbewegungen durch thoraxbewegungen ausgelost. Zentralbl Physiol 20, 298-302.
- BARMACK NH (2003): Central vestibular system: vestibular nuclei and posterior cerebellum. Brain Res Bull 60, 511-541.
- BARNSLEY L, LORD S & BOGDUK N (1994): Whiplash injury. Pain 58, 283-307.
- BORCHGREVINK G, SMEVIK O, HAAVE I, HARALDSETH O, NORDBY A & LEREIM I (1997): MRI of cerebrum and cervical columna within two days after whiplash neck sprain injury. Injury 28, 331-335.
- BRONSTEIN AM & HOOD JD (1986): The cervico-ocular reflex in normal subjects and patients with absent vestibular function. Brain Res 373, 399-408.
- BRONSTEIN AM, MORLAND AB, RUDDOCK KH & GRESTY MA (1995): Recovery from bilateral vestibular failure: implications for visual and cervico-ocular function. Acta Otolaryngol Suppl 520 Pt 2, 405-407.
- CROWE H (1928): Injuries to the cervical spine. Presentation to the anual meeting of the Western Orthopaedic Association. San Francisco.
- DE KLEYN A & STENVERS HW (1941): Tonic neck reflexes on the eye muscles in man. Proc. Kon. Ned. Akad. Wet. 44, 385-396.
- ECK JC, HODGES SD & HUMPHREYS SC (2001): Whiplash: a review of a commonly misunderstood injury. Am J Med 110, 651-656.
- ENGSTROM H, ADES HW, ENGSTROM B, GILCHRIST D & BOURNE G (1977): Structural changes in the vestibular epithelia in elderly monkeys and humans. Adv Otorhinolaryngol 22, 93-110.
- FISCHER AJEM, HUYGEN PLM, FOLGERING HT, VERHAGEN WIM & THEUNISSEN EJJM (1995): Vestibular hyperreactivity and hyperventilation after whiplash injury. J Neurol Sci 132, 35-43.
- FISCHER AJEM, VERHAGEN WIM & HUYGEN PLM (1997): Whiplash injury. A clinical review with emphasis on neuro-otological aspects. Clin Otolaryngol 22, 192-201.
- FREEMAN MD, CROFT AC, ROSSIGNOL AM, WEAVER DS & REISER M (1999): A review and methodologic critique of the literature refuting whiplash syndrome. Spine 24, 86-96.
- GDOWSKI GT, BELTON T & MCCREA RA (2001): The neurophysiological substrate for the cervico-ocular reflex in the squirrel monkey. Exp Brain Res 140, 253-264.

- GIMSE R, TJELL C, BJORGEN IA & SAUNTE C (1996): Disturbed eye movements after whiplash due to injuries to the posture control system. J Clin Exp Neuropsychol 18, 178-186.
- HEIKKILA HV & WENNGREN BI (1998): Cervicocephalic kinesthetic sensibility, active range of cervical motion, and oculomotor function in patients with whiplash injury. Arch Phys Med Rehabil 79, 1089-1094.
- HEIMBRAND S, BRONSTEIN AM, GRESTY MA & FALDON ME (1996): Optically induced plasticity of the cervico-ocular reflex in patients with bilateral absence of vestibular function. Exp Brain Res 112, 372-380.
- HIKOSAKA O & MAEDA M (1973): Cervical effects on abducens motoneurons and their interaction with vestibulo-ocular reflex. Exp Brain Res 18, 512-530.
- HUYGEN PLM, VERHAGEN, WIM & NICOLASEN MG (1991): Cervico-ocular reflex enhancement in labyrinthine-defective and normal subjects. Exp Brain Res 87, 457-464.
- HUYGEN PLM, VERHAGEN WIM, VAN HOOF JJ & HORSTINK MW (1989): Vestibular hyperreactivity in patients with idiopathic spasmodic torticollis. J Neurol Neurosurg Psychiatry 52, 782-785.
- JONSSON H JR, BRING G, RAUSCHNING W & SAHLSTEDT B (1991): Hidden cervical spine injuries in traffic accident victims with skull fractures. J Spinal Disord 4, 251-263.
- KANDEL ER, SCHWARTZ JH, JESSELL TM, MACK S & DODD J (2000): Principles of neural science. McGraw Hill, New York (N.Y.).
- LOVELL ME & GALASKO CS (2002): Whiplash disorders--a review. Injury 33, 97-101.
- MAEDA M (1979): Neck influences on the vestibulo-ocular reflex arc and the vestibulocerebellum. Prog Brain Res 50, 551-559.
- MERGNER T, SCHWEIGART G, BOTTI F & LEHMANN A (1998): Eye movements evoked by proprioceptive stimulation along the body axis in humans. Exp Brain Res 120, 450-460.
- MINTON R, MURRAY P, STEPHENSON W & GALASKO CS (2000): Whiplash injury--are current head restraints doing their job? Accid Anal Prev 32, 177-185.
- MULCH G & PETERMANN W (1979): Influence of age on results of vestibular function tests. Review of literature and presentation of caloric test results. Ann Otol Rhinol Laryngol Suppl 88, 1-17.
- NEDERHAND MJ, HERMENS HJ, IJZERMANS MJ, TURK DC & ZILVOLD G (2002): Cervical muscle dysfunction in chronic whiplash-associated disorder grade 2: the relevance of the trauma. Spine 27, 1056-1061.
- NEDERHAND MJ, IJZERMANS MJ, HERMENS HJ, BATEN CT & ZILVOLD G (2000): Cervical muscle dysfunction in the chronic whiplash associated disorder grade II (WAD-II). Spine 25, 1938-1943.

- OOSTERVELD WJ, KORTSCHOT HW, KINGMA GG, DE JONG HA & SAATCI MR (1991): Electronystagmographic findings following cervical whiplash injuries. Acta Otolaryngol 111, 201-205.
- PAIGE GD (1994): Senescence of human visual-vestibular interactions: smooth pursuit, optokinetic, and vestibular control of eye movements with aging. Exp Brain Res 98, 355-372.
- RONNEN HR, DE KORTE PJ, BRINK PR, VAN DER BIJL HJ, TONINO AJ & FRANKE CL (1996): Acute whiplash injury: is there a role for MR imaging?--a prospective study of 100 patients. Radiology 201, 93-96.
- SATO H, OHKAWA T, UCHINO Y & WILSON VJ (1997): Excitatory connections between neurons of the central cervical nucleus and vestibular neurons in the cat. Exp Brain Res 115, 381-386.
- SAWYER RN, THURSTON SE, BECKER KR, ACKLEY CV, SEIDMAN SH & LEIGH RJ (1994): The cervico-ocular reflex of normal human subjects in response to transient and sinusoidal trunk rotations. J Vestib Res 4, 245-249.
- SCHWEIGART G, CHIEN RD & MERGNER T (2002). Neck proprioception compensates for age-related deterioration of vestibular self-motion perception. Exp Brain Res 147, 89-97.
- SPITZER WO, SKOVRON ML, SALMI LR, CASSIDY JD, DURANCEAU J, SUISSA S & ZEISS E (1995): Scientific monograph of the Quebec Task Force on Whiplash-Associated Disorders: redefining "whiplash" and its management. Spine 20, 1S-73S.
- TABAK S, COLLEWIJN H, BOUMANS LJJM & VAN DER STEEN J (1997): Gain and delay of human vestibulo-ocular reflexes to oscillation and steps of the head by a reactive torque helmet. I. Normal subjects. Acta Otolaryngol 117, 785-795.
- VAN DIE GC & COLLEWIJN H (1986): Control of human optokinetic nystagmus by the central and peripheral retina: effects of partial visual field masking, scotopic vision and central retinal scotomata. Brain Res 383, 185-194.
- VERHAGEN AP, SCHOLTEN-PEETERS GG, DE BIE RA & BIERMA-ZEINSTRA SM (2004): Conservative treatments for whiplash. Cochrane Database Syst Rev, CD003338.

CHAPTER 2

Compensatory increase of the cervico-ocular reflex with age in healthy humans



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ABSTRACT

The cervico-ocular reflex (COR) is an ocular stabilization reflex that is elicited by rotation of the neck. It works in conjunction with the vestibulo-ocular reflex (VOR) and the optokinetic reflex (OKR) in order to prevent visual slip over the retina due to self motion.

The gains of the VOR and OKR are known to decrease with age (Paige, 1994). We have investigated whether the COR, a reflexive eye movement elicited by rotation of the neck, shows a compensatory increase and whether a synergy exists between the COR and the other ocular stabilization reflexes.

In the present study 35 healthy subjects of varying age (20-86 years) were rotated in the dark in a trunk-to-head manner (the head fixed in spaced with the body passively rotated under it) at peak velocities between 2.1 and 12.6 º/s as a COR stimulus. Another 15 were subjected to COR, VOR and OKR stimuli at frequencies between 0.04 Hz and 0.1 Hz. Three subjects participated in both tests. Position of the eyes was recorded with an infrared recording technique.

We found that the COR gain increases with increasing age and that there is a significant co variation between the gains of the VOR and COR, meaning that when VOR increases, COR decreases and vice versa. A nearly constant phase lag between the COR and the VOR of about 25º existed at all stimulus frequencies.

INTRODUCTION

The ocular stabilization reflexes serve to stabilize the visual image on the retina during head movements. Several sensory systems contribute to this process. The vestibulo-ocular reflex (VOR) moves the eyes on the basis of vestibular information opposite to the direction of head movement. It is mainly responsive to head movements with a high frequency (Tabak et al. 1997). The optokinetic reflex (OKR) responds to visual motion stimulation. It directs the eyes in the same direction as the visual slip on the retina. The cervico-ocular reflex (COR) is a reflexive eye response that is elicited by rotation of the neck. The proprioception of muscles and the facet joints of the cervical spine form the receptor part of this reflex (Hikosaka & Maeda, 1973). In contrast to the VOR, both OKR and COR respond optimally to head movements with a low velocity (Van Die and Collewijn, 1986; Mergner et al. 1998). In an optimal situation these stabilization reflexes work in conjunction at all head velocities in order to optimize the ocular response.

A problem in the synergy of compensatory reflexes is that the VOR and the OKR decrease with old age (Mulch & Petermann, 1979; Aust, 1991; Paige, 1994). In this paper we investigate how the COR changes with age. The question is whether the COR declines, similar to the other stabilization reflexes, or whether the COR increases in order to compensate for the loss of vestibular and optokinetic function. Because other factors, such as age related changes in mobility of the neck, may have an effect on the sensitivity of the neck proprioceptors, we have also explicitly studied the synergy of COR, OKR and VOR.

In a recent paper Schweigart et al. (2002) present evidence that the proprioceptive gain of the neck increases with age. Psychophysical responses to passive neck rotation were larger in older subjects. Meanwhile the responses to pure vestibular stimulation decreased with age. Schweigart et al. hypothesize that the increase in the cervical response is a compensatory mechanism for the deterioration of vestibular function. Also in labyrinthine defective subjects the COR is substantially higher than in normal controls (Bronstein & Hood, 1986; Huygen et al. 1991; Heimbrand et al. 1996). This shows that the strength of the COR is apparently plastic and can indeed be up regulated in the absence of vestibular input.

MATERIALS AND METHODS

STIMULATION

Cervical stimulation

In a laboratory situation an isolated COR response can only be elicited in the absence of visual or vestibular input by fixating the head in space in total darkness and by passive rotation of the body (trunk-to-head rotation). This situation is different from the situation in daily life where the body usually remains in the same position and the head rotates (head-to-trunk rotation). A further difference with the natural situation is that passive head movements are rare, so that muscle stiffness during natural head movement is presumably different than during our stimulation.

For measurement of the COR a rotating chair was used. The subject's head was fixed in space by a custom made bite board using Lactona hardening silicone impression material (Dental Techno Benelux, Rotterdam, The Netherlands) and the trunk was fixed to the chair at the shoulders by a double belt system. The chair was rotated sinusoidally about the vertical axis at various amplitudes and frequencies. The setup was capable of generating sine waves without any backlash at the point where the chair rotation changed direction. A sensor connected to the chair recorded chair position. Chair position was stored on hard disk along with the eye position data (see below).

We used the Cervical Range Of Motion (CROM) device to determine if the bite board fixed head was well stabilized in space. Rotation of the head was negligibly small. The CROM device is a device existing of a magnet and three compass like instruments situated in every direction of motion of the neck (lateroflexion, rotation, flexion, extension). It is used to determine the maximum range of motion of the different neck motions. The device has been validated in several studies (Capuano-Pucci et al. 1991; Youdas et al. 1991).

Vestibular stimulation

For the recording of the VOR the same chair was used. The only difference was that the bite board was now attached to the chair, rather than to the room, so that head and body moved together in space, but not with respect to each other. The position of the bite board was chosen so that the axis of rotation was under the midpoint of the interaural line. Like in the COR measurements all vestibular stimulation was performed in darkness.

Optokinetic stimulation

Visual stimulation consisted of white dots that moved sinusoidally in a field that was 60º wide and 45º high. The dots were generated by a pc and back projected on a translucent screen (235 cm broad and 170 cm wide) by means of an Infocus LP 335 data projector. The beam of this projector reflected on a mirror that was mounted on a Cambridge Technology step motor (model number 6900). Rotations of this mirror induced motion of the dots on the screen. The stimulus consisted of 50 dots that had a diameter of 0.8º. In order to minimize the contribution of foveal pursuit of a single dot in the pattern, all dots had a limited lifetime of 50 ms. The dots were homogeneously distributed over the screen, with the exception of an area of 6º in the center where no dot appeared. The subjects were instructed to keep fixation within this area, in order to prevent visual motion in the (peri) foveal region. The head and chair were both fixed with respect to the room.

Mirror position was stored on hard disk along with the eye position data (see next paragraph).

RECORDING OF EYE POSITION

Eye position was recorded by using an infrared eye tracking device (Eyelink®, SMI; see Van der Geest and Frens, 2002). After calibration of the device, both horizontal and vertical eye position could be recorded precisely with a resolution of 20 seconds of arc and a sampling frequency of 250 Hz. During the experiment the location of the eyes relative to the bite board mounted cameras was continuously monitored to make sure the subject's head was well stabilized by the bite board.

EXPERIMENTAL PROCEDURE

We performed two sets of experiments. In the first set (the COR test) we recorded the COR under a variety of stimulus parameters (amplitude and frequency) in a population of subjects balanced over a largely varying age. This test meant to identify the optimal stimulus parameters for the COR, and to study the effect of aging on this reflex. In the second set (the synergy test) we used a smaller range of stimulus parameters within the optimal range of the COR. In this range we tested not only the COR, but also the OKR and VOR. The main focus of this test was to test whether the gains of these reflexes correlate between subjects, and to investigate mutual phase relations.

COR test

For the cervical stimulation that was applied in the COR test, the chair was rotated at two different frequencies (0.1 Hz and 0.067 Hz) and four different amplitudes (5°, 10°, 15° and 20°). All rotations were around the 'straight ahead' position (i.e. transversal planes though both ears and both shoulders parallel) as the middle of the range of motion.

Five complete stimulus cycles were made in the dark, while the eye movements were recorded. As the COR is hypothesized to help in stabilization of the retinal image, the test subject was instructed to focus on an imaginary target located straight ahead at about 3 meters distance, briefly indicated by a laser dot before rotations started. The procedure was repeated for each combination of amplitude and frequency.

Subjects were divided into 4 groups with either in- or decreasing frequencies and in- or decreasing amplitudes to exclude any effects of learning or fatigue on COR gain. Statistical analysis (Student's t-test all $p > 0.1$) showed no difference between these groups. Therefore, for the remainder of the paper all data will be pooled across the order of frequencies and amplitudes.

Synergy test

In the synergy test we applied cervical, vestibular and optokinetic stimulation. All stimuli had an amplitude of 5°, and were applied in isolation (i.e. no combined visual/vestibular or cervical stimulation was given). Frequencies were 0.04, 0.06, 0.08, and 0.1 Hz. Like in the COR test all stimuli were applied with the head in the straight ahead position.

SUBJECTS

In the experiments a total of 47 subjects participated. 35 subjects (15 female, 20 male) were measured in the COR test, and 15 (6 female, 9 male) participated in the synergy test. Three subjects did both tests.

In the COR test, the mean age was 44.9 $\pm$ 18.4 years (range 20 – 82 years). In the synergy test, the mean age was 34.2 $\pm$ 13.8 years (range 23 – 64 years). All subjects signed informed consent and filled out a medical questionnaire. None of the subjects had a history of vestibular problems or cervical complaints nor did they use any form of tranquilizing medication (benzodiazepines, antihistamines). The experiments were approved by the ethics committee of the Erasmus MC and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

DATA ANALYSIS

Eye velocity was calculated by taking the derivative of the horizontal eye position signal (Figure 2.1). We removed blinks, saccades and fast phases using a 20 °/s threshold. On average the subjects made between one and two nystagmus fast phases per second. A sine wave was fitted through the remaining eye velocity signal. Stimulus velocity was derived from chair position (COR and VOR measurement) and mirror position (OKR measurement) data.
The gain of the response was defined as the amplitude of the eye velocity fit divided by the peak velocity of the stimulus movement. Phase differences were defined so that a movement with a difference of 0° was in phase with the stimulus, in the compensatory direction. Positive phase differences indicate a phase lag. All analyses were done with Matlab® 6.1 (the Mathworks Inc.).

RESULTS

COR TEST

Figure 2.2 shows COR gains of all subjects as a function of either frequency (figure 2.2A) or stimulus peak velocity (figure 2.2B). As the COR gain data can be correlated in a single curve to the various peak velocities but not to the different frequencies, the COR appears to be better determined by peak velocity than by frequency. This becomes more evident when the mean gain data at a peak velocity of 6.3°/s, which consist of two different combinations of frequencies and amplitudes (i.e. a combination of 0.067 Hz and 15° and a combination of 0.10 Hz and 10°), are subjected to a 2-tailed t-test. This test showed no difference between both mean gains ($p = 0.136$). This finding correlates with the findings of Mergner (1998). Therefore we will present our data as a function of peak velocity rather than of frequency.
In figure 2.3 mean gains are displayed for each peak velocity. The mean gain at the lowest peak velocity (2.1°/s) was 0.21 $\pm$ 0.025 (SEM) and this decreased with increasing peak velocities to 0.08 $\pm$ 0.010 (SEM) at a peak velocity of 12.6 °/s. Because the relation saturates at higher peak velocities, two straight lines were fitted through the gains as function of the peak velocity (figure 2.3). For the peak velocities below 7 º/s (solid line) the fitted slope of –0.014 s/° was significantly different from zero ($p = 0.0016$). For the peak velocities over 7 º/s (dashed line) the slope was –0.0011 s/º, which is not significantly different from zero ($p = 0.71$). These results show that the COR is a *low peak velocity* system.

Figure 2.4 presents the same data as shown in figure 2.3 but now the subjects were assigned to one of four different age groups, i.e. younger than 30 years (N = 10, mean age 24.5 $\pm$ 2.5 years), between 30 and 45 years of age (N = 8, mean age 35.0 $\pm$ 4.2 years), between 45 and 60 years (N = 10, mean age 51.6 $\pm$ 5.3 years) and older than 60 years (N = 7, mean age 72.3 $\pm$ 5.6 years). The oldest group (older than 60 years) seems to have a higher COR gain over all peak velocities.

