Oculomotor disorders in neck pain patients

Britta Castelijns Ischebeck

Oculomotor disorders in neck pain patients

Britta Kristina Castelijns Ischebeck

Acknowledgements: The work presented in this thesis was performed in the Department of Neuroscience of Erasmus MC in Rotterdam, The Netherlands and in the Spine& Joint Centre, Rotterdam, The Netherlands.

Cover: Sjoerd Cloos

Photo: Rob van Dalen

ISBN: 978-94-6332-439-7

Oculomotor Disorders In Neck Pain Patients

Oculomotorische functiestoornissen bij nekpatiënten

Proefschrift

ter verkrijging van de graad van doctor aan de

Erasmus Universiteit Rotterdam

op gezag van de

rector magnificus

Prof. dr. R.C.M.E. Engels

en volgens het besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op

16 januari 2019 om 9.30 uur

door

Britta Kristina Castelijns Ischebeck

geboren te Wuppertal (Duitsland)

Erasmus University Rotterdam

Promotiecommissie:

Promotor:	Prof.dr. M.A. Frens
	Prof.dr. G-J Kleinrensink
Overige leden:	Dr. J.J. van der Dobbelsteen
	Prof.dr. G.M. Ribbers
	Prof.dr. J. van der Steen
Copromotoren:	Dr. J.N. van der Geest
	Dr. J.P. van Wingerden
Paranimfen:	Karina Bölger
	Jurryt de Vries, MSc

In Gedenken an meinen Vater Ernst Friedrich Ischebeck

Inhoud

Chapter 1:

General introduction

INTRODUCTION NECK PAIN

In the western world the prevalence of people with chronic neck pain is increasing and accompanied by growing costs for the health care systems [1–6]. In the Netherlands the prevalence of chronic neck pain was estimated to be 14.3% (2009) [7]. Despite all efforts, recovery rates were not substantially improved over the last decades. Half of the patients with traumatic neck pain do not recover within the first three months. This has a significant impact on their lives [8–10]. While some individuals recover quickly and fully, others experience on-going pain and disability [11]. It is not known yet why the process of recovery differs so much between patients.

The onset of neck pain can be either traumatic or non-traumatic [1,3]. However, the distinction between these two types is rather arbitrary, as we do not know which impact leads to eventual trauma and causes damage [12,13]. Moreover, the impact of the trauma does not by definition explain the diverse symptoms of the patient [8,14] and we do not know whether the characteristics of the course of recovery are different between the two types of origin. Also other factors are predisposing factors for the prognosis [11]. Some patients suffer from severe symptoms after a mild trauma while others resume their normal lives after a high impact trauma [15]. We also do not know exactly what can be the long-term consequences of a mild trauma of the neck [16].

WHIPLASH ASSOCIATED DISORDERS (WAD)

One onset-based category is summarized as ‘Whiplash Associated Disorders’. The term whiplash trauma is defined as ‘an acceleration- deceleration mechanism of energy transfer to the neck that results from rear-end or side-impact motor vehicle collisions, but can also result from diving or other mishaps. The impact results in bony or soft-tissue injuries (whiplash injury), which in turn may lead to a variety of clinical manifestations called whiplash-associated disorders (WAD)’[17]. The annual incidence of Whiplash injury in the Netherlands is 30.000 to 50.000 [18]. No up-to-date Dutch data on the prevalence of specific symptoms after whiplash are available [19].

A typical whiplash trauma results from a rear end collision. To understand the biomechanical impact, knowledge of the motion pattern of the spine is essential [13]. During a rear end collision three phases are distinguished. S-curvature resulting from the head lagging behind the thorax (i.e., retraction), C-curvature characterized by head-neck extension, and rebound of the head from the head restraint [12]. In the initial phase, a nonphysiologic curvature characterized by flexion in upper cervical segments and extension in lower cervical segments occurs. In the middle phase, the spine is fully extended [12,13,20,21].

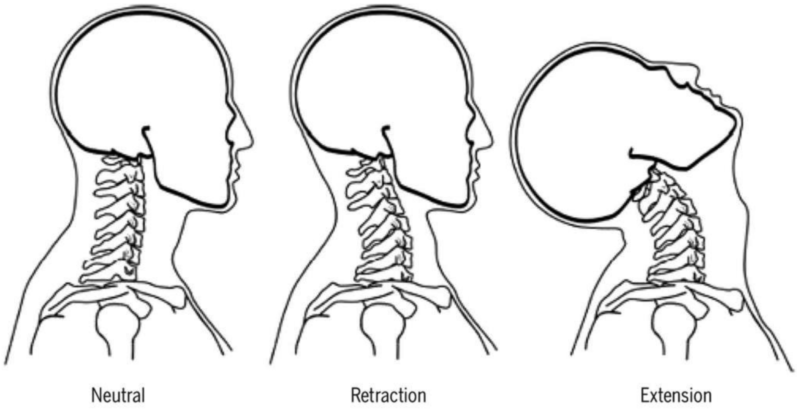

Figure 1: Initial phases of head-neck response to automotive rear impacts. The rear impact initiates with the occupant in a neutral upright position. As the thorax is accelerated anteriorly, the head remains stationary during the retraction phase, producing an S-shaped cervical spine curvature. Eventually, loads from the thorax are transferred up the cervical spine and the head-neck complex transitions into extension, with the cervical spine in an overall C-shaped extension curvature. The head eventually rebounds forward (not shown), and the cervical spine then transitions into flexion.[12]

The impact of a collision depends on different factors, such as speed, direction, position of body and head and awareness of the crash [13]. All of this, besides factors related to the car: bumper stiffness, stiffness of the backrest, position of the headrest etc.

Many injuries occur at the same time and cause a variety of pathogenic mechanisms [5,13,22,23]. The zygapophysial joints of C2-C3, C5-6 and/or C6-7 are most commonly affected [16]. The trauma results in stretching and impingement of the articular capsule, including the synovial fold and consequently in persistent sensitivity [24]. It can lead to a constant source of nociception and biomechanical consequences like instability and altered loading patterns and furthermore to nerve tissue impingement [23,25]. The clinical presentation of such a proprioceptive deficit consists of altered muscle response patterns, decreased (re)position sense and decreased range of motion [16,26–34]. In patients, the amount of primary and secondary motion is decreased [23,31,32,35–37]. Also, the quality of motion differs between patients and healthy individuals. Feipel et al. were the first to report differences in motion curves of the cervical spine in chronic neck pain patients in all primary motion directions (flexion/extension, rotation and lateral bending) [38]. The movement curves of the patients were less harmonic, with hesitations in movement. Later on, irregularities in movement were also found in other parameters, such as peak velocity, 'Jerk index', helical axis position and muscle recruitment [26,31,32,39–42]. With regard to the 'Jerk index', range of motion and joint position error, Sjölander et al. do report that patients with non-traumatic neck pain have the jerkiest movements and patients with WAD have the highest repositioning error and a higher variability in range of motion [32].

During trauma the muscles are exposed to an unphysiological level of stretch (muscle fascicle strain is 7% in the m.sternocleidomastoid and even 21% in the m.semispinalis capitis) [43]. However, lesions of the muscles can heal within hours and do not explain persistent pain and changed afferent information[5].

Ligament afferents have reflex projections to the gamma-motoneurons of the muscles and can possibly influence the sensitivity of muscle spindles during slow movements [24]. In animal models it is shown that stimulation of spinal ligaments initiates spinal muscle activity. Conceivably, the injured capsule sends abnormal signals to the spinal muscles to stiffen the cervical spine [5].

Identification of factors associated with poor recovery is accumulating the last years. However, understanding recovery pathways for individuals following whiplash injury continues to be a challenge [11,12]. Half of the patients with acute WAD develop chronic complaints, which can be physical and/or cognitive in nature [44]. The most commonly reported symptoms in WAD patients are neck pain, headache, decreased cervical range of motion, dizziness, visual complaints and cognitive dysfunction [5,19,33,34,45–50].

DIAGNOSTICS OF NECK PAIN PATIENTS

For many years, the diagnosis of neck pain patients focused on the exclusion of serious pathology by radiology and on the assessment of the psychosocial impact on daily life. Recently there has been a growing interest for disturbances of the sensorimotor system [22,27,36,51,52]. The term sensorimotor in this case describes the afferent, efferent and central connections and integrative mechanisms necessary for the maintenance of postural control and (cervical) spinal stability (figure 2) [51].

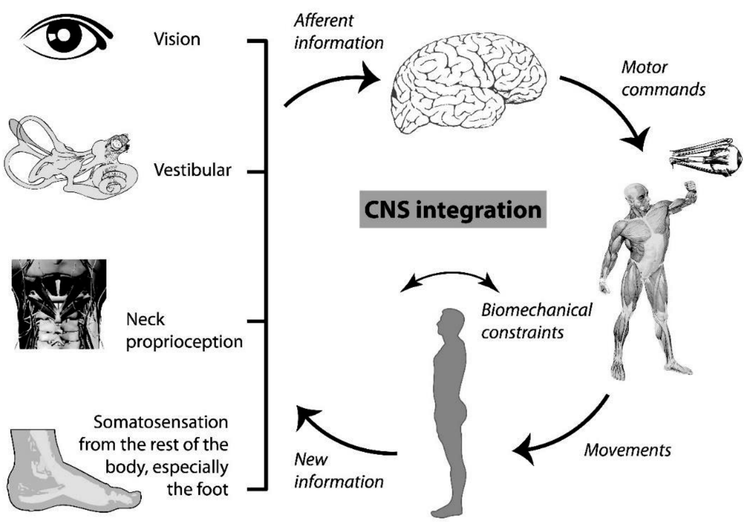

Figure 2: Sensorimotor function [51]

The clinical consequences of altered cervical proprioception are only partly known [34,51,53]. Although dizziness, unsteadiness, altered head control and visual disturbances are often mentioned, it is difficult to relate them to the variety of pathogenetic mechanisms [5,51,53]. Reason for this lack of recognition is that conventional testing methods (e.g. amount of pain or range of motion) in most instances cannot verify patients' subjective complaints [51,54].

Recently, several new tests for sensorimotor function were described [54–58]. Assessing sensorimotor impairment of the neck should involve: 1. proprioception, 2. postural stability and 3. oculomotor control.

Whereas the assessment and underlying concepts of proprioception and postural stability are well established, knowledge of oculomotor disorders in neck pain patients is insufficient right now. In the clinical practice, four different aspects of oculomotor control can be distinguished:

1. smooth pursuit eye movements
2. eye stabilization reflexes
3. gaze stability
4. head-eye coordination

The knowledge of the assessment and underlying concepts of these four aspects is limited. It is unknown why oculomotor disorders are present in neck pain patients, how the different aspects interact, and which complaints are caused by oculomotor disorders. This knowledge has to be improved to develop optimal assessment and therapy for neck pain patients. Currently, no specific clinical tests for neck pain patients with a structured guideline or normative values exist or are subject of discussion [29,53,59–64].

In this thesis we will mainly focus on eye stabilization reflexes.

Oculomotor control: Eye stabilization reflexes

Among physiotherapists knowledge of changes in eye stabilization reflexes, as part of the oculomotor system, is still minimal compared to knowledge of anatomical and biomechanical changes in patients[8].

Ocular stabilization reflexes guarantee the stabilization of vision even if the head is moving. Based on the sensory input, at least three eye stabilization reflexes can be distinguished: the optokinetic reflex (OKR), the vestibulo-ocular reflex (VOR) and the cervico-ocular reflex (COR). These three complementary reflexes receive input from different sensory systems and have distinct characteristics (for further information see table 1).

The OKR is mainly evoked by visual motion. The VOR receives input from the vestibulum, responding to movements of the head in space. The COR receives input from the mechanoreceptors, mainly the muscle spindles and joint sensors, of the upper cervical spine [65]. The COR responds to movements of the head relative to the trunk. Afferent information from the neck proprioceptors and the vestibulum is forwarded via the vestibular nuclei and further on to the flocculus in the cerebellar cortex. From the flocculus the efferent information is projected back to the vestibular nuclei and further to the oculomotor nuclei to control the extraocular muscles [66]. The central pathways of the VOR and the COR are the same, both reflexes converge to the vestibular nuclei [65].

Eye stabilization reflexes

The three eye stabilization reflexes can be described by their **gains** and **phases**.The **gain** is the magnitude of the eye movement in relation to the stimulus movement:

$$gain = \frac{velocity\ of\ the\ eye}{velocity\ of\ the\ stimulus}$$

The **phase** describes the delay of the eye movement after a stimulus (in degrees). A phase of 0 degrees means that the eye movement is exactly in phase with the stimulus. A phase lag of 180 degrees means that the eye movement is exactly in counter phase of the stimulus in case of a sinusoidal stimulation. Normally, in the three eye stabilization reflexes the phase lag is minimal (Kelders et al., 2003).

Reflex	Input	Output	Optimal stimulus range	Feedback system
COR	Proprioception of the neck (proprioceptive afferents of deep neck muscles and joint capsules of the upper cervical spine)	Eye movement in the same direction as the stimulus	Low velocities (in the order of 2 deg s^{-1}) [20]	Open loop reflex
VOR	Vestibular information (receptors in the semicircular canals and otolith organs)	Eye movement in the opposite direction of the stimulus	High frequencies	Open loop reflex
OKR	Visual motion	Eye movement in the same direction as the stimulus	Low to midrange velocities	Closed loop reflex

Table 1: Overview of thee eye stabilization reflexes

If these eye reflexes are not properly coordinated, the visual image is ‘slipping’ on the retina and the vision will be blurred during movement of the visual stimulus, the head, or the trunk [67–70]. Visual information processing will then be hampered and even, in some cases, impossible. It is not unlikely that impaired visual perception causes secondary effects such as difficulties concentrating, headache and difficulties reading and working on a computer. It is noteworthy that these effects are often reported by patients with (chronic) neck pain.

The levels of these three reflexes are subject to adaptation and ageing [68,71–74]. The VOR and OKR decrease and the COR increases with age [72,75]. In healthy humans, the VOR and the COR gain are inversely related: in people with a high VOR, the COR is low and vice versa [72]. Such a synergy between reflexes is important because under natural conditions all systems are involved in maintaining eye stabilization at the same time. This synergy is indicative for an optimizing adaptive process ensuring optimal visual information processing.

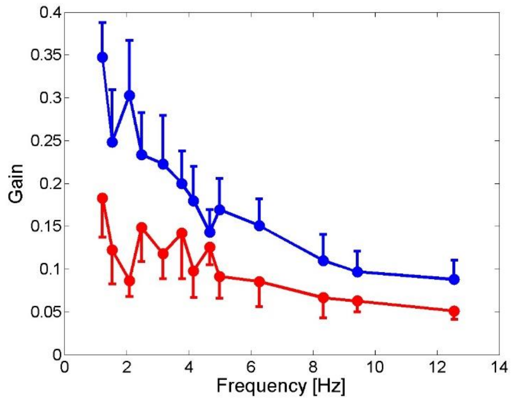

Figure 3: Gain of the COR (mean) in healthy controls (red line) and patients with WAD (blue line) [63]

However, the eye stabilization reflexes of patients with WAD differ [63,64]. The eye position traces of these patients show increased compensatory movements of the eyes, i.e. the COR, during passive rotation of the neck (figure 3). Moreover, COR levels increase without a compensating decrease of the VOR or OKR responses.

Outline of this thesis

The diagnostics of neck pain patients remains challenging. The last years, the knowledge of sensorimotor functioning of neck pain patients improved. However, we still do not understand why many patients report visual complaints and how we can integrate oculomotor disorders into neck pain diagnostics.

The general aim of this thesis is to gain knowledge of oculomotor disorders in (traumatic and non-traumatic) neck pain patients. This knowledge is highly necessary to improve the understanding of the complex entity of disorders in neck pain patients and to integrate visual complaints in the diagnostic process and therapy of these patients.

A more specific purpose is to make the therapeutic community more aware of the importance of central nervous system disorders, which become clear by eye reflex disturbances. This in its turn should contribute to a better understanding of the characteristics of the course of traumatic cervical spine lesions and hence to a better diagnosis and treatment of this group of patients so often misunderstood.

The first part of this thesis explores the existing evidence on oculomotor disorders in patients with Whiplash Associated Disorders and compares the different test methods **(chapter 2)**. In the second part it is investigated which neck pain patients have oculomotor disorders (**chapter 3-5**). In the third part of the study different aspects of oculomotor function are tested and artificially manipulated in a heterogeneous group of chronic neck pain patients and healthy controls **(chapter 6-9)**.

In the last part, a general discussion, including recommendations for further research and summary of our results described in this thesis are provided **(chapter 10 and 11)**.

We address the following research questions in this thesis:

1. *What is known about oculomotor problems in patients with Whiplash Associated Disorders?*

   Therefore, we present a comprehensive, systematic overview of the literature concerning altered eye movements in patients with WAD compared to healthy controls **(chapter 2)**.

2. *Are eye stabilization reflexes in a group of patients with long-lasting neck pain different to eye stabilization reflexes of healthy controls? Are the eye stabilization reflexes different in patients with comparable history, but different origin of complaints, i.e. traumatic versus non-traumatic?*

   The eye stabilization reflexes of chronic neck pain patients who apply for tertiary care rehabilitation are compared with healthy controls in a cross-sectional study. Furthermore, the patient group is divided into chronic traumatic, non-traumatic neck pain patients and patients with WAD. These groups are compared to clarify if the origin of complaints determines the alteration of eye reflexes **(chapter 3)**.

3. *Are eye stabilization reflexes altered in patients with nonspecific neck pain?*

   In a cross-sectional design the eye stabilization reflexes of a group of neck pain patients with less severe and shorter duration of complaints is compared to healthy controls **(chapter 4)**.

4. *What affects eye stabilization reflexes?*
   Possible relationships between patients' eye stabilization reflexes and their cervical motion profile (range of motion and joint position sense), personality traits (fear avoidance behavior, pain and stress, duration of symptoms), personal factors (age, gender, cultural background) and the complaints of the patient (level of disability, maximal duration of daily activities, fatigue and cognitive complaints) are explored in a cohort study **(chapter 5)**.

5. *Are eye stabilization reflexes and cervical joint position error as a parameter of cervical proprioception associated in patients with nonspecific neck pain?*

The association between eye stabilization reflexes and the cervical joint position error is studied with a cross-sectional design in a group of nonspecific neck pain patients **(chapter 6)**.

6. *What is the effect of neck torsion and target predictability on smooth pursuit eye movements and saccadic eye movements in healthy individuals?*
   Since in the clinical practice often the Smooth Pursuit Neck Torsion Test is used to assess oculomotor problems in neck pain patients, we explore the effect of different degrees of neck torsion and predictability on the test outcome in healthy individuals. Both smooth pursuit and saccadic eye movements are tested **(chapter 7)**.

7. *Does predictability and neck torsion influence smooth pursuit eye movements in patients with neck pain and healthy controls differently?*
   Smooth pursuit gains are measured during the applying of predictable and unpredictable moving stimuli in a heterogeneous group of patients with chronic neck pain and in healthy controls **(chapter 8)**.

8. *What is the effect of altered cervical input on the cervico-ocular reflex and the vestibulo-ocular reflex? Do the reflexes change gain in response to a temporary reduction of cervical proprioceptive output (hypokinesia), induced by passive immobilization of the neck? And do the reflexes change as result of temporary increased proprioceptive output (hyperkinesia)?*

   To study possible causes for altered eye stabilization reflexes in neck pain patients the influence of neck movement is tested. Temporary intensified versus minimized active neck movement is applied and the influence on eye stabilization reflexes is measured in healthy controls in a cross-over trial **(chapter 9)**.

References

1. Borghouts JA, Koes BW, Bouter LM. The clinical course and prognostic factors of non-specific neck pain: a systematic review. *Pain*. 1998;77(1):1-13. http://www.ncbi.nlm.nih.gov/pubmed/9755013.

2. Cecchi F, Molino-Lova R, Paperini A, et al. Predictors of short- and long-term outcome in patients with chronic non-specific neck pain undergoing an exercise-based rehabilitation program: a prospective cohort study with 1-year follow-up. *Intern Emerg Med*. 2011;6(5):413-421. doi:10.1007/s11739-010-0499-x.

3. Verhagen AP, Lewis M, Schellingerhout JM, et al. Do whiplash patients differ from other patients with non-specific neck pain regarding pain, function or prognosis? *Man Ther*. 2011;16(5):456-462. doi:10.1016/j.math.2011.02.009.

4. Hoving JL, de Vet HCW, Twisk JWR, et al. Prognostic factors for neck pain in general practice. *Pain*. 2004;110(3):639-645. doi:10.1016/j.pain.2004.05.002.

5. Curatolo M, Bogduk N, Ivancic PC, McLean S a, Siegmund GP, Winkelstein B a. The role of tissue damage in whiplash-associated disorders: discussion paper 1. *Spine (Phila Pa 1976)*. 2011;36(25 Suppl):S309-15. doi:10.1097/BRS.0b013e318238842a.

6. McLean SM, May S, Klaber-Moffett J, Sharp DM, Gardiner E. Risk factors for the onset of non-specific neck pain: a systematic review. *J Epidemiol Community Health*. 2010;64(7):565-572. doi:10.1136/jech.2009.090720.

7. Bala M, Bekkering T, Riemsma R, Harker J, Huyghen F, Kleijnen J. *Epidemiology of Chronic Pain in the Netherlands*. Rotterdam, The Netherlands; 2011. http://www.sip-platform.eu/tl_files/redakteur-bereich/National Initiatives/GRUNEN1112 Boek Chronic Pain.pdf.

8. Jull G. Whiplash Continues Its Challenge. *J Orthop Sport Phys Ther*. 2016;46(10):815-817. doi:10.2519/jospt.2016.0112.

9. Sterling M, Hendrikz J, Kenardy J. Compensation claim lodgement and health outcome developmental trajectories following whiplash injury: A prospective study. *Pain*. 2010;150(1):22-28. doi:10.1016/j.pain.2010.02.013.

10. Kamper SJ, Rebbeck TJ, Maher CG, McAuley JH, Sterling M. Course and prognostic factors of whiplash: a systematic review and meta-analysis. *Pain*. 2008;138(3):617-629. doi:10.1016/j.pain.2008.02.019.

11. Ritchie C, Sterling M. Recovery Pathways and Prognosis After Whiplash Injury. *J Orthop Sports Phys Ther*. 2016;46(10):1-30. doi:10.2519/jospt.2016.6918.

12. Stemper, Brian D., Corner BD. Whiplash-Associated Disorders: Occupant Kinematics and Neck Morphology. *J Orthop Sport Phys Ther*. 2016;46(10):834-844. doi:10.2519/jospt.2016.6846.

13. Ivancic PC. Mechanisms and Mitigation of Head and Spinal Injuries Due to Motor Vehicle Crashes. *J Orthop Sport Phys Ther*. 2016;46(10):826-833. doi:10.2519/jospt.2016.6716.

14. Li Q, Shen H, Li M. Magnetic resonance imaging signal changes of alar and transverse ligaments not correlated with whiplash-associated disorders. 2013:14-20. doi:10.1007/s00586-012-2490-x.

15. Kasch H, Stengaard-Pedersen K, Arendt-Nielsen L, Staehelin Jensen T. Headache, neck pain, and neck mobility after acute whiplash injury: a prospective study. *Spine (Phila Pa 1976)*. 2001;26(11):1246-1251. http://www.ncbi.nlm.nih.gov/pubmed/11389391.

16. Binder A. The diagnosis and treatment of nonspecific neck pain and whiplash. *Eura Medicophys*. 2007;43(1):79-89. http://www.ncbi.nlm.nih.gov/pubmed/17369782. Accessed September 11, 2013.

17. Spitzer WO, Skovron ML, Salmi LR, Cassidy JD, Duranceau J SS. Scientific monograph of the quebec task force on Whiplash-associated disorders: Redefining “whiplash” and its management. *Spine (Phila Pa 1976)*. 1995;20:1S-73S.

18. Consumer Safety Institute. Ongevallen en bewegen in Nederland. http://www.veiligheid.nl/onderzoek/ongevallen-en-bewegen-in-nederland-obin. Published 2009.

19. Bekkering GE, Hendriks HJM, Lanser K, Oostendorp RAB, G.G.M. PeetersV APV, Windt DAWM van der. KNGF-richtlijn Whiplash. *Ned Tijdschr voor Fysiother*. 2001;3(111):1-25. http://www.ohcbv.nl/hulppagina/documenten/kngfrichtlijn whiplash.pdf. Accessed September 11, 2013.

20. Grauer JN, Panjabi MM, Cholewicki J, Nibu K, Dvorak J. Whiplash produces an S-shaped curvature of the neck with hyperextension at lower levels. *Spine (Phila Pa 1976)*. 1997;22(21):2489-2494. doi:10.1097/00007632-199711010-00005.

21. Kaneoka K, Ono K, Inami S HK. Motion analysis of cervical vertebrae during whiplash loading. *Spine (Phila Pa 1976)*. 1999;24(8):763-770.

22. Falla D, Farina D. Neural and muscular factors associated with motor impairment in neck pain. *Curr Rheumatol Rep*. 2007;9(6):497-502. http://www.ncbi.nlm.nih.gov/pubmed/18177604.

23. Passatore M, Roatta S. Influence of sympathetic nervous system on sensorimotor function: whiplash associated disorders (WAD) as a model. *Eur J Appl Physiol*. 2006;98(5):423-449. doi:10.1007/s00421-006-0312-8.

24. Sjölander P, Johansson H, Djupsjöbacka M. Spinal and supraspinal effects of activity in ligament afferents. *J Electromyogr Kinesiol*. 2002;12(3):167-176. http://www.ncbi.nlm.nih.gov/pubmed/12086810.

25. Ivancic PC, Ito S, Tominaga Y, et al. Whiplash causes increased laxity of cervical capsular ligament. *Clin Biomech (Bristol, Avon)*. 2008;23(2):159-165. doi:10.1016/j.clinbiomech.2007.09.003.

26. Nederhand MJ, IJzerman MJ, Hermens HJ, Baten CT, Zilvold G. Cervical muscle dysfunction in the chronic whiplash associated disorder grade II (WAD-II). *Spine (Phila Pa 1976)*. 2000;25(15):1938-1943. http://www.ncbi.nlm.nih.gov/pubmed/10908937.

27. Elliott JM, Noteboom JT, Flynn TW, Sterling M. Characterization of acute and chronic whiplash-associated disorders. *J Orthop Sports Phys Ther*. 2009;39(5):312-323. doi:10.2519/jospt.2009.2826.

28. Feipel V, Salvia P, Klein H, Rooze M. Head repositioning accuracy in patients with whiplash-associated disorders. *Spine (Phila Pa 1976)*. 2006;31:E51-E58. doi:10.1097/01.brs.0000194786.63690.54.

29. Treleaven J, Jull G, LowChoy N. The relationship of cervical joint position error to balance and eye movement disturbances in persistent whiplash. *Man Ther*. 2006;11:99-106. doi:10.1016/j.math.2005.04.003.

30. Woodhouse A, Liljebäck P, Vasseljen O. Reduced head steadiness in whiplash compared with non-traumatic neck pain. *J Rehabil Med*. 2010;42(1):35-41. doi:10.2340/16501977-0484.

31. Woodhouse A, Vasseljen O. *Altered Motor Control Patterns in Whiplash and Chronic Neck Pain*. biomedcentral.com; 2008.

32. Sjölander P, Michaelson P, Jaric S, Djupsjöbacka M. Sensorimotor disturbances in chronic neck pain--range of motion, peak velocity, smoothness of movement, and repositioning acuity. *Man Ther*. 2008;13(2):122-131. doi:10.1016/j.math.2006.10.002.

33. Stenneberg MS, Rood M, de Bie R, Schmitt MA, Cattrysse E, Scholten-Peeters GG. To What Degree Does Active Cervical Range of Motion Differ Between Patients With Neck Pain, Patients With Whiplash, and Those Without Neck Pain? A Systematic Review and Meta-Analysis. *Arch Phys Med Rehabil*. October 2016.

doi:10.1016/j.apmr.2016.10.003.

34. Treleaven J. Dizziness, Unsteadiness, Visual Disturbances, and Sensorimotor Control in Traumatic Neck Pain. *J Orthop Sport Phys Ther*. 2017;47(7):492-502. doi:10.2519/jospt.2017.7052.

35. Heikkilä H V, Wenngren BI. Cervicocephalic kinesthetic sensibility, active range of cervical motion, and oculomotor function in patients with whiplash injury. *Arch Phys Med Rehabil*. 1998;79(9):1089-1094. http://www.ncbi.nlm.nih.gov/pubmed/9749689.

36. Sterling M, Jull G, Vicenzino B, Kenardy J, Darnell R. Development of motor system dysfunction following whiplash injury. *Pain*. 2003;103(1-2):65-73. http://www.ncbi.nlm.nih.gov/pubmed/12749960.

37. Dall'Alba PT, Sterling MM, Treleaven JM, Edwards SL, Jull G a. Cervical range of motion discriminates between asymptomatic persons and those with whiplash. *Spine (Phila Pa 1976)*. 2001;26(19):2090-2094. http://www.ncbi.nlm.nih.gov/pubmed/11698884.

38. Feipel V, Rondelet B, LePallec JP, DeWitte O, Rooze M. The use of disharmonic motion curves in problems of the cervical spine. *Int Orthop*. 1999;23(4):205-209. http://www.ncbi.nlm.nih.gov/pubmed/10591935.

39. Baydal-Bertomeu JM, Page AF, Belda-Lois JM, Garrido-Jaén D, Prat JM. Neck motion patterns in whiplash-associated disorders: quantifying variability and spontaneity of movement. *Clin Biomech (Bristol, Avon)*. 2011;26(1):29-34. doi:10.1016/j.clinbiomech.2010.08.008.

40. Antonaci F, Bulgheroni M, Ghirmai S, et al. 3D kinematic analysis and clinical evaluation of neck movements in patients with whiplash injury. *Cephalalgia*. 2002;22(7):533-542. http://www.ncbi.nlm.nih.gov/pubmed/12230595.

41. Falla D, Bilenkij G, Jull G. Patients with chronic neck pain demonstrate altered patterns of muscle activation during performance of a functional upper limb task. *Spine (Phila Pa 1976)*. 2004;29(13):1436-1440. http://www.ncbi.nlm.nih.gov/pubmed/15223935.

42. Falla D, Farina D, Dahl MK, Graven-Nielsen T. Muscle pain induces task-dependent changes in cervical agonist/antagonist activity. *J Appl Physiol*. 2007;102(2):601-609. doi:10.1152/japplphysiol.00602.2006.

43. Vasavada AN, Brault JR, Siegmund GP. Musculotendon and fascicle strains in anterior and posterior neck muscles during whiplash injury. *Spine (Phila Pa 1976)*. 2007;32(7):756-765. doi:10.1097/01.brs.0000259058.00460.69.

44. Carroll LJ, Holm LW, Hogg-Johnson S, et al. Course and prognostic factors for neck pain in whiplash-associated disorders (WAD): results of the Bone and Joint Decade 2000-2010 Task Force on Neck Pain and Its Associated Disorders. *J Manipulative Physiol Ther*. 2009;32(2 Suppl):S97-S107. doi:10.1016/j.jmpt.2008.11.014.

45. Ferrari R, Russell a S, Carroll LJ, Cassidy JD. A re-examination of the whiplash associated disorders (WAD) as a systemic illness. *Ann Rheum Dis*. 2005;64(9):1337-1342. doi:10.1136/ard.2004.034447.

46. Anstey R, Kongsted A, Kamper S, Hancock MJ. Are People With Whiplash-Associated Neck Pain Different From People With Nonspecific Neck Pain? *J Orthop Sports Phys Ther*. 2016;46(10):894-901. doi:10.2519/jospt.2016.6588.

47. Treleaven J. Dizziness, Unsteadiness, Visual Disturbances, and Postural Control Implications for the Transition to Chronic Symptoms After a Whiplash Trauma. *Spine (Phila Pa 1976)*. 2011;36:S211-S217.

48. Treleaven J, Jull G, Sterling M. Dizziness and unsteadiness following whiplash injury: characteristic features and relationship with cervical joint position error. *J Rehabil Med*. 2003;35(1):36-43. http://www.ncbi.nlm.nih.gov/pubmed/12610847.

49. Treleaven J, Takasaki H. Characteristics of visual disturbances reported by subjects with neck pain. *Man Ther*. 2014;19(3):203-207. doi:10.1016/j.math.2014.01.005.

50. Rodriquez AA, Barr KP, Burns SP. Whiplash: pathophysiology, diagnosis, treatment, and prognosis. *Muscle Nerve*. 2004;29(6):768-781. doi:10.1002/mus.20060.

51. Kristjansson E, Treleaven J. Sensorimotor function and dizziness in neck pain: Implications for assessment and management. *J Orthop Sport Phys Ther*. 2009;39(5):364-377. doi:10.2519/jospt.2009.2834.

52. Treleaven J, LowChoy N, Darnell R, Panizza B, Brown-Rothwell D, Jull G. Comparison of sensorimotor disturbance between subjects with persistent whiplash-associated disorder and subjects with vestibular pathology associated with acoustic neuroma. *Arch Phys Med Rehabil*. 2008;89(3):522-530. doi:10.1016/j.apmr.2007.11.002.

53. Treleaven J. Sensorimotor disturbances in neck disorders affecting postural stability, head and eye movement control. *Man Ther*. 2008;13(1):2-11. doi:10.1016/j.math.2007.06.003.

54. Michiels S, De Hertogh W, Truijen S, November D, Wuyts F, Van de Heyning P. The assessment of cervical sensory motor control: a systematic review focusing on measuring methods and their clinimetric characteristics. *Gait Posture*. 2013;38(1):1-7. doi:10.1016/j.gaitpost.2012.10.007.

55. De Hertogh WJ, Vaes PH, Vijverman V, De Cordt A, Duquet W. The clinical examination of neck pain patients: the validity of a group of tests. *Man Ther*. 2007;12(1):50-55. doi:10.1016/j.math.2006.02.007.

56. Michiels S, Hallemans A, Van de Heyning P, et al. Measurement of cervical sensorimotor control: The reliability of a continuous linear movement test. *Man Ther*. March 2014:2-7. doi:10.1016/j.math.2014.02.004.

57. Kristjansson E, Oddsdottir GL. “The Fly”: a new clinical assessment and treatment method for deficits of movement control in the cervical spine: reliability and validity. *Spine (Phila Pa 1976)*. 2010;35(23):E1298-305. doi:10.1097/BRS.0b013e3181e7fc0a.

58. Kristjansson E, Dall’Alba P, Jull G. A study of five cervicocephalic relocation tests in three different subject groups. *Clin Rehabil*. 2003;17(7):768-774. doi:10.1191/0269215503cr676oa.

59. Tjell C, Tenenbaum A, Sandstrom S. Smooth pursuit neck torsion test - A specific test for whiplash associated disorders? *J Whiplash Rel Disord*. 2002;1:9-24. doi:10.1300/J180v01n02_02.

60. Treleaven J, Jull G, Grip H. Head eye co-ordination and gaze stability in subjects with persistent whiplash associated disorders. *Man Ther*. 2011;16(3):252-257. doi:10.1016/j.math.2010.11.002.

61. Grip H, Jull G, Treleaven J. Head eye co-ordination using simultaneous measurement of eye in head and head in space movements: Potential for use in subjects with a whiplash injury. *J Clin Monit Comput*. 2009;23:31-40. doi:10.1007/s10877-009-9160-5.

62. Kongsted A, Jorgensen L V, Bendix T, Korsholm L, Leboeuf-Yde C. Are smooth pursuit eye movements altered in chronic whiplash-associated disorders? A cross-sectional study. *Clin Rehabil*. 2007;21:1038-1049. doi:10.1177/0269215507075519.

63. Kelders WP a, Kleinrensink GJ, van der Geest JN, et al. The cervico-ocular reflex is increased in whiplash injury patients. *J Neurotrauma*. 2005;22(1):133-137. doi:10.1089/neu.2005.22.133.

64. Montfoort I, Kelders WPA, Van Der Geest JN, et al. Interaction between ocular stabilization reflexes in patients with whiplash injury. *Invest Ophthalmol Vis Sci*. 2006;47:2881-2884. doi:10.1167/iovs.05-1561.

65. Hikosaka O, Maeda M. Cervical effects on abducens motoneurons and their interaction with vestibulo-ocular reflex. *Exp Brain Res*. 1973;18(5):512-530. http://www.ncbi.nlm.nih.gov/pubmed/4794882.

66. Corneil BD, Olivier E, Munoz DP, et al. Neck Muscle Responses to Stimulation of Monkey Superior Colliculus . II . Gaze Shift Initiation and Volitional Head Movements Neck Muscle Responses to Stimulation of Monkey Superior

Colliculus . II . Gaze Shift Initiation and Volitional Head Movements. 2012:2000-2018.

67. Barlow D, Freedman W. Cervico-Ocular Reflex in the Normal Adult. *Acta Otolaryngol*. 1980;89(3-6):487-496. doi:10.3109/00016488009127166.

68. Bronstein a M, Hood JD. The cervico-ocular reflex in normal subjects and patients with absent vestibular function. *Brain Res*. 1986;373(1-2):399-408. http://www.ncbi.nlm.nih.gov/pubmed/3487371.

69. Iwashita M, Kanai R, Funabiki K, Matsuda K, Hirano T. Dynamic properties , interactions and adaptive modifications of vestibulo-ocular reflex and optokinetic response in mice. *Sci Technol*. 2001;39:299-311.

70. Popov KE, Lekhel H, Faldon M, Bronstein a M, Gresty M a. Visual and oculomotor responses induced by neck vibration in normal subjects and labyrinthine-defective patients. *Exp Brain Res*. 1999;128(3):343-352. http://www.ncbi.nlm.nih.gov/pubmed/10501806.

71. Bronstein a M, Mossman S, Luxon LM. The neck-eye reflex in patients with reduced vestibular and optokinetic function. *Brain*. 1991;114 (Pt 1:1-11. http://www.ncbi.nlm.nih.gov/pubmed/1998877.

72. Kelders WP a, Kleinrensink GJ, van der Geest JN, et al. Compensatory increase of the cervico-ocular reflex with age in healthy humans. *J Physiol*. 2003;553(Pt 1):311-317. doi:10.1113/jphysiol.2003.049338.

73. Rijkaart DC, van der Geest JN, Kelders WP, de Zeeuw CI, Frens M a. Short-term adaptation of the cervico-ocular reflex. *Exp Brain Res*. 2004;156(1):124-128. doi:10.1007/s00221-004-1878-1.

74. Montfoort I, Van Der Geest JN, Slijper HP, De Zeeuw CI, Frens MA. Adaptation of the cervico- and vestibulo-ocular reflex in whiplash injury patients. *J Neurotrauma*. 2008;25:687-693. doi:10.1089/neu.2007.0314.

75. Paige GD. Senescence of human visual-vestibular interactions: smooth pursuit, optokinetic, and vestibular control of eye movements with aging. *Exp Brain Res*. 1994;98(2):355-372. http://www.ncbi.nlm.nih.gov/pubmed/8050519.

Chapter 2:

Eye movements in patients with WAD: a systematic review

Ischebeck, Britta K

de Vries, Jurryt

Van der Geest, Jos N

Janssen, Malou

Van Wingerden, Jan Paul

Kleinrensink, Gert Jan

Frens, Maarten A

published in: BMC Musculoskeletal Disorders 2016 Oct 21;17(1):441.

ABSTRACT

Background Many people with Whiplash Associated Disorders (WAD) report problems with vision, some of which may be due to impaired eye movements. Better understanding of such impaired eye movements could improve diagnostics and treatment strategies.

Objectives This systematic review surveys the current evidence on changes in eye movements of patients with WAD and explains how the oculomotor system is tested.

Study Design Systematic literature review according to the PRISMA guidelines.

Results Thirteen studies out of 833 unique hits were included. Nine studies reported impaired eye movements in patients with WAD and in four studies no differences compared to healthy controls were found. Different methods of eye movement examination were used in the nine studies: in four studies, the smooth pursuit neck torsion test was positive, in two more the velocity and stability of head movements during eye-coordination tasks were decreased, and in another three studies the cervico-ocular reflex was elevated.

Conclusions The thirteen reviewed studies about eye movement in patients with WAD report different results. When comparing the results of the relevant publications, one should realize that there are significant differences in test set-up and patient population. In the majority of studies patients show altered compensatory eye movements and smooth pursuit movements which may impair the coordination of head and eyes.

Keywords Whiplash Associated Disorders (WAD); problems with vision; oculomotor problems; systematic review

Introduction

People who suffer from chronic 'Whiplash Associated Disorders' (WAD) exhibit very distinct complaints[1]. 70% of patients complain of pain, dizziness and unsteadiness [2], while 50% report problems with vision[3].These problems with vision comprise concentration problems during reading, sensitivity to light, visual fatigue and eye strain [3]. The severity of problems with vision is higher in traumatic neck pain patients than in non-traumatic neck pain patients [3]. Problems in vision could be due to malfunction of the oculomotor system that is meant to keep the eye on a target [4,5]. Such oculomotor problems in WAD patients could be related to cervical sensorimotor disorders. The knowledge of cervical induced oculomotor system disorders is still limited [6]. This may be because of the complexity of the cervico-oculomotor system, that includes not only the central nervous system but also the proprioceptive system of the cervical spine (for review see e.g. [7]).

Eye movement control depends on eye position in the head and on the position of the head in space [8]. Head position is determined by integration of several sub-systems such as the vestibular system, visual information and proprioceptive system of the cervical spine [8,9]. Disturbed afferent cervical information is related to nystagmus, dizziness and deficits in balance [10,11].

The principal source of cervical afferent information is formed by mechanoreceptors in the upper cervical spine. Specifically in the deep upper cervical muscles (i.e. m. obliquus capitis superior and inferior, m. longus colli), the density of muscle spindles is extremely high compared to other muscles in the body [12,13]. Muscle spindles are part of the sensorimotor system [14]. In patients with WAD sensorimotor control is disturbed [14–17].

In attempts to reveal the complex relation between cervical sensorimotor disorders and visual problems several studies regarding oculomotor problems in patients with WAD have been published [3,18–23]. In all studies one of three distinct eye movement types were used to assess oculomotor problems in patients with WAD: eye stabilization reflexes, smooth pursuit eye movements and head-eye coordination.

Eye Stabilization reflexes

Eye stabilization reflexes preserve stable vision on the retina during head movement. At least three eye stabilization reflexes can be distinguished based on their sensory input: the cervico-ocular reflex (COR), the vestibulo-ocular reflex (VOR) and the optokinetic reflex (OKR). These three complementary reflexes have distinct characteristics and receive input from the cervical spine, the vestibulum and the eyes, respectively. The COR receives input from muscle spindles in the cervical spine, especially from the deep upper cervical muscles and joint capsules of C1 to C3 [24]. The central pathways of the VOR and the COR are the same; both reflexes converge at the vestibular nuclei [24]. The OKR pathways, however, are quite distinct from the COR and VOR pathways [25].

Smooth pursuit eye movements

Accurate smooth pursuit is essential to look at a moving object by keeping the retinal image steady within the foveal area. Ideally, smooth pursuit velocity matches the velocity of the moving object. Performing smooth pursuit eye movements properly requires the integration of visual, vestibular and cervical information [26].

Head-eye coordination

Head-eye coordination is the overall result of all systems in control of the visual system. During these tasks, the compensatory eye movements and the motor control of the neck co-operate, requiring integration of saccades, the COR, VOR, OKR and active neck movements.

This systematic review provides an overview of existing evidence on oculomotor system changes in patients with WAD and how this evidence was perceived. We aim to address the question of what is known about changed eye movements in patients with WAD. To our knowledge no reviews of the literature concerning oculomotor problems in patients with WAD have previously been published. Therefore, we present a comprehensive, systematic overview of the literature concerning changed eye movements in patients with WAD compared to healthy controls.

METHODS

The PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) were employed in this systematic literature review [27].

Information sources and search parameters

To be as comprehensive as possible, the following databases have been searched until September 2015: Embase, Medline (OvidSP), Web of Science, Scopus, Cinahl, SportDiscus, Cochrane, Pubmed Publisher and Google scholar. Keywords were derived from the research question and transformed to associated and free text words. The search strategy in Embase was based on the following combination of terms: 'cornea reflex'/exp OR 'eye movement'/exp OR 'eye movement disorder'/de OR 'oculomotor system'/de OR 'extraocular muscle'/de OR (((cornea* OR eye* OR ocular* OR cervicoocul* OR visual*) NEAR/6 (reflex* OR movement* OR pursuit* OR motilit* OR track*)) OR oculomotor* OR ((extraocular* OR ocular* OR eye*) NEAR/3 muscle*) OR 'smooth pursuit' OR (tracking NEAR/3 (perform* OR task*))):ab,ti) AND ('neck pain'/de OR 'neck injury'/de OR 'whiplash injury'/exp OR (((neck OR cervic* OR colli OR collum*) NEAR/6 (pain* OR hyperextension* OR ache OR injur* OR disorder* OR trauma* OR lesion* OR bruise*)) OR neckache* OR Cervicalgia* OR Cervicodynia* OR whiplash):ab,ti)

In addition, Medline (OvidSP), Web of Science, Scopus, Cinahl, SportDiscus, Cochrane, Pubmed Publisher and Google scholar were similarly searched with their own thesaurus used for indexing articles and free entries.

Study selection

For inclusion in the systematic review the following criteria had to be met: (1) participants in the study had to be 18 years or older; (2) patients had to have Whiplash Associated Disorders; (3) one of the outcome measures in the study had to be eye movements; (4) control subjects were healthy individuals; (5) the article was written in English, Dutch or German; (6) the original article was available in full text.

Data items and collection

Information was extracted from the included articles and presented in the evidence table (table 1), regarding (1) study, (2) sample size, (3) characteristics of the patients, (4) testing device for eye movements, (5) eye movements testing protocol, (6) results and (7) possible bias.

Risk of bias in individual studies

The validity and risk of bias of the included articles was checked by using the "Methodology Checklist 4: Case-control studies" version 2.0 and "Methodology Checklist 3: Cohort studies" version 3.0 provided by the Scottish Intercollegiate Guidelines Network (SIGN). The risk of bias table is presented in table 2. The appraisal of the articles was based on the description of the internal validity, i.e. the selection of subjects, exclusion of selection bias, clear definition of outcomes, blinding of assessors, reliable assessment of exposure, identification of potential confounders and provision of confidence intervals. For the studies the grading score has been set from "Low quality" (0), "Acceptable" (+) or "High quality" (++). In the present review, only articles graded as "Acceptable" or "High quality" were included. This criterion was set a priori. Methodological quality of the included articles was assessed blindly and independently by authors BI and JV. After both researchers appraised the selected articles, results were compared and any differences discussed after screening the article a second time.

Results

1. *Study selection*

A total of 833 studies were identified. As shown in figure 1, 13 studies remained after two screening phases.

In the first phase all articles were screened on relevance of the title and abstract. Nineteen of the included studies remained after the first screening. These studies met the inclusion criteria, according to the title and abstract. After the first full-text reading, two researchers agreed on seventeen of the nineteen studies. Six of these seventeen studies were excluded because they did not fulfil the inclusion criteria, regarding the participants [28,29] or the outcome parameter [3,18,30,31].

In two studies, the reviewers disagreed on the validity of the measurement protocol [32,33]. After a second reading and comparison of the differences, the researchers reached consensus. Both studies were included, resulting in 13 included studies.

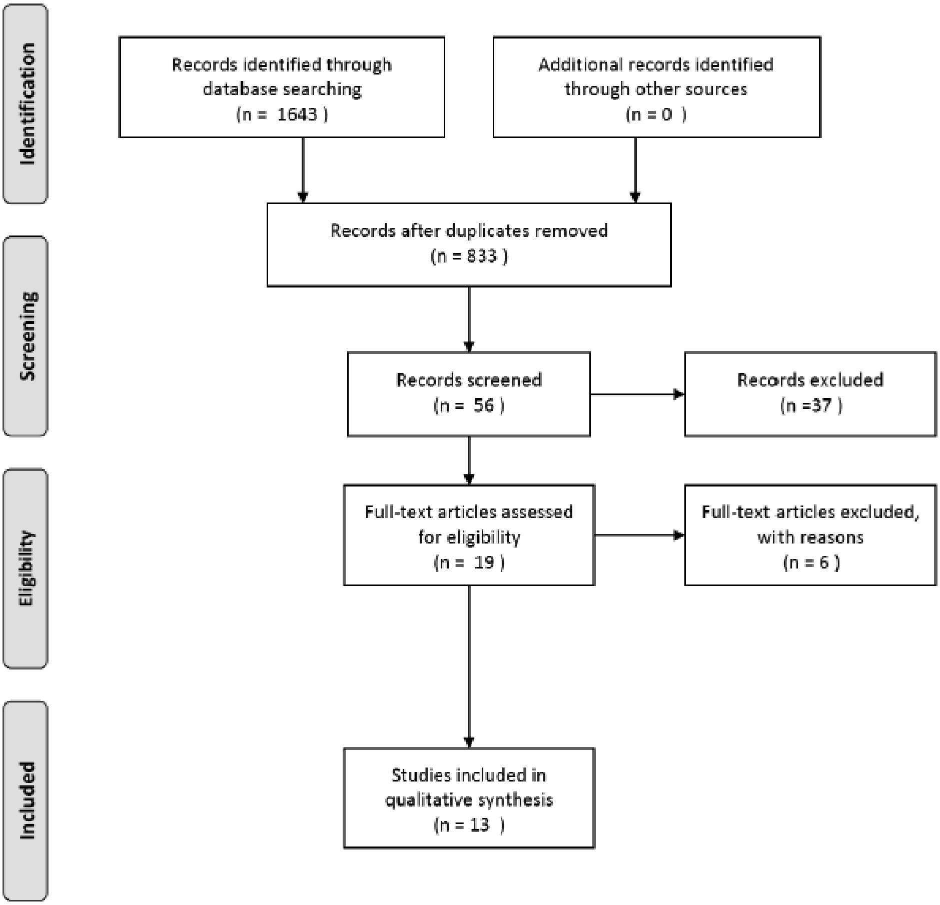

Figure 1: Flow Diagram of study selection

The methodological quality of all of the included studies was "acceptable" (+) according to the SIGN criteria checklist. This implies some weaknesses in the study, with an associated risk of bias. Most studies used rather small and heterogeneous populations (e.g. the time after accident of the patients varied from one months to seven years [32,34]). There was also limited information concerning raw data, possible confounders and patient characteristics (e.g. pain, anxiety and disability).

	internal validity: selection of subjects							internal validity: assessment		internal validity: confounding	internal validity: statistical analysis	overall assessment		
	appropriate research question	cases and controls from comparable population	same exclusion criteria	percentage of each group participating in the study	comparison between participants and non-participants	cases are clearly defined and differentiated from controls	established that controls are non-cases	prevention of primary exposure influencing case ascertainment	standard, valid and reliable exposure	identification of main potential confounders	confidence intervals	minimization the risk of bias	clear association between exposure and outcome	results directly applicable to patient group
Dispenza et al., 2011 [33]	+	?	-	Cases: 89% Controls: 100%	-	-	-	?	+	?	+	-	-	-
Grip et al., 2009 [39]	+	+	+	Cases: 100% Controls: 90%	+	+	+	d.n.a	+	?	+	++	+	+
Heikkila et al., 1998 [20]	+	?	+	Cases: 100% Controls: 100%	-	+	+	d.n.a.	-	+	+	+	+	+
Janssen et al., 2015 [40]	+	+	-	Cases: 99% Controls: 100%	-	+	+	d.n.a.	+	?	+	+	+	+
Kelders et al., 2005 [23]	+	?	?	Cases: 100% Controls: 100%	-	-	?	d.n.a.	+	+	+	+	+	+
Kongsted et al., 2007 [36]	+	+	+	Cases: 70% Controls: 90%	+	+	+	+	+	+	+	++	+	+
Montfoort et al., 2006 [21]	+	+	-	Cases: 100% Controls: 100%	-	?	?	?	+	?	-	+	-	-
Montfoort et al., 2008 [22]	+	?	?	Cases: 95% Controls: 100%	+	+	+	?	+	?	+	+	+	+
Prushansky et al., 2004 [35]	+	+	+	Cases : 100% Controls : 100%	-	+	+	d.n.a.	+	-	+	+	+	+
Tjell et al., 1998 [34]	-	+	-	Cases: 75% Controls: 100%	+	?	+	d.n.a.	+	+	+	+	+	-
Treleaven et al., 2005 [37]	+	?	?	Cases: 100% Controls: 100%	-	+	+	+	+	+	+	+	-	-
Treleaven et al., 2006 [16]	+	+	+	Cases: 100% Controls: 100%	+	+	+	+	+	?	-	+	+	+
Treleaven et al., 2008 [41]	+	+	-	Cases: 100% Controls: 100%	+	+	+	?	?	+	-	+	+	+
Treleaven et al., 2011 [19]	+	?	+	Cases: 100% Controls: 100%	+	+	+	?	+	+	+	++	+	+
+= yes; -= no; ++= high quality; += acceptable; - = unacceptable; d.n.a.= does not apply														

Table 2: risk of bias table presenting individual criteria in SIGN checklists for the 14 included studies

2. Study characteristics

The characteristics of the data that were extracted from the included studies (study, sample size, characteristics of the patients, eye movement testing instrument, testing protocol, results, and possible bias) are presented in table 1.

reference	sample	inclusion criteria	testing instrument	testing protocol	results	possible bias
Dispenza et al., 2011 [32]	33 WAD (36.5y, 21-53) 23 CON (30.4y, 19-49)	WAD (without loss of consciousness) 1-12 months after accident	video-oculography	SPNT	neutral: WAD 0.86, CON 0.87 right rotation: WAD 0.87 left rotation: WAD 0.86 SPNT-diff: WAD 0	type of WAD not described, selection of controls not described, no SP in rotated position tested in controls
Grip et al., 2009 [35]	6 WAD (28y) 20 CON (32y)	WAD > 3 months after accident	electro-oculography	gaze stability; sequential eye and head movement (SEHM)	gaze stability: WAD: head angle reduced (no exact data) SHEM: WAD: mean angular head velocity reduced (no exact data)	small population (n=7) no individual data, results presented in boxplots
Heikkila et al., 1998 [20]	27 WAD (38.8y, 18-66) 25 CON (34y, 25-40y)	acute WAD II, III (without loss of consciousness)	electro-oculography	SP	right rotation: WAD 2x abnormal left rotation: WAD 5x abnormal	only SP in neutral position tested, no torsion of the neck only quantity of abnormal scores provided, no individual data
Janssen et al., 2015 [36]	11 WAD, 44 non-WAD (44.2y, 25-67) 20 CON (28.4, 20-51)	WAD > 6 months after accident	video-oculography	SPNT	SPNTdiff predictably: WAD 0.08, non-WAD 0.05, CON 0.02 SPNT unpredictably: WAD 0.01, non-WAD 0.01, CON 0	no specification of grade of WAD
Kelders et al., 2005 [23]	8 WAD (32y, 25-42) 8 CON (35y, 30-45)	WAD I,II,III 5-36 months after accident	video-oculography	cervico-ocular reflex	COR higher in WAD than in CON *	little data provided, only graphs
Kongsted et al., 2007 [37]	34 WAD (39.4y, 20-51) 60 CON (40y, 18-63))	WAD I,II,III > 6 months after accident	electro-oculography	SPNT	neutral: WAD 0.9, CON 0.96 (median) right rotation: WAD 0.89, CON 0.94 left rotation: WAD 0.93, CON 0.95 SPNTdiff: WAD 0, CON 0	patient population heterogeneous regarding symptoms, disability and duration of symptoms
Montfoort et al., 2006 [21]	13 WAD (40y, 26-60) 18 CON (36y, 23-64)	WAD I, II	video-oculography	cervico-ocular reflex; vestibulo-ocular reflex; optokinetic reflex	COR: $P=2.9 \times 10^{-6}$* VOR: P=0.27 OKR: P= 0.25	only comparison between groups, no individual data
Montfoort et al., 2008 [22]	COR: 10 WAD (42y, 22-52), 10	WAD I,II	video-oculography	cervico-ocular reflex;	COR adaptation: WAD $\Delta G=0.13\pm0.24$,	no comparison between characteristics of patients and

	CON (31y, 18-54) VOR: 10 WAD (39y, 19-56), COR 30y, 24-39)			vestibulo-ocular reflex; optokinetic reflex	CON ∆G=-0.19±0.06* VOR adaptation: WAD ∆G=0.037±0.062, CON ∆G=-0.2±0.072*	controls, little data provided
Prushansky et al., 2004 [34]	26 WAD (40.3y, 25-55) 23 CON (34.2y, 18-54)	WAD II, III 6-84 months after accident	electro-oculography	SPNT	neutral: WAD 0.79*, CON 0.86 right rotation: WAD 0.74, CON 0.82 left rotation: WAD 0.75, 0.80 SPNTdiff: WAD 0.026, CON 0.035	remarkable variation in duration of neck pain
Tjell et al., 1998 [33]	50 WAD D (39y, 18-60) 25 WAD ND (34y, 21-63)	≥ WAD II > 6 months after accident	electro-oculography	SPNT	SPNTdiff: WAD D 0.14*; WAD ND 0.10*; CON 0.02	vague exclusion criteria for controls: tension in neck
Treleaven et al., 2005 [38]	100 WAD: 50 WAD D (35y, 19-46) 50 WAD ND (35y, 18-46) 50 CON (30y, 19-45)	WAD II > 3 months after accident	electro-oculography	SPNT	neutral: WAD ND 0.82, CON 0.88 * right rotation: WAD ND 0.78, CON 0.88* left rotation: WAD ND 0.74, CON 0.87* SPNTdiff: WAD D 0.11*; WAD ND 0.07, CON 0.01*	3 groups, but just two groups compared with each other (WAD D with WAD ND and WAD ND with controls)
Treleaven et al., 2006 [39]	50 WAD D (35.5y, 19-46) 50 WAD ND (35y, 18-46) 40 CON (29.6y, 19-45)	WAD II > 3 months after accident	electro-oculography	SPNT	WAD D: 45 abnormal SPNT scores WAD ND: 39 abnormal SPNT scores	only quantity of abnormal scores provided, no individual data
Treleaven et al., 2011 [19]	20 WAD (37y) 20 CON (33y)	WAD symptoms > 3 months, < 5 year	electro-oculography	gaze stability; sequential eye and head movement (SEHM)	gaze stability: WAD 27.7*/ 30.5*, CON 44.5/43.5 (degrees of head ROM right and left) WAD 16.9/20.2, CON 33.0/37.4*(head rotation velocity in degrees/sec) SHEM: WAD 23.6/30, CON 36.9*, WAD 30, CON 36.9/36.9* (head rotation velocity in degrees/sec)	remarkable variation in duration of neck pain

WAD = Whiplash associated disorder; WAD grade I = neck complaints of pain, stiffness or tenderness only but no physical signs are noted by the examining physician; WAD grade II = neck complaints and musculoskeletal signs as decreased range of motion and point tenderness in the neck; WAD grade III includes additional signs (decreased or absent deep tendon reflexes, weakness, and sensory deficits); **WAD D=** patients with WAD and dizziness; **WAD ND=** patients with WAD without dizziness; **CON**: healthy controls; y=mean years of age; **SPNT=** Smooth Pursuit Neck Torsion Test; **SP=** smooth pursuit; **SPNTdiff=** difference in SP gain between neutral and rotated position; **COR=** cervico-ocular reflex**; VOR=** vestibulo-ocular reflex; **ROM=** cervical range of motion; **SEHM=** sequential eye and head movement; ***=** indicates statistically significant differences between groups

Table 1: Evidence table of the included studies

Twelve studies were case control studies and one was a cohort study [20]. Nine studies used the classification of the Quebec Task Force on Whiplash Associated Disorders (WAD) [20–23,33,34,37–39]. In these studies patients were included with WAD grade 1 (complaints of neck pain, stiffness or tenderness only without physical signs that are noted by an examining physician), grade 2 (complaints of neck pain and musculoskeletal signs, such as a decreased range of motion and point tenderness in the neck) or grade 3 (includes additional signs such as decreased or absent deep tendon reflexes, weakness, and sensory deficits) [40].