A multivariate analysis was carried out, having two factors: 'age group' with four levels (corresponding to the age groups), and 'stimulus peak velocity' with 7 levels (2.1 °/s, 3.1 °/s, 4.2 °/s, 6.3 °/s, 8.4 °/s, 9.4 °/s and 12.6 °/s). This showed that the main effect of 'age group' reached significance [$F(3,30) = 7.39$, $p=0.001$]. LSD (Least Square Difference) post hoc analysis showed that the mean gains differed only between the group over 60 years and all other groups ($p < 0.001$ for each group). The main effect of peak velocity also reached significance [$F(3,28) = 6.00$, $p = 0.003$]. This means that the oldest group had increased COR gains at all peak velocities.

SYNERGY TEST

Figure 2.5 shows typical results of the synergy test of a typical subject, performed at 0.04 Hz. Note that the three reflexes result in qualitatively similar responses, that include smooth traces, interleaved with saccades and blinks. The occurrence of the latter two has about the same frequency in all reflex types.

Figure 2.6 shows the gain and phase relations of the three reflexes. In the upper panel the average gains are shown. Note that, since we used a fixed stimulus position amplitude in the synergy test, there is now a one-to-one relation between stimulus peak velocity and frequency. All gains are quite stable over the stimulus range of the synergy test. The gain of the COR decreases slightly with stimulus frequency ($p<0.05$), which is in line with the data of the COR test. The VOR slightly increases ($p<0.05$). The OKR is more or less constant within this stimulus range. Despite the fact that the VOR is more sensitive at higher frequencies, its gain is still higher than the COR gain, even at the tested low stimulus velocities.

In figure 2.6, lower panel a phase difference of 0º means that the reflex is compensatory (i.e. in phase with the stimulus for the COR and in counter phase with the stimulus for the VOR). As one can see, all 3 reflexes are roughly compensatory at all stimulation frequencies. A positive value indicates a phase lag with respect to the stimulus. The variability in the phase values at these low velocities is similar for the VOR and the COR. The variation is mutually uncorrelated, i.e. the phase of someone's VOR cannot be predicted from the COR or vice

versa (not shown). At all frequencies, the OKR is almost perfectly compensatory. Meanwhile, both the phase difference of the VOR and the COR significantly change in the same direction ($p<0.05$). The response increasingly lags the stimulus with increasing frequency in such a way that there is a more or less constant phase difference of about 25º between the reflexes at all frequencies.

The gain values of all subjects and at all frequencies are plotted in Figure 2.7. Note that there is a negative correlation between the VOR gain and the COR gain ($r= -0.42$; $p = 0.007$; Figure 2.7A). Meanwhile the OKR and VOR gain as well as the OKR gain and COR gain are mutually uncorrelated ($r<0.25$; $p >0.1$; Figure 2.7B and C). In these correlations, age can be a confounding factor. Indeed, both the COR and the VOR vary with age in the investigated population ($p<0.05$), while gain of the OKR remains constant ($p>0.05$; Figure 2.7D). There is an increase of COR gain with age, which is in line with the results of the COR test. Meanwhile the VOR gain decreases.

In table 2.1 the results of the synergy test are summarized for all frequencies separately. In general the trends that are observed for the pooled data (Figure 2.7) can be generalized to the separate frequencies. The exception to this are the data obtained at 0.1 Hz, where no correlations are found.

DISCUSSION

THE RELATION BETWEEN AGE AND THE COR

There is a large variation between the COR gains that have been reported in the literature (Barnes & Forbat, 1979; Barlow & Freedman, 1980; Bronstein & Hood, 1986; Huygen et al. 1991; Sawyer et al. 1994; Mergner et al. 1998). A possible explanation for this high variability could be a difference in subject characteristics between the groups that were investigated. Therefore, factors that may influence the COR gain should be identified. We investigated the hypothesis that age is an important factor determining the magnitude of the COR gain. This was inspired by the finding that there is an age related decline in the other ocular stabilization processes, i.e. the VOR and OKR (Paige 1994). This might either predict a similar decrease in the COR or an increase of COR gain with age, as an adaptation to the decline in the other reflexes.

It has been shown before that the COR can adapt to new circumstances. Huygen et al. (1991) and Bronstein & Hood (1986) reported that COR takes over part of the VOR in labyrinthine defective subjects. Here we report significantly larger gains at all rotational velocities in the group with people aged over 60 years when compared to the other age groups. Although only two different frequencies were tested, our data support the suggestion made by Mergner et al. (1998) that the COR is a peak velocity system instead of a frequency dependent system.

From our study it can be concluded that age plays an important role in the relation between peak velocity and COR gain and hence, in unstratified populations, accounts for a significant part of the variation (Figure 2.4). When doing research on COR in different patient groups, these groups should be stratified for age. This will lead to a smaller inter subject variation, which will make it easier to establish differences in the magnitude of COR gain between different groups.

The increase in COR gain with age can tell us something about the source of the decrease in VOR and OKR. As the COR and the other reflexes share the same effector (the extra ocular muscles), it is likely that the decrease in VOR and OKR is due to loss of sensory rather than motor function. Stronger proprioceptive signals accounting for the increase of the COR of the neck are in agreement with the psychophysical data of Schweigart et al. (2002; see introduction).

THE RELATION BETWEEN THE COR AND THE OTHER STABILIZATION REFLEXES

Although it is tempting to ascribe the age related changes in the COR to a compensation for the loss of other reflexes, other possible explanations exist. One such explanation could be the fact that elderly persons have a relatively stiffer neck in which the range of motion is smaller and the limits are reached earlier. Therefore the proprioception in the neck may be more important and thus more sensitive to neck rotation.

To test whether the COR strength is influenced by the strength of the other stabilization reflexes we tested the COR, VOR and OKR under a variety of identical experimental conditions. Within the frequency range tested there appeared to be a link between the properties of the COR and the VOR, and not so between the OKR and the other reflexes.

Firstly, within the age range of the subjects of the synergy test both the VOR and the COR correlate with age. The VOR decreases, and the COR increases (Figure 2.7D). At first sight this latter finding may seem to be at odds with the results of the COR test, where we concluded that only the oldest age group (> 60 yr) significantly differed from the other subjects. This is probably due to the differences in stimulus parameters. The synergy test was focused on the range where the COR had a relatively high value in all ages.

Secondly, there is a significant co variation between the individual gain parameters of the VOR and COR (Figure 2.7A and Table 2.1). This means that the strength of the COR can be partially predicted by the strength of the VOR. Again there is a negative relation: the higher the VOR is, the lower the COR.

Thirdly, the phase of the VOR and COR response both shift in the same direction as a function of stimulus frequency, resulting in a more or less constant phase difference between the two reflexes (Figure 2.6).

Taken together, these data support the hypothesis that there is a synergistic function of the COR and the VOR. The most straightforward explanation would be that the COR can compensate for loss of vestibular function. When the gain of the VOR is lower than desired, the COR can be up regulated. This is similar to the results observed in labyrinthine patients (Huygen, 1991; Bronstein & Hood, 1986). This can even hold, despite the difference in dynamic properties of both reflexes. The COR is most responsive at low velocities, whereas the VOR is responsive at high frequencies. However, even at low velocities the VOR often has a higher gain than the COR (Figure 2.6A). Such a compensation can obviously only be effective in the range where the COR is active, and will therefore not influence performance at high frequencies.

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REFERENCES

- AUST, G (1991): [The effect of age on vestibulo-ocular reactions] Der Einfluss des Lebensalters auf vestibulo-okulare Reaktionen. Laryngorhinootologie 70, 132-137.
- BARLOW D & FREEDMAN W (1980): Cervico-ocular reflex in the normal adult. Acta Otolaryngol 89, 487-496.
- BARNES GR & FORBAT LN (1979): Cervical and vestibular afferent control of oculomotor response in man. Acta Otolaryngol 88, 79-87.
- BRONSTEIN AM & HOOD JD (1986): The cervico-ocular reflex in normal subjects and patients with absent vestibular function. Brain Res 373, 399-408.
- CAPUANO-PUCCI D, RHEAULT W, AUKAI J, BRACKE M, DAY R & PASTRICK M (1991): Intratester and intertester reliability of the cervical range of motion device. Arch Phys Med Rehabil 72, 338-340.
- HEIMBRAND S, BRONSTEIN AM, GRESTY MA & FALDON ME (1996): Optically induced plasticity of the cervico-ocular reflex in patients with bilateral absence of vestibular function. Exp Brain Res 112, 372-380.
- HIKOSAKA O & MAEDA M (1973): Cervical effects on abducens motoneurons and their interaction with vestibulo-ocular reflex. Exp Brain Res 18, 512-530.
- HUYGEN PLM, VERHAGEN WIM & NICOLASEN MG (1991): Cervico-ocular reflex enhancement in labyrinthine-defective and normal subjects. Exp Brain Res 87, 457-464.
- MERGNER T, SCHWEIGART G, BOTTI F & LEHMANN A (1998): Eye movements evoked by proprioceptive stimulation along the body axis in humans. Exp Brain Res 120, 450-460.
- MULCH G & PETERMANN W (1979): Influence of age on results of vestibular function tests. Review of literature and presentation of caloric test results. Ann Otol Rhinol Laryngol Suppl 88, 1-17.
- PAIGE GD (1994): Senescence of human visual-vestibular interactions: smooth pursuit, optokinetic, and vestibular control of eye movements with aging. Exp Brain Res 98, 355-372.
- SAWYER RN, THURSTON SE, BECKER KR, ACKLEY CV, SEIDMAN SH & LEIGH RJ (1994): The cervico-ocular reflex of normal human subjects in response to transient and sinusoidal trunk rotations. J Vestib Res 4, 245-249.
- SCHWEIGART G, CHIEN RD, MERGNER T. (2002): Neck proprioception compensates for age-related deterioration of vestibular self-motion perception. Exp Brain Res. 147:89-97.
- TABAK S, COLLEWIJN H, BOUMANS LJJM, VAN DER STEEN J (1997): Gain and delay of human vestibulo-ocular reflexes to oscillation and steps of the head by a reactive torque helmet. I. Normal subjects. Acta Otolaryngol. 117:785-795.

- VAN DIE GC, COLLEWIJN H. (1986): Control of human optokinetic nystagmus by the central and peripheral retina: effects of partial visual field masking, scotopic vision and central retinal scotomata. Brain Res. 24:185-94.
- VAN DER GEEST JN, FRENS MA. (2002): Recording eye movements with video-oculography and scleral search coils: a direct comparison of two methods. J Neurosci Methods. 2002 Mar 15;114(2):185-95.
- YOUDAS JW, CAREY JR & GARRETT TR (1991): Reliability of measurements of cervical spine range of motion--comparison of three methods. Phys Ther 71, 98-104; discussion 105-106.

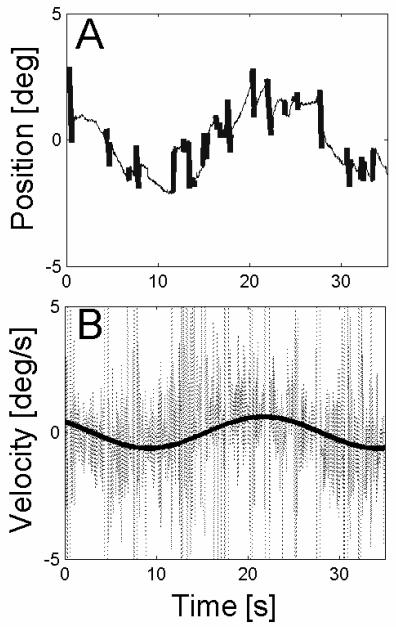


Figure 2.1 Eye response signal

A. Example of a raw horizontal eye position trace during stimulation at 0.04 Hz with an amplitude of 5º, taken from a 58 year old subject. Detected blinks, saccades and fast phases are shown as thick lines.

B. Eye velocity derived from the position data in panel A (dotted line). Through the eye velocity a sinus is fitted (fixed line) with three free parameters (amplitude, phase, and offset). Data from blinks, saccades and fast phases are not used for the fit.

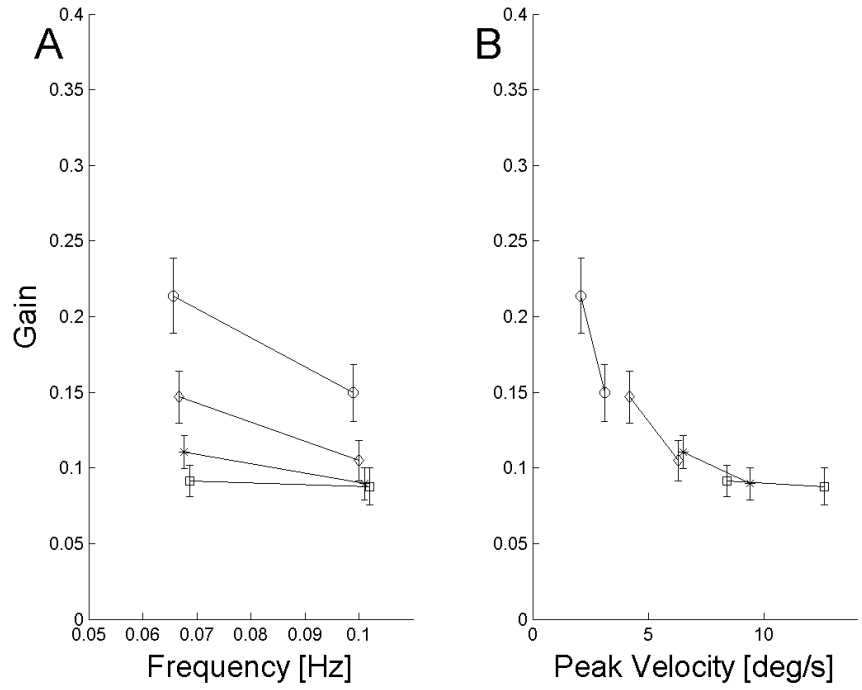


Figure 2.2 Gains plotted against frequency and peak velocity.

The errorbars represent standard errors of the mean. For clarity the data points at identical frequencies or peak velocities have been slightly shifted horizontally in both panel A and B. **o:** 5° stimulus amplitude; **◊:** 10°; ***:** 15°; **□:** 20°.

A. Gains plotted for each frequency. Every stimulus amplitude is represented by an individual line. There is much variation in gains between the different amplitudes. The lowest amplitude has the largest gains, whereas the highest amplitudes have the lowest gains.

B. Gains plotted as a function of peak velocity. Every amplitude is again represented by an individual line. Note that the individual lines are all at the same curve in panel B.

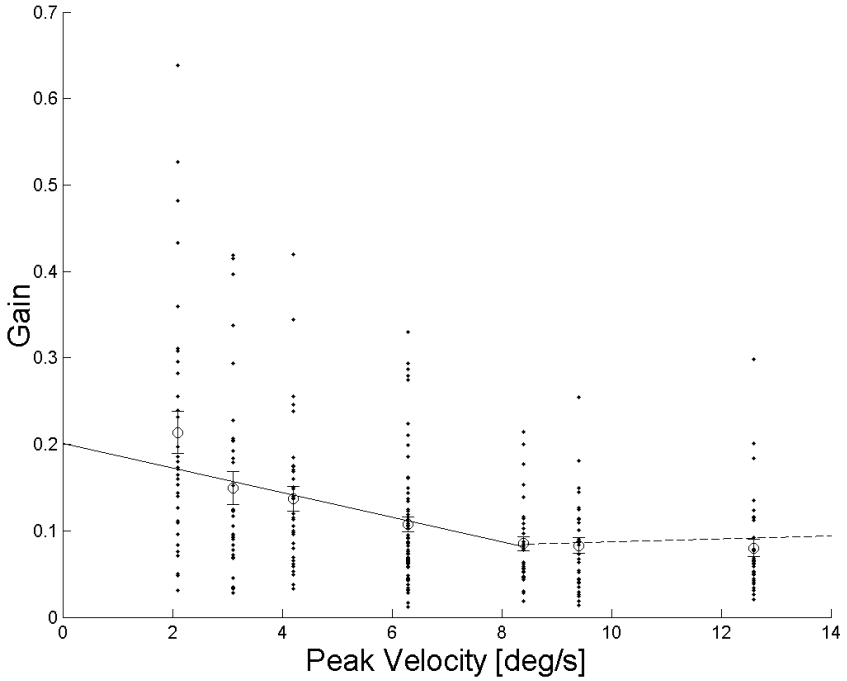


Figure 2.3 Gains plotted against peak velocity with individual data points and two fitted straight lines. Every individual COR gain is represented by a dot. Mean gains are represented by the circles with errorbars, which represent the standard errors of the mean. The dashed straight line is fitted through the individual data points with a stimulus peak velocity higher than 7 °/s. The solid line is fitted through the other individual data points.

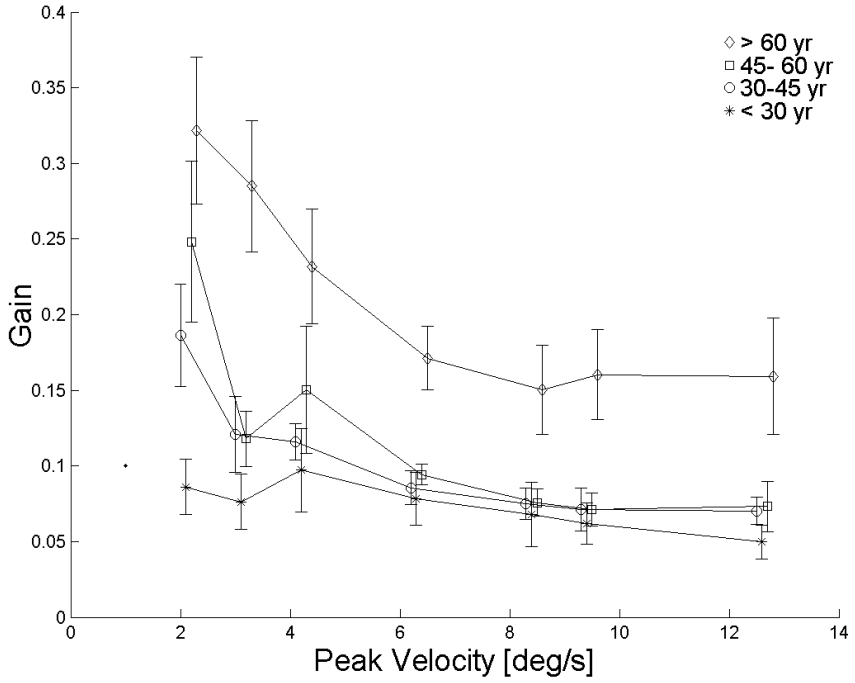


Figure 2.4 Mean gains plotted against peak velocity per age group.
Each age group is represented by a line. The vertical lines represent the standard error of the mean. Note the upward shift of the curve at all velocities for age >60 years. For clarity the data points have been slightly shifted horizontally.

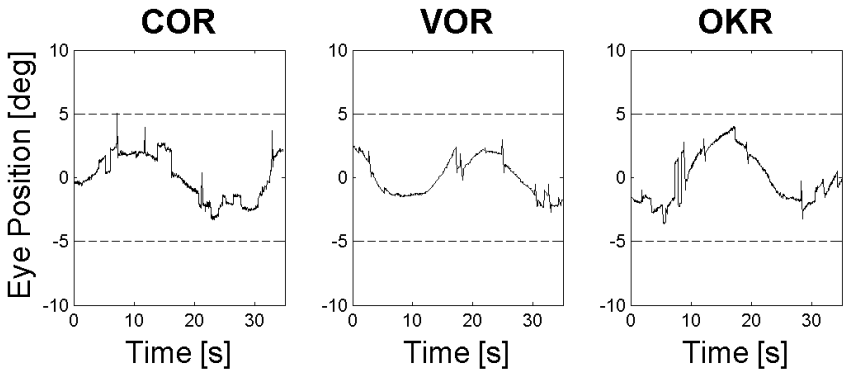


Figure 2.5 Typical traces from the synergy test

These graphs show horizontal position traces from a 26 year old subject, in response to cervical, vestibular and optokinetic stimulation respectively. Dashed lines indicate stimulus amplitude.

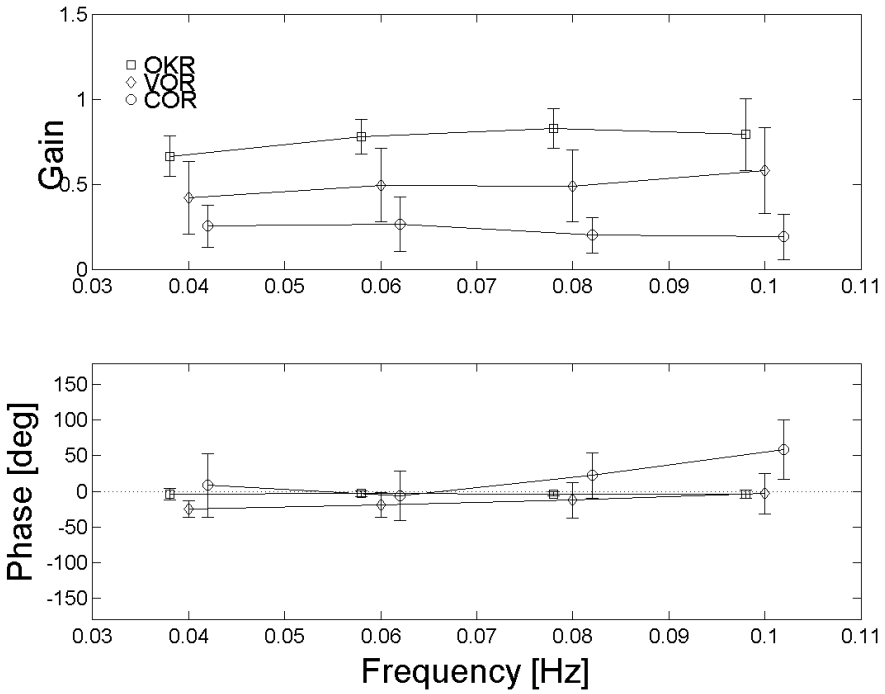


Figure 2.6 Mean gain and phase of the three stabilization reflexes as a function of stimulus frequency. Note that at all frequencies the OKR is strongest, followed by the VOR and the COR.

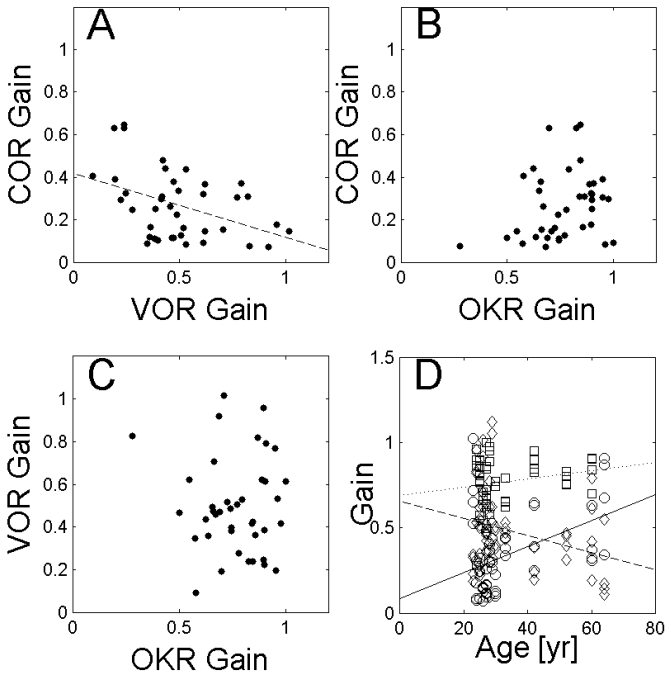


Figure 2.7 Correlations between the reflex gains mutually (A-C) and between gain and age (D). In panel A the dashed line is a linear fit. In panel D different symbols indicate the COR (solid line, **o**), the VOR (dashed line, ◊), and the OKR (dotted line, □).

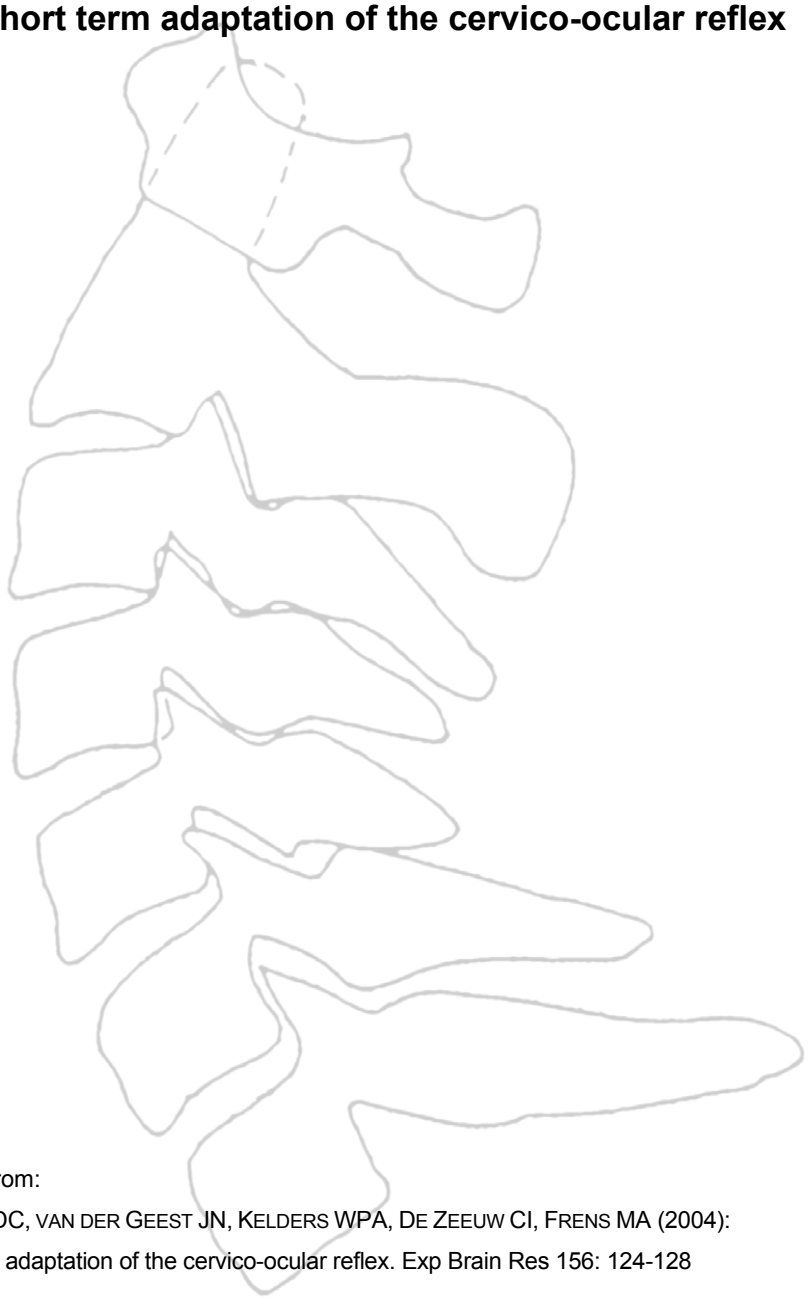
Frequency			Correlation
0.02	VOR	OKR	0.22
		COR	**-0.45**
	OKR	COR	0.17
0.04	VOR	OKR	0.24
		COR	**-0.46**
	OKR	COR	0.29
0.08	VOR	OKR	-0.23
		COR	**-0.38**
	OKR	COR	-0.0056
0.10	VOR	OKR	-0.20
		COR	-0.20
	OKR	COR	0.24

Table 2.1 Correlations between reflexes

Correlation between the gains of the different reflexes split out for the four stimulation frequencies of the synergy test. Bold correlations are significant ($p < 0.05$).

CHAPTER 3

Short term adaptation of the cervico-ocular reflex



Adapted from:

RIJKAART DC, VAN DER GEEST JN, KELDERS WPA, DE ZEEUW CI, FRENS MA (2004):

Short term adaptation of the cervico-ocular reflex. Exp Brain Res 156: 124-128

ABSTRACT

The cervico-ocular reflex (COR) works in conjunction with the vestibulo-ocular reflex (VOR) and the optokinetic reflex (OKR) in order to prevent visual slip over the retina during head movement. The COR induces eye movements in response to proprioceptive signals from the neck. We investigated whether the COR gain can be adapted by inducing a mismatch between vision and neck proprioception, in analogy to VOR adaptation. Thirteen healthy subjects were rotated in the dark in a trunk-to-head manner (the head fixed in spaced while the body passively rotated sinusoidally with a peak velocity of 1.25 °/s). Eye movements were recorded with infrared video oculography under various adaptive conditions. Analysis showed a significant adaptation of the cervico-ocular reflex after only 10 minutes of stimulation.

INTRODUCTION

The cervico-ocular reflex (COR) is an eye stabilization reflex that receives its sensory input from the proprioception of the neck. The receptors are located in the muscles and the facet joints of the cervical spine (Hikosaka & Maeda,1973). The COR works in conjunction with the vestibulo-ocular reflex (VOR) and the optokinetic Reflex (OKR) in order to prevent visual slip during head movement. The VOR moves the eyes on the basis of vestibular information. The OKR responds to visual motion stimulation. In contrast to the VOR, the COR and the OKR respond optimally at low head movement velocity (Van Die and Collewijn, 1986;Mergner et al.1998; Kelders et al. 2003). In a laboratory situation an isolated COR response can be elicited by passive rotation of the body in the absence of visual or vestibular input by fixating the head in space in total darkness (trunk-to-head rotation). This situation is different from the situation in daily life where the body usually remains in the same position and the head rotates (head-to-trunk rotation).

In a recent paper Kelders et al. (2003) reported that the COR gain (eye velocity / trunk velocity) increases with age. Moreover, there is a significant negative correlation between the gains of the VOR and COR. Kelders et al. hypothesized that the age related increase of the cervical response is a compensatory mechanism for loss of the vestibular function. Also in labyrinthine defective subjects the COR is found to be enhanced (Bronstein & Hood, 1986; Huygen et al.1991; Heimbrand et al.1996). The compensation mechanism is reversible, since the cervical response decreases after vestibular recovery (Bronstein et al.1995). This suggests that the COR is apparently modifiable over at least longer periods of time (weeks to years).

It has been well established that the VOR gain can be rapidly adapted by inducing a mismatch between the visual and vestibular information. The average time that is needed for rapid VOR adaptation is in the order of one hour. These short term adaptive changes in VOR gain can be evoked either by fitting subjects with magnifying, miniaturizing, or reversing spectacles during normal behaviour or by moving a visual stimulus concurrently with the movement of the head (Zee, 1989; Koizuka et al. 2000; Shelhamer et al. 2002; Watanabe et al. 2003).

It has been reported that the COR follows the same neural pathways as the VOR (Gdowski and McCrea, 2000). We examined whether the COR gain can also be rapidly adapted by inducing a mismatch between visual stimulation and neck proprioception, in analogy to VOR adaptation, in which a mismatch is created between visual and vestibular input. This will help us to further understand the mechanisms that underlie the synergy in the reflexes that stabilize the eye during changing conditions in health and disease.

MATERIALS AND METHODS

SUBJECTS

Thirteen healthy human subjects (24-36 years of age; five females and eight males) with no history of any neurological or vestibular disorder gave informed consent to perform in all conditions of this study. The experimental procedures were approved by the local ethical committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

PARADIGM

For the cervical stimulation the body was sinusoidally rotated at a frequency of 0.04 Hz with respect to the head. The amplitude of the chair movement was 5º. These are the conditions for which the COR gain is highest (Kelders et al. 2003). The amplitude was well within the range of comfortable neck rotations in all subjects. All rotations were about the vertical axis with the 'straight ahead' position (i.e. transversal planes through both ears and both shoulders parallel) as the middle of the range of motion. As the COR is hypothesized to help in stabilization of the retinal image, the test subject was instructed to focus on an imaginary target located straight ahead at about 3 meters distance, briefly indicated by a laser dot before rotations started. The experiment consisted of three phases: a pre phase, an adaptation phase and a post phase.

In the pre phase the baseline COR response was measured. For two minutes cycles (i.e. ~7 full cycles) were made in the dark, while the eye movements were recorded.

During the adaptation phase the cervical stimulation continued as in the pre phase but simultaneously a moving visual stimulus was presented. This adaptation phase lasted for 10 minutes (i.e. ~35 full cycles) and consisted of one of the following six conditions:

Suppression conditions:

1. Rotating the visual stimulus with amplitude of 10º in counter phase of the chair (figure 3.1A Contra).
2. Keeping the visual stimulus stable (figure 3.1A Fixed).

Enhancement conditions:

3. Rotating the visual stimulus in phase with the chair, with amplitude of 10º (figure 3.1A Ipsi).

4. Rotating the visual stimulus in phase with the chair, with amplitude of 17.1º (figure 3.1A Ipsi).

Control conditions:

5. Rotating in total darkness
6. Rotating the visual stimulus in phase with the chair, with amplitude of 5º (figure 3.1A Ipsi).

During the post phase the COR response was measured under identical conditions as the pre phase, to test effect of adaptation.
In the enhancement conditions the visual stimulus provided the subject with visual velocity information that was larger than the cervical input, in the control condition this information was either identical or absent and in the suppression condition the visual stimulation was lower or in counter phase with the cervical input.
To exclude influences between the adaptation series, the conditions were separated in time for more than 24 hours for each subject. In order to minimize effects of training, the different conditions were given in a random order to each subject. There was no correlation between the ranking of a condition in time and the absolute size of the effect. Therefore we pooled the data of all subjects

APPARATUS

Subjects were seated on a rotating chair, driven by a motor (Harmonic Drive, Germany). The trunk was fixed to the chair at shoulder level by a double belt system. A sensor connected to the chair recorded chair position. Head position was fixed in space by means of a bite board. The Cervical Range of Motion (CROM) device showed that the bite board fixed head was well stabilized in space and that the rotation of the head induced by the moving chair was negligibly small.

VISUAL STIMULATION

The visual stimulus consisted of about 55 dots that had a diameter of 0.2°. The dots were homogeneously but randomly distributed over the screen. The dots were generated by a PC and back projected on a translucent screen (235 cm broad, 170 cm long and at 153 cm from the subject) by means of a data projector Infocus LP 335. The beam of this projector reflected on a mirror that was mounted on a Cambridge Technology stepping motor (model number 6900). Rotations of this mirror induced motion of the dots on the screen. Mirror position was stored on hard disk along with the eye position data (see below).

EYE MOVEMENT MEASUREMENT

The eye movements were recorded by infrared video oculography (Eyelink SMI, Germany) (Van der Geest et al.2002). After calibration of the device both horizontal and vertical eye movements could be recorded precisely with a resolution of 20 seconds of arc and a sampling frequency of 250 Hz. During the experiment the position of the eyes relative to the biteboard mounted cameras was continuously monitored to make sure subject's head was well stabilized by the biteboard.

ANALYSIS

Eye velocity was calculated by taking the derivative of the horizontal eye signal. A sine wave was fitted through the velocity signal after removal of fast phases, using a 20 °/s threshold (figure 3.1B). The gain of the response was defined as the amplitude of the eye velocity fit divided by the maximum velocity of the chair movement which was the same in all conditions: 1.25 °/s.
The gain value of the COR in the pre adaptation phase differed strongly between subjects (0.13-0.87). In order to compare subjects we normalized the gain changes.
The normalized gain change (ΔG) was calculated by dividing the gain change by the gain in the pre phase;

$$\Delta G = \frac{Gpost - Gpre}{Gpre}$$

RESULTS

All subjects had clear and significant COR gains in the pre phase. Although the head was fixated in space, while the chair rotated their trunk, most subjects perceived the illusion that their head was turning with respect to a stationary trunk. Note that both Cervical range of motion device (see chapter 2) and the space fixed eye movement registration showed no actual head movement. The eye movements were in the same direction as the movement of the trunk i.e., in the opposite direction of illusory head movements.
Figure 3.2 shows two examples of pre- and post adaptation data for two representative subjects. Panel A shows that the slow phase velocity of the reflexive eye movements decreases after a condition in which the chair is moving but the visual stimulation is stable

(suppression, condition 2). Panel B shows the condition in which the visual stimulation is moving in phase with the chair but with a larger amplitude (enhancement, condition 3), resulting in an increase in slow phase eye velocity.

Figure 3.3 shows the average normalized gain change (ΔG) as a function of the amplitude of the visual adaptation stimulus. For each amplitude the gain is represented by a circle. The control conditions, in which the visual stimulus was either identical or absent, are indicated by the dotted line.

There is no clear linear relation between screen movement amplitude and gain change. Therefore we pooled the data, putting data together of the two experiments for suppression, enhancement and the control condition and performed a repeated measures ANOVA. This showed a significant effect of condition (suppression, control, enhancement; $p=0.012$). Student's t-tests showed that the normalized gain changes did not differ between the suppression condition ($\Delta G = -0.17 \pm 0.13$ standard error of the mean) and the control condition ($\Delta G = 0.14 \pm 0.21$; $p=0.10$) nor between the enhancement condition and the control condition ($\Delta G = 0.21 \pm 0.19$; $p=0.76$). However the difference between suppression and enhancement conditions was significant (difference of 0.38 ± 0.23). The smallest gain decrease (condition 2) was the only condition that yielded a gain change that was significantly different from 0 ($\Delta G = -0.26 \pm 0.08$; $p=0.0085$). Given the outcome of the ANOVA, no post hoc correction was done for the t-tests.

DISCUSSION

Our study investigated the rapid adaptation of the COR by inducing a mismatch between visual stimulation and cervical proprioception in analogy to VOR adaptation. We found that there was a significant difference in COR adaptation change between the suppression and the enhancement conditions.