All thirteen studies included a healthy control group.

3. *Outcome measures*

The principal outcome measure of the current review was eye movements, being the main subject of investigation in all included studies. However, different tests for eye movements were used among the included studies. The different tests were: (1) tests for head-eye coordination, integrating compensatory eye movements and neck movement tests; (2) smooth pursuit tests and (3) compensatory eye movement tests, including the VOR and the COR. Also for these three different tests, two different eye movement measurement techniques were used: electro-oculography and video-oculography.

<u>Head-eye coordination</u>

In two studies several parameters concerning the head-eye coordination were tested using two different tests [19,35]. One of the tests was gaze stability during active head rotation. The other test was the sequential head and eye movement (SHEM) test. During the gaze stability test, the subject has to keep the eyes focused on a point straight ahead while rotating the neck actively. During the SHEM test, the subject has to move the eyes first to one side, followed by an active head motion. Subsequently the subject first moves the eyes and then the head back to the starting position. During these tasks the compensatory eye movements and the motor control of the neck co-operate, requiring integration of saccades, the COR, VOR, OKR and active neck movements. In both tasks the patients executed the head movements slower compared to controls. During the gaze stability test, head range of motion was smaller in patients.

<u>Smooth pursuit eye movements</u>

Smooth pursuit eye movements were tested in eight studies [20,32–34,36–39]. During the smooth pursuit neck torsion (SPNT) test, the influence of a rotated cervical spine on the smooth pursuit eye movement is tested [33,41].

In one study the smooth pursuit eye movements were tested only in neutral position and not in a neck rotated position [20]. In this study, two of the 26 tested patients were classified with a dysfunctional gain (i.e. the ratio between the movement of the eyes and the movement of the stimulus). In seven studies the more complex SPNT test was used [32–34,36–39]. In three of those seven studies the primary outcome parameter, the 'SPNTdiff' (the difference between the gain in neutral and in rotated position) was significantly higher in patients compared to healthy controls (WAD 0.14/0.11/0.08, controls

0.02/0.01/0.02) [33,36,38]. Three other studies did not find any differences between cases and controls [32,34,37]. One study provided only the number of patients with an altered SPNTdiff compared to controls, but did not provided the median values of the SP gain [39]. One other study also provided only the number of individuals with an altered SP in neutral position [20]. In one study the SPNT difference of patients with WAD was larger for predictably moving targets compared to unpredictably moving targets. This difference was not seen in healthy controls and patients with non-traumatic neck pain [36].

Eye stabilization reflexes

In three studies the COR and the VOR were measured [21–23]. These eye stabilization reflexes were tested in a custom setting with an infrared eye tracking device in a darkened room (further description of the measurement method in [42]). All studies reported a significantly higher COR gain in patients with WAD. One study described that both the COR and VOR gain could adapt in healthy controls, but not in patients [22].

In summary, as shown in table 1, nine of the thirteen studies reported differences between patients with WAD and healthy controls [16,19,21–23,33,35,36,38]. Velocity of eye movements is decreased and eye movements are less coordinated in patients than in healthy controls. In four of the eight studies which used the SPNT test, the smooth pursuit movements in the neck-rotated position were slower in the patient group compared to the healthy controls [33,36,38,39]. In all five studies which used the tests for eye stabilization reflexes and the head-eye coordination tests, the WAD group performed worse than the healthy control group [19,21–23,35]. In the discussion section we will discuss extensively the variety of outcome parameters in the tests for oculomotor deficits. Generally, patients with WAD had an elevated COR and had more problems in stabilizing the head and gaze during stability tasks and sequential movement tasks.

Four studies did not find differences between patients and healthy controls [20,32,34,37]. The results were explained with a different analysis of the data [37], differences in symptom severity of the patient group and attentional deficits of the patients [32,34]. Heikkilä et al. found differences in patients after a whole battery of oculomotor tests, but no differences in the SPNT test alone [20].

In general, most studied studies lack details in the description of patient characteristics [16,20–23,32–36]. Heterogeneity in patient population may be an important factor in confounding the results of eye movement tests.

Discussion

The current review provides an overview of present knowledge on altered eye movements in WAD patients. The majority of studies in this review confirm the possibility of eye movement impairments in WAD patients. This underlines the necessity to include an examination of eye movement impairments in the diagnostic process of patients with WAD. There are various methods that address different aspects of eye movement. Regrettably a general consensus on eye movement examination does not yet exist. The thirteen studies included in this review are evaluated by the specific aspect of oculomotor problems that are tested, the clinical applicability and test validity.

Head-eye coordination

Two studies used a series of tests to analyze the head-eye coordination [19,35]. The purpose of this method is to evaluate over-all head-eye coordination disturbances. This method does not allow discrimination as to which part of the system is causing the actual disturbance. The head-eye coordination tests were developed for clinical use, are well described and relatively easy to execute. However, due to the requirement of active cervical movements and the combination of cervical, vestibular and visual input, it is not possible to draw specific conclusions about eye movements in isolation. The studies included in this review did not provide substantial information on the validity of this method. However, in another study that was excluded from this review as it was not performed on WAD patients the discriminative validity and reliability were considered sufficient when three out of five test scored positive [43].

Smooth pursuit eye movements

Eight studies focused on smooth pursuit eye movements by using the SPNT test [20,32–34,36–39]. The SPNT test is developed for clinical use and eye movements are measured with electro-oculography. One point of concern is the diversity in analyzing the recordings. The accuracy, reliability and non-standardized interpretation is a source of bias [37,44,45]. In this review the four studies that did not find differences between patients with WAD and healthy subject were all SPNT test studies. This may lead to the conclusion that the discriminating capacity of this test is less than that of the other methods.

In addition, as in the head-eye coordination method, it remains unclear what exactly is causing the recorded disturbance. In a recent study on the SPNT test the question was raised whether confounding factors such as pain experience or impaired cognitive functioning may affect test outcomes [36]. Based on these findings the SPNT test should be used with care in the clinical setting.

Eye stabilization reflexes

Solitary cervical induced eye movements were investigated in three studies. These studies focused on eye stabilization reflexes and measured the COR in isolation. COR gain was measured without influence of visual, vestibular or cervical motor information [21–23]. Therefore it is impossible to influence COR gain deliberately, which makes the COR an objective outcome measure of oculomotor function. However, the experimental setup for the COR test is complex and it is necessary to perform the test in a completely darkened room.

A future challenge would be the conversion of the existing test into a less expensive and easy to perform test, suitable for the clinical practice. Recording of eye stabilization reflexes is relatively new. The present studies provide little information on validity of the test.

The optimal test for eye movement impairments does not exist yet. Comparing all three methods in one patient group may clarify which method is most applicable to evaluate oculomotor problems in patients with WAD. At present the head-eye coordination measurements seem the most suitable for clinical use. Particularly when training head-eye disturbances is used as therapeutic intervention. When a test comprises multiple (sub-) systems, it remains difficult to determine the most important factor in the observed change. However, this knowledge is necessary for successful treatment of the patient. To enhance therapeutic interventions, more insight in etiological relations between WAD and oculomotor dysfunction is essential. Eye stabilization reflexes, more than the smooth pursuit method, may enhance our comprehension of the complex interaction between of the cervico-oculomotor system and the coherence of neck pain symptoms.

Conclusion

In the majority of studies included in this review, patients show altered compensatory eye movements and smooth pursuit movements which may impair the coordination of head and eyes.

In this review three methods of eye movement examination are found. The used methods and the patient populations significantly differ. An optimal test to measure oculomotor problems in patients with WAD does not exist yet.

At the present time, the head-eye coordination tests may be the most suitable method for clinical use. Further studies of eye stabilization reflexes can help to clarify the etiology of oculomotor problems in patients with WAD.

Acknowledgements

The authors wish to thank Wichor Bramer, biomedical information specialist at Erasmus MC, for the support with the literature search.

We are grateful for the financial support of TC2N (EU Interreg; MF & JG), and Stichting Coolsingel (MF).

References

1. Curatolo M, Bogduk N, Ivancic PC, McLean S a, Siegmund GP, Winkelstein B a. The role of tissue damage in whiplash-associated disorders: discussion paper 1. *Spine (Phila Pa 1976)*. 2011;36(25 Suppl):S309-15. doi:10.1097/BRS.0b013e318238842a.

2. Treleaven J, Jull G, Sterling M. Dizziness and unsteadiness following whiplash injury: characteristic features and relationship with cervical joint position error. *J Rehabil Med*. 2003;35(1):36-43. http://www.ncbi.nlm.nih.gov/pubmed/12610847.

3. Treleaven J, Takasaki H. Characteristics of visual disturbances reported by subjects with neck pain. *Man Ther*. 2014;19(3):203-207. doi:10.1016/j.math.2014.01.005.

4. Hülse. Klinik der Funktionsstörungen des Kopfgelenkbereiches. In: Hülse M, Neuhuber WL WH, ed. *Der Kranio-Zervikale Übergang*. Berlin: Sprin; 1998:43-97.

5. Wolff H. Störungen des kraniozervikalen Übergang (Kopfgelenkbereich). In: Wolff H, ed. *Neurophysiologische Aspekte Des Bewegungssystems*. Berlin: Springer; 1996.

6. Westergren H, Freeman MD, Malmström E-M. The whiplash enigma: Still searching for answers. *Scand J Pain*. 2014;5(4):226-228. doi:10.1016/j.sjpain.2014.08.003.

7. Treleaven J. Sensorimotor disturbances in neck disorders affecting postural stability, head and eye movement control. *Man Ther*. 2008;13:2-11. doi:10.1016/j.math.2007.06.003.

8. Corneil BD. The neural base of gaze shifts. In: Liversedge S, Gilchrist I, Everling S, eds. *Oxford Handbook on Eye Movements*. ; 2011:1-35.

9. Treleaven J, LowChoy N, Darnell R, Panizza B. Comparison of sensorimotor disturbance between subjects with persistent whiplash-associated disorder and subjects with vestibular pathology associated with …. *Arch Phys …*. 2008;89(3):522-530. http://www.sciencedirect.com/science/article/pii/S0003999307017455.

10. Cohen L. Role of eye and neck proprioceptive mechanisms in body orientation and motor coordination. *J Neurophysiol*. 1961;(24):1-11.

11. Biemond A, Jong JMBVDE. On cervical nystagmus and related disorders. *Brain*. 1969;92:437-458.

12. Boyd-Clark LC, Briggs C a., Galea MP. Muscle Spindle Distribution, Morphology, and Density in Longus Colli and Multifidus Muscles of the Cervical Spine. *Spine (Phila Pa 1976)*. 2002;27(7):694-701. doi:10.1097/00007632-200204010-00005.

13. Kulkarni V, Chandy MJ, Babu KS. Quantitative Study of Muscle Spindles in Suboccipital Muscles of Human Foetuses. 2001;(December):355-359.

14. Falla D, Farina D. Neural and muscular factors associated with motor impairment in neck pain. *Curr Rheumatol Rep*. 2007;9(6):497-502. http://www.ncbi.nlm.nih.gov/pubmed/18177604.

15. Hodges PW. Pain and motor control: From the laboratory to rehabilitation. *J Electromyogr Kinesiol*. 2011;21(2):220-228. doi:10.1016/j.jelekin.2011.01.002.

16. Treleaven J, Jull G, LowChoy N. The relationship of cervical joint position error to balance and eye movement disturbances in persistent whiplash. *Man Ther*. 2006;11(2):99-106. doi:10.1016/j.math.2005.04.003.

17. Kristjansson E, Treleaven J. Sensorimotor function and dizziness in neck pain: implications for assessment and management. *J Orthop Sports Phys Ther*. 2009;39(5):364-377. doi:10.2519/jospt.2009.2834.

18. Storaci R, Manelli A, Schiavone N, Mangia L. Whiplash injury and oculomotor dysfunctions: clinical–posturographic correlations. *Eur Spine …*. 2006;15(12):1811-1816. http://link.springer.com/article/10.1007/s00586-006-0085-0.

19. Treleaven J, Jull G, Grip H. Head eye co-ordination and gaze stability in subjects with persistent whiplash associated disorders. *Man Ther*. 2011;16:252-257. doi:10.1016/j.math.2010.11.002.

20. Heikkilä H V, Wenngren BI. Cervicocephalic kinesthetic sensibility, active range of cervical motion, and oculomotor function in patients with whiplash injury. *Arch Phys Med Rehabil*. 1998;79(9):1089-1094. http://www.ncbi.nlm.nih.gov/pubmed/9749689.

21. Montfoort I, Kelders WPA, Van Der Geest JN, et al. Interaction between ocular stabilization reflexes in patients with whiplash injury. *Invest Ophthalmol Vis Sci*. 2006;47:2881-2884. doi:10.1167/iovs.05-1561.

22. Montfoort I, Van Der Geest JN, Slijper HP, De Zeeuw CI, Frens MA. Adaptation of the cervico- and vestibulo-ocular reflex in whiplash injury patients. *J Neurotrauma*. 2008;25:687-693. doi:10.1089/neu.2007.0314.

23. Kelders WP a, Kleinrensink GJ, van der Geest JN, et al. The cervico-ocular reflex is increased in whiplash injury patients. *J Neurotrauma*. 2005;22(1):133-137. doi:10.1089/neu.2005.22.133.

24. Hikosaka O, Maeda M. Cervical effects on abducens motoneurons and their interaction with vestibulo-ocular reflex. *Exp Brain Res*. 1973;18(5):512-530. http://www.ncbi.nlm.nih.gov/pubmed/4794882.

25. Van Die GC, Collewijn H. 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*. 1986;383(1-2):185-194. http://www.ncbi.nlm.nih.gov/pubmed/3768688.

26. Lencer R, Trillenberg P. Neurophysiology and neuroanatomy of smooth pursuit in humans. *Brain Cogn*. 2008;68(3):219-228. doi:10.1016/j.bandc.2008.08.013.

27. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*. 2009;6(7):e1000097. doi:10.1371/journal.pmed.1000097.

28. Mergner T, Schweigart G, Botti F, Lehmann A. Eye movements evoked by proprioceptive stimulation along the body axis in humans. *Exp Brain Res*. 1998;120:450-460.

29. Kongsted A, Jorgensen L V, Leboeuf-Yde C, Qerama E, Korsholm L, Bendix T. Are altered smooth pursuit eye movements related to chronic pain and disability following whiplash injuries? A prospective trial with one-year follow-up. *Clin Rehabil*. 2008;22:469-479. doi:10.1177/0269215507082141.

30. Freitag P, Greenlee MW, Wachter K, Ettlin Th M, Radue EW. fMRI response during visual motion stimulation in patients with late whiplash syndrome. *Neurorehabil Neural Repair*. 2001;15:31-37. http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L32800193.

31. Bexander CSM, Hodges PW. Cervico-ocular coordination during neck rotation is distorted in people with whiplash-associated disorders. *Exp Brain Res*. 2012;217(1):67-77. doi:10.1007/s00221-011-2973-8.

32. Dispenza F, Gargano R, Mathur N, Saraniti C, Gallina S. Analysis of visually guided eye movements in subjects after whiplash injury. *Auris Nasus Larynx*. 2011;38:185-189. doi:10.1016/j.anl.2010.08.007.

33. Tjell C, Rosenhall U. Smooth pursuit neck torsion test: A specific test for cervical dizziness. *Am J Otol*. 1998;19:76-81. http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L28070287.

34. Prushansky T, Dvir Z, Pevzner E, Gordon CR. Electro-oculographic measures in patients with chronic whiplash and healthy subjects: A comparative study. *J Neurol Neurosurg Psychiatry*. 2004;75:1642-1644. doi:10.1136/jnnp.2003.031278.

35. Grip H, Jull G, Treleaven J. Head eye co-ordination using simultaneous measurement of eye in head and head in space movements: Potential for use in subjects with a whiplash injury. *J Clin Monit Comput*. 2009;23:31-40. doi:10.1007/s10877-009-9160-5.

36. Janssen M, Ischebeck BK, de Vries J, Kleinrensink G-J, Frens MA, van der Geest JN. Smooth Pursuit Eye Movement Deficits in Patients With Whiplash and Neck Pain are Modulated by Target Predictability. *Spine (Phila Pa 1976)*.

2015;40(19):E1052-E1057. doi:10.1097/BRS.0000000000001016.

37. Kongsted A, Jørgensen L V, Bendix T, Korsholm L, Leboeuf-Yde C. Are smooth pursuit eye movements altered in chronic whiplash-associated disorders? A cross-sectional study. *Clin Rehabil*. 2007;21(11):1038-1049. doi:10.1177/0269215507075519.

38. Treleaven J, Jull G, LowChoy N. Smooth pursuit neck torsion test in whiplash-associated disorders: Relationship to self-reports of neck pain and disability, dizziness and anxiety. *J Rehabil Med*. 2005;37:219-223. doi:10.1080/16501970410024299.

39. Treleaven J, Jull G, LowChoy N. The relationship of cervical joint position error to balance and eye movement disturbances in persistent whiplash. *Man Ther*. 2006;11:99-106. doi:10.1016/j.math.2005.04.003.

40. Spitzer WO, Skovron ML, Salmi LR, Cassidy JD, Duranceau J SS. Scientific monograph of the quebec task force on Whiplash-associated disorders: Redefining “whiplash” and its management. *Spine (Phila Pa 1976)*. 1995;20:1S-73S.

41. Tjell C, Tenenbaum A, Sandstrom S. Smooth pursuit neck torsion test - A specific test for whiplash associated disorders? *J Whiplash Rel Disord*. 2002;1:9-24. doi:10.1300/J180v01n02_02.

42. Kelders WP a, Kleinrensink GJ, van der Geest JN, et al. Compensatory increase of the cervico-ocular reflex with age in healthy humans. *J Physiol*. 2003;553(Pt 1):311-317. doi:10.1113/jphysiol.2003.049338.

43. Della Casa E, Affolter Helbling J, Meichtry A, Luomajoki H, Kool J. Head-Eye movement control tests in patients with chronic neck pain; Inter-observer reliability and discriminative validity. *BMC Musculoskelet Disord*. 2014;15. doi:10.1186/1471-2474-15-16.

44. Collewijn H. Eye movement recording. In: JG R, ed. *Vision Research, a Practical Guide to Laboratory Methods*. 1st ed. Oxford: Oxford University Press; 1999:245-185.

45. Hess CW, Muri R, Meienberg O. Recording of horizontal saccadic eye movements: methodological comparison between electro-oculography and infrared reflection oculography. *Neuro Ophthalmol*. 1986;6:189-197.

Chapter 3:

Eye stabilization reflexes in traumatic and non-traumatic chronic neck pain patients

Ischebeck, Britta K

de Vries, Jurryt

Janssen, Malou

van Wingerden, Jan Paul

Kleinrensink, Gert- Jan

van der Geest, Jos N

Frens, Maarten A

published in: Musculoskeletal Science and Practice 2017;29:72-77. doi:10.1016/j.msksp.2017.03.004.

ABSTRACT

Background Many chronic neck pain patients experience problems with vision. These problems are possibly induced by deviations of the eye stabilization reflexes. It is not known whether these eye reflex alterations occur both in traumatic and non- traumatic neck pain patients.

Objective To investigate if the cervico-ocular reflex (COR) and the vestibulo-ocular reflex (VOR) are changed in tertiary care patients with prolonged, chronic neck pain with various origin of complaints.

Design Cross sectional study

Methods Ninety-one chronic neck pain patients were subdivided into three groups by origin of complaints, and compared with healthy controls. COR and VOR gains were measured with an infrared eye tracking device with the subject sitting on a rotating chair in a darkened room and with the head fixed.

Results Neck pain patients had a higher COR gain (median 0.41, IQR 0.289) compared with healthy controls (median 0.231, IQR 0.179). The mean COR gain did not differ between the three patient groups (Whiplash Associated Disorders 0.444 (SD 0.221); traumatic group 0.397 (SD0.205); non-traumatic 0.468 (SD0.236)). There was no difference in VOR gain between the groups.

Conclusion Chronic neck pain patients, who already received primary care, still have an elevated cervico-ocular reflex. The origin of complaints did not seem to be associated with this deviant oculomotor behavior.

Keywords cervico-ocular reflex, vestibulo-ocular reflex, chronic neck pain patients, whiplash associated disorders

INTRODUCTION

Patients with chronic neck pain suffer from various complaints. Besides diminished range of motion, pain, headache and cognitive dysfunction [1–4], half of the patients report vision-related problems (e.g. concentration problems during reading, sensitivity to light and eye strain) [5–7]. Especially in patients with Whiplash Associated Disorders (WAD) visual disturbances might be related to deficits in oculomotor control [8]. The oculomotor system receives eye and body position information via eye stabilization reflexes using information from the eyes, the vestibulum and the cervical spine [9,10]. The vestibulo-ocular reflex (VOR) receives positional input from the vestibulum whereas the cervico-ocular reflex (COR) receives input from the muscle spindles and joint capsules in the (upper) cervical spine [9]. The VOR and COR work in conjunction to stabilize the visual image on the retina during head and trunk movements in space. Previous studies showed that the synergy between the COR and VOR can be disturbed in neck pain patients, due to altered cervical sensory input [11–13]. Patients' COR gain (that is, the amplitude of eye velocity fit compared to the stimulus velocity) is elevated without a compensatory decrease of the VOR gain, that is often observed in healthy individuals [11–13]. The optokinetic reflex which receives information from the eyes, remains unchanged in patients with WAD [11]. Despite the promising results of the studies of Kelders et al. and de Vries et al., their patient groups are diffuse with respect to duration of complaints, cause of complaints and previous treatments [12,13]. In the present patient group the option of natural recovery is minimized by increasing the minimum duration of complaints to 6 months. It is unknown how long COR and VOR reflex deviations persist, or whether the reflexes might prove chronically maladjusted. To our knowledge, no information is available on eye stabilization reflexes in severely impaired chronic neck pain patients. Studying oculomotor function in this patient population is of particular interest, since these chronic patients still do report sensorimotor, visual and cognitive dysfunction, even after multiple treatments. Furthermore, in this study both traumatic and non-traumatic neck pain patients are included, with an extra subdivision of the traumatic group. Finally, in this study all patients received earlier, but unsuccessful treatment.

The first aim of the present study is to investigate the eye stabilization reflexes in a group of unsuccessfully treated patients with long-lasting neck pain and compare these outcomes with a group of healthy controls.

The second aim is to determine whether there are differences in eye stabilization reflexes in patients with comparable history, but different origin of complaints, i.e. traumatic versus non-traumatic. In order to specify if a certain traumatic impact is determinative for alteration of eye stabilization reflexes, the traumatic group will be divided into a whiplash associated disorders (WAD) group as defined by Spitzer at al. and patients with a traumatic impact, but no whiplash acceleration-deceleration mechanism of energy transfer to the neck [14]. Most of the patients in the WAD group have had a car accident with a whiplash mechanism, associated with or without blunt trauma to the head. The patients of the traumatic group have had no direct trauma to the neck or the head.

Right now, the underlying mechanisms of eye reflex alterations are still unknown. It can be argued that patients with WAD have, due to the high traumatic impact on the cervical spine, a more distinct reflex alteration than non-WAD and non-traumatic neck pain patients. However, eye stabilization reflexes may be, besides due to anatomical damage, also altered due to sensorimotor changes or behavioral factors [2,11]. It is worthwhile to investigate this influence as it may aid in diagnosis and assessing the effectiveness of treatments.

METHODS

Participants

Patients with chronic neck pain were included from the population of the Spine & Joint Centre Rotterdam, a Dutch rehabilitation center for patients with chronic neck complaints. All patients took part of the study prior to their rehabilitation. Participants with neck pain were included if they 1) were referred to the Spine & Joint Centre with the diagnosis of chronic neck pain (pain primarily in the neck for more than six months); 2) had received primary care physiotherapy more than 9 times without benefit (actual intervention not specified); 3) were between the age of 18 and 65 years; 4) were able to understand and speak the Dutch language and 5) were physically able to undergo COR and VOR measurements (which involved sitting immobilized in a chair for 30 minutes).

The participants with neck pain were divided into three groups: Group 1. patients with WAD grade 2 or 3 [14] (WAD group); Group 2. patients with a traumatic origin of the complaints, but no motor vehicle accident and no direct impact on the neck (e.g. falling of a horse or bicycle, traumatic delivery) (Traumatic neck pain group [T]); Group 3. patients with a non-traumatic origin of complaints (Non-traumatic neck pain group [NT]).

Participants in the healthy control group were recruited among co-workers and students and had no personal or legal relationship with the investigator. The inclusion criteria were 1) aged between 18 and 65; 2) able to understand and speak the Dutch language; 3) without any complaints of the cervical spine (including cervicogenic headache and dizziness) in the last 5 years; and 4) without any history of neck trauma. Exclusion criteria were 1) suffering from any neurological disorder, or vestibular or visual problems prior to the neck pain; and 2) having fractures or surgery in the cervical spine, temporomandibular joint or head in the past.

All participants were without any ocular abnormalities that could not be corrected by wearing glasses or contact lenses. They were recruited and tested between January 2012 and January 2015. The study was approved by the local ethical board of the Erasmus MC and all participants gave prior written informed consent.

Experimental setup

The experimental setup was identical to the setup described in an earlier study [13]. In short, infrared video-oculography [Eyelink 1, SMI, Germany [15]] at a sample rate of 250 Hz was used for the recording of monocular (left) eye positions while people were rotated using a motor driven rotatable chair

(Harmonic Drive, Germany). The motor induced continuous sinusoidal chair rotations around the vertical axis without any backlash. The position of the chair was recorded with sensors and stored on the computer.

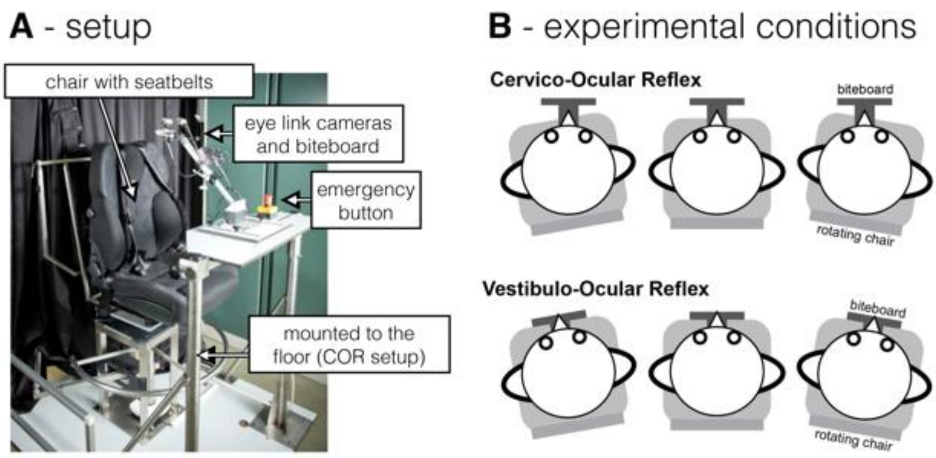

Figure 1: Panel A shows a photograph of the chair and the position of the cameras and the bite board in the COR setup. Panel B shows the measurement of the vestibular ocular reflex (VOR) with the bite board attached to the chair, and the cervico-ocular reflex (COR) with the bite board attached to the floor, whilst the chair is rotating back and forth.