The gain change of the cervico-ocular reflex obtained here is relatively small. This is probably due to the fact that the adaptation phase lasted only ten minutes. From the literature it appears that the average adaptation period of the VOR is about one hour (Zee, 1989; Koizuka, 2000; Shelhamer, 2002; Watanabe, 2003). Hence, an elongated adaptation phase might be more effective in changing the COR gain. We did a pilot experiment with an adaptation phase of 20 minutes. However, after this experiment the subjects complained about pain in the neck, and the results were highly variable. Probably other factors interfere with the experiment such as an increased stiffness or even a painful neck.

As mentioned in the results, no linear relation could be observed between the magnitude of the visual cervical mismatch error in the adaptation phase and the induced gain change. One explanation for this might be that the system adapts slower to larger mismatches, because a bigger change has to be made. This seems to be in agreement with the VOR adaptation data of Shelhamer et al. (1994) and of Robinson et al. (2003), who describe a similar phenomenon during saccade adaptation in the monkey.

The finding that the gain of the COR can be rapidly adjusted when deficits occur in the stabilization of the retinal image shows that the COR is a functional reflex whose output is actively controlled. This is important to further understand the previously reported synergy between the stabilization reflexes (Kelders et al. 2003).

Under natural conditions the stabilization reflexes such as the VOR, OKR and COR contribute simultaneously to the stabilization of the eyes. However, when one of these reflexes is altered, due for instance to trauma or aging (Paige 1994), other reflexes can compensate. Mechanisms, such as VOR adaptation and COR adaptation, are therefore likely to sub serve optimal oculomotor control.

REFERENCES

- BRONSTEIN AM, HOOD JD (1986): The cervico-ocular reflex in normal subjects and patients with absent vestibular function. Brain Res 373:399-408
- BRONSTEIN AM, MORLAND AB, RUDDOCK KH, GRESTY MA (1995): Recovery from bilateral vestibular failure: implications for visual and cervico-ocular function. Acta Otolaryngol Suppl 520 Pt 2:405-7
- GDOWSKI GT, MCCREA RA (2000): Neck proprioceptive inputs to primate vestibular nucleus neurons. Exp Brain Res 135:511-26
- HEIMBRAND S, BRONSTEIN AM, GRESTY MA (1996). Optically induced plasticity of the cervico-ocular reflex in patients with bilateral absence of vestibular function. Exp Brain Res 112: 372-380
- HIKOSAKA O, MAEDA M (1973): Cervical effects on abducens motoneurons and their interaction with vestibulo-ocular reflex. Exp Brain Res 18:512-30
- HUYGEN PLM, VERHAGEN WIM, NICOLASEN MG (1991): Cervico-ocular reflex enhancement in labyrinthine-defective and normal subjects. Exp Brain Res 87:457-64
- KELDERS WPA, KLEINRENSINK GJ, VAN DER GEEST JN, FEENSTRA L, DE ZEEUW CI, FRENS MA (2003) Compensatory increase of the cervico-ocular reflex with age in healthy humans.J Physiol. 2003
- KOIZUKA I, KATSUMI N, HATTORI K, OKADA T, KATO I (2000): Effect of adaptive plasticity of linear vestibulo-ocular reflex upon angular vestibulo-ocular reflex. Auris Nasus Larynx 27:89-93
- MERGNER T, SCHWEIGART G, BOTTI F, LEHMANN A (1998): Eye movements evoked by proprioceptive stimulation along the body axis in humans. Exp Brain Res 120:450-60
- ROBINSON FR, NOTO CT, BEVANS SE (2003): Effect of visual error size on saccade adaptation in monkey.J Neurophysiol 90(2):1235-44
- SHELHAMER M, PENG GC, RAMAT S, PATEL V (2002): Context-specific adaptation of the gain of the oculomotor response to lateral translation using roll and pitch head tilts as contexts. Exp Brain Res 146:388-393
- SHELHAMER M, TILIKET C, ROBERTS D, KRAMER PD, ZEE DS. Short-term vestibulo-ocular reflex adaptation in humans. II. Error signals.Exp Brain Res. 1994;100(2):328-36.
- VAN DER GEEST JN, FRENS MA. (2002) Recording eye movements with video-oculography and scleral search coils: a direct comparison of two nethodes. J Neurosci Methods 114(2):185-95

- VAN DIE GC, COLLEWIJN H (1986): Control of human optokinetic nystagmus by the central and peripheral retina: effects of partial visual field masking, scotopic vision and central retinal scotomata. Brain Res 383:185-194
- WATANABE S, HATTORI K, KOIZUKA I (2003): Flexibility of vestibulo-ocular reflex adaptation to modified visual input in human. Auris Nasus Larynx 30 Suppl:29-34
- ZEE DS (1989): Adaptation and the ocular motor system. Bull Soc Belge Ophtalmol 237:191-207

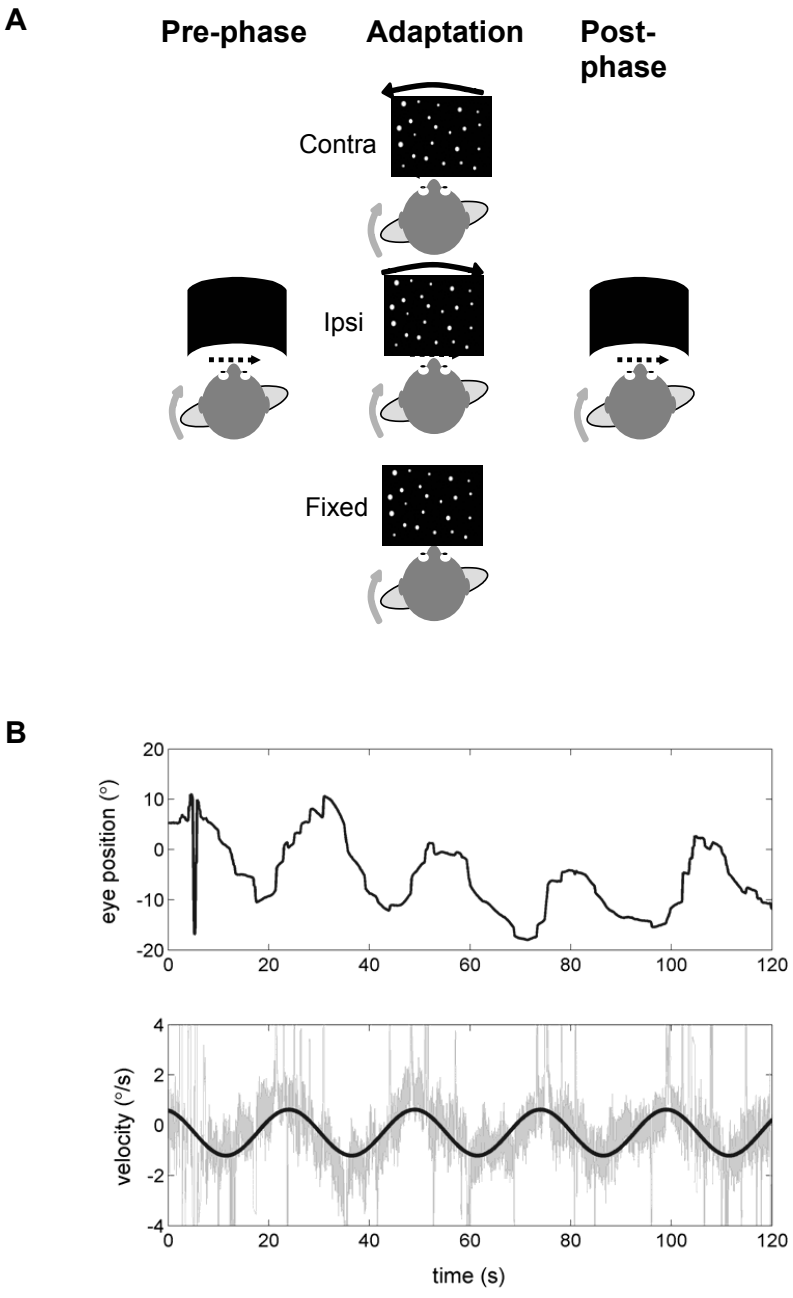


Figure 3.1 Paradigm and eye responses

A. Paradigm

The gray curved arrow shows the movement of the trunk induced by the rotating chair. The curved arrow above the rectangles represents the direction of the visual stimulus, and the dotted arrow shows

the direction of the reflexive eye movement. In the pre phase (left side) subjects were rotated in complete darkness. In the adaptation phase (middle column) a visual stimulus was presented according to the 3 types of conditions. Contra: the random dot pattern in front of the subject moves in the opposite direction of the chair. Ipsi: the pattern moves with the rotation chair in the same direction. Fixed: the screen stands still while the chair rotates. During the pre and post phase the rotations were in darkness.

B. Eye movement recordings and analysis

The upper panel shows the raw data of one individual subject aged 25 years at amplitude of 5º with a stimulus of 0.04 Hz in the pre phase of an experiment. After 5 seconds the subject blinked.

Here we plot the eye position against time for two minutes. The lower panel shows the eye velocity. A sine wave is fitted through the slow component of the eye velocity signal. The gain of this subject was 0.78.

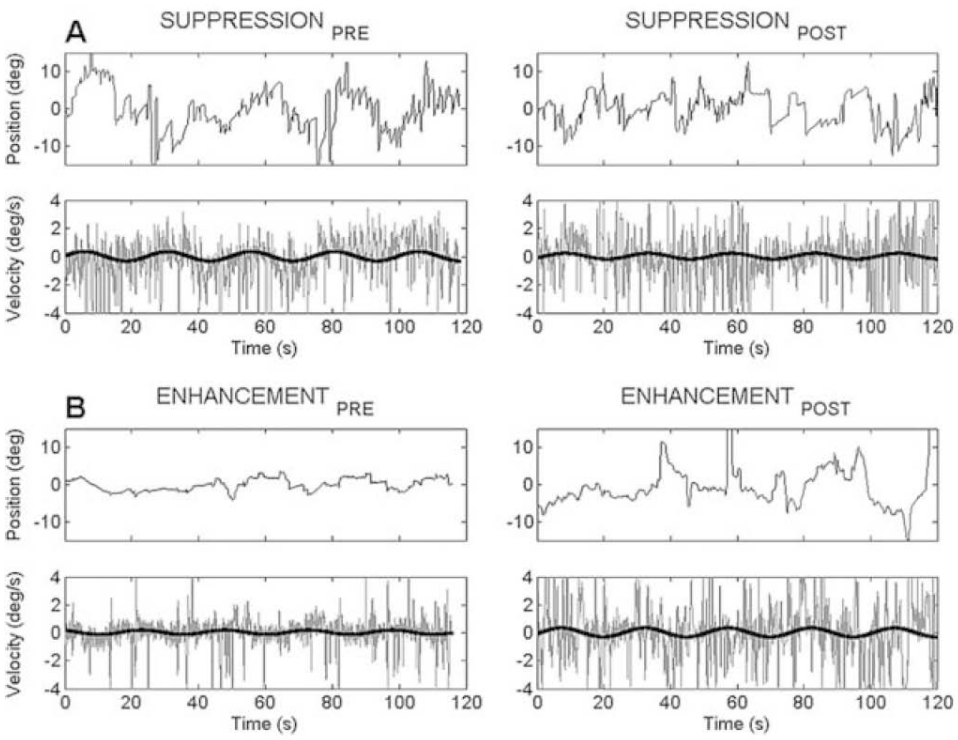


Figure 3.2 Raw data traces

This graph shows the eye position and velocity traces before and after adaptation in two conditions (from two representative subjects). Same format as Figure 2.1B.

A. Gain suppression

Condition 2: visual stimulation not moving

B. Gain enhancement

Condition 3: visual stimulation in phase with an amplitude of 10^{o}

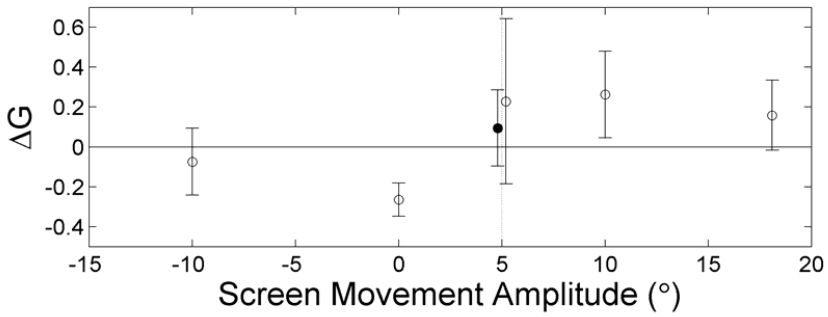
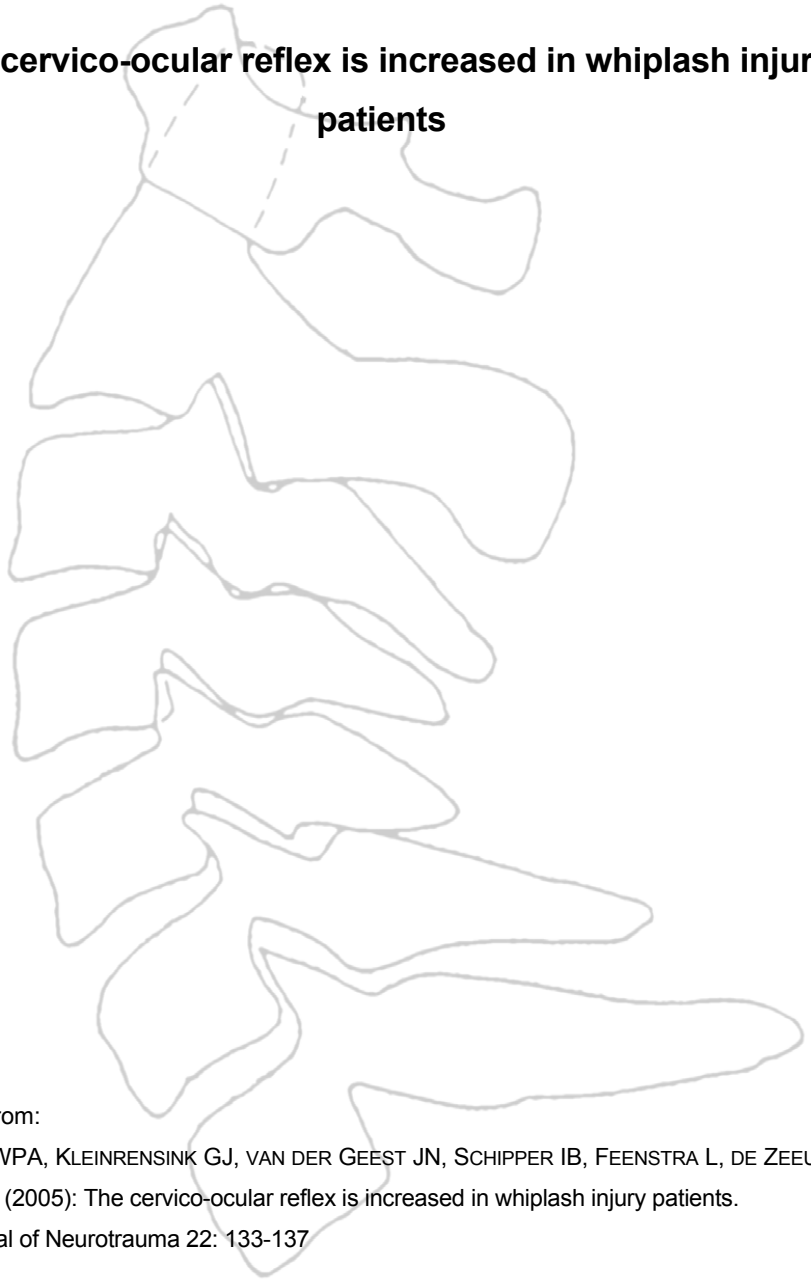


Figure 3.3 Mean gains plotted against screen movement amplitude.

For each amplitude the mean gain is represented by the circle with error bars, which represent standard errors of the mean. The open circles represent adaptation periods with visual stimulus, the black circle represent the adaptation period in the dark. The control conditions, where the visual stimulus was either identical or absent, are indicated by the dotted line. These two control conditions are plotted slightly offside for reasons of clarity.

CHAPTER 4

The cervico-ocular reflex is increased in whiplash injury patients



Adapted from:

KELDERS WPA, KLEINRENSINK GJ, VAN DER GEEST JN, SCHIPPER IB, FEENSTRA L, DE ZEEUW CI, FRENS MA (2005): The cervico-ocular reflex is increased in whiplash injury patients. The Journal of Neurotrauma 22: 133-137

ABSTRACT

Whiplash associated disorders (WAD) are a major problem in the western world, which put a large financial burden on modern society and which evoke an emerging debate on the true nature of their origin. To date there is no generally accepted test that allows us to diagnose WAD objectively. Because whiplash injury causes dysfunction of proprioception in the neck, we investigated the characteristics of the cervico-ocular reflex (COR) of presumptive WAD patients. These patients and age matched healthy controls were rotated at different stimulus peak velocities in the dark while their head was fixed in space. The gain values of the COR were significantly increased in the patient population at a wide range of stimulus peak velocities with maximum difference at the lower frequencies ($p = 0.037$, ANOVA). Hence, although larger numbers of patients should be measured, the COR gain appears to be a parameter that may permit an objective diagnosis of WAD.

INTRODUCTION

Whiplash associated disorders (WAD) are a major medical problem in the western world. WAD is the term, adopted by the Quebec Task Force, for the clinical entities associated with a whiplash injury (Spitzer et al. 1995). WAD is characterized by a combination of neck and head pain and attention deficits following a whiplash injury to the cervical region. The Quebec Task Force defines whiplash as an acceleration-deceleration mechanism of energy transfer to the neck. It may result from rear end or side impact motor vehicle collisions, but can also occur during diving and other mishaps. The impact may result in bony or soft tissue injuries (Spitzer et al. 1995). Each year costs related to WAD amount to 300 million dollars in the Netherlands and to 29 billion dollars in the United States (Freeman et al. 1999). The annual incidence may be as high as 3.8 per 1000 population (Barnsley et al. 1994) and is still rising. In the UK the incidence has increased more than fivefold between 1984 and 1994, since the introduction of compulsory seatbelts in cars (Minton et al. 2000). Signs and symptoms can vary widely and may include neck pain and stiffness, headache, vertigo, tinnitus, visual disturbances and fatigue (Eck et al. 2001). In 6 to 18% of the cases the patients suffer from permanent disability (for review see Lovell and Galasko 2002). The cause for such chronicity is not clear. Some researchers found an abnormal psychological response to pain or other psychiatric disturbances, while others have suggested zygoapophyseal joint pain as the reason for chronic neck pain after a whiplash injury (Lovell and Galasko 2002).

To date, objective and reliable tests to diagnose WAD are not available. CT and MRI scans of the brain and cervical spine usually do not show abnormalities (Ronnen et al. 1996; Borchgrevink et al. 1997). Here, we explored the possibility that the cervico-ocular reflex (COR) may be altered in WAD patients. This reflex, which stabilizes the eye following neck movements, might be affected because proprioception in the facet joints of the cervical spine and deep muscles of the neck may be disturbed in WAD patients (Gimse et al. 1996). In daily life the COR works in conjunction with the vestibulo-ocular reflex (VOR) and optokinetic reflex (OKR) to prevent visual slip over the retina due to self motion (Barlow and Freedman 1980).

The vestibulo-ocular reflex (VOR), which is predominantly induced by activation of the semicircular canals, is mainly responsive to contraversive head movements at high frequency (Tabak et al. 1997). The optokinetic reflex (OKR) on the other hand is mainly evoked by ipsiversive visual motion stimulation at low frequencies. In general all these stabilization reflexes operate together at the various head velocities to optimize the ocular response.

Plasticity in gain values of the COR has already been demonstrated for both short term and long term processes under non pathological conditions. These include for example changes in COR due to aging (Kelders et al. 2003) or visual cervical training (Rijkaart et al. 2004). Thus changes in COR gain could equally well be induced by pathological causes such as WAD. For the present study we restricted ourselves to COR measurements of WAD patients who experienced a head-to-tail collision.

MATERIALS AND METHODS

SUBJECTS

We tested 8 patients with symptoms of whiplash injury (grades 1 and 2) after a head-to-tail car collision (WAD diagnosis and gradation was made according to Spitzer et al. 1995). These included 6 women and 2 men varying from 25 to 42 years in age with a mean of 32. Six patients were included after a visit to the Emergency Department of the Erasmus MC. Two others were included through coworkers. Patients with fractures or dislocations of one or more bones of the neck or with cervical arthrosis were excluded for safety reasons. The whiplash injury occurred 0.5 to 36 months prior to our measurement. Eight age matched healthy subjects were investigated for control; these included 2 women and 6 men varying from 30 to 45 years in age with a mean of 35. A structured interview (use of seatbelts, airbags, headrests, velocity at impact, anticipation of the crash, cervical and neurological symptoms) was taken from every patient and informed consent was signed. None of the subjects had a history of vestibular problems nor did they use any form of tranquilizing or vestibular sedative medication (benzodiazepines, antihistamines, betahistine).
The local medical ethical committee approved the experiments, in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

SETUP

Isolated COR responses were elicited in the absence of visual or vestibular input by passively rotating the body in total darkness, while the head was fixed in space (trunk-to-head rotation). The subject's head was fixed in space by a custom made bite board using Lactona hardening silicone impression material (Dental Techno Benelux, Rotterdam, The Netherlands) and the trunk was fixed to the rotating chair at the shoulders by a double belt system. A Cervical Range Of Motion (CROM) device was used to determine whether the bite board fixed head was stabilized sufficiently (Capuano-Pucci et al. 1991; Youdas et al.

1991). Chair position recorded by a connected sensor was stored on hard disk along with the eye position data. Eye movements were recorded by using an infrared eye tracking device with a resolution of 20 seconds of arc and a sampling frequency of 250 Hz. (Eyelink®, SMI). Both horizontal and vertical eye movements were calibrated.

STIMULUS PARADIGMS

Rotations about the vertical axis were made at four different frequencies (0.1 Hz, 0.067 Hz, 0.05 Hz and 0.04 Hz) and four different amplitudes (5°, 10°, 15° and 20°). The amplitude was limited to 20°, because WAD patients complained of neck pain in the end range of motion.
All rotations were done with the 'straight ahead' position (coronal planes through both ears and both shoulders parallel) as the middle of the range of motion. As the COR is hypothesized to help in stabilization of the retinal image, the test subject was instructed to focus on an imaginary target located straight ahead at about 3 meters distance, briefly indicated by a laser dot before rotations started. This procedure was used for all amplitudes and frequencies.

ANALYSIS

Eye velocity was calculated by taking the derivative of the horizontal eye position signal (Figure 4.1). We removed blinks, saccades and fast phases using a 20°/s threshold. On average the subjects made between one and two nystagmus fast phases per second. A sine wave was fitted through the remaining eye velocity signal. Stimulus velocity was derived from chair position data.
The gain of the response was defined as the amplitude of the eye velocity fit divided by the peak velocity of the chair movement.
Statistical analysis was done with one way analysis of variance (ANOVA).
All analyses were done with Matlab® 6.1 (the Mathworks Inc.).

RESULTS

In both WAD patients and age matched control subjects the stimulus paradigms evoked nystagmus like movements that were composed of slow compensatory eye movements and fast resetting saccades (Figure 4.2). The amplitude of the compensatory response, i.e. the actual COR, was considerably larger in WAD patients than in controls (Figures 4.2 and 4.3).

The mean gain values during COR in patients were significantly higher over the whole range of stimulus peak velocities ($p = 0.037$, ANOVA). This difference even existed at the higher peak velocities, which generally evoked relatively small responses (Figure 4.3). We present our data as a function of peak velocity rather than of frequency because it was shown earlier that the COR is a peak velocity dependent system, rather than a frequency dependent system (Mergner et al. 1998; Kelders et al. 2003).

As far as could be detected in our small population of WAD patients there was no relation between the gain of the COR and the length of the period between the trauma and the measurement (which varied from 2 weeks to 3 years). In both patients and controls the phase lag re stimulus increased with stimulus peak velocity and varied from 0º to 90º (data not shown). We did not observe any significant difference in phase values between the two groups at any of the stimulus paradigms.

DISCUSSION

The present study shows that the gain of the COR of WAD patients is increased over a wide range of peak velocities. So far other attempts have failed to find this correlation (Holtmann et al. 1993; Fischer et al. 1995). We found that it is essential to compare the COR of WAD patients to control subjects that are matched for age, because the gain values of their COR depend on age (Kelders et al. 2003). This increase in COR gain of the elderly may reflect in part a compensatory mechanism for a decrease of their vestibulo-ocular reflex (Kelders et al. 2003). This hypothesis is supported by the fact that WAD patients sometimes also show hypo caloric responses (Chester 1991; Claussen and Claussen 1995; Vibert and Hausler 2003). Alternatively, the COR gains may be increased in elderly persons because of a relatively stiff neck that affects their proprioceptive input. This latter hypothesis also seems to hold in the light of our current results, because all WAD patients appeared to have problems in the end range of their neck motion. Possibly, the sensitivity to proprioceptive inputs is increased in these patients to avoid neck pain in the end range of motion of the neck and consequently the gain of the COR will increase.

We can conclude that COR measurements are very sensitive to detect cervical injury, but it remains to be elucidated to what extent this test is specific for WAD syndrome. Other diseases such as cervical arthrosis may show similar aberrations. Further research will have to reveal to what extent this objective test may be used to specifically determine the diagnosis and prognosis of WAD patients or to evaluate their therapy.

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REFERENCES

- BARLOW D, FREEDMAN W (1980): Cervico-ocular reflex in the normal adult. Acta Otolaryngol 89: 487-496.
- BARNSLEY L, LORD S, BOGDUK N (1994): Whiplash injury. Pain 58: 283-307
- BORCHGREVINK G, SMEVIK O, HAAVE I, HARALDSETH O, NORDBY A, LEREIM I (1997): MRI of cerebrum and cervical columna within two days after whiplash neck sprain injury. Injury 28: 331-335
- CAPUANO-PUCCI D, RHEAULT W, AUKAI J, BRACKE M, DAY R, PASTRICK M (1991): Intratester and intertester reliability of the cervical range of motion device. Arch Phys Med Rehabil 72: 338-340
- CHESTER JB, JR. (1991): Whiplash, postural control, and the inner ear. Spine 16: 716-720
- CLAUSSEN CF, CLAUSSEN E (1995): Neurootological contributions to the diagnostic follow-up after whiplash injuries. Acta Otolaryngol Suppl 520 Pt 1: 53-56
- ECK JC, HODGES SD, HUMPHREYS SC (2001): Whiplash: a review of a commonly misunderstood injury. Am J Med 110: 651-656
- FISCHER AJEM, HUYGEN PLM, FOLGERING HT, VERHAGEN WIM, THEUNISSEN EJJM (1995): Vestibular hyperreactivity and hyperventilation after whiplash injury. J Neurol Sci 132: 35-43.
- FREEMAN MD, CROFT AC, ROSSIGNOL AM, WEAVER DS, REISER M (1999): A review and methodologic critique of the literature refuting whiplash syndrome. Spine 24: 86-96.
- GIMSE R, TJELL C, BJORGEN IA, SAUNTE C (1996): Disturbed eye movements after whiplash due to injuries to the posture control system. J Clin Exp Neuropsychol 18: 178-186
- HOLTMANN S, REIMAN V, SCHOPS P (1993): [Clinical significance of cervico-ocular reactions]. Zur klinischen Bedeutung zerviko-okularer Reaktionen. Laryngorhinootologie 72: 306-310.
- KELDERS WPA, KLEINRENSINK GJ, VAN DER GEEST JN, FEENSTRA L, DE ZEEUW CI, FRENS MA (2003): Compensatory increase of the cervico-ocular reflex with age in healthy humans. J Physiol 553: 311-317
- LOVELL ME, GALASKO CS (2002): Whiplash disorders--a review. Injury 33: 97-101
- MERGNER T, SCHWEIGART G, BOTTI F, LEHMANN A (1998): Eye movements evoked by proprioceptive stimulation along the body axis in humans. Exp Brain Res 120: 450-460.
- MINTON R, MURRAY P, STEPHENSON W, GALASKO CS (2000): Whiplash injury--are current head restraints doing their job? Accid Anal Prev 32: 177-185

- RIJKAART DC, VAN DER GEEST JN, KELDERS WPA, DE ZEEUW CI, FRENS MA (2004): Short-term adaptation of the cervico-ocular reflex. Exp Brain Res 156: 124-128
- RONNEN HR, DE KORTE PJ, BRINK PR, VAN DER BIJL HJ, TONINO AJ, FRANKE CL (1996): Acute whiplash injury: is there a role for MR imaging?--a prospective study of 100 patients. Radiology 201: 93-96
- SPITZER WO, SKOVRON ML, SALMI LR, CASSIDY JD, DURANCEAU J, SUISSA S, ZEISS E (1995): Scientific monograph of the Quebec Task Force on Whiplash-Associated Disorders: redefining "whiplash" and its management. Spine 20: 1S-73S
- VIBERT D, HAUSLER R (2003): Acute peripheral vestibular deficits after whiplash injuries. Ann Otol Rhinol Laryngol 112: 246-251
- YOUDAS JW, CAREY JR, GARRETT TR (1991): Reliability of measurements of cervical spine range of motion--comparison of three methods. Phys Ther 71: 98-104; discussion 105-106

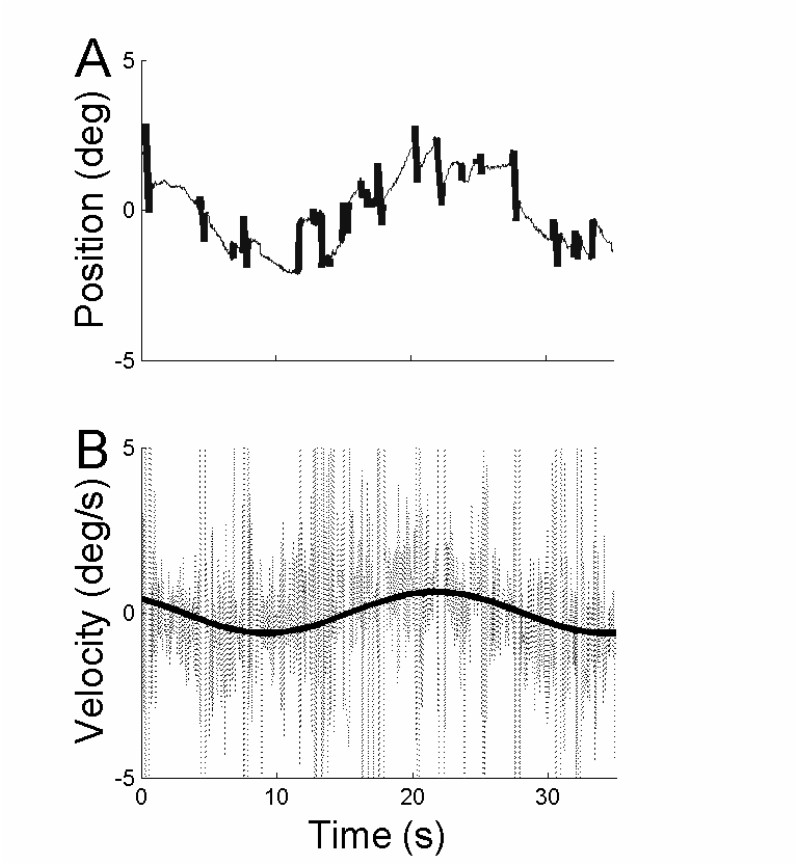


Figure 4.1 Analysis of eye movements

A. Example of a raw horizontal eye position trace during stimulation at 0.04 Hz with an amplitude of 5º, taken from a 58 year old, healthy subject. Detected blinks, saccades and fast phases are shown as thick lines.

B. Eye velocity derived from the position data in panel A (dotted line). Through the eye velocity a sine wave is fitted (fixed line) with three free parameters (amplitude, phase, and offset). Data from blinks, saccades and fast phases are not used for the fit.

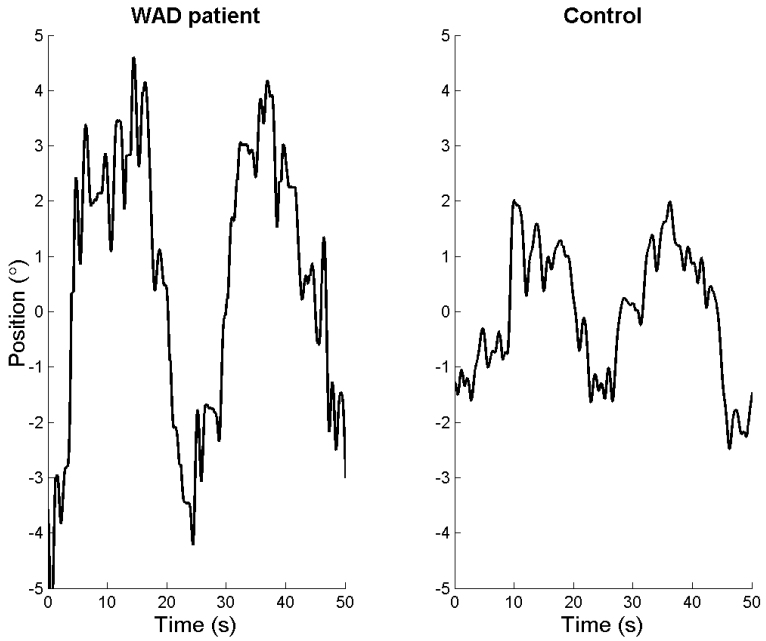


Figure 4.2 Eye position traces of a typical WAD patient (left panel) and normal control (right panel) at 0.04 Hz with an amplitude of 5º.

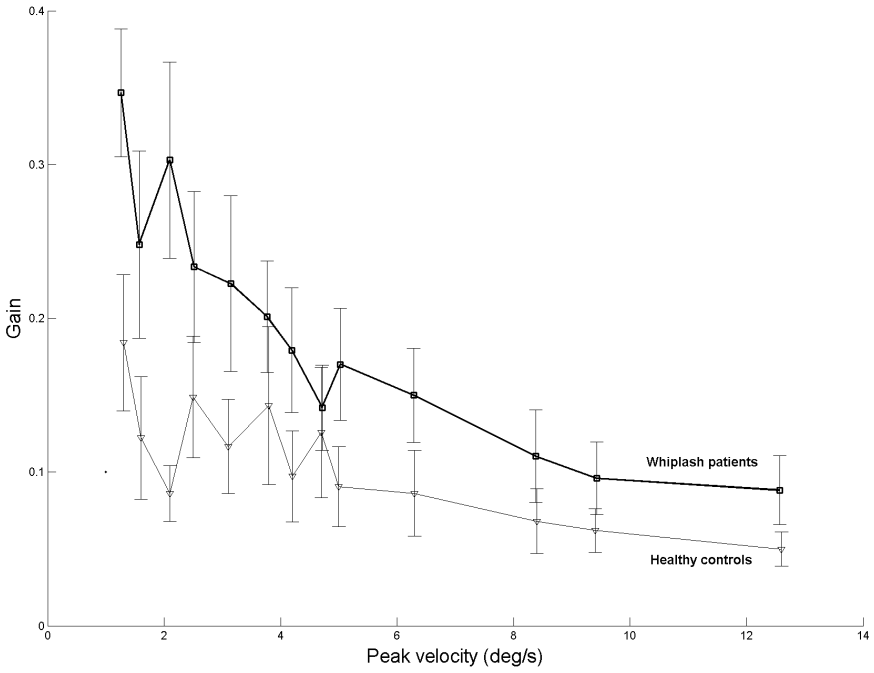
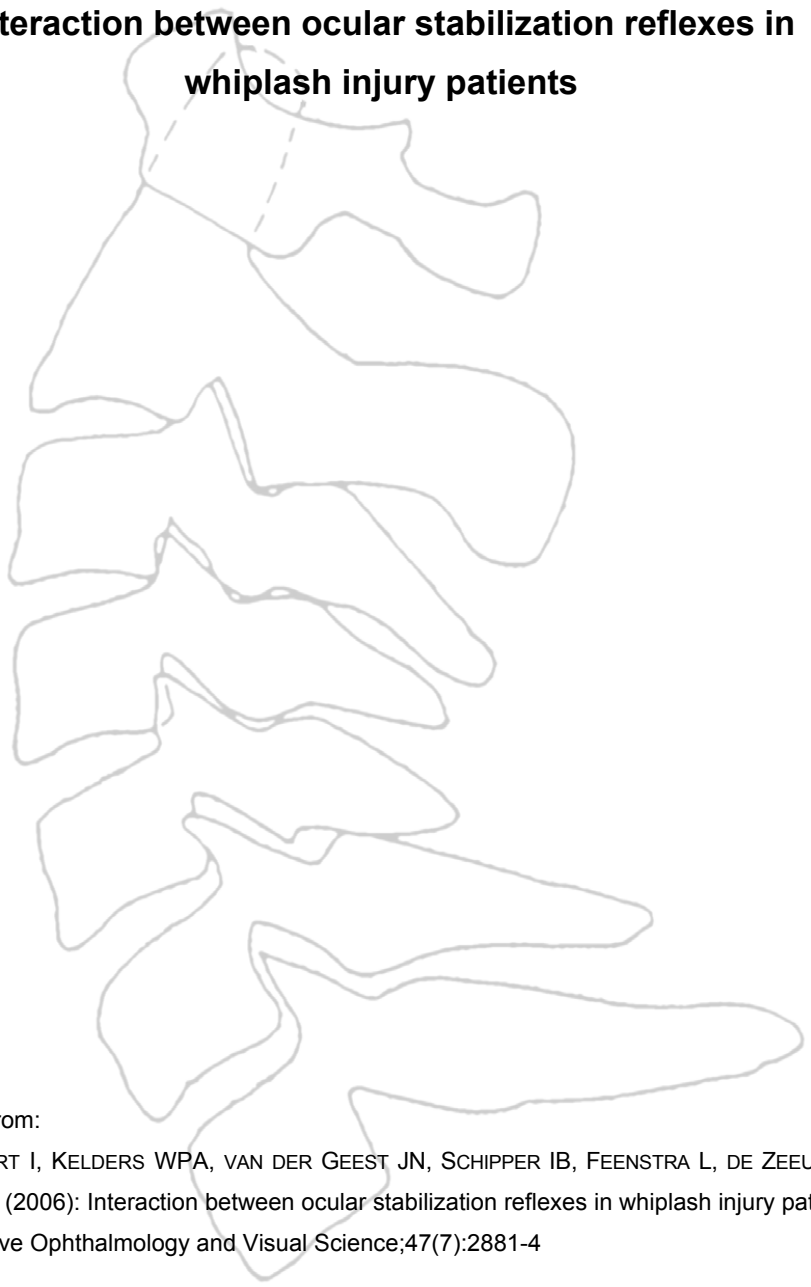


Figure 4.3 COR gain is elevated in WAD patients.