The trunk was fixed to the chair at shoulder level by a double-belt system (figure 1a). Head position was fixed by means of a custom-made bite board. The bite board was positioned with the axis of chair rotation under the midpoint of the inter-aural line and fixed to the floor to guarantee a fixed head position. In this case, rotation of the chair in complete darkness induced pure cervical stimulation, which elicits the COR in isolation (figure 1b). In the COR stimulation, the chair rotated for 134 seconds with an amplitude of 5.0 degrees and a frequency of 0.04 Hz. This yielded five full sinusoidal rotations of the chair with peak velocity of 1.26 degrees/s.

When the bite board was mounted to the chair, rotation of the chair in complete darkness induced pure vestibular stimulation, eliciting the VOR in isolation (figure 1b). In the VOR stimulation, the chair rotated for 33 seconds with an amplitude of 5.0 degrees and a frequency of 0.16 Hz. This yielded five full sinusoidal rotations of the chair with peak velocity of 5.03 degrees/s.

In both eye movement stimulations, which were ran in complete darkness, participants were instructed to look at a position directly in front of the set-up which was briefly indicated by means of a laser dot.

Data Analysis

All data processing was done with custom-written scripts in Matlab R2013a (The MathWorks Inc., Natick, MA). Eye movement reflexes were analyzed by looking at the eye velocity relative to the chair or stimulus velocity, referred to as the gain of the eye movement. Eye velocity was calculated by taking the derivative of the horizontal eye position signal. Blinks, saccades and fast phases were removed (using a 20 degrees-per-second threshold) and a sine wave was fitted through the eye velocity signal data. The gain of the response was defined as the amplitude of the eye velocity fit divided by the peak velocity of the chair rotation (COR: 1.26 degrees/s; VOR: 5.03 degrees/s). A gain of 1 thus reflects that the peak velocity of the eye was the same as the peak velocity of the stimulus.

Statistical Analysis

Differences in the eye stabilization reflexes between patients with chronic neck pain and healthy controls were statistically assessed by non-parametric statistics using Mann-Whitney tests. Correlations between the gains of the COR and VOR, as well as between these gains and age and gender, were statistically assessed using Spearman's correlations.

To assess the effect of the origins of complaints, we compared the eye stabilization reflexes between the three groups (WAD, T and NT) with the Kruskal-Wallis test.

An alpha level of $p < 0.05$ was considered significant for all statistical tests. The data was analyzed with IBM SPSS Statistics for Windows, version 20 (IBM Corp., Armonk, NY).

RESULTS

117 participants completed the measurements successfully. The VOR measurement of three patients (2x WAD; 1x NT) and one healthy control were discarded due to technical errors.

The comparison of eye stabilization reflexes between 91 patients with chronic neck pain [45 male, 84 female; median age 42 (IQR 19); median VAS pain 56 (min-max: 11-90; IQR 39)] and 30 healthy controls [(16 male, 14 female; median age 25 (IQR 6)] are summarized in table 1 and figure 2. The COR gain of patients with chronic neck pain was significantly higher than the COR gain of healthy controls, but the VOR gain did not differ between the two groups. In the WAD group and in the traumatic group, the gain of the COR was moderately correlated with age. There was no correlation between COR and age in the non-traumatic group (table 4).

	patients	controls	Mann-Whitney-test
n	91	30	
age (median, IQR)	42 (19)	25 (6)	U=605.5, Z=-5.856, p<0.001
gender	65% female	46% female	U= 1578.0, Z=-1.866, p=0.062
VOR (median, IQR)	0.7 (0.302)	0.7 (0.255)	U= 1399.5, Z= -0.041, p=0.968
COR (median, IQR)	0.41 (0.289)	0.231 (0.179)	U= 659.5, Z= -4.235, p<0.001

Table 2: Eye stabilization reflexes in patients and healthy controls. VOR= vestibulo-ocular reflex; COR= cervico-ocular reflex; IQR= interquartile range

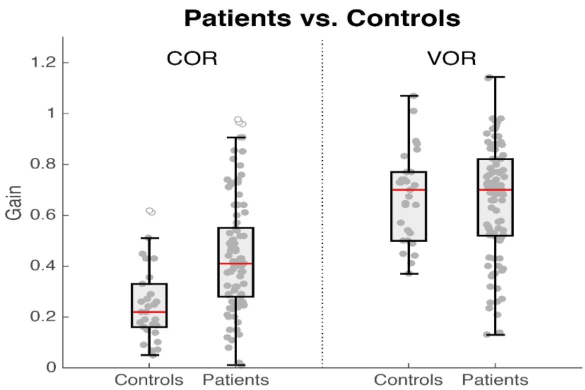

Figure 2: Boxplot of COR and VOR gain in patients and healthy control group. Thick horizontal line in the grey box line = median; grey box = IQR, grey dots = individual gain values; open circles = outliers. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

In both groups no correlations between the eye stabilization reflexes and age or gender were found (table 2).

	VOR	age	gender
COR	CT: -0.014 (p=0.944) PT: -0.054 (p=0.617)	CT: -0.052 (p=0.786) PT: 0.002 (p=0.984)	CT: 0.154 (p=0.415) PT: 0.144 (p=0.173)
VOR		CT: -0.019 (p=0.923) PT: 0.186 (p=0.083)	CT: -0.07 (p=0.716) PT: -0.036 (p=0.742)
age			CT: -0.077 (p=0.684) PT: 0.025 (p=0.814)

Table 3: Correlations (correlation coefficient and p-value) between the different variables (gain of the COR and VOR, age and gender) for the two groups (PT= patients; CT= controls)

We observed no effect of the origin of the neck pain when we compared the three different patient groups (table 3 and figure 3). Both the COR and VOR gains were similar between patients with WAD, with a traumatic origin and with a non-traumatic origin.

	WAD	T	NT	Kruskal-Wallis
n	28	16	47	
age (median, IQR)	40; 21	42; 22	44; 17	H(2)= 6.604, p= 0.037
gender	59% female	65% female	68% female	H(2)= 4.603, p= 0.100
VOR (median, IQR)	0.695; 0.386	0.680; 0.397	0.712; 0.299	H(2)= 0.351, p= 0.839
COR (median, IQR)	0.420; 0.372	0.395; 0.182	0.468; 0.330	H(2)= 0.903, p= 0.637

Table 4: Eye stabilization reflexes in the three different patient groups. VOR= vestibulo-ocular reflex; COR= cervico-ocular reflex; WAD= Whiplash group; T= traumatic group; NT= non-traumatic group; IQR= interquartile range

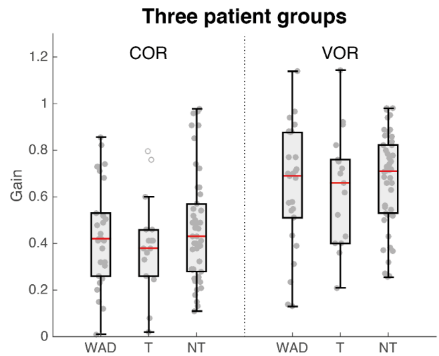

Figure 3: Boxplot of COR and VOR gain in the three patient groups. Thick horizontal line in the grey box line = median; grey box = IQR, grey dots = individual gain values; open circles = outliers. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

	VOR	age	gender
COR	WAD: -0.099 (p=0.631) T: -0.185 (p=0.494) NT: -0.03 (p= 0.843)	WAD: 0.561 (p=0.002) T: -0.615 (p=0.011) NT: -0.118 (p=0.429)	WAD: 0.097 (p=0.622) T: -0.14 (p=0.604) NT: 0.255 (p= 0.083)
VOR		WAD: 0.148 (p=0.470) T: 0.156 (p= 0.565) NT: 0.172 (p=0.254)	WAD: -0.139 (p=0.5) T: 0.098 (p= 0.718) NT: -0.047 (p=0.758)
age			WAD: -0.186 (p=0.343) T: 0.24 (p= 0.371) NT: -0.077 (p= 0.605)

Table 5: Correlations (correlation coefficient and p-value) between the different variables for the three different patient groups

DISCUSSION

The current study aimed at the question whether eye stabilization reflexes are altered in unsuccessfully treated chronic neck pain patients and whether there are differences in eye stabilization reflexes between traumatic and non-traumatic patients. The results of this study show that chronic neck pain patients have an elevated COR and an unchanged VOR gain compared with healthy controls. Furthermore, traumatic and non-traumatic neck pain patients have similar COR and VOR gains. Apparently, changes in eye stabilization reflexes are not predominantly caused by a traumatic physical impact.

Chronic neck pain patients who experience neck pain for at least six months, still show an elevated COR and an unchanged VOR. Apparently, COR does not diminish automatically in chronic neck pain patients even when they receive paramedical treatment. It appears that in this severely impaired patient group (with a median reported VAS pain of 56) the persistence of altered reflexes depends on other -non temporary- factors. Studies show that chronic neck pain patients demonstrate irregular cervical movement strategies and diminished cervical range of motion [3,16]. Sensorimotor impairment is suggested as underlying cause for these specific motion patterns [16–18]. It is hypothesized that this specific motion characteristic may lead to altered reflexes [19]. Consequently, the COR remains augmented as long as cervical afferent information is hampered by this sensorimotor impairment. Cervical sensorimotor impairment includes disturbed mechanisms of muscle control (altered activation pattern of muscles) and changed muscle properties (e.g. fatty degeneration of the cervical extensor muscles) [16–18,20–24]. It would be of high clinical relevance to determine if eye stabilization reflexes regulate themselves after diminishing of this sensorimotor disturbances. This could be studied by measuring the effect of specific sensorimotor training on altered eye stabilization reflexes [18,19,25].

In the current study besides the COR, also the VOR was measured. It is yet unclear why the VOR does not adapt in neck pain patients and we can only speculate about the cause. In healthy individuals, age dependent decrease of the VOR is caused by degeneration of the vestibular system [26]. The COR adapts to this alteration with increased gain. However, in neck pain patients not the vestibular system, but the cervical system changes [11,12]. This change affects the COR without an effect on the VOR, thereby changing the correlation between the two reflexes. Apparently, while VOR gain seems conditional for COR gain, this does not automatically imply that COR gain is also conditional for VOR gain.

The second result of this study is that the three groups of chronic neck pain patients with traumatic and non-traumatic origin of complaints have comparable gains of the eye stabilization reflexes. A whiplash trauma seems to be no prerequisite for the development of oculomotor disorders. Thus, in the studied population, the origin of complaints, whether traumatic or non- traumatic do not determine alteration of reflexes and can no longer be seen as negative predictive factor for the development of altered eye stabilization reflexes. This implies that the alteration is dependent of other, presently unknown, factors which can possibly be changed by treatment. These factors are not explored in the current study. To get more insight into the underlying mechanisms of changed reflexes, it would be useful to study the influence of a variety of patient characteristics (sensorimotor function, degree of disability and pain, duration of complaints, cervical range of motion) and behavioral factors, like e.g. fear avoidance behavior, fatigue and stress on eye stabilization reflexes.

With respect to possible confounding in the current study, we paid attention to influence of age on reflex gain. In this study there is a significant age difference between patients and healthy controls (the healthy control group was younger than the patient group). Nevertheless, the impact of age on the COR seems to be negligible. Age dependent increase of the COR is only seen in healthy individuals of 60 years and older [27]. In the current study the correlation between the COR gain and age differs in the two traumatic groups. The correlation in the WAD group is positive and in the traumatic group negative (table 4). We can only speculate about this reversed correlation between COR and age between the groups. It could be related to differences in patient characteristics between the groups, e.g., in neck mobility and in duration of the complaints.

It is point of discussion whether a negative correlation exists between the VOR- and the COR gain in healthy individuals. Two studies report a moderate negative relationship between COR and VOR gain [11,27], but in the present study and in the study of de Vries et al. this correlation could not be confirmed[13].

CONCLUSION

Severely impaired chronic neck pain patients have an elevated COR and an unchanged VOR compared to healthy controls. This elevation seems to be independent of the traumatic or non-traumatic origin of complaints. The group of neck pain patients with altered eye stabilization reflexes is thereby bigger than suspected. Maybe persistent sensorimotor disorders of the cervical spine are a perpetuating factor for eye reflex alteration.

REFERENCES

1. Treleaven J. Dizziness, Unsteadiness, Visual Disturbances, and Postural Control Implications for the Transition to Chronic Symptoms After a Whiplash Trauma. *Spine (Phila Pa 1976)*. 2011;36:S211-S217.
2. Curatolo M, Bogduk N, Ivancic PC, McLean S a, Siegmund GP, Winkelstein B a. The role of tissue damage in whiplash-associated disorders: discussion paper 1. *Spine (Phila Pa 1976)*. 2011;36(25 Suppl):S309-15. doi:10.1097/BRS.0b013e318238842a.
3. Stenneberg MS, Rood M, de Bie R, Schmitt MA, Cattrysse E, Scholten-Peeters GG. To What Degree Does Active Cervical Range of Motion Differ Between Patients With Neck Pain, Patients With Whiplash, and Those Without Neck Pain? A Systematic Review and Meta-Analysis. *Arch Phys Med Rehabil*. October 2016. doi:10.1016/j.apmr.2016.10.003.
4. Anstey R, Kongsted A, Kamper S, Hancock MJ. Are People With Whiplash-Associated Neck Pain Different From People With Nonspecific Neck Pain? *J Orthop Sports Phys Ther*. 2016;46(10):894-901. doi:10.2519/jospt.2016.6588.
5. Treleaven J, Takasaki H. Characteristics of visual disturbances reported by subjects with neck pain. *Man Ther*. 2014;19(3):203-207. doi:10.1016/j.math.2014.01.005.
6. Hülse. Klinik der Funktionsstörungen des Kopfgelenkbereiches. In: Hülse M, Neuhuber WL WH, ed. *Der Kranio-Zervikale Übergang*. Berlin: Sprin; 1998:43-97.
7. Wolff H. Störungen des kraniozervikalen Übergang (Kopfgelenkbereich). In: Wolff H, ed. *Neurophysiologische Aspekte Des Bewegungssystems*. Berlin: Springer; 1996.
8. Ischebeck BK, de Vries J, Van der Geest JN, et al. Eye movements in patients with Whiplash Associated Disorders: a systematic review. *BMC Musculoskelet Disord*. 2016;17(1):441. doi:10.1186/s12891-016-1284-4.
9. Hikosaka O, Maeda M. Cervical effects on abducens motoneurons and their interaction with vestibulo-ocular reflex. *Exp Brain Res*. 1973;18(5):512-530. http://www.ncbi.nlm.nih.gov/pubmed/4794882.
10. Van Die GC, Collewijn H. 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*. 1986;383(1-2):185-194. http://www.ncbi.nlm.nih.gov/pubmed/3768688.
11. Montfoort I, Kelders WP a, van der Geest JN, et al. Interaction between ocular stabilization reflexes in patients with whiplash injury. *Invest Ophthalmol Vis Sci*. 2006;47(7):2881-2884. doi:10.1167/iovs.05-1561.
12. Kelders WP a, Kleinrensink GJ, van der Geest JN, et al. The cervico-ocular reflex is increased in whiplash injury patients. *J Neurotrauma*. 2005;22(1):133-137. doi:10.1089/neu.2005.22.133.
13. de Vries J, Ischebeck BK, Voogt LP, et al. Cervico-ocular Reflex Is Increased in People With Nonspecific Neck Pain. *Phys Ther*. 2016;96(8):1190-1195. doi:10.2522/ptj.20150211.
14. Spitzer WO, Skovron ML, Salmi LR, Cassidy JD, Duranceau J SS. Scientific monograph of the quebec task force on Whiplash-associated disorders: Redefining "whiplash" and its management. *Spine (Phila Pa 1976)*. 1995;20:1S-73S.
15. van der Geest JN, Frens M a. Recording eye movements with video-oculography and scleral search coils: a direct comparison of two methods. *J Neurosci Methods*. 2002;114(2):185-195. http://www.ncbi.nlm.nih.gov/pubmed/11856570.
16. Sjölander P, Michaelson P, Jaric S, Djupsjöbacka M. Sensorimotor disturbances in chronic neck pain--range of motion, peak velocity, smoothness of movement, and repositioning acuity. *Man Ther*. 2008;13(2):122-131. doi:10.1016/j.math.2006.10.002.
17. Baydal-Bertomeu JM, Page AF, Belda-Lois JM, Garrido-Jaén D, Prat JM. Neck motion patterns in whiplash-associated disorders: quantifying variability and spontaneity of movement. *Clin Biomech (Bristol, Avon)*. 2011;26(1):29-34. doi:10.1016/j.clinbiomech.2010.08.008.
18. Kristjansson E, Treleaven J. Sensorimotor function and dizziness in neck pain: implications for assessment and management. *J Orthop Sports Phys Ther*. 2009;39(5):364-377. doi:10.2519/jospt.2009.2834.
19. Röijezon U, Clark NC, Treleaven J. Proprioception in musculoskeletal rehabilitation: Part 1: Basic science and principles of assessment and clinical interventions. *Man Ther*. 2015;20(3):368-377. doi:10.1016/j.math.2015.01.008.
20. Hodges PW. Pain and motor control: From the laboratory to rehabilitation. *J Electromyogr Kinesiol*. 2011;21(2):220-

228. doi:10.1016/j.jelekin.2011.01.002.

21. Falla D, Farina D. Neural and muscular factors associated with motor impairment in neck pain. *Curr Rheumatol Rep*. 2007;9(6):497-502. http://www.ncbi.nlm.nih.gov/pubmed/18177604.
22. Treleaven J, Jull G, LowChoy N. The relationship of cervical joint position error to balance and eye movement disturbances in persistent whiplash. *Man Ther*. 2006;11:99-106. doi:10.1016/j.math.2005.04.003.
23. Elliott J, Jull G, Noteboom JT, Darnell R, Galloway G, Gibbon WW. Fatty infiltration in the cervical extensor muscles in persistent whiplash-associated disorders: a magnetic resonance imaging analysis. *Spine (Phila Pa 1976)*. 2006;31(22):E847-55. doi:10.1097/01.brs.0000240841.07050.34.
24. Karlsson A, Leinhard OD, Åslund U, et al. An Investigation of Fat Infiltration of the Multifidus Muscle in Patients With Severe Neck Symptoms Associated With Chronic Whiplash-Associated Disorder. *J Orthop Sports Phys Ther*. 2016;46(10):886-893. doi:10.2519/jospt.2016.6553.
25. Clark NC, Röijezon U, Treleaven J. Proprioception in musculoskeletal rehabilitation. Part 2: Clinical assessment and intervention. *Man Ther*. 2015;20(3):378-387. doi:10.1016/j.math.2015.01.009.
26. Paige GD. Senescence of human visual-vestibular interactions: smooth pursuit, optokinetic, and vestibular control of eye movements with aging. *Exp Brain Res*. 1994;98(2):355-372. http://www.ncbi.nlm.nih.gov/pubmed/8050519.
27. Kelders WP a, Kleinrensink GJ, van der Geest JN, et al. Compensatory increase of the cervico-ocular reflex with age in healthy humans. *J Physiol*. 2003;553(Pt 1):311-317. doi:10.1113/jphysiol.2003.049338.

Chapter 4:

Cervico-ocular Reflex Is Increased in People with Nonspecific Neck Pain

de Vries, Jurryt

Ischebeck, Britta K

Voogt, Lennard P

Janssen, Malou

Frens, Maarten A

Kleinrensink, Gert-Jan

van der Geest, Jos N

published in: Physical Therapy 2016;96. doi:10.2522/ptj.20150211.

ABSTRACT

Background Neck pain is a widespread complaint. People experiencing neck pain often present an altered timing in contraction of cervical muscles. This (altered) afferent information elicits the cervico-ocular reflex (COR), which stabilizes the eye in response to trunk-to-head movements. The vestibulo-ocular reflex (VOR) elicited by the vestibulum is thought to be unaffected by afferent information from the cervical spine.

Objective Measurement of COR and VOR in people with non-specific neck pain.

Design Cross-sectional design according to the STROBE statement.

Methods An infrared eye-tracking device was used to record the COR and the VOR while the participant was sitting on a rotating chair in darkness. Eye velocity was calculated by taking the derivative of the horizontal eye position. Parametric statistics were performed.

Results The mean COR gain in the control group (N= 30) was 0.26 (SD= 0.15), against 0.38 (SD= 0.16) in the non-specific neck pain group (N= 37). Analyses of covariance were performed to analyze differences in COR and VOR gains with age and gender as covariates. Analyses of covariance showed a significantly increased COR in people with neck pain (p= 0.046). The VOR between the control group with a mean VOR of 0.67 (SD= 0.17) and the non-specific neck pain group with a mean VOR of 0.66 (SD=0.22) was not significantly different (p= 0.203).

Limitations Measuring eye movements while the participant is sitting on a rotating chair in complete darkness is technically complicated.

Conclusions This study suggests that people with non-specific neck pain have an increased COR. The COR is an objective non-voluntary eye reflex and an unaltered VOR. This study shows that an increased COR is not restricted to traumatic neck pain patients.

INTRODUCTION

Neck pain is a major problem worldwide, and is a common reason for individuals to seek care from physiotherapists and manual therapists.[1, 2] In addition to pain, concomitant symptoms are often present, including headache (65% of cases), dizziness (31%)[3], and visual disturbances.[4] Visual disturbances in people with neck pain might be related to deficits in oculomotor control.[5-8] In the majority of people with neck pain, a specific cause cannot be identified, and the term "non-specific neck pain" is used.[9, 10]

People experiencing neck pain often present functional disorders (such as an altered timing in contraction) of the cervical muscles, such as the m. longus colli and the m. longus capitis.[11-13] These cervical muscles provide information to, and receive information from, the central nervous system.[14-16] Animal studies have showed that pain has profound effects on muscle spindle afferents.[17, 18] In humans, cervical pain leads to, for instance, a worse joint position sense indicating a disturbed proprioception.[19-21] Afferent information from the cervical muscles is sent to the vestibular nuclei where it converges with other information regarding head movements relayed by the visual and vestibular systems.[22] It can be argued that incongruences between the cervical, vestibular, and visual systems are likely to be associated with dizziness and decreased postural stability.[23]

The cervical afferents are not only important for controlling head movements. They are also involved in the cervico-ocular reflex (COR). The COR stabilizes the eye in response to trunk-to-head movements.[24-26] The COR operates in conjunction with the vestibulo-ocular reflex (VOR). The VOR stabilizes the eye in response to vestibular input, i.e., movements of the head in space. The COR is elicited by proprioception of the facet joints of the cervical spine and deep muscles of the neck. The strength of the COR can be modified as a result of altered visual input[27] and by immobilization of the cervical spine by means of a stiff neck collar.[28] The COR increases in people aged over 60 years as a compensatory mechanism for the sensory loss of the vestibulum.[29]. In people with a Whiplash Associated Disorder (WAD), this compensatory mechanism is not seen[28, 30]. The strength of the COR is increased in people with WAD although there is no compensatory decline in VOR.[30, 31] To date, no research on COR in people with non-specific neck pain has been conducted.

Here we describe the two eye movement reflexes (COR and VOR) in people with non-specific neck pain who are likely to have deficits in neck proprioception.[32] Therefore, we expect that the COR but not the VOR will be altered, compared to healthy controls.

METHODS

The guidelines of the STROBE statement (Strengthening the Reporting of Observational Studies in Epidemiology)[33] were used for the outline of this paper.

Design Overview
We conducted a cross-sectional study involving participants with neck pain and healthy controls.

Setting and Participants
Participants with neck pain were recruited via physiotherapy practices in Rotterdam, The Netherlands. People with non-specific neck pain were asked personally by their physiotherapist to participate in the study. These physiotherapists had been briefed about the study and had information letters for the patients. If patients formally consented to being contacted by the investigator, the physiotherapist contacted the investigator. Healthy controls were recruited by means of an information letter spread among co-workers, students, and other people in the Erasmus University Medical Center and the Rotterdam University of Applied Sciences having no personal or legal relationship with the investigator. All participants were recruited and tested between October 2012 and September 2014. The study was approved by the local ethical board of the Erasmus MC. All participants gave prior written informed consent.

Participants with neck pain were eligible if they 1) were between the ages of 18 and 65 years; 2) spoke Dutch; 3) experienced non-specific neck pain (defined as the sensation of mild to moderate pain and discomfort in the neck area with possible radiation to the thoracic spine and one or both shoulders) continuously for less than one year; and 4) were physically able to undergo COR and VOR measurements (which involved sitting immobilized in a chair for 30 minutes). Participants were excluded if they: 1) used medication that influenced alertness or balance (*e.g.*, benzodiazepines, barbiturates); 2) suffered from any neurological disorder, or had vestibular or visual problems; or 3) had a history of neck trauma (a history would make the diagnosis specific instead of non-specific). Healthy controls were eligible if they; 1) were between the ages of 18 and 65; 2) spoke Dutch; 3) had not experienced any complaints of the cervical spine (including cervicogenic headache and dizziness) in the last 5 years; and 4) were without a history of neck trauma.

Demographic and Clinical Characteristics
Participants filled in a standard demographic questionnaire (gender and age were measured and labeled as possible confounders). In participants with neck pain, the intensity of perceived pain was evaluated using a numeric pain rating scale (NRPS), the functional disability due to neck pain was evaluated using the Neck Disability Index (NDI), and the Dizziness Handicap Inventory (DHI) was used to assess the perceived handicap due to dizziness. The NRPS, NDI, and DHI have shown good psychometric properties in people with neck pain.[34-36]

In all participants, the cervical range of motion (CROM) was measured with a CROM device (Performance Attainment Associates, USA). The CROM device consists of a magnet and three compass-like instruments positioned in the three directions of neck mobility (rotation, flexion/extension, and lateroflexion). The CROM measures the maximum range of motion (in degrees) in each of these directions.[37]

Recording of Reflexive Eye Movements
Monocular (left) eye positions were recorded by infrared video-oculography (Eyelink 1, SMI, Germany:

see van der Geest & Frens[38]) at a sample rate of 250 Hz. Eye position was calibrated using the built-in nine-point calibration routine. Eye movements were recorded during either cervical or vestibular stimulation in complete darkness by rotating the chair in which the participant was seated. The chair was attached to a motor (Harmonic Drive, Germany) that ensured sinusoidal chair rotation without any backlash. The trunk was fixed to the chair at shoulder level by a double-belt system. A sensor connected to the chair recorded chair position, and stored the data on a computer along with eye positions.

In both stimulation paradigms (COR and VOR), participants were instructed to keep their eyes open during the stimulation and to look at a position directly in front of the set-up. This position was briefly indicated by means of a laser dot before the rotation started. Head position was fixed in both conditions by means of a custom-made biteboard. In both stimulation paradigms, the position of the biteboard was set so that the axis of rotation was under the midpoint of the inter-aural line.

During the COR stimulation, the biteboard was mounted to the floor to fix the position of the head in space (see Figure 1). Rotation of the chair induced pure cervical stimulation, which elicits the COR in isolation. The chair was rotated for 134 seconds around the vertical axis with an amplitude of 5.0 degrees and a frequency of 0.04 Hz. This yielded 5 full sinusoidal rotations of the chair with a peak velocity of 1.26 degrees/s. During the VOR stimulation, the biteboard was mounted to the chair so that rotation of the chair induced pure vestibular stimulation (see Figure 1). The chair was rotated for 33 seconds around the vertical axis with an amplitude of 5.0 degrees and a frequency of 0.16 Hz. This yielded 5 full sinusoidal rotations of the chair with a peak velocity of 5.03 degrees/s.

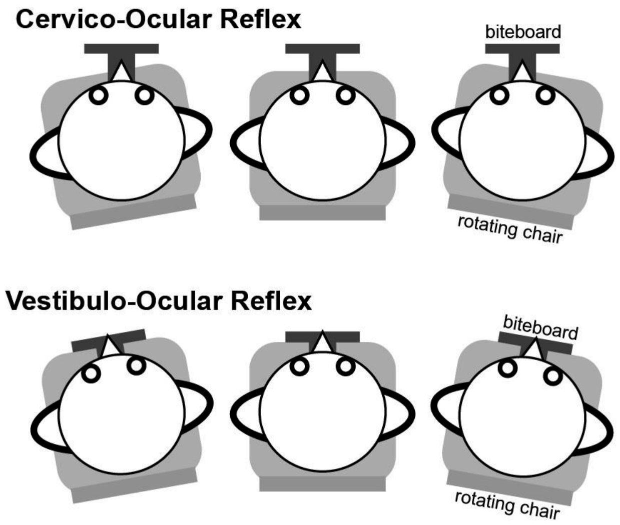

Figure 1. A schematic representation of the experimental set-up. In both paradigms the participants had to look at a position directly in front of the set-up. For the COR, the body of the subjects was rotated while the head of the participants was held fixed relative to the floor to fixate the position of the head in space. For the VOR, the body of the subjects was rotated while the head of the participants was held fixed relative to the chair.