The mean gain values (± SEM) during COR are presented as a function of stimulus peak velocity for both patients and controls. The mean gain values of the whiplash injury patients are plotted as a thick black line, while the lower thin line represents the mean gain values of the age matched control group.

CHAPTER 5

Interaction between ocular stabilization reflexes in whiplash injury patients



Adapted from:

MONTFOORT I, KELDERS WPA, VAN DER GEEST JN, SCHIPPER IB, FEENSTRA L, DE ZEEUW CI, FRENS MA (2006): Interaction between ocular stabilization reflexes in whiplash injury patients. Investigative Ophthalmology and Visual Science;47(7):2881-4

ABSTRACT

Purpose: In the last few decades the car has become a more and more popular means of transport, which has lead to an increasing number of rear end car collisions and consequently resulted in more patients with whiplash associated disorders (WAD). Recently we found that the gain of one of the ocular stabilization reflexes, i.e. the cervico-ocular reflex (COR) is elevated in whiplash injury patients. The COR responds to proprioceptive signals from the neck and acts in conjunction with the vestibulo-ocular reflex (VOR) and optokinetic reflex (OKR) to preserve stable vision of the external world on the retina during head motion. Therefore we investigated whether the reported elevation of the COR in WAD was accompanied by changes in VOR and/or OKR.

Methods: Eye movements of 13 patients and 18 age matched healthy controls were recorded with an infrared eye tracking device.

Results: Analysis confirmed a significant increase in COR gain in whiplash patients. Meanwhile the VOR gain and OKR gain remained the same. No correlation was found between the gains of the reflexes in individual subjects. This is in contrast with earlier observations in elderly and labyrinthine defective subjects, who showed an increase in COR gain accompanied by a decrease in VOR gain.

Conclusions: An impaired neck motion, altered proprioception of the neck, or disorganization in the process of VOR plasticity could explain the lack of change in VOR gain.

INTRODUCTION

As the grade of traffic increases, rear end car collisions occur more frequently and as a result whiplash associated disorders (WAD) have become a common phenomenon in the Western doctors' office. Especially since the introduction of the obliged occupant protecting seatbelt use the incidence has increased (Thomas, 1990). The term WAD is adopted by the Quebec Task Force (QTF) and refers to a variety of clinical manifestations, such as neck and head pain, but also visual disturbances, tinnitus, dizziness and fatigue are presented by patients (Eck et al. 2001). The QTF defined whiplash as an acceleration-deceleration mechanism of energy transfer to the neck. It may result from rear end or side impact motor vehicle collision, but can also occur during diving or other mishaps. The impact may result in bony or soft tissue injuries (Spitzer et al. 1995). Although the mechanism seems clear, the variety of signs and symptoms makes it an extensive disorder. Furthermore, though in the majority of cases the physical complaints disappear in time, between 6 and 18% of the patients have permanent disability (Lovell & Galasko, 2002).

Despite clear complaints, it is difficult to find objective standards to produce evidence for the presence of the ailment in patients with WAD. However, Nederhand et al. found a decreased relaxation ability of the cervical trapezoid muscles (Nederhand et al. 2000) and Kelders et al. (2005) recently found that the gain of one of the ocular stabilization reflexes, i.e., the cervico-ocular reflex (COR), is elevated in whiplash injury patients as compared to an age matched control group (see chapter 4).

The COR acts in conjunction with the vestibulo-ocular reflex (VOR) and optokinetic reflex (OKR) to preserve stable vision of the external world on the retina during head motion. It is elicited by rotation of the neck, thereby stimulating proprioceptive afferents from deep neck muscles and joint capsula from C1 – C3 to the vestibular nucleus (Hikosaka & Maeda, 1973) and leads to eye movements that oppose the direction of the head movement.

The VOR can be subdivided into rotational and translational components that are induced by stimulation of the semicircular canals and the otolith organs respectively. When the head is turned the VOR moves the eyes in the opposite direction, responding optimally to high frequencies (Tabak et al. 1997). The OKR is stimulated by visual motion and uses the relative velocity of the image on the peripheral retina to generate eye movements in the same direction. Both OKR and COR respond best at low head movement velocities (Van Die & Collewijn, 1986; Mergner et al. 1998; Kelders et al. 2003). The gain values of the COR are increased over a broad range of velocities (ranging from 1.2 º/s to 12.8 º/s) in whiplash injury patients, although the largest difference was found at lower velocities (Kelders et al. 2005).

In healthy subjects the COR gain can be modified after 10 minutes of concurrent visual and cervical stimulation (Rijkaart et al. 2004). In patients with absent vestibular function the COR

gain is also increased (Bronstein & Hood, 1986; Huygen et al. 1991; Bronstein et al. 1995; Bouyer & Watt, 1999) as it does with age (aged over 60 years (Kelders et al. 2003)). Meanwhile in elderly persons the gain of the VOR and OKR is decreased (Mulch & Petermann, 1979; Aust, 1991; Paige, 1994). Earlier, in chapter 2 (Kelders et al. 2003), we reported a co variation between the gains of the COR and VOR in healthy humans: i.e., when the VOR is relatively high, the COR is low and vice versa.

Because the ocular stabilization reflexes work in parallel, we studied the OKR, COR, and VOR in patients with WAD. We investigated whether the reported elevation of the COR in WAD was accompanied by changes in VOR, OKR or both. Investigating the stabilization reflexes helps to increase the understanding of the neuro anatomical basis of OKR, COR, and VOR characteristics and therefore gives a better understanding of motor control and helps to unravel the mechanisms that underlie WAD.

MATERIALS AND METHODS

SUBJECTS

Thirteen patients with a mean age of 40 (range 26-60 years) who visited the Emergency Department of the Erasmus MC with symptoms of isolated whiplash injury (WAD grades 1&2 according to Spitzer et al. (1995)) following a head-to-tail car collision were included. Patients with a history of vestibular problems, recent use of tranquilizing medication, fractures or dislocations of bones of the neck or cervical arthrosis were excluded. Of every patient factors concerning the car crash, such as velocity at impact, anticipation of the crash, signs and symptoms, use of seatbelt, headrest and airbag were collected by interview. Also 18 age matched healthy controls with a mean age of 36 (range 23-64 years) were asked to participate in the trial. For age stratification the control group used in chapter 4 (Kelders et al. 2005) was extended by 10 control subjects. All participants had clear vision and no one used any form of tranquilizing or vestibular sedative medication. Every subject gave informed consent. In accordance with the ethical standards laid down in the 1964 Declaration of Helsinki the experiments were approved by the medical ethical committee of the Erasmus MC.

EXPERIMENTAL SETUP

A projection screen and a custom made rotating chair were used to record COR, VOR, and OKR responses. Details of the experimental setup are described in chapter 2 (Kelders et al. 2003).

COR recordings

By passively rotating the body while fixating the subject's head (trunk-to-head rotation) isolated COR responses were recorded in the absence of visual or vestibular input. The subject's head was fixed in space by means of a custom made bite board (Dental Techno Benelux, Rotterdam, The Netherlands) and the trunk was fixed to the chair by a double belt system at shoulder level. A cervical range of motion device was used to demonstrate that the head was sufficiently stabilized in space with a negligibly small head movement induced by chair motion (see chapter 2).

VOR recordings

In contrast to the setup used for the recordings of the COR responses, the bite board was attached to the chair so trunk and head moved passively together. As in COR recordings, the room was totally darkened.

OKR recordings

The stimulus was generated by a personal computer using Matlab 6.1 (Mathworks Inc.) and consisted of 50 sinusoidally moving white dots with a diameter of 0.8º in a 60º wide and 45º high field. The dots were projected on a 235 cm broad and 170 cm wide translucent screen through an Infocus LP 335 data projector. This projector back projected the image on the screen using a mirror, attached to a Cambridge Technology step motor (model number 6900), for reflection. The dots were homogenously distributed over the screen and had a limited lifetime of 50 ms to prevent foveal pursuit of single dots. No dots were shown in the central area of 6º. Rotations of the mirror induced motion of the dots. Subjects were instructed to keep fixating at the centre of the dots free area to prevent visual motion in the (peri) foveal region while their head was also fixed with the help of the bite board.

Chair location, mirror positions as well as eye position data were stored on hard disk. Eye movements were recorded by using an infrared eye tracking device (EyeLink, SMI, Germany) assembled to the same construction as the bite board, with a resolution of 20 sec of arc and a sampling frequency of 250 Hz (van der Geest & Frens, 2002). The positions of the eyes relative to the cameras were constantly observed to ensure stabilization of the subject's head during recordings.

Stimulus Paradigms

For optokinetic and cervical/vestibular stimulation, the mirror and chair respectively were rotated at four different frequencies (0.1, 0.08, 0.06 and 0.04 Hz) with an amplitude of 5º about the vertical axis. For both COR and VOR recordings, subjects were instructed to focus on an imaginary target located straight ahead on the screen, briefly indicated in advance by a laser dot.

ANALYSIS

Eye velocity was calculated by taking the derivative of the horizontal eye position signal, identical to what was done in earlier experiments described in chapter 2 (Kelders et al. 2003). Although the eye reflexes were never perfectly symmetrical in both groups, resulting in small drift towards the left or right, no differences in symmetry were found between the whiplash patients and healthy subjects. After removal of blinks, saccades, and fast phases using a 20 º/s threshold, a sine wave was fitted to the velocity signal. The gain of the response was defined as the amplitude of the eye velocity fit divided by the maximum velocity of the chair. Outliers were removed. Further analyses were done with Kolmogorov-Smirnov (KS) tests and linear regression using Matlab 6.1 (Mathworks Inc.).

RESULTS

Gain values were independent of stimulus frequencies within the range that we presented, as was also described in chapter 2 (Kelders et al. 2003). Therefore, data were pooled over all frequencies.

The three reflex gain values of the age matched subjects at all frequencies are plotted in figure 5.1 (controls A,C,E, patients B,D,F). In chapter 2 (Kelders et al. 2003) we describe an increased COR gain in elderly (> 60 years) and in whiplash injury patients (Kelders et al. 2005). Also in this study, a higher COR gain was found in WAD patients as compared to healthy controls (Figure 5.1 A, B, KS test, $p = 2.9 * 10^{-6}$). The gains of the OKR and VOR do not show a significant change (VOR gain p = 0.27, OKR gain p = 0.25). The gain values of patients remain consistent with those of healthy controls. (Figure 5.1 C - F). Previously, Kelders et al. (2003) also found a negative correlation between the COR gain and VOR gain in healthy subjects. Figure 5.2A shows a similar correlation for healthy participants (r = -0.38, p = 0.01), but not for patients (r = 0.01, p = 0.95). Furthermore both reflexes are not significantly correlated with the OKR in either controls (r = 0.26, p = 0.08, r = -0.02, p = 0.9 respectively, Figure 5.2B), or patients (r = 0.09, p = 0.05, r = 0.16, p = 0.31 respectively,

Figure 5.2C). Although the COR gain increases with age in controls ($r = 0.32$, $p < 0.02$), such a difference does not appear in patients ($r = -0.05$, $p > 0.7$; Figure 5.3).

DISCUSSION

In WAD patients the COR gain values are significantly increased compared to healthy controls. The gain rise with age was not seen in patients, which could indicate that the whiplash injury cancels out this age related effect. After stratifying for age, the values remained higher, similar to what was seen in Kelders et al. (2005). Also, in contrast with normal controls, no synergy was found between the COR and VOR in the patient group. Furthermore, no correlation was found between the remaining eye reflex combinations either in patients or in controls. However, an age related decay in VOR and OKR in normal subjects has been reported (Mulch & Petermann, 1979; Aust, 1991; Paige, 1994). The increase in COR gain in elderly might be an adjustment for the decline in VOR gain. Moreover, in persons with bilateral labyrinthine defects, the COR partly takes over for the diminished VOR by rising (Bronstein & Hood, 1986; Huygen et al. 1991; Heimbrand et al. 1996) and decreasing again after restoration of the vestibular apparatus (Bronstein et al. 1995). In earlier experiments, Rijkaart et al. (2004) showed that the COR is able to adapt after only 10 minutes of incongruent simultaneous visual and cervical stimulation.

A decrease in VOR gain might have been responsible for an increase in COR gain in our whiplash patients, as is seen in elderly and in labyrinthine defective subjects. However, a higher COR gain could also be the cause of a decline in VOR gain. Earlier experiments showed that the VOR gain can be adapted in one hour by non corresponding vestibular and visual information (Zee, 1989; Koizuka et al. 2000; Shelhamer et al. 2002; Watanabe et al. 2003). Contrary to the latter theory, the COR gain was elevated without a decline in the gain of the vestibulo-ocular reflex in WAD patients.

Three hypotheses can provide an explanation for this lack of synergy in whiplash injury patients.

Firstly, perhaps a decreased mobility of the neck leads to an alteration in proprioception of the neck, which in turn results in an augmented gain of the cervico-ocular reflex without any problems in the VOR pathway.

Secondly, it may be that adaptation of the VOR requires sufficient head motion and because of an impaired neck motion there is too little adaptive input for the VOR to induce a negative adaptation in VOR gain. It is known that the VOR responds best at high velocities, while the COR is most responsive at low frequencies. This could explain the absent decrease in VOR gain.

Thirdly, perhaps there is a disorganization in the process of VOR plasticity due to micro trauma in the VOR pathway, e.g. in the flocculonodular area of the cerebellum. The latter

hypothesis will be subject to more research in the near future when we will perform VOR adaptation experiments in whiplash injury patients.

Although a variety of complaints such as head and neck pain, visual disturbances, tinnitus, dizziness and fatigue are associated with whiplash injuries (Eck et al. 2001), it can be speculated to what degree abnormalities in COR gain are responsible for the reported signs and symptoms. Although the correlation between them is striking, it does not prove causation. However, the results might explain some symptoms. The improperly tuned VOR and COR may lead to complaints such as dizziness and visual problems like reading problems. The absence of synergy between the COR and VOR as well as head and neck pain may induce fatigue complaints.

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REFERENCES

- AUST G (1991): [The effect of age on vestibulo-ocular reactions]. Der Einfluss des Lebensalters auf vestibulo-okulare Reaktionen. Laryngorhinootologie 70, 132-137.
- BOUYER LJ & WATT DG (1999): "Torso Rotation" experiments. 4: the role of vision and the cervico-ocular reflex in compensation for a deficient VOR. J Vestib Res 9, 89-101.
- BRONSTEIN AM & HOOD JD (1986): The cervico-ocular reflex in normal subjects and patients with absent vestibular function. Brain Res 373, 399-408.
- BRONSTEIN AM, MORLAND AB, RUDDOCK KH & GRESTY MA (1995): Recovery from bilateral vestibular failure: implications for visual and cervico-ocular function. Acta Otolaryngol Suppl 520 Pt 2, 405-407.
- ECK JC, HODGES SD & HUMPHREYS SC. (2001): Whiplash: a review of a commonly misunderstood injury. Am J Med 110, 651-656.
- HEIMBRAND S, BRONSTEIN AM, GRESTY MA & FALDON ME (1996): Optically induced plasticity of the cervico-ocular reflex in patients with bilateral absence of vestibular function. Exp Brain Res 112, 372-380.
- HIKOSAKA O & MAEDA M (1973): Cervical effects on abducens motoneurons and their interaction with vestibulo-ocular reflex. Exp Brain Res 18, 512-530.
- HUYGEN PLM, VERHAGEN WIM & NICOLASEN MG (1991): Cervico-ocular reflex enhancement in labyrinthine-defective and normal subjects. Exp Brain Res 87, 457-464.
- KELDERS WPA, KLEINRENSINK GJ, VAN DER GEEST JN, FEENSTRA L, DE ZEEUW CI & FRENS MA (2003): Compensatory increase of the cervico-ocular reflex with age in healthy humans. J Physiol 553, 311-317.
- KELDERS WPA, KLEINRENSINK GJ, VAN DER GEEST JN, SCHIPPER IB, FEENSTRA L, DE ZEEUW CI & FRENS MA (2005): The cervico-ocular reflex is increased in whiplash injury patients. J Neurotrauma 22, 133-137.
- KOIZUKA I, KATSUMI N, HATTORI K, OKADA T & KATO I (2000): Effect of adaptive plasticity of linear vestibulo-ocular reflex upon angular vestibulo-ocular reflex. Auris Nasus Larynx 27, 89-93.
- LOVELL ME & GALASKO CS (2002): Whiplash disorders--a review. Injury 33, 97-101.
- MERGNER T, SCHWEIGART G, BOTTI F & LEHMANN A (1998): Eye movements evoked by proprioceptive stimulation along the body axis in humans. Exp Brain Res 120, 450-460.
- MULCH G & PETERMANN W (1979): Influence of age on results of vestibular function tests. Review of literature and presentation of caloric test results. Ann Otol Rhinol Laryngol Suppl 88, 1-17.