Data Processing and Analyses

Eye velocity was calculated by taking the derivative of the horizontal eye position signal. After removal of blinks, saccades, and fast phases (using a 20 degrees-per-second threshold), a sine wave was fitted through the eye velocity signal data. Stimulus velocity was derived from chair position (COR and VOR measurement) data. The gain of the response was defined as the amplitude of the eye velocity fit divided by the peak velocity of the chair rotation (COR: 1.26 degrees/s, VOR: 5.03 degrees/s). Therefore, a gain of one reflects that the peak velocity of the eye was the same as the peak velocity of the chair rotation. All data processing was done with Matlab R2013a (The MathWorks Inc., Natick, MA).

Statistical Analysis

Descriptive statistics were computed for the entire sample for the gains of the COR and VOR (outcome parameters), NDI, DHI, perceived pain, CROM (outcome variables), and age and gender (possible confounders). Since the data was distributed normally (Kolmogorov-Smirnov test), parametric statistics were applied. Two analyses of covariance (ANCOVA) were performed to analyze differences in COR and VOR gains, respectively, between healthy controls and participants with neck pain with age and gender as covariates. Correlations between the gains (outcome parameters) and outcome variables were assessed using Pearson correlation coefficients. An alpha level of $P < 0.05$ was considered significant for all statistical tests. The data was analyzed with IBM SPSS Statistics for Windows, version 22 (IBM Corp., Armonk, NY).

RESULTS

Forty-one participants with neck pain and 30 healthy controls participated in the study. Eye movement recordings were successful in 37 participants with neck pain. In two participants, it was not possible to track the eye of the participant; in one participant, calibration of the eye tracking failed, and in one participant we failed to store the data properly on the hard disk.

Table 1 shows the group characteristics. Healthy controls were on average 13.8 years younger than participants with neck pain. There was a correlation between the VOR gain and age in the control group ($r=0.370$, $p=0.048$). In the neck pain group, there was no correlation

between the VOR gain and age ($r=0.163$, $p=0.364$). No other correlations between age, COR

gain, VOR gain, and the CROM were found within each group (all $r <0.291$).

	Control (N=30)		**Neck pain (N=37)**	
	Mean (SD)	95% CI	Mean (SD)	95% CI
Age in years	28.3 (9.1)	25.7, 32.3	42.1 (12.3)*	36.5, 44.9
Male/female	15/15	-	12/25	-
COR	0.26 (0.15)	0.21, 0.32	0.38 (0.16)*	0.31, 0.42
VOR	0.67 (0.17)	0.61, 0.74	0.66 (0.22)	0.56, 0.72

CROM Rotation	139 (18)	133, 146	134 (27)	126, 145
CROM flexion/extension	133 (23)	123, 139	111 (25)*	103, 122
Pain	-	-	4.1 (2.0)	3.5, 4.8
Neck Disability Index	-	-	23.4 (12.8)	20.5, 28.4
Dizziness Handicap Inventory	-	-	18.2 (17.3)	12.3, 24.7

Tabel 1: Comparison of demographic and questionnaire data between asymptomatic controls and participants with neck pain. NDI scores range from 0 (no disability) to 100 (maximal disability), DHI scores range from 0 (no disability) to 100 (maximal disability), CROM= cervical range of motion. Age and gender were identified as possible confounders.
* Significant difference between control and neck pain group at $p < 0.05$.

Participants with neck pain showed an increased COR after controlling for age and gender, $F(1,62) = 4.15$, $p= 0.046$, $\eta^2=0.063$), but no significant difference in VOR $F(1,58)= 1.66$ $p= 0.203$, $\eta^2=0.028$), compared to healthy controls. The CROM was reduced in participants with non-specific neck pain in the vertical plane (flexion/extension, $F(1,60)= 4.21$, $p= 0.045$, $\eta^2=0.066$), but not in the horizontal plane (Rotation, $F(1,60)= 0.33$, $p= 0.568$, $\eta^2=0.005$).

The correlation between the gains of the two eye movement reflexes was not significant when the data were pooled ($r= 0.211$, $p=0.102$; Figure 2), or analyzed per group, neck pain group ($r= 0.304$, $p=0.091$) and in the control group ($r= 0.152$, $p=0.431$).

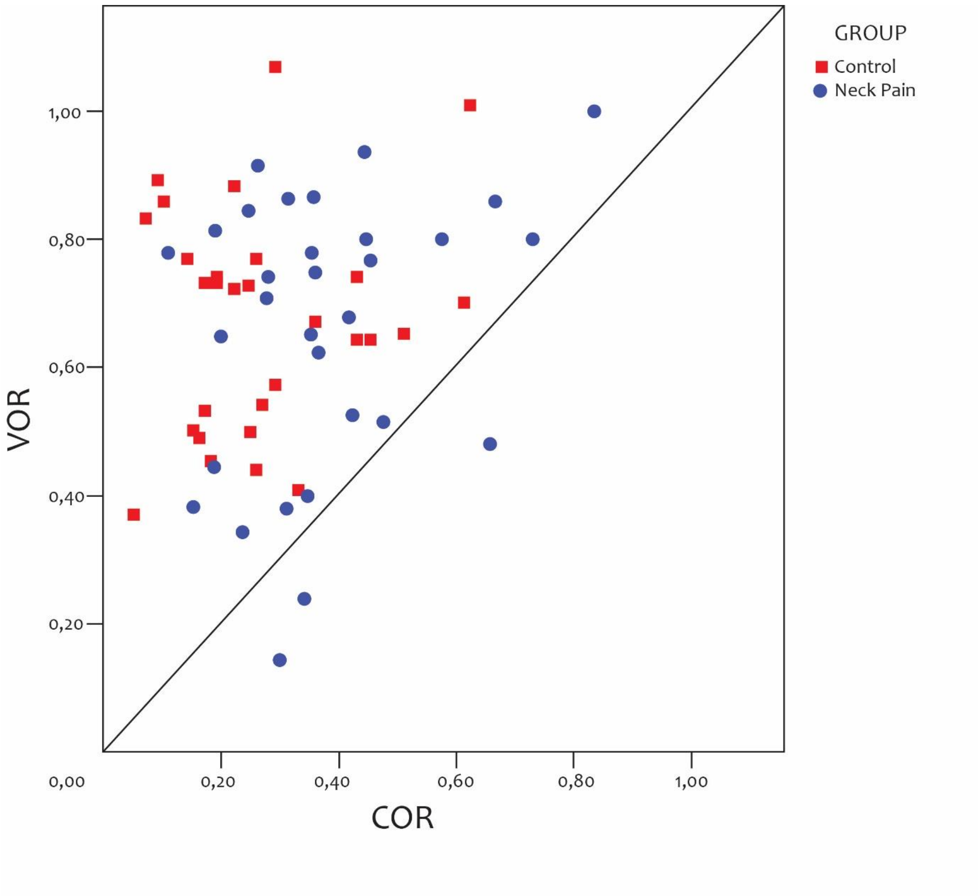

Figure 2. Scatterplot of the COR and VOR for all participants. In addition, correlations between the COR or VOR on the one hand, and pain levels, location of the neck pain, range of motion of the cervical spine, NDI, or DHI scores on the other hand were not significant (r between 0.037 and -0.233, all p > 0.172). The correlation between COR gain and pain level at the moment of measurement was close to significance (r= -0.304, p=0.07).

Discussion

We observed a higher COR but an unaltered VOR in a group of participants with non-specific neck pain group compared to a group of healthy controls. This is the first study investigating the COR in non-traumatic neck pain. Similar results were obtained in a previous study in people with WAD.[5] This suggests that an increased COR is not restricted to specific patient groups with neck pain.

An explanation for an increased COR in people with neck pain could be altered afferent information from the cervical spine. In the cervical spine, the information from muscles is a dominant source of information.[39, 40] Deficits in afferent information are suggested by MRI studies showing a widespread presence of fatty infiltrates in the neck muscles of patients with chronic whiplash[41] and to a lesser extent in idiopathic neck pain.[42] Furthermore, muscles of the cervical spine (especially in the suboccipital region) have an exceptionally high density of muscle spindles.[43, 44] An alteration of afferent information of the cervical spine is therefore likely to affect the COR.

Another explanation is that people with neck pain avoid movements in the end-range of motion. This could also alter afferent information of the cervical spine and, in turn, affect the COR. Our data suggest that this might be the case for the vertical plane where we observed a reduction in the range of motion in participants with neck pain. However, the higher age in the non-specific neck pain group could also explain the reduced range of motion.[45] In the rotational plane, there was no difference between the two groups in contrast to other studies.[46] This difference could be explained by the low to moderate neck pain and disability levels in our neck pain group.

Normally, the afferent information from the vestibular and cervical system cooperate in order to maintain a clear visual image during head and eye movements [47]. Our findings suggest that the VOR does not compensate for the increased COR in the neck pain group. This mismatch between COR and VOR could lead to visual disturbances ,[4] dizziness,[48] and postural control disturbances.[49-51] In our study, we found no correlation between pain levels, dizziness and the COR. This lack of correlation could be explained by the fact that the study population scored rather low on both the DHI and NPRS.

Measuring eye movements in patients might be useful for diagnostic and therapeutic purposes. For instance, it is not possible to influence COR deliberately. This makes the COR an objective outcome measure of oculomotor function that could be used as an additional test in clinical settings. This objectivity contrasts with other rather subjective outcome measures used to diagnose neck pain, such as questionnaires on disabilities and pain intensity. However, objectively quantifying the ocular reflexes also has some limitations. For instance, eye movements need to be measured with adequate precision and accuracy. In the present study, we measured reflexive eye movements by means of video-oculography.[38, 52, 53] Measuring eye movements while the participant is sitting on a rotating chair in complete darkness is technically complicated. Furthermore, video-oculography is rather expensive. A cheaper and easier way to measure eye movements is by means of electro-oculography (EOG). Although this method is widely used in clinical settings, it is less suitable for recording VOR and COR eye movements due to its limited accuracy and reliability.[52, 53]

Another limitation is related to the fact that that we only observed group effects. It would be interesting to investigate the possibility of assessing oculomotor control on an individual level, or as part of a function profile of people with neck pain. Another interesting question yet to be answered is whether it is possible to use the COR as an outcome measure to evaluate the effectiveness of interventions in people with neck pain. In a future study, we will make a direct comparison of the COR between people with non-specific neck pain, people with WAD, and people without neck pain. It might well be that there is an difference between in the COR between these groups. Another interesting direction for future research could be to investigate the relationship between COR and visual complaints, which occur frequently in people with neck pain[4].

We conclude that a deficit in eye stabilization function, namely an increased COR, can also be observed patients suffering from neck pain without any direct causes, i.e., non-specific neck pain. We suggest that the evaluation of oculomotor control in patients with neck pain and concomitant symptoms such as decreased postural stability might be worthwhile in clinical settings.[54]

Acknowledgments

The authors wish to thank all the willing participants, and the physical therapists in Rotterdam who informed their patients of the possibility of taking part in this study.

We are grateful for the financial support of TC2N (EU Interreg; MF & JG), and Stichting Coolsingel (MF). The authors have no conflict of interest relevant to the content of this paper.

References

1. Côté P, Cassidy JD, Carroll L. The Saskatchewan Health and Back Pain Survey: The Prevalence of Neck Pain and Related Disability in Saskatchewan Adults. *Spine.* 1998;23(15):1689-1698.
2. Hogg-Johnson vdVG, Carroll LJ, Holm LW, Cassidy JD, Guzman J, Côté P, Haldeman S, Ammendolia C, Carragee E, Hurwitz E, Nordin M, Peloso P. The Burden and Determinants of Neck Pain in the General Population: Results of the Bone and Joint Decade 2000–2010 Task Force on Neck Pain and Its Associated Disorders. *Spine.* 2008;33:39-51.
3. Leaver AM, Maher CG, McAuley JH, Jull GA, Refshauge KM. Characteristics of a new episode of neck pain. *Manual Therapy.* 2012(0).
4. Treleaven J, Takasaki H. Characteristics of visual disturbances reported by subjects with neck pain. *Manual Therapy.* 6// 2014;19(3):203-207.
5. Kelders K, van der Geest, Schipper, Feenstra, Zeeuw, and Frens. The Cervico-Ocular Reflex Is Increased in Whiplash Injury Patients *Journal of Neurotrauma.* 2005;22(1):133-137.
6. Tjell R. Smooth pursuit neck torsion test: a specific test for cervical dizziness. *American Journal of Otology.* 1998;19(1):76-81.
7. Treleaven J, Jull G, Grip H. Head eye co-ordination and gaze stability in subjects with persistent whiplash associated disorders. *Manual Therapy.* 6// 2011;16(3):252-257.
8. Storaci R, Manelli A, Schiavone N, Mangia L, Prigione G, Sangiorgi S. Whiplash injury and oculomotor dysfunctions: clinical–posturographic correlations. *European Spine Journal.* 2006;15(12):1811-1816.
9. Bogduk N. Neck Pain. *Aust. Fam. Physician.* 1984;13:26-30.
10. Borghouts JAJ, Koes BW, Bouter LM. The clinical course and prognostic factors of non-specific neck pain: a systematic review. *Pain.* 7// 1998;77(1):1-13.
11. Falla D, Jull G, Hodges PW. Feedforward activity of the cervical flexor muscles during voluntary arm movements is delayed in chronic neck pain. *Experimental Brain Research.* 2004/07/01 2004;157(1):43-48.
12. O'Leary S, Falla D, Jull G, Vicenzino B. Muscle specificity in tests of cervical flexor muscle performance. *Journal of Electromyography and Kinesiology.* 2// 2007;17(1):35-40.
13. Boyd-Clark LCB, C. A. and; Galea, M. P. . Muscle Spindle Distribution, Morphology, and Density in Longus Colli and Multifidus Muscles of the Cervical Spine. *Spine.* 2002;27(7):694-701.
14. Bolton PS, Kerman IA, Woodring SF, Yates BJ. Influences of neck afferents on sympathetic and respiratory nerve activity. *Brain Research Bulletin.* 1998;47(5):413-419.
15. Hellström F, Roatta S, Thunberg J, Passatore M, Djupsjöbacka M. Responses of muscle spindles in feline dorsal neck muscles to electrical stimulation of the cervical sympathetic nerve. *Experimental Brain Research.* 2005;165(3):328-342.
16. Kalaska. Central neural mechanisms of touch and proprioception. *Canadian journal of physiology and pharmacology.* 1994;72(5):542-545.
17. Djupsjöbacka M, Johansson H, Bergenheim M, Wenngren BI. Influences on the γ-muscle spindle system from muscle afferents stimulated by increased intramuscular concentrations of bradykinin and 5-HT. *Neuroscience Research.* 6// 1995;22(3):325-333.
18. Thunberg J, Hellström F, Sjölander P, Bergenheim M, Wenngren B-I, Johansson H. Influences on the fusimotor-muscle spindle system from chemosensitive nerve endings in cervical facet joints in the cat: possible implications for whiplash induced disorders. *Pain.* 3// 2001;91(1–2):15-22.
19. Chen X, Treleaven J. The effect of neck torsion on joint position error in subjects with chronic neck pain. *Manual Therapy.* 2013;18(6):562-567.
20. Kristjansson J. A study of five cervicocephalic relocation tests in three different subject groups. *Clinical Rehabilitation.* 2003;17(7):768-674.
21. de Vries J, Ischebeck BK, Voogt LP, et al. Joint position sense error in people with neck pain: A systematic review. *Manual Therapy.* (0).
22. Corneil BD, Olivier E, Munoz DP. Neck Muscle Responses to Stimulation of Monkey Superior Colliculus. II. Gaze Shift Initiation and Volitional Head Movements. *Journal of Neurophysiology.* October 1, 2002 2002;88(4):2000-2018.

23. Kristjansson T. Sensorimotor function and dizziness in neck pain: implications for assessment and management. *Journal of Orthopaedic Sports and Physical Therapy.* 2009;39(5).

24. Barany. Augenbewgungen durch Thoraxbewegungen ausgelost. *Zentralbl Physiol.* 1906;20:298-302.

25. Barany. Uber enige Augen- Und Halsmuskelreflexe beei Neugeborene. *Acta Otolaryngol (Stockh).* 1918/1919;1:97-102.

26. Reisman JE, Anderson JH. Compensatory eye movements during head and body rotation in infants. *Brain research.* Apr 10 1989;484(1-2):119-129.

27. Rijkaart DC, Geest JN, Kelders WP, Zeeuw CI, Frens MA. Short-term adaptation of the cervico-ocular reflex. *Experimental Brain Research.* 2004;156(1):124-128.

28. Montfoort I, Van Der Geest JN, Slijper HP, De Zeeuw CI, Frens MA. Adaptation of the cervico- and vestibulo-ocular reflex in whiplash injury patients. *J Neurotrauma.* Jun 2008;25(6):687-693.

29. Kelders K, van der Geest, Feenstra, de Zeeuw, and M A Frens. Compensatory increase of the cervico-ocular reflex with age in healthy humans. *Journal of Physiology.* 2003;553(1):311-317.

30. Montfoort I, Kelders WP, van der Geest JN, et al. Interaction between ocular stabilization reflexes in patients with whiplash injury. *Invest Ophthalmol Vis Sci.* Jul 2006;47(7):2881-2884.

31. Gimse R, Tjell C, Bjôrgen IA, Saunte C. Disturbed Eye Movements after Whiplash Due to Injuries to the Posture Control System. *Journal of Clinical and Experimental Neuropsychology.* 1996/04/01 1996;18(2):178-186.

32. Strimpakos N. The assessment of the cervical spine. Part 1: Range of motion and proprioception. *J Bodywork Mov Ther.* 2011;15(1):114-124.

33. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *The Lancet.* //;370(9596):1453-1457.

34. L. Vereeck ST, F.L. Wuyts, P.H. Van De Heyning. Internal consistency and factor analysis of the Dutch version of the Dizziness Handicap Inventory. *Acta oto-laryngologica.* 2007;127:788-795.

35. Ailliet L, Rubinstein SM, de Vet HCW, van Tulder MW, Terwee CB. Reliability, responsiveness and interpretability of the neck disability index-Dutch version in primary care. *European Spine Journal*. 2014/05/17 2014:1-6.

36. Cleland JA, Childs JD, Whitman JM. Psychometric Properties of the Neck Disability Index and Numeric Pain Rating Scale in Patients With Mechanical Neck Pain. *Archives of Physical Medicine and Rehabilitation.* 1// 2008;89(1):69-74.

37. Williams M, Williamson E, Gates S, Cooke M. Reproducibility of the cervical range of motion (CROM) device for individuals with sub-acute whiplash associated disorders. *European Spine Journal.* 2012;21(5):872-878.

38. van der Geest JN, Frens MA. Recording eye movements with video-oculography and scleral search coils: a direct comparison of two methods. *Journal of Neuroscience Methods.* 3/15/ 2002;114(2):185-195.

39. Proske U, Gandevia SC. The Proprioceptive Senses: Their Roles in Signaling Body Shape, Body Position and Movement, and Muscle Force. *Physiological Reviews.* October 1, 2012 2012;92(4):1651-1697.

40. Hogervorst T, Brand RA. Mechanoreceptors in joint function. *Journal of Bone and Joint Surgery - Series A.* 1998;80(9):1365-1378.

41. Elliott JM. Are There Implications for Morphological Changes in Neck Muscles After Whiplash Injury? *Spine.* 2011;36:S205-S210.

42. Elliott JMP, A.R. Jull, G.A. Wyk, L. Galloway, G.G O'Leary, S.P. Differential Changes in Muscle Composition Exist in Traumatic and Nontraumatic Neck Pain. *Spine.* 2014;39:39–47.

43. Liu J-X, Thornell L-E, Pedrosa-Domellöf F. Muscle Spindles in the Deep Muscles of the Human Neck: A Morphological and Immunocytochemical Study. *Journal of Histochemistry & Cytochemistry.* February 1, 2003 2003;51(2):175-186.

44. Kulkarni V CM, Babu K S Quantitative study of muscle spindles in suboccipital muscles of human foetuses. *Neurology India.* 2001 49(4):355-359.

45. Hole DE, Cook JM, Bolton JE. Reliability and concurrent validity of two instruments for measuring cervical range of motion: effects of age and gender. *Manual Therapy.* 11// 1995;1(1):36-42.

46. Dall'Alba PTBHS, Michele M. MPhty; Treleaven, Julia M. BPhty; Edwards, Sandra L. MPhtySt; Jull, Gwendolen A. PhD. Cervical Range of Motion Discriminates Between Asymptomatic Persons and Those With Whiplash. *Spine.* 2001;26:2090-2094.

47. Rubin AM, Young JH, Milne AC, Schwarz DWF, Fredrickson JM. Vestibular-neck integration in the vestibular nuclei. *Brain research.* 10/10/ 1975;96(1):99-102.

48. Treleaven J. Dizziness, Unsteadiness, Visual Disturbances and Postural Control- Implications for the Transition to Chronic Symptoms Following a Whiplash Trauma. *Spine.* 2011.

49. Treleaven J, Clamaron-Cheers C, Jull G. Does the region of pain influence the presence of sensorimotor disturbances in neck pain disorders? *Man Ther.* 2011;16(6):636-640.

50. Treleaven J. Dizziness, unsteadiness, visual disturbances, and postural control: implications for the transition to chronic symptoms after a whiplash trauma. *Spine.* 2011;36(25 Suppl):S211-217.

51. Silva AG, Cruz AL. Standing balance in patients with whiplash-associated neck pain and idiopathic neck pain when compared with asymptomatic participants: A systematic review. *PHYSIOTHER. THEORY PRACT.* Jan 2013;29(1):1-18.

52. Hess CW MR, Meienberg O. Recording of horizontal saccadic eye movements: methodological comparison between electro-oculography and infrared reflection oculography. *Neuro Ophthalmol.* 1986;6:189–197.

53. Collewijn. *Eye movement recording*. Oxford: Oxford University Press; 1999.

54. Treleaven J. Sensorimotor disturbances in neck disorders affecting postural stability, head and eye movement control-Part 2: Case studies. *Man Ther.* 2008;13(3):266-275.

4

Chapter 7:

Small effects of neck torsion on healthy human voluntary eye movements

Janssen, Malou

de Vries, Jurryt

Ischebeck, Britta K

Frens, Maarten A

van der Geest, Jos N

published in European Journal of Applied Physiology 2013;113:3049-57.

ABSTRACT

Purpose Although several lines of research suggest that the head and eye movement systems interact, previous studies reported that applying static neck torsion does not affect smooth pursuit eye movements in healthy controls. This might be due to several methodological issues. Here we systematically investigated the effect of static neck torsion on smooth pursuit and saccadic eye movement behavior in healthy subjects.

Methods In twenty healthy controls we recorded eye movements with video-oculography while their trunk was in static rotation relative to the head (7 positions from 45 degrees to the left to 45 degrees to right). The subject looked at a moving dot on the screen. In two separate paradigms we evoked saccadic and smooth pursuit eye movements, using both predictable and unpredictable target motions.

Results Smooth pursuit gain and saccade peak velocity decreased slightly with increasing neck torsion. Smooth pursuit gains were higher for predictable target movements than for unpredictable target movements. Saccades to predictable targets had lower latencies but reduced gains compared to saccades to unpredictable targets. No interactions between neck torsion and target predictability were observed.

Conclusion Applying static neck torsion has small effects on voluntary eye movements in healthy subjects. These effects are not modulated by target predictability.

Keywords: smooth pursuit eye movement, saccadic eye movement, proprioception, neck torsion, human

INTRODUCTION

Humans can shift their gaze voluntarily for optimal visual processing. New objects can be viewed by executing saccadic eye movements that rapidly redirect the line of sight, whilst moving objects can be followed using smooth pursuit eye movement. In daily life, these eye movements occur together with head movements, to ensure that gaze shifts are fast, accurate and efficient. It is not surprising that several lines of research suggest that the head movement system and the eye movement system interact [1,2].

Electrical stimulation of the frontal eye fields in monkeys evokes a saccadic eye movement [3]. However, it also results in contraction of neck muscles that yield head movement in the same direction as the saccade, even when the stimulation is at subthreshold level and no saccade is executed [1]. A similar finding has been observed for the supplementary eye fields [4]. Electrophysiological recordings from eye movement structures, like the frontal eye fields [5] and the superior colliculus (an important area for eye head co-ordination) [6], show that some cells in these areas modulate their responses based on altered cervical afferent input due to changes in head position. Some clinical studies have reported affected smooth pursuit gains following static rotation of the head relative to the body in patients with neck pain due to, for instance, Whiplash Associated Disorder [2,7,8] or cervical spondylosis [9]. These findings underlie the Smooth Pursuit Neck Torsion (SPNT) test used to assess the degree of eye movement impairments relating to clinical neck pain populations [10].

In healthy subjects, on the other hand, neck torsion seems to affect eye movements minimally at most [2,10,11]. Although this is usually welcomed in clinical practice, as it increases the discriminative ability of the SPNT, the lack of neck torsion effects in non-patient populations might be the result of reduced sensitivity due to various methodological issues. Firstly, most of these clinical studies focused on smooth pursuit eye movements and less so on saccadic eye movements. Secondly, smooth pursuit eye movements were evoked by a predictably moving target. Therefore, any decline in smooth pursuit performance due to changes in low-level motor processes might well be compensated for by higher level cognitive processes that predict target motion[12–14]. Thirdly, only a few neck rotations are applied in the SPNT, being one extreme (30 or 45 degrees to the left or right) and one neutral (straight ahead) rotation. Moreover, neck rotation was usually enforced by holding the head manually. Fourthly, eye movements were recorded by means of electro-oculography (EOG) which is known to be limited in its accuracy and reliability [15,16]. Although an influence of neck torsion on eye movements in healthy subjects is expected given the alleged interaction between head and eye movement systems, these methodological issues might hamper observing such an effect.

In the present study, we measured eye movements by means of video-oculography and systematically investigated the effect of neck torsion on both smooth pursuit and saccadic eye movements. We displayed targets with predictable and unpredictable movements and used a custom-made bite board to fixate the head while applying a range of static rotations to the trunk. We hypothesized that increased neck torsion would yield small changes on eye movement characteristics which are more pronounced for unpredictably moving targets than for predictably moving targets. In addition, we expect that unpredictably moving targets would yield less optimal eye movements, showing longer saccadic latencies and reduced gains.

METHODS

Subjects

Twenty healthy subjects participated in each of the two experimental paradigms (smooth pursuit eye movements and saccadic eye movements); 16 subjects participated in both paradigms. None of the subjects had a history of trauma, neck complaints or neurological conditions. In all subjects, vision was normal or corrected-to-normal. In the smooth pursuit paradigm, subjects (10 male, 10 female) were on average 28.4 years old (range 20-51 years); in the saccade paradigm subjects (9 male, 11 female) were on average 27.9 years old (range 21-44 years). All subjects gave informed consent to participate in this study, which was approved by the local ethical board.

Apparatus

The paradigms were performed in a darkened and quiet room. Subjects were seated in a custom-made rotatable chair. Body movements were restricted by seat belts. Head movements were restrained by means of a bite board. Rotating the chair to a fixed position, while keeping the head pointing straight ahead, induced static neck torsion.

Visual stimuli were generated in Matlab (version 2008) and back-projected by a projector (Infocus LP 335) on a translucent screen, placed 168 cm in front of the subject. In both the saccade and smooth pursuit paradigm the visual target was a single red dot of 0.5 degrees of visual angle in diameter that was displayed on a black background. We will refer to this dot as the target.

Eye movements were measured at 250 Hz with an infrared eye-tracking device (Eyelink I, SMI, Germany, see [17]).

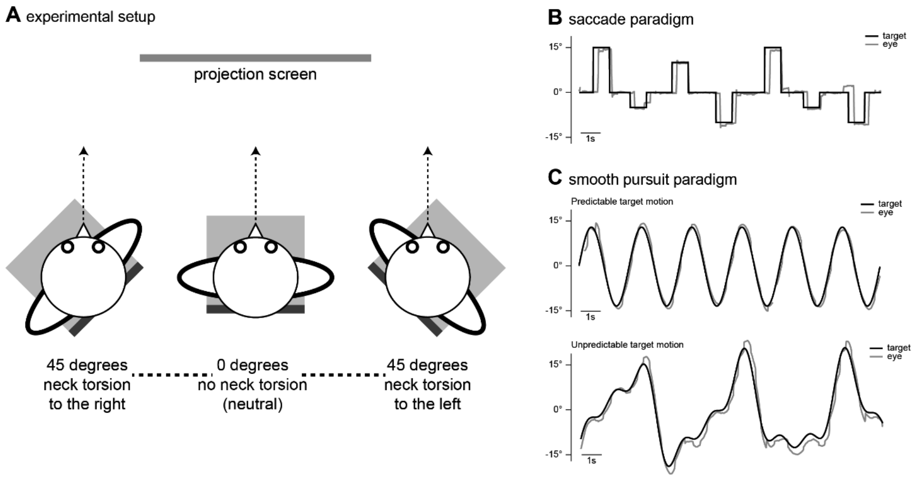

Figure 1. Experimental setup and paradigms. Panel A shows a schematic representation of the experimental setup: the body of the subjects could rotated to a static position while the head faced forwards toward the screen on which the target was presented. Panel B shows an example of the saccade paradigm: eye movement responses (grey line) in response to a target (black line) that jumped from a center to a peripheral position and back again. Panel C shows examples of the smooth pursuit paradigm: eye movement responses (grey line) in response to a predictably (top) or unpredictably (bottom) moving smooth pursuit target (black line).

Paradigms

Subjects participated in two experimental paradigms: saccades and smooth pursuit. Each paradigm consisted of multiple runs. In both paradigms and in each run, the chair was rotated to one out of seven positions to induce static neck torsion, i.e., the trunk was rotated while the head was kept pointing straight ahead (figure 1A). These seven chair rotations were 15, 30, 45 degrees to the left or to the right, and a neutral rotation (0 degrees straight ahead, i.e., the head and trunk were aligned).

In the saccade paradigm subjects were instructed to look at target while it jumped on the screen (Figure 1B). At the beginning of a trial, the target was presented at the center of the screen. After a random interval of 0.8 to 1.6 seconds, the target disappeared and immediately appeared unpredictably at one out of six possible locations. These locations were 5, 10, or 15 degrees of visual angle to the left or right site from the center. After a random interval of 0.8 to 1.6 seconds the target disappeared from that location and immediately appeared at the center of the screen, indicating the beginning of the next trial. In each trial, two saccades were therefore evoked. The first centrifugal saccade was directed to an unpredictable position whereas the second saccade was always directed towards the center (centripetal) and therefore was predictable with respect to its direction and amplitude. We note that target predictability is confounded with the initial eye position but this is unlikely to have a significant impact (see discussion). Each of the six possible locations was used in ten trials, yielding 120 trials in total per run. The duration of the target display and the order of used target locations were randomized in each run. A run lasted about 2 minutes.

In the smooth pursuit paradigm subjects were instructed to look at the target while it moved gradually from left to right on the screen in the horizontal plane (Figure 1C). There were two conditions in this paradigm: a predictable motion condition and an unpredictable motion condition. In the predictable condition the target moved according to a single sinusoid with frequency of 0.4 Hz and a peak to peak amplitude of 27 degrees. In the unpredictable condition the target moved according to a sum of three sinusoids with different frequencies and amplitudes (Sum of Sines stimulation, Soeching et al. 2010). One of the sinusoids had a frequency of 0.4 Hz and a peak to peak amplitude of 27 degrees, like the predictably moving target. In a single run, the other two (non-harmonic) sinusoids were one of the following pairs: 0.182 and 0.618 Hz, 0.222 and 0.578 Hz or 0.268 and 0.532 Hz. Note that for each combination the average frequency was 0.4 Hz. Three different combinations were used randomly between runs to prevent learning. In each run, the predictable condition was performed first for about 30 seconds, followed by the unpredictable condition for about 30 seconds. In between conditions was a brief pause of about 5 seconds. A run lasted little over 1 minute.

Procedure

The order of the chair rotations was pseudo-randomized across subjects. In the first run the chair was in neutral rotation (0 degrees), followed by a 45 degrees chair rotation either to the left or the right in the second run. In the third run the chair was rotated 45 degrees to the other direction. In the following runs the four remaining rotations were applied in a pseudo-random order across subjects. In the smooth pursuit paradigm only, an additional measurement was made with neutral chair rotation in the fourth run. In both paradigms, a neutral chair rotation (0 degrees) was used for the final run. The smooth pursuit paradigm entailed nine runs, the saccade paradigm entailed eight runs.

In 12 of the 16 subjects who performed in both paradigms, the two paradigms were executed in two sessions on two separate days; in the other four subjects the paradigms were performed in a single session. For these subjects, the chair was rotated to a specific position and a run of the smooth pursuit paradigm was followed by a run of the saccade paradigm.

Analysis

The recorded eye data were parsed for events (blinks, saccades and fixations) and eye positions using the built-in EyeLink software, and subsequently analyzed off-line using custom-written software in Matlab (version 2008b).

In the saccade paradigm, the primary saccades following a change in target position, either away or toward the center, were marked and extracted for each subject and in each run. For each saccade, the latency (i.e., the time between change in target location and saccade onset), the amplitude and peak velocity were determined. Saccades with a latency smaller than 50 ms, an amplitude below 2 degrees or above 30 degrees of visual angle, with a duration over 150 ms, and/or with a vertical component above 2 degrees of visual angle were discarded. Saccadic amplitude was transformed into a gain value, being the amplitude divided by the size of the target jump.

Saccades were grouped in 12 categories according to six trial types (i.e., the combination of two directions of the saccade (leftward or rightward), and three sizes of the initial target jump away from the center) and two phases within a trial (the unpredictable jump away from the center, evoking a centrifugal saccade, and the predictable change towards the center evoking a centripetal saccade). The median values of the three saccade parameters of interest (latency, gain, and peak velocity) were calculated over the 10 trials for each of the 12 saccade categories and each of the eight runs separately. The two values of the two runs when the chair was rotated in the neutral position were averaged within each subject. Data were averaged over the direction of chair rotation, since a preliminary analysis showed no effect of the direction of chair rotation.

Statistical analyses were performed by means of repeated measurements ANOVAs, which included four factors (“neck torsion” with four levels: 0, 15, 30 and 45 degrees of chair rotation; “predictability” with two levels: predictable (centripetal) target jumps vs. unpredictable (centrifugal) target jumps; “direction” with 2 levels: left or right; and “amplitude” with three levels: 5, 10 or 15 degrees of visual angle). For each of the three outcome parameters of the saccade paradigm (latency, gain, and peak velocity) a separate ANOVA was performed.

In the smooth pursuit paradigm, instantaneous eye velocity signals were calculated from the eye position signals. The numbers of saccadic intrusions (amplitude > 1.0 degrees) were counted in a time window of 30 seconds, starting one second after the commencement of recording. Saccades and square waves, as well as eye blinks were removed from the velocity signals. For the predictable condition, a sinusoid with a frequency of 0.4 Hz was fitted through the eye velocity data. This yielded a gain and a phase lag of the smooth pursuit eye movement. The gain was defined as the fitted eye velocity amplitude divided by the target velocity amplitude (fixed at 2*pi*0.4*13.5 = 33.9 degrees/s). For the unpredictable condition a sum of three sinusoids, with frequencies matching the three target frequencies, was fitted through the eye velocity data. This yielded three fitted eye velocity amplitudes. The gain of the unpredictable smooth pursuit eye movement was defined as the fitted amplitude for 0.4 Hz divided by the target velocity amplitude at 0.4 Hz (fixed at 2*pi*0.4*13.5 = 33.9 degrees/s).

The gains, phase lags, and the number of saccadic intrusions of the second and third measurement, when the chair was rotated in the neutral position, were averaged, to obtain values for this chair rotation (the first measurement in this rotation was discarded). For each subject, all 14 gains (obtained for 7 chair rotations and 2 target movement conditions [predictable and unpredictable]) were normalized by dividing them by the median of the 7 gains obtained in the predictable condition. The number of saccadic intrusions were normalized similarly using the median number of saccades for the 7 chair rotations in the predictable condition. Data were averaged over the direction of chair rotation, since a preliminary analysis showed no effect of the direction of chair rotation.

Statistical analyses were performed by means of repeated measurements ANOVAs, which included two factors (“neck torsion” with four levels: 0, 15, 30 and 45 degrees of degrees of chair rotation; “predictability” with two levels: predictable vs. unpredictable smooth pursuit target motion). For each of the three outcome parameters of the smooth pursuit paradigm (gain, phase difference and number of saccadic intrusions) a separate ANOVA was performed.

All statistical analyses were performed using SPSS (Version 20). Significance level was set at 5%. In the result section we will focus on the effects of chair rotation and target predictability (and their interaction with other factors) on the various outcome measures of saccadic and smooth pursuit eye movements.

RESULTS

Saccadic eye movements

The data of one subject was discarded, because almost all her predictable centripetal saccades had latencies below 50 ms, leaving 19 subjects to be included in the analysis.

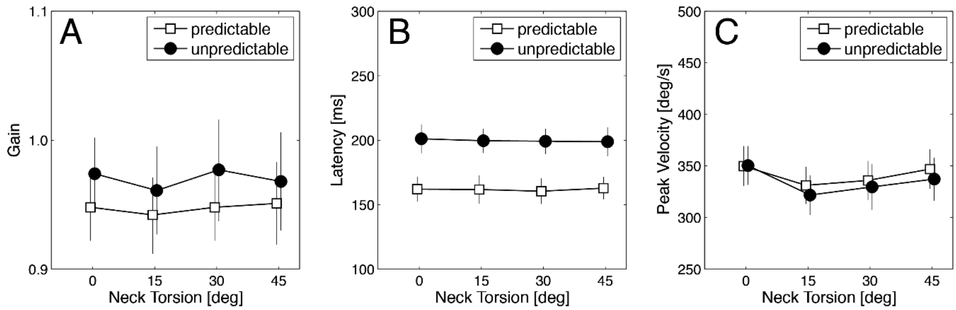

Figure 2: Saccadic gains (panel A), latencies (panel B) and peak velocities (panel C) for each of the four eccentricities of chair rotation, for predictable centripetal saccades (closed circles) and unpredictable centrifugal saccades (open squares). Error bars represent 95% confidence interval.

Saccadic gain (figure 2A) was not affected by neck torsion and none of the interactions involving neck torsion reached significance. Predictability did affect saccade gain ($F(1,18) = 8.25$, $p = .01$, partial $\eta^2 = .34$): unpredictable centrifugal saccades had higher gains (0.97 ± 0.02) than predictable centripetal saccades (0.95 ± 0.01). The interaction between predictability and amplitude ($F(2,17) = 27.65$, $p < .00$, partial $\eta^2 = .77$) showed that the gains of unpredictable centrifugal saccades decreased with amplitude (1.00 ± 0.02, 0.97 ± 0.02, and 0.94 ± 0.01, for 5, 10, and 15 degrees amplitude, resp., $F(2,17) = 20.56$, $p < .00$, partial $\eta2 = .71$), whereas the gains of predictable centripetal saccades did not (0.92 ± 0.02, 0.96 ± 0.01, and 0.96 ± 0.01, for 5, 10, and 15 degrees amplitude, resp., $F(2,17) = 9.38$, $p = .00$, partial $\eta2 = .53$). The interaction between predictability and direction ($F(1,18) = 6.13$, $p = .02$, partial $\eta^2 = .25$), showed that the difference in gain between leftward saccades and rightward saccades was smaller for predictable centripetal saccades (0.94 ± 0.02 vs. 0.95 ± 0.01) than for unpredictable centrifugal saccades (0.95 ± 0.02 vs. 1.00 ± 0.01, $T(18) = 2.501$, $p = .02$) The main effect of direction ($F(1,18) = 7.93$, $p = .01$, partial $\eta^2 = .31$) showed that rightward saccades had a higher gain (0.97 ± 0.02) than leftward saccades (0.94 ± 0.01). The main effect of amplitude ($F(2,17) = 8.26$, $p = .00$, partial $\eta^2 = .49$) showed that, overall, saccade gain differed between amplitudes (0.96 ± 0.02, 0.97 ± 0.02 and 0.95 ± 0.01 for 5, 10, and 15 degrees amplitude, resp.).

Saccadic latency (figure 2B) was not affected by neck torsion and none of the interactions involving neck torsion reached significance. Predictability did affect latency ($F(1,18) = 82.37$, $p < .00$, partial $\eta^2 = .82$): unpredictable centrifugal saccades had longer latencies (193 ± 5 ms) than predictable centripetal saccades (166 ± 6 ms). The interaction between predictability and amplitude ($F(2,17) = 12.21$, $p = .00$, partial $\eta^2 = .59$) showed that latencies of unpredictable centrifugal saccades increased with amplitude (194 ± 5 192 ± 5, and 214 ± 5 ms for 5, 10, and 15 degrees amplitude, resp., $F(2,17) = 105.27$, $p < .00$, partial $\eta^2 = .93$), whereas the latencies of predictable centripetal saccades did not (166 ± 6, 155 ± 5, and 165 ± 5 ms for 5, 10, and 15 degrees amplitude, resp., $F(2,17) = 44.76$, $p < .00$, partial $\eta^2 = .84$). There was no interaction between predictability and saccade direction and there was no main effect of direction. The main effect of amplitude showed that, overall, saccade latency differed between amplitudes (180 ± 5, 173 ± 4, and 189 ± 4 ms for 5, 10, and 15 degrees amplitude, resp., $F(2,17) = 100.66$, $p < .00$, partial $\eta^2 = .92$).

Saccadic peak velocity (figure 2C) was significantly affected by neck torsion ($F(3,16) = 6.39$, $p = .01$, partial η2 = .55). Post-hoc analysis using paired t-tests showed that the peak velocity at neutral position (350 ± 9 deg/s) was significantly different from the peak velocity at 15 degrees (327 ± 9 deg/s , $p = .00$) and at 30 degrees neck torsion (333 ± 10 deg/s , $p = .01$), but not from the peak velocity at 45 degrees neck torsion (342 ± 9 deg/s). The peak velocities between 15 degrees and 45 degrees neck torsion differed as well ($p = .04$). None of the interactions involving neck torsion reached significance. Predictability did not affect peak velocity. The interaction between predictability and amplitude ($F(2,17) = 51.10$, $p < .00$, partial η2 = .86) was significant. Post-hoc comparisons showed that peak velocity increases with amplitude for predictable saccades (239 ± 6, 351 ± 9, and 425 ± 10 deg/s, for 5, 10, and 15 degrees amplitude, resp., $F(2,17) = 406.63$, $p < .00$, partial η2 = .98), but less so for unpredictable saccades (253 ± 7, 352 ± 9, and 399 ± 10 deg/s, for 5, 10, and 15 degrees amplitude, resp., $F(2,17) = 305.82$, $p < .00$ partial η2 = .97). There was no interaction between predictability and saccade direction. There was no main effect of direction. The main effect of target amplitude showed that, overall, peak velocity differed between amplitudes (246 ± 6 deg/s, 355 ± 9 deg/s and 412 ± 10 deg/s for 5, 10, and 15 degrees, resp., $F(2,17) = 395.40$, $p < .00$, partial η2 = .98).

In neutral chair rotation, the within-subject correlations between predictable centripetal saccades and unpredictable centrifugal saccades were significant for all parameters measured: saccade gains ($r = .78$), latencies ($r = .57$), and peak velocities ($r = .79$).

We also compared the mean gain, latency and peak velocity between both runs in neutral rotation (i.e., between run 1 and run 8) to assess possible effects of learning and/or fatigue. No differences in gain or latency were found. Peak velocities of saccades in the first run (350 ± 12 deg/s) were somewhat higher than the second run in neutral rotation (328 ± 12 deg/s; $F(1,17) = 7.01$, $p = .02$, partial $\eta^2 = .29$).

Smooth pursuit eye movements
All 20 subjects were included in the analyses.

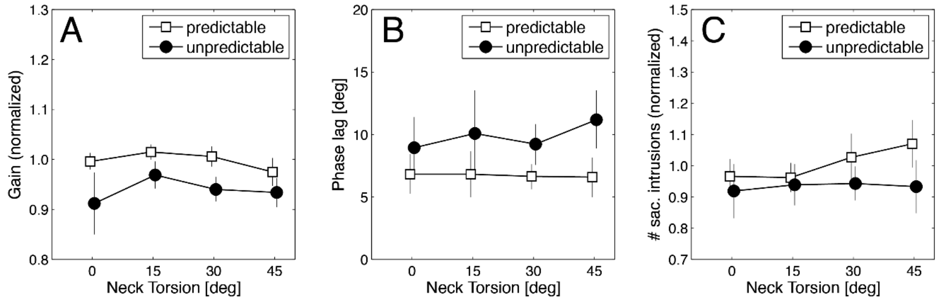

Figure 3: Normalized smooth pursuit gain (panel A), phase lags (panel B) and normalized number of saccadic intrusions (panel C) for each of the four eccentricities of chair rotation, for predictably moving targets (closed circles) and unpredictably moving targets (open squares). Error bars represent 95% confidence interval.

Smooth pursuit gain (figure 3A) was affected by neck torsion (0.95 ± 0.02, 0.99 ± 0.01, 0.97 ± 0.01 and 0.95 ± 0.01, for 0, 15, 30 and 45 degrees chair rotation, resp., $F(3,17) = 4.98$, $p = .01$, partial $\eta 2 = .47$). Predictability did affect smooth pursuit gain ($F(1,19) = 22.74$, $p < 00$, partial $\eta 2 = .55$): predictably moving targets yielded higher smooth pursuit gains (1.00 ± 0.00) than unpredictably moving targets (0.94 ± 0.12). The interaction between predictability and neck torsion was not significant.

Phase lags (figure 3B) were affected by neck torsion (9.2 ± 0.5, 8.6 ± 0.6, 8.0 ± 0.5 and 9.1 ± 0.6 degrees, for 0, 15, 30 and 45 degrees chair rotation, respectively ($F(3,17) = 3.39$, $p = .04$, partial $\eta 2 = .37$). Phase lag was higher for unpredictably moving targets (10.3 ± 0.6 degrees) than for predictably moving targets (6.9 ± 0.6 degrees, $F(1,19) = 4.50$, $p = .05$, partial $\eta 2 = .19$). No interaction between neck torsion and predictability was present.

The normalized number of saccadic intrusions (figure 3C) was not affected by neck torsion. Predictability did affect the number of saccadic intrusions ($F(1,19) = 7.22$, $p = .02$, partial $\eta 2 = .28$): predictably moving targets resulted in more saccades (1.01 ± .01) than unpredictably moving targets (0.93 ± 0.03). The interaction between predictability and neck torsion was just not significant ($F(3,17) = 3.04$, $p = .06$, partial $\eta 2 = .35$). A post-hoc analysis suggested that for predictably moving targets the number of saccadic intrusions increased with increasing neck torsion (93 ± .04, .96 ± .02, 1.03 ± .04 and 1.07 ± .04 intrusions, for 0, 15, 30 and 45 degrees chair rotation, resp., $F(3,17) = 3.90$, $p = .03$, partial $\eta 2 = .41$). For unpredictably moving targets, the number of saccadic intrusions was not affected by neck torsion.

Individual smooth pursuit gains ($r = .46$) and number of saccadic intrusions ($r = .79$) correlated between predictably moving targets and unpredictably moving targets across 20 subjects in the neutral rotation. Smooth pursuit gains did not correlate with number of saccadic intrusions for predictably ($r = .14$) and unpredictably ($r = .05$) moving targets.

We compared smooth pursuit gains and numbers of saccades to predictably moving targets between both runs in neutral rotation (i.e., between run 4 and run 9) to assess possible effects of learning and/or fatigue. No significant differences were found in smooth pursuit gains or numbers of saccadic intrusions.

Finally, for the neutral chair rotation, we observed no correlation between the average gain of predictable saccades and the gain of predictable smooth pursuit (r = .32), nor between the average gain of unpredictable saccades and the gain of unpredictable smooth pursuit (r = .19), using the data of the 16 subjects who participated in both paradigms. Also, we did not see marked differences between the four subjects who performed both paradigms in a single session and the 12 subjects who performed both paradigms in two separate sessions.

DISCUSSION

In this study, we systematically investigated the effect of neck torsion on voluntary eye movements. Using a thorough methodological approach using video-oculography and a range of neck torsions, we found that smooth pursuit as well as saccadic eye movement performance were only mildly affected by static rotation of the trunk relative to the head. The effect was most prominent, but nonetheless small, for smooth pursuit eye movements. Using a range of neck torsions from 45 degrees to the left to 45 degrees to the right, a maximum of 5% percent change in smooth pursuit gain was observed. Gain was maximal at 15 degrees torsion, but similar gains were observed for neutral (0 degrees) and extreme (45 degrees) neck torsions. For saccadic eye movements, only peak velocity seems to be influenced by neck torsion, and gain and latency were not. Neutral and extreme neck torsions yielded comparable saccadic peak velocities. These findings of small effects of neck torsion on healthy human voluntary eye movements are in line with previous reports[2,7,8,11].

Interestingly enough, optimal performance, as reflected by high gains, was not always encountered at neutral rotations of the trunk, i.e., when the head and trunk were aligned (see figure 2A and 3A). Indeed, some subjects spontaneously reported that they found it more convenient to perform the task when they were rotated a little sideways, although this varied between subjects. However, we did not measure this “preferential direction” reliably for proper analysis in the present study. It is recommended that it is taken into account in the design of future studies.

The lack of effect of neck torsion might be explained by an adaptive process. Increased neck torsion could have only transient effects on eye movement control as it is conceivable that the oculomotor system adapts to static changes in afferent cervical input caused by increased neck torsion. This notion could be tested in a setup that allows for applying dynamic chair rotation while presenting visual stimuli (see, e.g.[18,19]). In this way, one could disentangle transient from sustained effects of neck torsion on oculomotor control.

In both the saccadic and smooth pursuit paradigm we manipulated the predictability of the target movements. As expected, unpredictable target jumps yielded higher saccadic latencies. Previous studies suggest that more time is needed in planning a saccade in response to an unpredicted target jump [20,21]. An increased latency might also allow for executing a more accurate saccade [22]. In the present study, gains were higher for increased latencies. The observed interaction between peak velocity and amplitude seems to be in line with previously reported increased peak accelerations for predictable large saccades [23]. An increase in peak velocities could be related to the concurrent increase in gain, given the link between saccade amplitude and velocity which is known as the main sequence [24]. Also in the present study we found this relationship by manipulating the size of the target jump.

In our saccade paradigm, saccades were either predictable or unpredictable with respect to direction and amplitude. However, predictable saccades were always centripetal, whereas unpredictable saccades were always centrifugal. Initial eye position could therefore be a confounding factor [25]. Eye position, however, does not play a role in saccade generation on a low level. Structures like the superior colliculus and the brainstem encode saccadic direction, amplitude, duration and velocity, independent of initial eye position [26]. Saccadic latencies are more likely to be controlled by cognitive processes that take target predictability into account. These cognitive processes are part of a higher level of oculomotor control in which the frontal eye fields, for instance, play a role [26]. We therefore argue that the differences in saccadic latencies are not caused by different initial eye positions but rather by target predictabilities.

For smooth pursuit movements, unpredictable target movements impaired smooth pursuit behavior. As expected, adding a frequency component above 0.4 Hz had a decremental effect on smooth pursuit gain of the 0.4 frequency component [12]. This effect was found to be present for all neck rotations. However, reduced gains did not lead to an increased number of saccadic intrusions in response to unpredictably moving targets. This could be explained by the notion that it is not useful to make a saccade to a location that is unlikely to be the correct position of the target, since it moves unpredictably. In line with previous research, phase lags increased in the unpredictable condition for which smooth pursuit gain was decreased [27].

In the Smooth Pursuit Neck Torsion (SPNT) test [10] smooth pursuit is measured in response to predictable target motion. Importantly, smooth pursuit performance is compared between neutral position and a position with (extreme) neck torsion, which circumvents issues related to between-subject differences that are, for instance, related to variations in cognitive abilities. We observed that the effect of neck torsion was not affected by target predictability. This suggests that one does not need to use unpredictable targets to compare groups of subjects, for instance, patients with neck pain and healthy controls. Even so, it might be worthwhile to use both predictable and unpredictable target motions to investigate how cognitive factors affect oculomotor behavior in patients with neck pain. For instance, patients with cognitive impairments due to frontal lobe degeneration show deficits in predicting target movements during smooth pursuit [28]. It has been reported that patients with neck pain due to WAD also show more self-reports of cognitive complaints [29]. It could be that these patients are less able to predict target motion and therefore show impairments in smooth pursuit performance. Although speculative, this impairment could be more pronounced in more challenging circumstances, i.e., when the neck patient is in extreme torsion. However, both the effect of target predictability itself and its potential interaction with neck torsion has not been investigated in patients with neck pain.

The present study has several limitations. For instance, our subjects were rather young and it is known that eye movement performance changes with age [30]. Therefore, one cannot extrapolate the current findings to the general population. Furthermore, we only tested eye movements and neck torsion in the horizontal plane. Given the distinct neuronal pathways for horizontal and vertical eye movements [26], it might be that neck torsion in different planes (tilt and roll) might yield different results.

In conclusion, applying static neck torsion to healthy human subjects resulted in minimal changes in oculomotor control, not only for smooth pursuit eye movements, but also for saccadic eye movements. These effects were not modulated by target predictability, which, in itself, had clear effects on saccadic and smooth pursuit performance.

Our findings are in line with previous observations about the effect of neck torsion on smooth pursuit eye movements in healthy individuals. As in the SPNT test, we did not find significant differences between no neck torsion (neutral rotation, 0 degrees) and extreme neck torsion (45 degrees rotation). Therefore, the methodological issues mentioned in the introduction do not seem to reduce the clinical relevance of the SPNT test to assess the cervical afferent influence on smooth pursuit eye movements. However, the use of video-oculography allows for a more detailed analysis of smooth pursuit behavior including saccadic intrusions and phases. Using more chair rotations provides a more complete view of the effect of neck torsion, for instance, by taking an individual torsion preference into account. Finally, using both predictable and unpredictable targets could give more insight in the interaction between (impaired) cognitive processes and smooth pursuit. Therefore, when given the opportunity, we recommend that future studies, for instance on the oculomotor control of patients with neck pain, include both predictably and unpredictably moving targets and use a range of neck torsions. This could be a useful and informative supplement of the SPNT test, although we realize that this might be difficult in clinical practice. Further studies are warranted to investigate how the head and eye movement systems interact to produce efficient gaze shifts in humans.

REFERENCES

1. Corneil BD, Elsley JK, Nagy B, Cushing SL. Motor output evoked by subsaccadic stimulation of primate frontal eye fields. *Proc Natl Acad Sci*. 2010;107(13):6070-6075. doi:10.1073/pnas.0911902107.

2. Treleaven J, LowChoy N, Darnell R, Panizza B, Brown-Rothwell D, Jull G. Comparison of sensorimotor disturbance between subjects with persistent whiplash-associated disorder and subjects with vestibular pathology associated with acoustic neuroma. *Arch Phys Med Rehabil*. 2008;89(3):522-530. doi:10.1016/j.apmr.2007.11.002.

3. Bruce CJ, Goldberg ME, Bushnell MC, Stanton GB. Primate frontal eye fields. II. Physiological and anatomical correlates of electrically evoked eye movements. *J Neurophysiol*. 1985;54(3):714-734. doi:10.1152/jn.1985.54.3.714.

4. Chapman BB, Pace MA, Cushing SL, Corneil BD. Recruitment of a contralateral head turning synergy by stimulation of monkey supplementary eye fields. *J Neurophysiol*. 2012;107(6):1694-1710. doi:10.1152/jn.00487.2011.

5. Fukushima K, Akao T, Saito H, Kurkin SA, Fukushima J, Peterson BW. Representation of Neck Velocity and Neck-Vestibular Interactions in Pursuit Neurons in the Simian Frontal Eye Fields. *Cereb Cortex*. 2010;20(5):1195-1207. doi:10.1093/cercor/bhp180.

6. Corneil BD, Munoz DP, Chapman BB, Admans T, Cushing SL. Neuromuscular consequences of reflexive covert orienting. *Nat Neurosci*. 2008;11(1). http://www.ncbi.nlm.nih.gov/pubmed/18059264.

7. Tjell C, Tenenbaum A, Sandstrom S. Smooth pursuit neck torsion test - A specific test for whiplash associated disorders? *J Whiplash Rel Disord*. 2002;1:9-24. doi:10.1300/J180v01n02_02.

8. Prushansky T, Dvir Z, Pevzner E, Gordon CR. Electro-oculographic measures in patients with chronic whiplash and healthy subjects: a comparative study. *J Neurol Neurosurg Psychiatry*. 2004;75(11):1642-1644. doi:10.1136/jnnp.2003.031278.

9. Gabr M, El-Beheiry F, Soliman AA, El-Mahdi M, El-Mougy M, El-Akkad N. Smooth pursuit neck torsion test in patients with cervical spondylosis. *Egypt J Otolaryngol*. 2010;26:37-44. http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&DbFrom=pubmed&Cmd=Link&LinkName=pubmed_pubmed&LinkReadableName=Related Articles&IdsFromResult=417959&ordinalpos=3&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum.