- NEDERHAND MJ, IJZERMAN MJ, HERMENS HJ, BATEN CT & ZILVOLD G (2000): Cervical muscle dysfunction in the chronic whiplash associated disorder grade II (WAD-II). Spine 25, 1938-1943.
- PAIGE GD (1994): Senescence of human visual-vestibular interactions: smooth pursuit, optokinetic, and vestibular control of eye movements with aging. Exp Brain Res 98, 355-372.
- RIJKAART DC, VAN DER GEEST JN, KELDERS WPA, DE ZEEUW CI & FRENS MA (2004): Short-term adaptation of the cervico-ocular reflex. Exp Brain Res.
- SHELHAMER M, PENG GC, RAMAT S & PATEL V (2002): Context-specific adaptation of the gain of the oculomotor response to lateral translation using roll and pitch head tilts as contexts. Exp Brain Res 146, 388-393.
- SPITZER WO, SKOVRON ML, SALMI LR, CASSIDY JD, DURANCEAU J, SUISSA S & ZEISS E (1995): Scientific monograph of the Quebec Task Force on Whiplash-Associated Disorders: redefining "whiplash" and its management. Spine 20, 1S-73S.
- TABAK S, COLLEWIJN H, BOUMANS LJJM & VAN DER STEEN J (1997): Gain and delay of human vestibulo-ocular reflexes to oscillation and steps of the head by a reactive torque helmet. I. Normal subjects. Acta Otolaryngol 117, 785-795.
- THOMAS J (1990): Road traffic accidents before and after seatbelt legislation--study in a district general hospital. J R Soc Med 83, 79-81.
- VAN DER GEEST JN & FRENS MA (2002): Recording eye movements with video-oculography and scleral search coils: a direct comparison of two methods. J Neurosci Methods 114, 185-195.
- VAN DIE GC & COLLEWIJN H (1986): Control of human optokinetic nystagmus by the central and peripheral retina: effects of partial visual field masking, scotopic vision and central retinal scotomata. Brain Res 383, 185-194.
- WATANABE S, HATTORI K & KOIZUKA I (2003): Flexibility of vestibulo-ocular reflex adaptation to modified visual input in human. Auris Nasus Larynx 30 Suppl, S29-34.
- ZEE DS (1989): Adaptation and the ocular motor system. Bull Soc Belge Ophtalmol 237, 191-207.

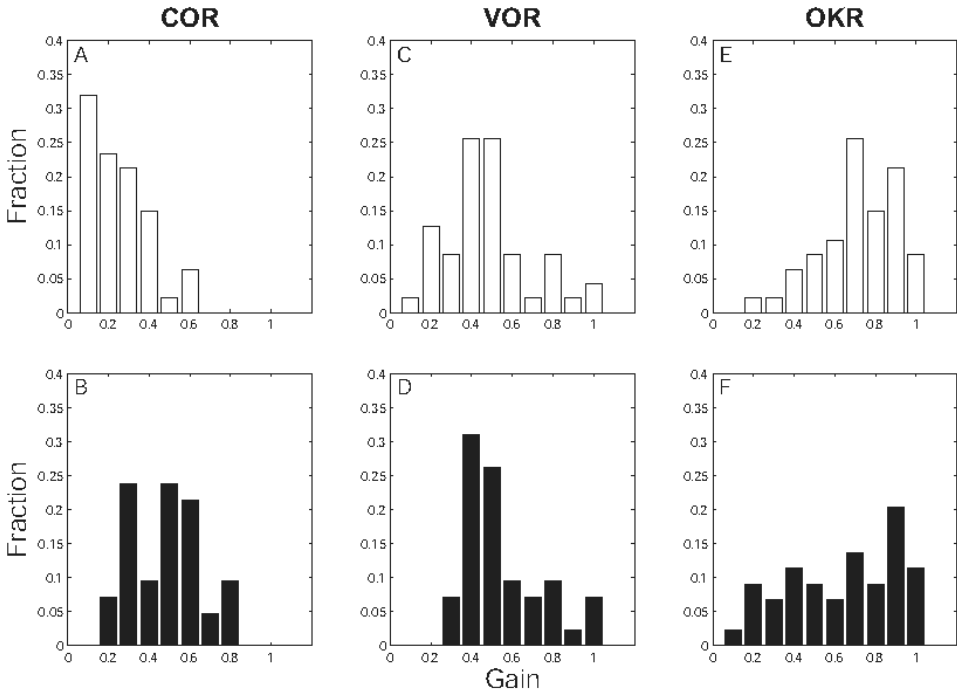


Figure 5.1 The fractions of COR, VOR, and COR gains pooled for the whole range of stimulus peak velocities. The results of the age matched healthy controls and whiplash patients are plotted in panels A,C, E and B,D,F respectively.

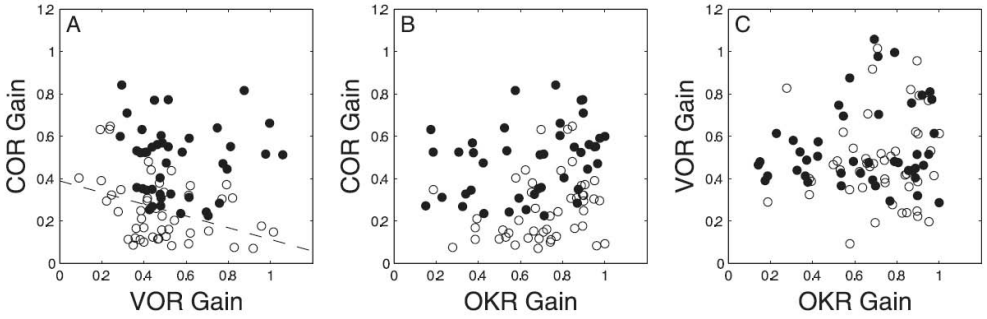


Figure 5.2 Correlations between the reflex gains (A-C).
Different symbols indicate the whiplash patients (closed circles,•) and controls (open circles, ○). In A the dotted line is a orthogonal fit through the data of the healthy subjects (slope = -0.4581). In the remaining data no significant correlation could be found, therefore no fitting line is shown.

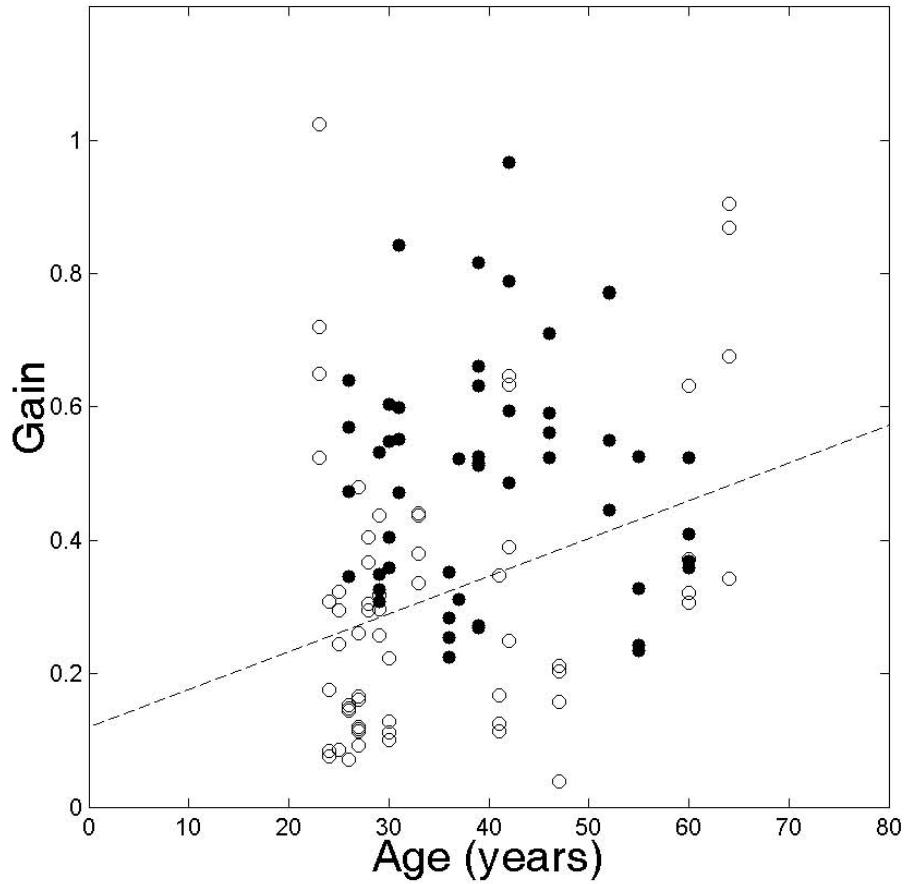


Figure 5.3 Correlation between the COR gain and age.

Different symbols indicate the whiplash patients (closed circles,•) and controls (open circles, ○). The dotted line is fitted trough the data of the healthy subjects by means of linear regression (slope = 0.0057 yr^{-1})

CHAPTER 6

Discussion

A major problem in the diagnosis of whiplash associated disorder (WAD) is the large variety in signs and symptoms. There are no objective test results to help in the diagnosis of WAD. As many of the WAD related symptoms are either vestibular (dizziness) or oculomotor (reading problems) related, and because motor responses are objectively quantifiable, we set out to find an objective measurement for WAD in the compensatory eye movement domain.

In the otolaryngology practice ENG testing (electronystagmography) is frequently used in the diagnosis of patients with complaints of vertigo. ENG tests mostly two of the eye stabilization reflexes, i.e. the vestibulo-ocular reflex (VOR) and the optokinetic reflex (OKR).

As the third eye stabilization reflex, the cervico-ocular reflex (COR) relies on input from the cervical proprioceptive system (Hikosaka & Maeda, 1973), and since the primary affected area in whiplash is the neck, we focused on this reflex in our investigations, and on the relation between the COR and the other eye stabilization reflexes. A problem in COR measurements is the small amplitude of the reflex and the large intra individual difference in gains. Therefore it is important to identify factors influencing COR gain and to use sensitive and state of the art measuring equipment.

COR CHARACTERISTICS

Our data confirm earlier findings that the COR is most responsive at low stimulus intensity. We were also able to confirm earlier findings by Mergner et al. (1998), that the COR seems to be a peak velocity dependent system rather than a frequency dependent system.

COR AND AGE

In chapter 2 we report the rise of COR gain in age groups over 60 years. This can be explained by two different theories. Firstly, VOR decreases with age (Mulch & Petermann, 1979; Aust, 1991; Paige, 1994), while COR is reported to compensate for a decrease in VOR gain (Bronstein & Hood, 1986; Huygen et al. 1991; Bronstein et al. 1995) and thus is enhanced in aging individuals.

Secondly, neck mobility decreases with age, and possibly proprioceptive signals from the neck decline. This could be the basis for an up regulation of COR gain with age.

SYNERGY BETWEEN OCULAR STABILIZATION REFLEXES IN HEALTHY SUBJECTS

In our synergy experiments on healthy subjects we found that, within the age range measured, both VOR and COR correlate with age. The VOR decreases while the COR increases. These findings confirm the results on the relation between VOR gain and age as reported in the literature (Mulch & Petermann, 1979; Aust, 1991; Paige, 1994) and they confirm our earlier experiments with another group of subjects.

In the same experiments we found a negative correlation between VOR and COR, meaning that when the VOR gain is relatively high, the COR gain is relatively low and vice versa. It therefore seems that there is a synergistic function of the COR and the VOR and that the COR can compensate for loss of vestibular function. This confirms the results observed in labyrinthine defective patients (Bronstein & Hood, 1986; Huygen et al. 1991). It is also in line with the case report that demonstrated a patient with a temporary bilateral labyrinthine function loss where COR gain increased to 0.51 and dropped again to 0.15 after labyrinthine function recovery (Bronstein et al. 1995). Even though the reflexes do not function optimally at the same frequencies (the COR is a low velocity reflex, the VOR a high velocity reflex), this theory can hold, because even at low velocities the VOR often has a higher gain than the COR. Because of the low velocity range of the COR, this compensation will not influence performance at the high frequencies where the VOR is normally optimal.

ADAPTATION OF COR

By inducing a mismatch between visual stimulation and cervical proprioception in a similar fashion as VOR adaptation, we found a small but significant difference in COR adaptation change between the suppression and the enhancement conditions (chapter 3).

We only found a small difference, probably because we had a short adaptation phase of 10 minutes. For the VOR, the optimal adaptation period is about one hour (Zee, 1989; Koizuka et al. 2000; Shelhamer et al. 2002; Watanabe et al. 2003), so a larger adaptation difference might be possible if the adaptation period is lengthened. Unfortunately we could not confirm this hypothesis as all subjects complained of pain in the neck after a period of more then 20 minutes of continuous trunk-to-head rotation and the results were highly variable. Probably increased cervical stiffness and pain influence the results.

No linearity was found between the magnitude of the mismatch between visual stimulus and cervical stimulus in the adaptation phase and the induced gain change. This can be explained by a slower adaptation to larger mismatches, because a larger change has to be made. This seems to be in agreement with the VOR adaptation data of Shelhamer et al. (1994) and with Robinson et al. (2003), found a similar result in the monkey.

Under physiological circumstances, the COR can be regarded as a functional reflex of which the output is actively controlled because it adjusts rapidly to movement of the retinal image.
When we look at the synergy between the stabilization reflexes (Kelders et al. 2003) in this light, it seems that under natural conditions VOR, OKR and COR work together to stabilize the retinal image. When one of the eye stabilization reflexes changes due to trauma or aging (Paige, 1994), the other reflexes can compensate through mechanisms like COR and VOR adaptation.

COR IN THE WHIPLASH PATIENT

From chapter 4 it can be concluded that the gain of the COR of WAD patients is increased in all of the measured stimulus peak velocities, a correlation that has never been established before (Holtmann et al. 1993; Fischer et al. 1995). In order to compare the COR of WAD patients to healthy controls it is essential to match those groups for age, because COR gain strongly depends on age as described in chapter 2 (Kelders et al. 2003).
An explanation for the increase in COR gains in elderly persons, besides the compensation for age related VOR decrease is a relative increase in cervical stiffness that supposedly alters their proprioception and thus their COR to avoid pain in the end range of motion of the neck. This could explain the COR increase in whiplash patients because they all had problems in the end range of their neck motion, as measured with the CROM device (see chapter 2, materials and methods, cervical stimulation).
Another explanation for the COR gain increase are the hypo caloric responses (i.e. a less than normal reaction on caloric stimulation of the vestibular end organs with hot and cold water in the external ear canal) in WAD patients that are sometimes found in the literature (Chester, 1991; Claussen and Claussen, 1995; Vibert and Hausler, 2003). The increased COR would then function as a compensatory mechanism for the decrease in VOR functionality. We could not confirm this hypothesis (see chapter 5).

SYNERGY BETWEEN OCULAR STABILIZATION REFLEXES IN WHIPLASH PATIENTS

In the group of whiplash injury patients that we describe in chapter 5 the COR is significantly increased compared to healthy age matched controls, just like in a different group in chapter 4. We did not find an effect of old age on the magnitude of the COR as in the healthy subjects, described in chapter 2. This implies that the whiplash injury cancels out this age related effect. In the patient group there was no synergy between VOR and COR as we found in the healthy controls from both chapter 2 and 5. Just like in chapter 2 there is no synergy between the other eye stabilization reflexes (VOR and OKR, and COR and OKR,

respectively), neither in the patient group, nor in the control group. The increase in COR gain in our patient group could be the result of a decreased VOR gain, just like in the aging person or the labyrinthine defective patient (Bronstein & Hood, 1986; Huygen et al. 1991; Heimbrand et al. 1996). An alternative explanation is that the relation is vice versa, i.e. that the increased COR induces a decline in VOR gain. However, we found that the COR gain in WAD patients was increased without either a decreased VOR gain or an increase in VOR gain as found by Fisher et al. (1995), which seems to counter both theories.

Three possible hypotheses can explain this lack of synergy in our whiplash injury patient group. Firstly, a decrease in neck mobility could result in an altered neck proprioception, which leads to an increase in COR without an effect on the VOR pathway. An alternative explanation is that perhaps VOR adaptation requires sufficient head motion to get enough VOR input. When neck motion is impaired there could be too little input to induce a negative adaptation in VOR gain. The VOR responds best at high velocities (Tabak et al. 1997), while the COR functions best at low peak velocities. This provides a possible explanation for the lack of VOR gain decrease. A third possible explanation for the lack of change in VOR gain in whiplash injury patients is that VOR plasticity is affected because of micro trauma in the VOR pathway, e.g. in the flocculonodular area of the cerebellum.

CONCLUSIONS AND SUGGESTIONS FOR FUTURE RESEARCH

We can conclude that COR measurements are very sensitive to detect cervical injury, but it remains to be elucidated to what extent this test is specific for WAD syndrome. Other diseases such as cervical arthrosis may show similar aberrations. Further research is needed to determine to what extent this objective test may be used to establish the diagnosis and prognosis of WAD patients in specific, or to evaluate their therapy.

Also the lack of a golden standard for the diagnosis of whiplash makes it hard to validate an instrument such as the cervico-ocular reflex as a diagnostic tool. Ideally a sensitivity and specificity should be calculated, but unfortunately to date that seems to hold no clinical relevance due to the small amount of whiplash patients measured and the absence of a golden standard.

Therefore in the future it would be wise to study more patients with a whiplash trauma. It would also be recommendable to study patients with different causes of cervical complaints like cervical arthrosis and cervical myalgia. This way it might be possible to distinguish these groups from the whiplash injury group by their specific COR values.

Concerning patient symptoms, dizziness is a well known complaint among WAD patients. In the past experiments have been conducted where local anaesthesia in the neck of humans and transsection of muscles in the neck of animals produced symptoms of dizziness (Brandt

& Bronstein, 2001). In future experiments one could try to differentiate WAD patients with and without complaints of dizziness based on their COR specifics.

In the near future COR and VOR adaptation tests will be performed in both healthy controls and whiplash injury patients to see whether whiplash patients really do have a deficit in VOR adaptation, which would make a lesion in the VOR pathway more likely, as hypothesized in the discussion on chapter 5.

If measurement of the cervico-ocular reflex can be established as an objective method to diagnose WAD patients, the various treatments for WAD could be evaluated quantitatively and compared by doing regular follow up of COR measurements before the treatment commences and as it proceeds. It would be clinically relevant to try to link COR gain values to patient symptoms, e.g. pain scores and dizziness.

It would be interesting to try to correlate a measurement of COR gain in the (sub) acute phase to the course of the complaints. Maybe it is possible to find a cut-off point that predicts which patients that suffered a whiplash injury develop a whiplash associated disorder (WAD) and which patients will be symptom free after a certain amount of time. Again, for this large numbers of patients are needed to participate.