10. Tjell C, Rosenhall U. Smooth pursuit neck torsion test: a specific test for cervical dizziness. *Am J Otol*. 1998;19(1):76-81. http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&DbFrom=pubmed&Cmd=Link&LinkName=pubmed_pubmed&LinkReadableName=Related Articles&IdsFromResult=9455954&ordinalpos=3&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum.

11. Treleaven J, Jull G, LowChoy N. Smooth pursuit neck torsion test in whiplash-associated disorders: Relationship to self-reports of neck pain and disability, dizziness and anxiety. *J Rehabil Med*. 2005;37:219-223. doi:10.1080/16501970410024299.

12. Barnes GR, Donnelly SF, Eason RD. Predictive velocity estimation in the pursuit reflex response to pseudo-random and step displacement stimuli in man. *J Physiol*. 1987;389:111-136. http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&DbFrom=pubmed&Cmd=Link&LinkName=pubmed_pubmed&LinkReadableName=Related Articles&IdsFromResult=3681722&ordinalpos=3&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum.

13. Barnes GR, Collins CJS. Internally generated smooth eye movement: its dynamic characteristics and role in randomised and predictable pursuit. In: ; 2008:441-449. doi:10.1016/S0079-6123(08)00665-1.

14. Matsuoka K, Ueda Y. Frequency characteristics of the smooth pursuit component in tracking eye movements. *Ergonomics*. 1986;29(2):197-214. doi:10.1080/00140138608968260.

15. Hess CW, Muri R, Meienberg O. Recording of Horizontal Saccadic Eye Movements: Methodological Comparison

Between Electro-Oculography and Infrared Reflection Oculography. *Neuro-Ophthalmology*. 1986;6(3):189-197. doi:10.3109/01658108608997351.

16. Collewijn H. Eye movement recording. In: JG R, ed. *Vision Research, a Practical Guide to Laboratory Methods*. 1st ed. Oxford: Oxford University Press; 1999:245-185.

17. van der Geest JN, Frens M a. Recording eye movements with video-oculography and scleral search coils: a direct comparison of two methods. *J Neurosci Methods*. 2002;114(2):185-195. http://www.ncbi.nlm.nih.gov/pubmed/11856570.

18. Kelders WP a, Kleinrensink GJ, van der Geest JN, et al. Compensatory increase of the cervico-ocular reflex with age in healthy humans. *J Physiol*. 2003;553(Pt 1):311-317. doi:10.1113/jphysiol.2003.049338.

19. Montfoort I, Van Der Geest JN, Slijper HP, De Zeeuw CI, Frens MA. Adaptation of the Cervico- and Vestibulo-Ocular Reflex in Whiplash Injury Patients. *J Neurotrauma*. 2008;25(6):687-693. doi:10.1089/neu.2007.0314.

20. Gagnon D, O'Driscoll GA, Petrides M, Pike GB. The effect of spatial and temporal information on saccades and neural activity in oculomotor structures. *Brain*. 2002;125(Pt 1):123-139. http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&DbFrom=pubmed&Cmd=Link&LinkName=pubmed_pubmed&LinkReadableName=Related Articles&IdsFromResult=11834598&ordinalpos=3&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum.

21. Wegner AJ, Fahle M. Alcohol and visually guided saccades: gap effect and predictability of target location. *Psychopharmacology (Berl)*. 1999;146(1):24-32. http://www.ncbi.nlm.nih.gov/pubmed/10485961.

22. McSorley E, Findlay JM. Saccade target selection in visual search: Accuracy improves when more distractors are present. *J Vis*. 2003;3(11):20. doi:10.1167/3.11.20.

23. Alvarez TL, Semmlow JL, Yuan W, Munoz P. Comparison of disparity vergence system responses to predictable and non-predictable stimulations. *Cah Psychol Cogn*. 2002;21(2):243-261. http://www.researchgate.net/publication/285916891_Comparison_of_disparity_vergence_system_responses_to_predictable_and_non-predictable_stimulations.

24. Bahill AT, Clark MR, Stark L. The main sequence, a tool for studying human eye movements. *Math Biosci*. 1975;24(3-4):191-204. doi:10.1016/0025-5564(75)90075-9.

25. Collewijn H, Erkelens CJ, Steinman RM. Binocular co-ordination of human horizontal saccadic eye movements. *J Physiol*. 1988;404:157-182. http://www.ncbi.nlm.nih.gov/pubmed/3253429.

26. Leigh RJ, Zee D. Neurology of eye movements, 4th edn. In: *Oxford UP*. 4th ed. New York; 2006.

27. Paige GD. Senescence of human visual-vestibular interactions: smooth pursuit, optokinetic, and vestibular control of eye movements with aging. *Exp Brain Res*. 1994;98(2):355-372. http://link.springer.com/article/10.1007/BF00228423.

28. Coppe S, Orban de Xivry J-J, Yüksel D, Ivanoiu A, Lefèvre P. Dramatic impairment of prediction due to frontal lobe degeneration. *J Neurophysiol*. 2012;108(11):2957-2966. doi:10.1152/jn.00582.2012.

29. Sullivan MJL, Hall E, Bartolacci R, Sullivan ME, Adams H. Perceived cognitive deficits, emotional distress and disability following whiplash injury. *Pain Res Manag*. 2002;7(3):120-126. http://www.ncbi.nlm.nih.gov/pubmed/12420020.

30. Munoz DP, Broughton JR, Goldring JE, Armstrong IT. Age-related performance of human subjects on saccadic eye movement tasks. *Exp brain Res*. 1998;121(4):391-400. http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&DbFrom=pubmed&Cmd=Link&LinkName=pubmed_pubmed&LinkReadableName=Related Articles&IdsFromResult=9746145&ordinalpos=3&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum.

Chapter 8:

Smooth Pursuit Eye Movement Deficits in Patients with Whiplash and Neck Pain are Modulated by Target Predictability

Janssen, Malou

Ischebeck, Britta K

de Vries, Jurryt

Frens, Maarten A

van der Geest, Jos N

published in Spine (Phila Pa 1976). 2015;40(19):E1052-E1057.

ABSTRACT

Study Design This is a cross-sectional study.

Objective The purpose of this study is to support and extend previous observations on oculomotor disturbances in patients with neck pain and whiplash-associated disorders (WADs) by systematically investigating the effect of static neck torsion on smooth pursuit in response to both predictably and unpredictably moving targets using video-oculography.

Summary of Background Data Previous studies showed that in patients with neck complaints, for instance due to WAD, extreme static neck torsion deteriorates smooth pursuit eye movements in response to predictably moving targets compared with healthy controls.

Methods Eye movements in response to a smoothly moving target were recorded with video-oculography in a heterogeneous group of 55 patients with neck pain (including 11 patients with WAD) and 20 healthy controls. Smooth pursuit performance was determined while the trunk was fixed in 7 static rotations relative to the head (from 45° to the left to 45° to right), using both predictably and unpredictably moving stimuli.

Results Patients had reduced smooth pursuit gains and smooth pursuit gain decreased due to neck torsion. Healthy controls showed higher gains for predictably moving targets compared with unpredictably moving targets, whereas patients with neck pain had similar gains in response to both types of target movements. In 11 patients with WAD, increased neck torsion decreased smooth pursuit performance, but only for predictably moving targets.

Conclusion Smooth pursuit of patients with neck pain is affected. The previously reported WAD-specific decline in smooth pursuit due to increased neck torsion seems to be modulated by the predictability of the movement of the target. The observed oculomotor disturbances in patients with WAD are therefore unlikely to be induced by impaired neck proprioception alone.

Keywords smooth pursuit, whiplash, neck pain, neck torsion, stimulus predictability, human, eye movements, diagnostic test, video-oculography, proprioception.

INTRODUCTION

Patients with neck pain often present with headaches, dizziness, as well as visual problems[1,2], which can be related to problems in eye movement control [3-6]. This includes smooth pursuit, which is an eye movement that is executed to keep track of a moving object [7]. The smooth pursuit neck torsion test (SPNT) is a clinical test that has been developed to diagnose patients with cervical dizziness (reported sensitivity/specificity: 90%/91%) [4]. This test is based on the observed decrease in smooth pursuit performance in patients due to static neck torsion (placing the head in rotated position while keeping the trunk stationary). Smooth pursuit performance is reflected by the smooth pursuit gain, i.e., the velocity of the eye movement relative to the velocity of the moving object. A gain of 1 implies perfect smooth pursuit. A decline in smooth pursuit performance with increased neck torsion was not observed in healthy controls. A later study validated the SPNT for diagnosing patients with whiplash associated disorder (WAD), and reported high diagnostic value in discriminating these patients from others with cervical complaints [8]. Additional studies that used the SPNT reproduced these findings of gain decline and specificity for WAD patients [9,10]. However, several factors impede proper assessment of these findings. First, subjects were fixated manually, which reduces the comparison and reproducibility between measurements since one cannot make sure that the same neck torsion is applied at all times. Second, eye movement recordings were commonly done by means of electro-oculography (EOG), which is quite unreliable to detect small changes in eye position as well as relatively slow eye movements [11]. Finally, a limited variety of neck torsions was usually applied (either none or very prominent, i.e., about 45 degrees of head rotation relative to the body). A final important limitation is related to the predictable motion of the object used to evoke smooth pursuit. With such a predictable motion, the sought-for modifications in smooth pursuit behavior might be compensated for by adequate prediction of target motion[7,12-15]. This confounding factor can be avoided by using an unpredictably moving target.

In this research we studied the effects of neck torsion and target predictability on smooth pursuit eye movement in patients with various origins of neck pain, avoiding the issues mentioned above. We expect that increased neck torsion would have more detrimental effects on smooth pursuit performance in patients than in healthy controls. Furthermore, we hypothesized an interaction between target predictability and neck torsion, with the SPNT with unpredictably moving targets being more affected.

METHODS

Subjects

Twenty healthy controls and 55 patients with neck pain participated in this experiment. Healthy controls were recruited among the hospital and university staff: they formed a heterogeneous group of 10 males and 10 females, being on average 28.4 years old (range 20-51 years). None of the control subjects had a history of trauma, neck complaints or neurological conditions. All had normal or corrected to normal vision. Importantly, none of the controls had experienced severe neck pain in the last six months.

For the patients, we looked at a heterogeneous group with various origins of their complaints, both traumatic and non-traumatic. Patients were included with support of the Spine and Joint Centre Rotterdam, a rehabilitation center for patients with chronic neck complaints, as well as regular physical therapists. In total, 55 patients (21 males, 34 females, mean age 44.2 years, range 25-67 years) were included. All patients experienced chronic pain the neck for more than six months which impaired their behavior in daily life. The patients were diagnosed as having Whiplash Associated Disorder (WAD, n=11) or not (non-WAD, n=44) according to experienced physicians of the Spine and Joint Centre Rotterdam, with use of the criteria of Spitzer [16].

All participants gave informed consent and the study was approved by the local review board.

Apparatus

The methodology has been described in detail elsewhere [17]. Briefly, subjects were seated in a custom-made rotatable chair. Rotating the chair to a fixed position, while keeping the head pointing straight ahead induced static neck torsion. Eye movements in response to a moving red dot on a black background were recorded by means of video-oculography (resolution noise < 0.01 degrees, velocity noise < 3 degrees/s, sample rate 250 Hz) [18].

Experiment

Seven chair rotations were used: a neutral rotation (0 degrees straight ahead, i.e., the head and trunk were aligned) and a rotation of 15, 30, 45 degrees to the left or to the right (figure 1). The experiment consisted of nine runs in which the chair was positioned in a specific rotation. Each eccentric rotation was applied once and the neutral rotation was applied three times. In each run, conditions were applied.

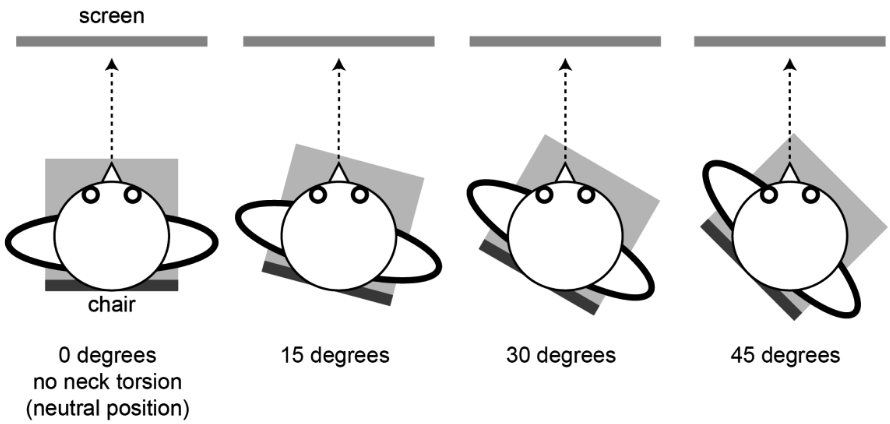

Figure1: Schematic representation of the chair rotation conditions. While the head was fixated by means of a bite board, the torso was held in a fixed rotation to the right or to the left, which induced static neck torsion. The subject was asked to follow a single moving dot that was projected on the screen in front.

There were two conditions in this experiment: a predictable motion condition and an unpredictable motion condition. In the predictable condition the target moved according to a single sinusoid with frequency of 0.4 Hz and a peak to peak amplitude of 27 degrees. In the unpredictable condition the target moved according to a sum of three sinusoids with different frequencies and amplitudes. One of the sinusoids had a frequency of 0.4 Hz and a peak to peak amplitude of 27 degrees, like the predictably moving target. Three unpredictable stimuli were used randomly between runs to prevent learning. In each run, the predictable condition was performed first, followed by the unpredictable condition. Both conditions lasted about 33 seconds.

Procedure

The order of the seven chair rotations was pseudo-randomized across subjects, Neutral rotation was measured three times at the 1st, 5th and 9th run. The experiment lasted about 20 minutes.

Analysis

The recorded eye data were parsed for events (blinks, saccades and fixations) and eye positions using the built-in EyeLink software, and subsequently analyzed off-line using custom-written software in Matlab (version 2008b).

Instantaneous eye velocity signals were calculated from the eye position signals. The numbers of saccadic intrusions (amplitude > 1.0 degrees) were counted in a time window of 30 seconds, starting one second after the commencement of recording. Saccades and square waves, as well as eye blinks, were removed from the velocity signals. For the predictable condition, a sinusoid with a frequency of 0.4

Hz was fitted through the eye velocity data. This yielded a gain of the smooth pursuit eye movement. The gain was defined as the fitted eye velocity amplitude divided by the target velocity amplitude (fixed at 2*pi*0.4*13.5 = 33.9 degrees/s). For the unpredictable condition a sum of three sinusoids, with frequencies matching the three target frequencies, was fitted through the eye velocity data. These combinations were 0.4 Hz combined with one of three frequency pairs (0.182 and 0.618 Hz, 0.222 and 0.578 Hz or 0.268 and 0.532 Hz), that were on average all 0.4 Hz. This yielded three fitted eye velocity amplitudes. The gain of the unpredictable smooth pursuit eye movement was defined as the fitted amplitude for 0.4 Hz divided by the target velocity amplitude at 0.4 Hz (fixed at 2*pi*0.4*13.5 = 33.9 degrees/s).

Number of saccadic intrusions was determined since an increased number of saccades during smooth pursuit eye movement is associated with worse performance [19,20]. The gains and the number of saccadic intrusions of the second and third measurement at neutral position, were averaged, to obtain values for this chair rotation (the first measurement in this rotation was discarded). Data for each chair rotation eccentricity to the left and to the right were combined by taking the average of the two values, since a preliminary analysis showed no effect of the direction of chair rotation.

Statistical analyses were performed using all the complete measurements by means of repeated measurements ANOVAs, which included one between-subject factor “Group” with two levels (patients vs. controls) and two within-subject factors (“Neck Torsion” with four levels: 0, 15, 30 and 45 degrees of chair rotation; “Predictability” with two levels: predictable vs. unpredictable smooth pursuit target motion). For both outcome parameters (gain and number of saccadic intrusions) a separate ANOVA was performed. Correlations between the smooth pursuit gain and the number of saccadic intrusions were assessed using Pearson’s correlation coefficient.

For each subject we also calculated the Smooth Pursuit Neck Torsion (SPNT) difference, similar to the previous studies [4,8,21]. The SPNT difference is defined as the difference between the average gain in the neutral position and the gain in the most eccentric measured positions, averaged over left and right. In most cases this was the 45 degree torsion. The SPNT difference was analyzed using a repeated measurement ANOVA with one between-subject factor “Group” with two levels (patients vs. controls) and one within-subject factors (“Predictability” with two levels: predictable vs. unpredictable moving targets). We also analyzed the groups of neck pain patients (WAD and non-WAD) separately.

RESULTS

Study population

In total 55 patients with neck pain were included. The data of one patient was discarded due to eye movement recording problems. 45 patients (including 7 WAD patients) were measured in all seven chair rotations.

The other nine patients provided only a partial data set. Five patients could not reach 45 degrees neck torsion and measurements at these eccentricities were skipped. Another four patients could not complete the measurements due to complaints of fatigue or too much pain and only the first three measurements (0 degrees, 45 degrees to the left and to the right) were performed. However, the partial data of these nine patients could be included in the analysis of the Smooth Pursuit Neck Torsion difference.

The experiment was performed successfully in all 20 controls. Their results have been reported in more detail previously [17].

Smooth pursuit gains

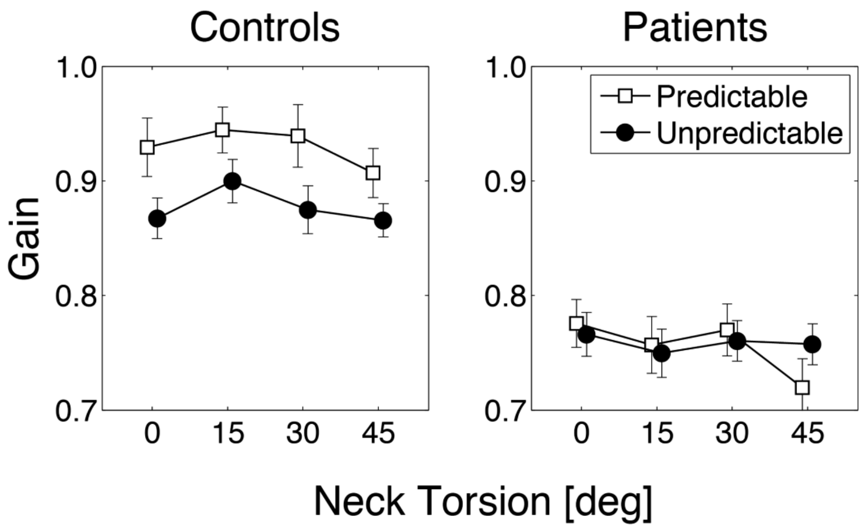

Figure 2: Smooth pursuit gains per group (20 Controls and 45 Patients), for each of the four eccentricities of chair rotation (Neck Torsion), and for predictably moving targets (open squares) and unpredictably moving targets (closed circles). Error bars represent Standard Error of the Mean.

Smooth pursuit gains of patients and controls are shown in figure 2. The overall ANOVA showed that the 20 healthy controls had higher smooth pursuit gains (0.90 ± 0.03) than the 45 neck pain patients (0.76 ± 0.02, $F(3,62) = 18.12$, $p < 0.00$, partial $\eta^2 = 0.22$). A significant main effect of Neck Torsion on smooth pursuit gain ($F(3,62) = 2.80$, $p = 0.05$, partial $\eta^2 = 0.12$) showed that gains decreased a little with increasing neck torsion (0.84 ± 0.02, 0.84 ± 0.02, 0.84 ± 0.02 and 0.82 ± 0.02, for 0, 15, 30 and 45 degrees respectively). No interaction between Neck Torsion and Predictability was observed ($p = 0.10$). The interaction between Neck Torsion and Group failed to reach significance ($p = 0.06$).

Predictability affected smooth pursuit gain significantly ($F(1,64) = 4.36$, $p = 0.04$, partial $\eta^2 = 0.06$): gains for predictably moving targets were higher than for unpredictably moving targets (0.85 ± 0.02 vs. 0.82

± 0.02, resp.). Predictability showed a significant interaction with Group ($F(1,64) = 4.48$, $p = 0.04$, partial $\eta^2 = 0.07$): healthy controls had a higher gain for predictably moving targets (0.93 ± 0.03) than for unpredictably moving targets (0.88 ± 0.03, $p < 0.00$), whereas patients had similar gains in both conditions (0.76 ± 0.03 vs 0.76 ± 0.02, resp., $p = 0.98$). The interaction involving all three factors was not significant ($p = 0.63$).

The ANOVA performed on the number of saccadic intrusions showed no effect of Group ($p = 0.11$) and none of the interactions involving Group reached significance (all $p > 0.30$). We did observe a small effect of Neck Torsion ($F(3,54) = 3.03$, $p = 0.04$, partial $\eta^2 = 0.14$): more eccentric positions evoked slightly more saccadic intrusions (70.5 ± 2.1, 71.2 ± 2.5, 73.6 ± 2.5 and 73.9 ± 2.1 saccadic intrusions, for 0, 15, 30 and 45 degrees neck torsion, respectively). We also observed a small effect of Predictability on number of saccadic intrusions ($F(1,56) = 15.32$, $p < 0.00$, partial $\eta^2 = 0.22$), with unpredictably moving targets evoking fewer saccadic intrusions (69.5 ± 1.9) than predictably moving targets (75.6 ± 2.5). The interaction between Neck Torsion and Predictability was weak but just significant ($F(3,54) = 3.00$, $p = 0.04$, partial $\eta^2 = 0.14$). The number of saccadic intrusions increased slightly more with neck torsion for predictably moving targets (from 73.0 to 78.1 intrusions, at 0 and 45 degrees chair rotation, resp.) than for unpredictably moving targets (from 67.9 to 69.8 intrusions).

There was no correlation between the smooth pursuit gain and the number of saccadic intrusions in controls ($r^2 = 0.014$, $p = 0.62$) or in patients ($r^2 = 0.06$, $p = 0.72$) in the neutral condition.

Smooth Pursuit Neck Torsion (SPNT) difference

The SPNT difference could be calculated for all 20 controls and 54 patients, thereby including those patients who skipped measurements at certain chair rotations. The SPNT difference was calculated using a chair rotation of 30 degrees in five patients, and the maximum chair rotation of 45 degrees in 49 patients.

We first compared all patients to controls. Analysis showed no main effect of Group ($F(1) = 0.73$, $p = 0.40$, partial $\eta^2 = 0.01$). The SPNT difference was higher for predictably moving targets than for unpredictably moving targets (-0.04 ± 0.01 vs. -0.01 ± 0.01, resp., $F(1) = 5.39$, $p = 0.02$, partial $\eta^2 = 0.07$). There was no interaction between Group and Predictability ($p = 0.38$).

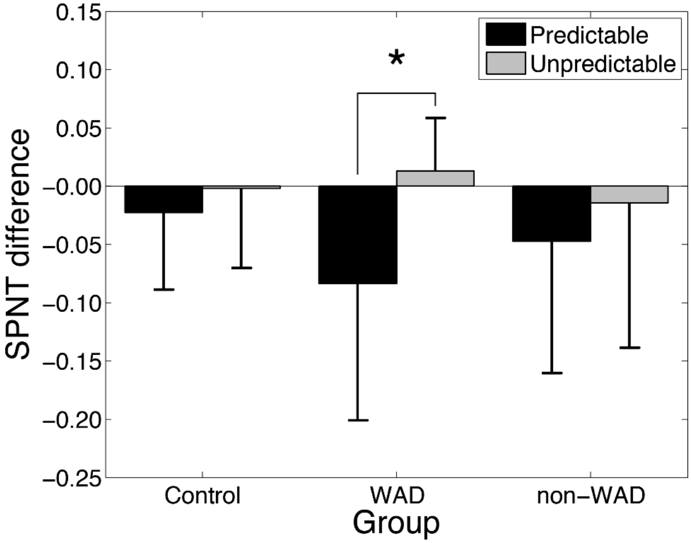

Figure 3: Smooth Pursuit Neck Torsion (SPNT) differences for each of the three groups (Controls, WAD patients and non-WAD patients) and the two stimulus conditions (predictably moving targets and unpredictably moving targets). Error bars represent Standard Deviations. * $p < 0.05$

We also looked at the effect of target predictability on the SPNT difference in healthy controls, in WAD patients, and in non-WAD patients separately (figure 3). In healthy controls and in non-WAD patients, the SPNT difference was not significantly different between predictably and unpredictably moving targets (controls: -0.02 ± 0.07 vs. -0.00 ± 0.07, resp., $t(19) = -1.27$, $p = 0.22$; non-WAD patients: -0.05 ± 0.11 vs. -0.01 ± 0.12, resp., $t(42) = 1.77$, $p = 0.09$). In WAD patients, however, the SPNT difference was larger for predictably than for unpredictably moving targets (-0.08 ± 0.12 vs. 0.01 ± 0.05, resp., $t(10) = 3.21$, $p = 0.01$).

Comparisons between the three groups for predictably and unpredictably moving targets separately showed that the SPNT differences in WAD patients did not differ from that of controls or non-WAD patients (all $p > 0.12$).

Discussion

We investigated the effect of neck torsion and target predictability on smooth pursuit eye movements in patients with neck pain. As expected based on previous reports, patients with neck pain showed lower smooth pursuit gains than healthy controls [4,8-10,21,22]. Moreover, smooth pursuit gains in patients decreased with increasing torsion of the neck, which is in line with several previous studies [4,8,10]. However, this decrease in gain was not different between patients and controls. This finding was supported by the analysis according to Smooth Pursuit Neck Torsion (SPNT) test. The differences in smooth pursuit gains between most eccentric neck rotations and neutral rotations were the same in patients with neck pain as in controls.

Target predictability, however, affected smooth pursuit gains differently in healthy controls and patients. In line with previous studies using predictably moving stimuli, we observed the performance of patients with neck pain was impaired compared to healthy controls [4,8-10,21,22]. However, smooth pursuit performance of healthy controls decreased when targets moved unpredictably, which might be explained by the fact that these subjects are adequately able to predict the movement of the target when the target moved in a simple fashion [23,24]. In contrast, the performance of patients with neck pain was the same for both conditions. This novel finding could suggest that the constant pain in their neck already hampered adequate prediction of the straightforward trajectory of a target. A similar hypothesis was put forward by Prushansky and colleagues [23], who suggested that observed deficits in eye movement performance in WAD patients were related to pain. Another explanation is that patients with neck pain are too distracted by the pain in their neck to perform optimally when the task is less challenging. In this respect it is worth to note that some patients spontaneously mentioned they found it hard to keep focused when the target moved predictably. This lack of focus could explain the lower gains for the predictably moving targets. Future studies in patients with neck pain might incorporate tests of concentration and attention to assess their effects on smooth pursuit performance. Moreover, to correlate pain experience with performance, a detailed analysis of pain experience might be fruitful.

We also aimed to differentiate between patients with Whiplash (WAD) and non-WAD. In accordance with previous reports we observed that for predictably moving targets the SPNT difference was larger in WAD patients than in controls and non-WAD patients [8-10,21]. In our population this difference was not significant, probably due to a lack of power. However, the SPNT differences disappeared completely when we used unpredictably moving targets. The observation that in WAD patients the SPNT difference is altered to a large extent by target predictability, raises the question whether the observed effect of increased neck torsion on smooth pursuit performance is due to eye movement deficits alone, as suggested by previous research [25]. If this was the case, increased neck torsion in WAD patients would also lead to lower gains for unpredictably moving targets. This was not observed. Therefore, the reduced gains for predictably moving targets induced by increased neck torsion could well be caused by confounding factors such as pain experience or impaired cognitive functioning (e.g. attention). This explanation is supported by previous observations showing that WAD patients have normal reflexive saccadic eye movements, but impaired voluntary ones which was explained by the authors as being caused by (pre-)frontal dysfunction [26].

A strength of the present study was the use of a high-quality video-oculography to record smooth pursuit eye movements and the range of applied neck torsions from extreme left to extreme right. A limitation is the relatively small number of subjects in the two patient groups. Moreover, not all patients could be measured in all chair rotation eccentricities. Therefore, too few subjects remained to make the favorable separation into two patient groups in the overall ANOVA. On the other hand, all patients could be included in the SPNT test. Furthermore, groups differed in age and since eye movements are altered when getting older, a more even age distribution would be recommended for future studies [27-29].

In conclusion, the differential effects of neck torsion in WAD patients, non-WAD patients and controls on smooth pursuit performance seem to be modulated by the predictability of the target trajectory. The observed oculomotor disturbances in WAD patients are therefore unlikely to be induced by impaired neck proprioception alone. Future studies investigating the relationship between impaired neck proprioception and eye movement control could take this property of the visual stimulus into account.