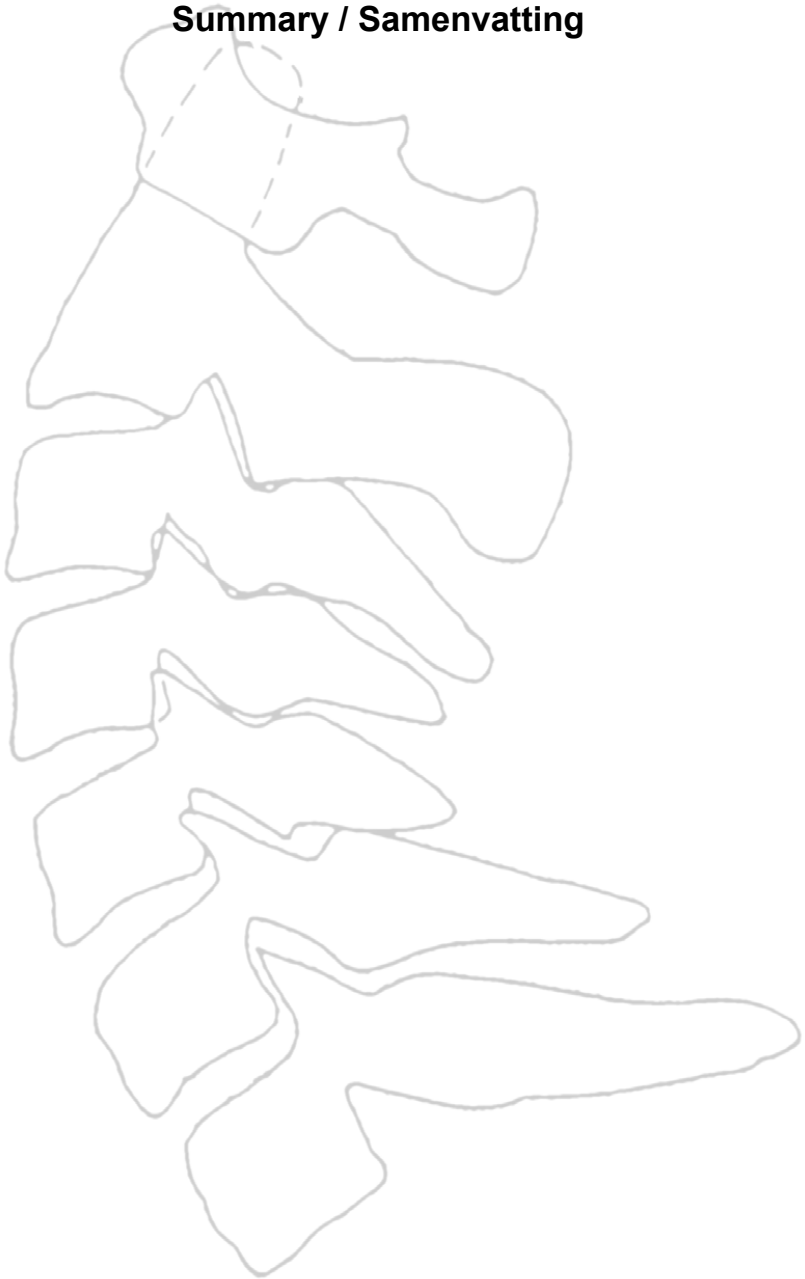
REFERENCES

- AUST G (1991): [The effect of age on vestibulo-ocular reactions]. Der Einfluss des Lebensalters auf vestibulo-okulare Reaktionen. Laryngorhinootologie 70, 132-137.
- BRANDT T & BRONSTEIN AM (2001): Cervical vertigo. J Neurol Neurosurg Psychiatry 71, 8-12.
- BRONSTEIN AM & HOOD JD (1986): The cervico-ocular reflex in normal subjects and patients with absent vestibular function. Brain Res 373, 399-408.
- BRONSTEIN AM, MORLAND AB, RUDDOCK KH & GRESTY MA (1995): Recovery from bilateral vestibular failure: implications for visual and cervico-ocular function. Acta Otolaryngol Suppl 520 Pt 2, 405-407.
- FISCHER AJEM, HUYGEN PLM, FOLGERING, HT, VERHAGEN WIM & THEUNISSEN EJJM (1995): Vestibular hyperreactivity and hyperventilation after whiplash injury. J Neurol Sci 132, 35-43.
- HEIMBRAND S, BRONSTEIN AM, GRESTY MA & FALDON ME (1996): Optically induced plasticity of the cervico-ocular reflex in patients with bilateral absence of vestibular function. Exp Brain Res 112, 372-380.
- HIKOSAKA O & MAEDA M (1973): Cervical effects on abducens motoneurons and their interaction with vestibulo-ocular reflex. Exp Brain Res 18, 512-530.
- HUYGEN PLM, VERHAGEN WIM & NICOLASEN MG (1991): Cervico-ocular reflex enhancement in labyrinthine-defective and normal subjects. Exp Brain Res 87, 457-464.
- KELDERS WPA, KLEINRENSINK GJ, VAN DER GEEST JN, FEENSTRA L, DE ZEEUW CI & FRENS MA (2003): Compensatory increase of the cervico-ocular reflex with age in healthy humans. J Physiol 553, 311-317.
- KOIZUKA I, KATSUMI N, HATTORI K, OKADA T & KATO I (2000): Effect of adaptive plasticity of linear vestibulo-ocular reflex upon angular vestibulo-ocular reflex. Auris Nasus Larynx 27, 89-93.
- MERGNER T, SCHWEIGART G, BOTTI F & LEHMANN A (1998): Eye movements evoked by proprioceptive stimulation along the body axis in humans. Exp Brain Res 120, 450-460.
- MULCH G & PETERMANN W (1979): Influence of age on results of vestibular function tests. Review of literature and presentation of caloric test results. Ann Otol Rhinol Laryngol Suppl 88, 1-17.
- PAIGE GD (1994): Senescence of human visual-vestibular interactions: smooth pursuit, optokinetic, and vestibular control of eye movements with aging. Exp Brain Res 98, 355-372.

- ROBINSON FR, NOTO CT & BEVANS SE (2003): Effect of visual error size on saccade adaptation in monkey. J Neurophysiol 90, 1235-1244.
- SHELHAMER M, PENG GC, RAMAT S & PATEL V (2002): Context-specific adaptation of the gain of the oculomotor response to lateral translation using roll and pitch head tilts as contexts. Exp Brain Res 146, 388-393.
- SHELHAMER M, TILIKET C, ROBERTS D, KRAMER PD & ZEE DS (1994): Short-term vestibulo-ocular reflex adaptation in humans. II. Error signals. Exp Brain Res 100, 328-336.
- TABAK S, COLLEWIJN H, BOUMANS LJJM & VAN DER STEEN J (1997): Gain and delay of human vestibulo-ocular reflexes to oscillation and steps of the head by a reactive torque helmet. I. Normal subjects. Acta Otolaryngol 117, 785-795.
- WATANABE S, HATTORI K & KOIZUKA I (2003): Flexibility of vestibulo-ocular reflex adaptation to modified visual input in human. Auris Nasus Larynx 30 Suppl, S29-34.
- ZEE DS (1989): Adaptation and the ocular motor system. Bull Soc Belge Ophtalmol 237, 191-207.

CHAPTER 7

Summary / Samenvatting



SUMMARY

The cervico-ocular reflex (COR) is an ocular stabilization reflex that is elicited by rotation of the neck. It works in conjunction with the vestibulo-ocular reflex (VOR) and the optokinetic reflex (OKR) in order to prevent visual slip over the retina due to self motion.

The gains of the VOR and OKR are known to decrease with age. In chapter 2 we have investigated whether the COR shows a compensatory increase and whether a synergy exists between the COR and the other ocular stabilization reflexes. We describe the results of a study with 35 healthy subjects of varying age (20-86 years). The subjects, seated in a specially developed chair, were rotated in the dark in a trunk-to-head manner (the head fixed in spaced with the body passively rotated under it) at peak velocities between 2.1 and 12.6 º/s as a COR stimulus. Another 15 subjects were given COR, VOR and OKR stimuli at frequencies between 0.04 Hz and 0.1 Hz. Three subjects participated in both tests. Position of the eyes was recorded with an infrared recording technique.

We found that the COR gain increases with rising age and that there is a significant covariation between the gains of the VOR and COR, meaning that when VOR increases, COR decreases and vice versa. A nearly constant phase lag between the COR and the VOR of about 25º existed at all stimulus frequencies.

In chapter 3 we investigated whether the COR can be adapted by inducing a mismatch between vision and neck proprioception, in analogy to VOR adaptation. Thirteen healthy subjects were rotated in the dark in a trunk-to-head manner (the head fixed in space while the body passively rotated sinusoidally with a peak velocity of 1.25 °/s). Eye movements were recorded under various adaptive conditions. Analysis showed a small but significant reduction in COR gain in the suppression conditions. This means that the COR can be modified after only ten minutes of concurrent visual and cervical stimulation.

In chapter 4 we describe COR measurements in whiplash patients. To date there is no generally accepted test that allows an objective diagnosis of whiplash associated disorder (WAD). Because whiplash injury causes dysfunction of proprioception in the neck, we investigated the characteristics of the COR of presumptive WAD patients. Eight patients and eight age matched healthy controls were rotated at different stimulus peak velocities in the dark while their head was fixed in space. The gain values of the COR were significantly increased in the patient population compared to healthy subjects at a wide range of stimulus peak velocities with maximum difference at the lower peak velocities. Hence, although larger numbers of patients should be measured, the COR gain appears to be a parameter that may permit an objective diagnosis of WAD.

In chapter 5 we investigated whether the reported elevation of the COR in whiplash injury patients is accompanied by changes in VOR and / or OKR gains. Eye movements of thirteen

patients and eighteen age matched healthy controls were recorded. Analysis confirmed a significant increase in COR gain in whiplash patients. Meanwhile the VOR gain and OKR gain remained the same. No correlation was found between the gains of the reflexes in individual subjects. This is in contrast with earlier observations in elderly and labyrinthine defective subjects, who showed an increase in COR gain accompanied by a decrease in VOR gain. An impaired neck motion, altered proprioception of the neck or disorganization in the process of VOR plasticity could explain the lack of change in VOR gain.

We conclude that the quickly adaptable and age dependent COR is a sensitive instrument to differentiate whiplash injury patients from healthy controls. Even though, further measurements with larger numbers of both patients and controls have to be conducted to establish whether more forms of cervical pain produce a rise in COR gain and to try and establish a cut-off point for WAD patients.

SAMENVATTING

De Cervico-Oculaire Reflex (COR) is een oogstabilisatie reflex die wordt opgewekt door draaien van de nek. De reflex werkt samen met de vestibulo-oculaire reflex (VOR) en de optokinetische reflex (OKR) om het optreden van “visual slip”, het verschuiven van het beeld op het netvlies door beweging van het hoofd, te voorkomen.

Het is bekend dat de gains van de VOR en de OKR kleiner worden naarmate de leeftijd vordert. In hoofdstuk 2 hebben we het onderzoek beschreven naar de compensatoire verhoging van de COR bij stijgende leeftijden en naar de samenwerking (synergie) tussen de COR en de andere oogstabilisatie reflexen. We beschrijven de resultaten van een studie met 35 gezonde proefpersonen met verschillende leeftijden, variërend van 20 tot 86 jaar. De proefpersonen werden zittend op een speciaal ontworpen draaistoel rondgedraaid op een zogenaamde “trunk-to-head” manier (het hoofd staat vast in de ruimte terwijl het lichaam er over een zekere hoek onder doordraait) met pieksnelheden van 2,1 tot 12,6 º/s. Nog eens 15 proefpersonen kregen COR, VOR en OKR stimuli aangeboden met frequenties van 0,04 tot 0,1 Hz. Drie proefpersonen namen deel aan beide proeven. Oogposities werden geregistreerd met een infrarode registratie techniek.

We vonden dat de COR-gain toeneemt met de leeftijd en dat er een significante covariatie is tussen de gains van de VOR en de COR. Dit betekent dat wanneer de VOR toeneemt, de COR afneemt, en andersom. Er bestond een bijna constante fasevertraging (“phase lag”) tussen de COR en de VOR van 25 graden op alle stimulusfrequenties.

In hoofdstuk 3 hebben we het onderzoek beschreven naar de COR adaptatie als gevolg van een wanverhouding tussen het beeld en de nek proprioceptie die werd aangeboden op een zelfde manier als bij de VOR adaptatie. Dertien gezonde proefpersonen werden in het donker rondgedraaid op een “trunk-to-head” manier met een pieksnelheid van 1,25 graden per seconde. Oogbewegingen werden geregistreerd onder verschillende adaptatie omstandigheden. Analyse van de resultaten liet zien dat er een kleine maar significante daling van de gain was in de suppressie omstandigheden. Dit betekent dat de COR al na tien minuten gezamenlijke visuele en cervicale stimulatie geadapteerd kan worden.

In hoofdstuk 4 beschrijven we de COR metingen bij whiplashpatiënten. Tot op de dag van vandaag is er geen algemeen geaccepteerde test die een objectieve diagnose van whiplash associated disorder (WAD) mogelijk maakt. Omdat een whiplash letsel een dysfunctie van de proprioceptie in de nek kan veroorzaken hebben we de eigenschappen van de COR gemeten van patiënten waarvan werd aangenomen dat ze een WAD hadden. Hiertoe werden acht patiënten en acht in leeftijd gelijke gezonde proefpersonen op verschillende stimulus pieksnelheden in het donker rondgedraaid terwijl hun hoofd gefixeerd was. De gain-waarden van de COR waren significant verhoogd in de patiëntenpopulatie in vergelijking met

de gezonde proefpersonen bij een breed spectrum van stimulus pieksnelheden. Het grootste verschil werd op de laagste pieksnelheden gevonden. De COR lijkt daarom een parameter te zijn die een objectieve diagnose van whiplash mogelijk maakt, hoewel er nog grotere aantallen patiënten gemeten zouden moeten worden om dat zeker te stellen.

In hoofdstuk 5 onderzochten we of de verhoogde COR-gains die we eerder na een whiplash trauma vonden ook gepaard gaat met verandering in gains van de VOR of OKR. Hiertoe registreerden we de oogbewegingen van dertien patiënten en achttien voor de leeftijd gelijke gezonde controlepersonen. Analyse van de resultaten bevestigde de significante verhoging van de COR gain, zoals in eerdere experimenten ook werd gevonden. De gains van de VOR en OKR veranderden echter niet. Er werd geen correlatie gevonden tussen de reflexen in individuele patiënten, dit in tegenstelling tot eerdere observaties bij ouderen en patiënten met afwezige labyrintfunctie, die een verhoging van de COR gain lieten zien in combinatie met een afname van de VOR gain.

We concluderen dat de snel te adapteren en leeftijdsafhankelijke COR een gevoelig instrument is om whiplashpatiënten te onderscheiden van gezonde controlepersonen. Toch zullen er meer experimenten met grotere aantallen patiënten en controlepersonen verricht meten worden om vast te stellen of meer vormen van cervicale pijn een verhoging van de COR gain kunnen veroorzaken en om een afkappunt voor WAD vast te kunnen stellen.

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CURRICULUM VITAE

Willem Kelders werd op 18 maart 1975 geboren in het Brabantse Schijndel. Na de lagere school ging hij naar het R.K. Gymnasium “Beekvliet” te Sint-Michielsgestel. Op 18-jarige leeftijd begon hij met de studie Geneeskunde aan de Rijksuniversiteit Limburg, de latere Universiteit Maastricht. Tijdens zijn studie was hij als “kidney-racer” werkzaam bij de afdeling Algemene Heelkunde van het academisch ziekenhuis Maastricht, waar hij “non-heart beating” donornieren begeleidde tussen explantatie in Maastricht en transplantatie in het ontvangende ziekenhuis. Tijdens zijn co-schappen assisteerde hij Dr. M.B. Oude Ophuis bij zijn promotieonderzoek naar Glutathion-S-transferase bij plaveiselcelcarcinomen in het hoofd-hals gebied.

Na het behalen van het artsendiploma werkte hij korte tijd als poortarts en AGNIO heelkunde in het Atrium Medisch Centrum te Kerkrade, waarna hij verhuisde naar Amsterdam om als AGNIO KNO-heelkunde in het Antoni van Leeuwenhoek ziekenhuis te werken.

Vanaf augustus 2000 werkt hij op de afdeling KNO-heelkunde van het Erasmus MC, eerst als AGNIO en later als AGIKO onder Prof.dr. L. Feenstra. Van maart 2001 tot april 2003 werkte hij aan zijn promotieonderzoek op de afdeling Neurowetenschappen onder begeleiding van Prof.dr. C.I. de Zeeuw, Prof.dr. M.A. Frens, Prof.dr. L. Feenstra en Dr. G.J. Kleinrensink. In april 2003 werd begonnen met de opleiding tot KNO-arts, eerst onder leiding van Prof.dr. L. Feenstra, later onder leiding van Prof.dr. R.J. Baatenburg de Jong. Hij hoopt de opleiding te voltooien per 1 november 2007.

De auteur woont samen met Gilles van Baar.

LIST OF PUBLICATIONS

1. DAEMEN JHC, OOMEN APA, KELDERS WPA, KOOTSTRA G (1997):
   The Potential Pool of Non-Heart-Beating Donor Kidneys.
   Clinical Transplantation 11: 149-154

2. WALTHER G, KELDERS WPA, COENEN NH, DUPREEZ N, DE GROOT M (1997)
   Open Window Thoracostomy for Thoracic Empyema.
   Chest Southern Africa '97
   Windhoek, Namibia, Aug 31–Sept 4, 1997

3. KELDERS WPA, PEETERS F (1999):
   Een protocol voor het gebruik van antidepressiva? Bezint eer ge begint!
   Nederlands Tijdschrift voor Geneeskunde 143 (13): 695

4. KELDERS WPA, OUDE OPHUIS MB, ROELOFS HMJ, PETERS WHM, MANNI JJ (2002):
   The association between Glutathione S-transferase P1-genotype and plasma level in patients with head and neck cancer. Laryngoscope 112: 462-466

5. KELDERS WPA, KLEINRENSINK GJ, VAN DER GEEST JN, FEENSTRA L, DE ZEEUW CI, FRENS MA (2003): The Compensatory increase of the cervico-ocular reflex with age in healthy humans. The Journal of Physiology 553-1: 311-317

6. KELDERS WPA, GOVAERE F, BOUMANS LJJM (2004): Acute vestibulaire uitval: een foto waard? Nederlands tijdschrift voor Keel-, Neus- Oorheelkunde 10 (1): 37-40

7. RIJKAART DC, VAN DER GEEST JN, KELDERS WPA, DE ZEEUW CI, FRENS MA (2004): Short-term adaptation of the cervico-ocular reflex. Exp Brain Res 156: 124-128

8. KELDERS WPA, BOUMANS LJJM, FEENSTRA L (2004): De huisarts en KNO-aandoeningen: Duizeligheid. Modern Medicine 28 (1): 6-9

9. KELDERS WPA, KLEINRENSINK GJ, VAN DER GEEST JN, SCHIPPER IB, FEENSTRA L, DE ZEEUW CI, FRENS MA (2005): The cervico-ocular reflex is increased in whiplash injury patients. J Neurotrauma 22: 133-137

10. MONTFOORT I, KELDERS WPA, VAN DER GEEST JN, SCHIPPER IB, FEENSTRA L, DE ZEEUW CI, FRENS MA (2006): Interaction between ocular stabilization reflexes in whiplash injury patients. Invest Ophthalmol Vis Sci. 47 (7): 2881-2884.

LIST OF ABBREVIATIONS

ANOVA	analysis of variance
BERA	brainstem evoked response audiometry
COR	cervico-ocular reflex
CROM	cervical range of motion
CT	computed tomography
EEG	electro encephalography
EMG	electro myography
ENG	electro nystagmography
Gain	response magnitude divided by stimulus magnitude
Gpost	gain after adaptation
Gpre	gain before adaptation
Hz	Hertz
KNO	keel-, neus en oor
KS	Kolmogorov-Smirnov
LD	labyrinthine defective
LSD	least square difference
MRI	magnetic resonance imaging
OKR	optokinetic reflex
QTF	Quebec task force
SEM	standard error of the mean
SMI	SensoMotoric Instruments GmbH
VOR	vestibulo-ocular reflex
WAD	whiplash associated disorder