REFERENCES

1. Treleaven J, Takasaki H. Characteristics of visual disturbances reported by subjects with neck pain. *Manual Therapy* 2014;19:203-7.
2. Leaver AM, Maher CG, McAuley JH, et al. Characteristics of a new episode of neck pain. *Manual Therapy* 2013;18:254-7.
3. Kelders W, Kleinrensink G, Van Der Geest J, et al. The Cervico-Ocular Reflex Is Increased in Whiplash Injury Patients *Journal of Neurotrauma* 2005;22:133-7.
4. Tjell C, Rosenhall U. Smooth pursuit neck torsion test: a specific test for cervical dizziness. *Am J Otol* 1998:76-81.
5. Treleaven J, Jull G, Grip H. Head eye co-ordination and gaze stability in subjects with persistent whiplash associated disorders. *Manual Therapy* 2011;16:252-7.
6. Storaci R, Manelli A, Schiavone N, et al. Whiplash injury and oculomotor dysfunctions: clinical–posturographic correlations. *Eur Spine J* 2006;15:1811-6.
7. Barnes G, Collins C. Internally generated smooth eye movement: its dynamic characteristics and role in randomised and predictable pursuit. In Christopher K, Leigh RJ eds. *Progress in Brain Research*: Elsevier, 2008:441-9.
8. Tjell C, Tenenbaum A, Sandström S. Smooth pursuit neck torsion test-a specific test for whiplash associated disorders? *Journal of Whiplash & Related Disorders* 2002;1:9-24.
9. Treleaven J, Jull G, LowChoy N. The relationship of cervical joint position error to balance and eye movement disturbances in persistent whiplash. *Manual Therapy* 2006;11:99-106.
10. Treleaven J, LowChoy N, Darnell R, et al. Comparison of sensorimotor disturbance between subjects with persistent whiplash-associated disorder and subjects with vestibular pathology associated with acoustic neuroma. *Archives of Physical Medicine and Rehabilitation* 2008;89:522-30.
11. Hess C, Muri R, Meienberg O. Recording of horizontal saccadic eye movements: methodological comparison between electro-oculography and infrared reflection oculography. *Neuro-Ophthalmology* 1986;6:189-97.
12. Barnes G, Asselman P. The mechanism of prediction in human smooth pursuit eye movements. *The Journal of Physiology* 1991;439:439-61.
13. Barnes GR. Cognitive processes involved in smooth pursuit eye movements. *Brain and Cognition* 2008;68:309-26.
14. Matsuoka K, Ueda Y. Frequency characteristics of the smooth pursuit component in tracking eye movements. *Ergonomics* 1986;29:197-214.
15. Soechting J, Rao H, Juveli J. Incorporating prediction in models for two-dimensional smooth pursuit. *PLoS ONE* 2010;5:e12574.
16. Spitzer W, Skovron M, Salmi L, et al. Scientific monograph of the quebec task force on Whiplash-associated disorders: Redefining “whiplash” and its management. *Spine (Phila Pa 1976)* 1995:15-20.
17. Janssen M, Vries J, Ischebeck B, et al. Small effects of neck torsion on healthy human voluntary eye movements. *European Journal of Applied Physiology* 2013;113:3049-57.
18. Geest van der J, Frens M. Recording eye movements with video-oculography and scleral search coils: a direct comparison of two methods. *Journal of Neuroscience Methods* 2002;114:185-95.
19. Karoumi Bb, Saoud M, d'Amato T, et al. Poor performance in smooth pursuit and antisaccadic eye-movement tasks in healthy siblings of patients with schizophrenia. *Psychiatry Research* 2001;101:209-19.
20. Clementz BA, Sweeney JA, Hirt M, et al. Pursuit gain and saccadic intrusions in first-degree relatives of probands with schizophrenia. *Journal of Abnormal Psychology* 1990;99:327-35.
21. Treleaven J, Jull G, N L, et al. Smooth pursuit neck torsion test in whiplash-associated disorders: relationship to self-reports of neck pain and disability, dizziness and anxiety. *J Rehabil Med* 2005;37:219-23.
22. Della Casa E., Affolter Helbling J., Meichtry A., et al. Head-Eye movement control tests in patients with chronic neck pain; Inter-observer reliability and discriminative validity. *BMC Musculoskeletal Disorders* 2014;15:11.
23. Prushansky T, Dvir Z, Pevzner E, et al. Electro-oculographic measures in patients with chronic whiplash and healthy subjects: a comparative study. *Journal of Neurology, Neurosurgery & Psychiatry* 2004;75:1642-4.
24. Kongsted A, Jørgensen L, Leboeuf-Yde C, et al. Are altered smooth pursuit eye movements related to chronic pain and disability following whiplash injuries? A prospective trial with one-year follow-up. *Clinical Rehabilitation* 2008;22:469-79.

25. Paige GD. Senescence of human visual-vestibular interactions: smooth pursuit, optokinetic, and vestibular control of eye movements with aging. *Exp Brain Res* 1994:355-72.
26. Mosimann UP, Müri RM, Felblinger J, et al. Saccadic eye movement disturbances in whiplash patients with persistent complaints. *Brain* 2000;123:828-35.
27. Pelak V. Ocular motility of aging and dementia. *Current Neurology and Neuroscience Reports* 2010;10:440-7.
28. Kelders W, Kleinrensink G, van der Geest J, et al. Compensatory increase of the cervico-ocular reflex with age in healthy humans. *The Journal of Physiology* 2003;553:311-7.
29. Munoz D, Broughton J, Goldring J, et al. Age-related performance of human subjects on saccadic eye movement tasks. *Experimental Brain Research* 1998;121:391-400.

Chapter 9:

The influence of cervical movement on eye stabilization reflexes: a randomized trial

Ischebeck, Britta K

de Vries, Jurryt

van Wingerden, Jan Paul

Kleinrensink, Gert-Jan

Frens, Maarten A

van der Geest, Jos N

published in: Experimental Brain Research . 2018;236(1):297-304. doi:10.1007/s00221-017-5127-9.

The trial is registered in the ISRCTN registry with trial ID ISRCTN55660633.

ABSTRACT

Objective: To investigate the influence of the amount of cervical movement on the cervico-ocular reflex (COR) and vestibulo-ocular reflex (VOR) in healthy individuals.

Summary of Background data: Eye stabilization reflexes, especially the COR, are changed in neck pain patients. In healthy humans, the strength of the VOR and the COR are inversely related.

Methods: In a cross-over trial the amplitude of the COR and VOR (measured with a rotational chair with eye tracking device) and the active cervical range of motion (CROM) was measured in 20 healthy participants (mean age 24.7). The parameters were tested before and after two different interventions (hyperkinesia: 20 min of extensive active neck movement; and hypokinesia: 60 min of wearing a stiff neck collar). In an additional replication experiment the effect of prolonged (120 minutes) hypokinesia on the eye reflexes were tested in 11 individuals.

Results: The COR did not change after 60 minutes of hypokinesia but did increase after prolonged hypokinesia (median change 0.220; IQR 0.168, p=0.017). The VOR increased after 60 minutes of hypokinesia (median change 0.155, IQR 0.26, p=0.003), but this increase was gone after 120 minutes of hypokinesia. Both reflexes were unaffected by cervical hyperkinesia.

Conclusions: Diminished neck movements influences both the COR and VOR, although on a different time scale. However, increased neck movements do not affect the reflexes. These findings suggest that diminished neck movements could cause the increased COR in patients with neck complaints.

Keywords: eye stabilization reflexes, cervico-ocular reflex, vestibulo-ocular reflex, cervical range of motion, neck pain patients, oculomotor disturbances

Introduction

In patients with neck pain and Whiplash Associated Disorders (WAD) oculomotor disturbances have been described [1–7], which may be attributed to altered cervical functioning [8–11]. Here we studied the effects of neck (im-) mobilization on the eye stabilization reflexes as part of the oculomotor system in healthy subjects.

To guarantee clear vision the vestibulo-ocular reflex (VOR) and the cervico-ocular reflex (COR) work in conjunction to stabilize the visual image on the retina. The VOR receives input from the vestibulum, responding to movements of the head in space. The COR receives input from the mechanoreceptors, mainly the muscle spindles and joint sensors, of the upper cervical spine [12]. The COR responds to movements of the head relative to the trunk.

It is important that the reflexes are properly adjusted to each other, even in circumstances when one of them is changed. Both reflexes are indeed quite plastic, in the sense that they adapt to perturbations and changes of input. In laboratory settings, it has been observed that the VOR and COR adapt to experimentally perturbed visual and vestibular input [6,13–15]. However, little is known about the adaption of the reflexes to perturbed cervical input.

The overall aim of the present study was to elucidate the effect of altered cervical input on COR and VOR. This latter reflex was not taken into account in our previous study [6]. Here we will also investigate whether the synergy of reflexes is altered and whether the changes of reflexes are directly related to changes in active range of motion. The first objective is to assess the changes in COR and VOR gain in response to a temporary reduction of cervical proprioceptive output (hypokinesia), induced by passive immobilization of the neck. We first study if one hour of neck immobilization is sufficient to observe changes in the eye stabilization reflexes. Then, we replicate our previous experiment using a two-hour immobilization period.

The second objective is to study reflex adaptation as result of temporary increased proprioceptive output (hyperkinesia), rather than immobilization.

The assessment of both reflexes in the same subjects under several neck (im-) mobilization conditions, allows us to assess the suggested interactions between the cervical and vestibular eye movement systems [2,5]. Adjustment of theses reflexes is essential for optimal oculomotor control and will prevent vision problems. This study elucidates the synergy of eye stabilization reflexes and how changes in one reflex affects the other. This information is essential to enhance our understanding of oculomotor problems in neck pain patients.

MATERIALS AND METHODS

Participants

Twenty healthy adults (mean age 24.7 years (range 20-33), 12 male, 8 female) were recruited from the Erasmus MC to participate in the main experiment (hypokinesia and hyperkinesia). For the current replication experiment (prolonged hypokinesia) eleven healthy subjects (mean age 29.3 (22-48), 4 male, 7 female) were recruited (four of them also participated in the main experiment). All participants had no history of neck complaints (including no cervicogenic headache or dizziness) and no known neurological, visual or vestibular disorders. They all had normal or corrected-to-normal visual acuity and no one used any form of tranquilizing medication. The local ethical board of the Erasmus MC, which is in accordance with the Declaration of Helsinki 1975, revised Hong Kong 1989, approved this study and all participants gave prior written informed consent.

Intervention

In the main experiment, two types of intervention were applied in a cross-over design: hypokinesia and hyperkinesia. Directly before and after the intervention, the eye stabilization reflexes and the active range of motion were measured.

In the *hypokinesia* intervention, the neck was immobilized by using a stiff neck collar (size 4, Laerdal Stifneck® Select™) for one hour. In the *hyperkinesia* intervention, active neck movement in all possible directions of movement was evoked by having the participants move their neck excessively in all directions for twenty minutes. The participants were instructed to move their head as far as possible, following visual cues (left, right rotation, side bending, flexion, extension and combined movements). During the experiment they were motivated to keep moving their neck without rest.

Each participant of the main experiment received both interventions on two different days separated by 6 or 7 days. The order of the two interventions was pseudo-randomized and balanced across participants.

In the replication experiment, eleven participants wore the neck collar for two hours (*prolonged hypokinesia*). This experiment took place two weeks after the end of the main experiment.

Experimental Setup

Monocular (left) eye positions were recorded by infrared video-oculography (Eyelink 1, SMI, Germany: see [16]) at a sample rate of 250 Hz. Eye position was calibrated using the built-in nine-point calibration routine.

Participants were seated in a comfortable rotatable chair (figure 1A). The trunk of the participant was fixed to the chair at shoulder level by a double-belt system. The chair was attached to a motor (Harmonic Drive, Germany) which induced continuous sinusoidal chair rotations around the vertical axis without any backlash. A sensor connected to the chair recorded chair position, which was stored on the computer along with eye positions.

The subjects head was fixed by means of a custom-made bite board, which was positioned with the axis of chair rotation under the midpoint of the inter-aural line. The bite board could be fixed to the floor or to the chair (figure 1B). During the COR stimulation, the bite board, mounted to the floor, fixed the position of the head in space. Measurements took place in complete darkness inducing pure cervical stimulation, which elicits the COR in isolation. During this stimulation, the chair rotated for 134 seconds with an amplitude of 5.0 degrees and a frequency of 0.04 Hz. This yielded five full sinusoidal rotations of the chair with peak velocity of 1.26 degrees/s. When the bite board was mounted to the chair, rotation of the chair in complete darkness induced pure vestibular stimulation, eliciting the VOR in isolation. During the VOR stimulation, the chair rotated for 33 seconds with an amplitude of 5.0 degrees and a frequency of 0.16 Hz. This yielded five full sinusoidal rotations of the chair with peak velocity of 5.03 degrees/s. In both eye movement stimulations participants were instructed to look at a position directly in front of the set-up. This position was briefly indicated by means of a laser dot in the completely darkened room.

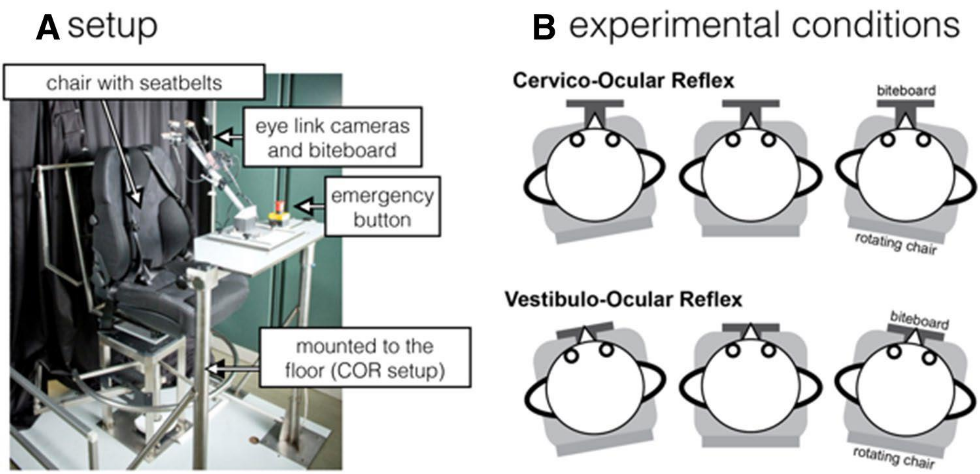

Figure 1: Panel A shows a photograph of the chair and the position of the cameras and the bite board in the COR setup. Panel B shows the measurement of the vestibular ocular reflex (VOR) with the bite board attached to the chair, and the cervico-ocular reflex (COR) with the bite board attached to the floor, whilst the chair is rotating back and forth

The amount of the active cervical range of motion (CROM) in both the horizontal and vertical planes was also measured before and after an intervention using the CROM measurement device (Performance Attainments Associates, USA; http://www.spineproducts.com/) [17]. The CROM device consists of two gravity dependent goniometers and one compass dial on a head-mounted frame allowing measurement of ROM in three planes. A magnetic yoke consisting of two bar magnets held anteriorly and posteriorly is supplied to reduce the influence of thorax rotation. Participants have to rotate their head in all directions (left, right rotation, side bending, flexion, extension and combined movements) as far as possible. The range of motion is measured in 2° increments.

Data Analysis

Eye movement reflexes were analyzed by looking at the eye velocity relative to the chair or stimulus velocity. The phase was not detected. All data processing was done with custom-written scripts in Matlab

R2013a (The MathWorks Inc., Natick, MA). The same analysis was used for all interventions. Eye velocity was calculated by taking the derivative of the horizontal eye position signal. After removal of blinks, saccades and fast phases (using a 20 degrees-per-second threshold), a sine wave was fitted through the eye velocity signal data. The gain of the response was defined as the amplitude of the eye velocity fit divided by the peak velocity of the chair rotation (COR: 1.26 degrees/s; VOR: 5.03 degrees/s).

A gain of 1 thus reflects that the peak velocity of the eye was the same as the peak velocity of the stimulus. Gain changes were defined as the difference in gain before and after the intervention.

Statistical analyses were done using SPSS 22 (IBM Corp., Armonk, NY). Descriptive statistics were computed for the gains of the two eye movement reflexes and the cervical range of motion before and after the interventions. Since the number of subjects was low, and data was not distributed normally (Shapiro-Wilk test: $p<0.05$), non-parametric statistics were applied. For each intervention the changes in COR and VOR gains, and changes of the cervical ranges of motion (horizontal and vertical) were statistically assessed using the Wilcoxon signed rank test. The differences in the changes between the two interventions was assessed using as well the Wilcoxon signed rank test. A correlation analysis (Spearman-Rho) was performed to determine any correlation between the five variables.

An alpha level of $p < 0.05$ was considered significant for all statistical tests. Reported values are medians and inter-quartile ranges.

Results

In the main experiment, COR recording failed in two participants, and VOR recording failed in another participant, in both interventions due to technical reasons. In one participant the COR and VOR recording failed in the hyperkinesia condition and in one other participant, VOR recording failed in the hyperkinesia condition. Statistical analyses were done on the remaining participants. The results of the main experiment are summarized in table 1 and shown in figure 3.

INTER-VENTION	**HYPOKINESIA**							**HYPERKINESIA**						
	n	**before**	**after**	**change**		**cor-relation**		**n**	**before**	**after**	**change**		**cor-relation**	
		median (IQR)	**median (IQR)**	**median (IQR)**	**p-value**	**r**	**p-value**		**median (IQR)**	**median (IQR)**	**median (IQR)**	**p-value**	**r**	**p-value**
COR (gain)	14	0.214 (0.216)	0.307 (0.178)	0.049 (0.263)	0.397	0.03	0.911	17	0.257 (0.522)	0.403 (0.448)	0.052 (0.365)	0.435	0.35	0.163

VOR (gain)	15	0.568 (0.21)	0.736 (0.275)	0.155 (0.26)	0.003	0.45	0.091	16	0.672 (0.245)	0.686 (0.192)	-0.011 (0.23)	0.642	0.32	0.226
CROM horizontal (degrees)	16	141° (10°)	140° (18°)	-5.5° (14°)	0.005	0.77	0.001	19	140° (14°)	148° (10°)	1 (8°)	0.208	0.75	<0.001
CROM vertical (degrees)	16	144.5° (24°)	132.5° (16°)	-8° (17°)	0.044	0.71	0.002	19	138° (32°)	150° (28°)	2 (25°)	0.198	0.75	<0.001

Table 1: Gains of the eye reflexes and cervical range of motion recorded before and after the two interventions, the change of gain/ range of motion and the correlation between the two recordings. COR = gain of cervico-ocular reflex; VOR = gain of vestibulo-ocular reflex (gain= eye velocity divided by stimulus velocity); CROM horizontal= active range of movement of the neck in the horizontal plane in degrees; CROM vertical= active range of movement of the neck in the vertical plane in degrees

Hypokinesia

Sixty minutes of wearing the stiff neck collar did not influence the COR gain, but it increased VOR gain by 29.6%. The cervical range of motion decreased slightly in the horizontal plane and in the vertical plane. The gains of the reflexes before and after the intervention were not correlated. The cervical ranges of motion before and after the intervention did correlate.

Hyperkinesia

Twenty minutes of intensified neck movements did not change COR, nor VOR gains. The cervical ranges of motions were also not affected. Both COR gains and VOR gains were not correlated before and after the intervention. The cervical ranges of motion were correlated.

Hypokinesia versus hyperkinesia

A direct comparison of the hypokinesia and hyperkinesia interventions in the sixteen participants who performed both interventions successfully, shows that the COR gain changes were not different between the two interventions (difference in gain change: -0.059 median +- 0.56 IQR, p = 0.463). The increase in VOR gain after wearing a neck collar for an hour was different from the decrease in VOR gain in the hyperkinesia intervention (0.105 +- 0.33, p=0.039). The changes in cervical ranges of motion were significant in both planes (horizontal: -6° +- 17°, p=0.004, vertical: -12° +-29°, p=0.025).

Prolonged hypokinesia

In the replication experiment, eleven participants wore the stiff neck collar for two hours. In one subject both the COR and VOR recordings failed and in one other subject the VOR recording failed. The results are shown in table 2. In figure 2 exemplary eye movement velocity traces of the VOR and COR of different subjects before and after the hypokinesia interventions are shown (sections a-h).

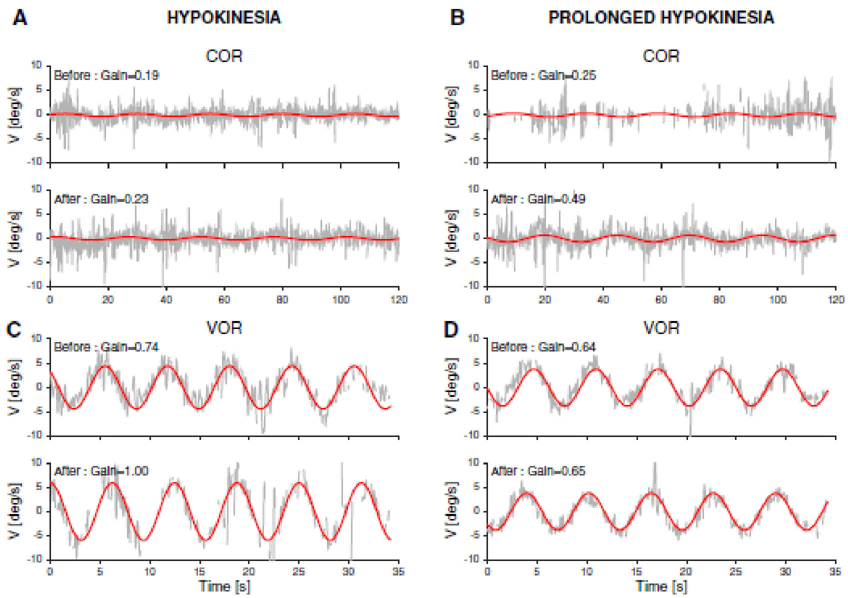

Figure 2: Exemplary eye movement velocity traces of the VOR and COR before and after 60 minutes or 120 minutes (prolonged) hypokinesia (of different subjects). Red line = the fit through the raw eye movement velocities (grey line). A= COR traces before and after hypokinesia; B= COR traces before and after prolonged hypokinesia; C= VOR traces before and after hypokinesia; D= VOR traces before and after prolonged hypokinesia

COR gain increased after prolonged neck immobilization by 81.8%, while VOR gain and the cervical ranges of motion did not change. The cervical ranges of motion did not change significantly in both the horizontal (-5° +- 12°, p = 0.294) and vertical planes (-8° +-20°, p=0.79). The before and after measurements were not correlated for the COR, but they were for the range of motion and the VOR. A between group-comparison of the hypokinesia and prolonged hypokinesia interventions showed that COR and VOR gain changes differ between the two interventions (difference in COR gain change 0.124 +- 0.228, p = 0.048 and the VOR gain change 0.092 +- 0.224, p=0.003, figure 3).

PROLONGED HYPOKINESIA		**before**	**after**	**change**		**correlation**	
	n	**median (IQR)**	**median (IQR)**	**median (IQR)**	**p-value**	**r**	**p-value**
COR (gain)	10	0.242 (0.375)	0.440 (0.349)	0.220 (0.168)	0.017	0.52	0.128
VOR (gain)	9	0.733 (0.209)	0.709 (0.278)	-0.031 (0.215)	0.314	0.68	0.042

CROM horizontal (degrees)	11	142° (24°)	134° (24°)	-2° (18°)	0.383	0.73	0.011
CROM vertical (degrees)	11	138° (32°)	130° (30°)	-8° (25°)	0.305	0.88	0.001

Table 2: Gains of the eye reflexes and cervical range of motion recorded before and after the prolonged hypokinesia intervention, the change of gain/ range of motion (including p-value) and the correlation between the two recordings (including p-value) (COR= cervico-ocular reflex; VOR= vestibulo-ocular reflex; CROM horizontal= active range of movement of the neck in the horizontal plane; CROM vertical= active range of movement of the neck in the vertical plane)

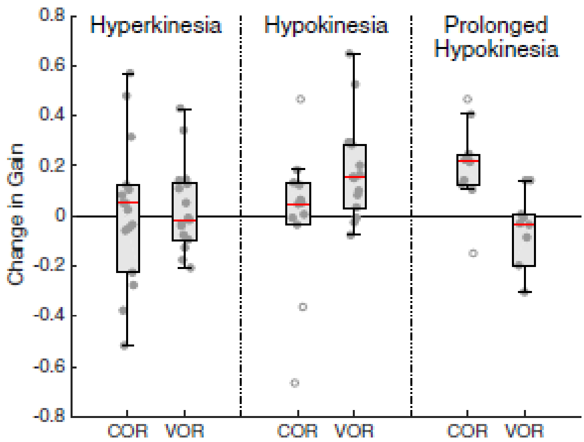

Figure 3: Boxplot of the changes in COR and VOR gains following the three different interventions. Red line= median; grey box= IQR, grey dots= individual gain values; open circles= outliers

Correlations

When we collapsed all data across all interventions, changes in the reflexes (COR and VOR) were not correlated (table 3). Subjects who moved their head more in the horizontal plane, also did so in the vertical plane. As well subjects who tended to move their heads more in the horizontal plan tended to exhibit smaller changes in VOR gains.

	VOR	**CROM horizontal**	**CROM vertical**
COR	0.081 (0.638)	0.015 (0.927)	-0.02 (0.904)
VOR		-0.369 (0.019)	0.005 (0.975)
CROM horizontal			0.537 (0.000)

Table 3: Correlations (correlation coefficient r and p-value) between the gains of COR and VOR and the range of motion in the horizontal and vertical planes.

Discussion

The present study aimed to elucidate the role of neck movements in the adaptive mechanisms of the cervico-ocular reflex (COR) and the vestibulo-ocular reflex (VOR). Thereto we temporarily immobilized the head relative to the trunk (hypokinesia) or asked participants to move their neck extensively (hyperkinesia). While COR gain does not adapt after one hour hypokinesia or after hyperkinesia, it increases after two hours of hypokinesia. VOR gain increases slightly after one hour hypokinesia, but was not changed after two hours hypokinesia nor after hyperkinesia. The influence of the maximal range of cervical motion on the eye stabilization reflexes seems to be negligible.

The changes in COR reflex are in line with the ‘upregulation theory’: if the output of the vestibulum and the neck is reduced by minimalizing the movement of the head and spine, reflex responsiveness is increased to receive enough information which is needed to stabilize the posture [6,13]. While the COR did not adapt after a shorter period of time, we replicated our previous findings of an increase in COR gains after two hours of hypokinesia [6]. This finding suggest that the COR adapts rather gradually to changed circumstances. In general, the exact time course of sensory adaptation following a stimulus change depends on the availability of sensory vestibular, visual and proprioceptive information and on the amplitude of the stimulus and the response. For instance, proprioceptive systems adapt slower to diminished sensory stimuli and faster to increased sensory stimuli [18].

Considering the importance of proper interaction of COR and VOR in relation to vision, we set out to measure the response of the VOR in response to hypokinesia as well. We observed that after one hour of hypokinesia the VOR was increased (while the COR was not altered). However, after two hours of neck immobility the VOR was no longer affected (while at this time we did observe an increased COR). The different time-courses could be explained by a nonlinear reaction of the VOR. When the COR is not adapted yet to the immobilization of the neck, the VOR adapts to improve oculomotor control. However, when after a longer period the COR finally does adapt, the change in VOR is no longer required. This shows that it takes some time for the two reflexes to balance out their interaction in response to changes in the environment. A similar effect is found in postural control experiments [18,19]. In our view, the results of the hypokinesia and prolonged hypokinesia experiment can be explained by the experience that the COR as a low gain reflex needs more time to adapt than the high gain VOR. However, it should be noted that in the present study the two reflexes were evoked at different frequencies. Therefore, the idea of compensatory interactions between the COR and the VOR needs to examined further in a more elaborate experiment which uses a broader range of frequencies.

From a clinical point of view this study helps to comprehend the frequently diffuse and confusing symptoms of neck pain patients. Neck pain patients show sensorimotor disturbances that are often related to pain, diminished range of motion, quality of movement, and oculomotor disturbances [3,10,20–23]. These oculomotor disturbances can provoke blurred vision, dizziness and the need to concentrate more than usual when reading [24]. Part of these problems could be attributed to disturbed eye stabilization reflexes [2,5]. In patients with WAD and in chronic idiopathic neck pain patients the normally weak COR is found to be increased [2,5,25,26]. Based on the findings in this study, it can be speculated that reflex alterations are not completely dependent on the origin of complaints, but do also depend on the amount of movement. From our studies we can conclude that in healthy controls limitation of neck motion affects the COR [6]. If a patient decreases neck motion due to e.g. disturbed motor control, pain, illness perceptions of fear of motion, the oculomotor system has to deal with reduced afferent sensory information from the cervical spine. In healthy controls the temporary increase of the COR is reversible [6]; it is unknown if altered reflexes are reversible in patients also. It will be crucial to understand how patients with disturbed eye reflexes, i.e. an increased COR gain, will react to augmented neck motion. From a therapeutic perspective it would be exciting if improved quality and increased neck motion would help to normalize COR gain and reduce visual problems of neck pain patients.

An alternative explanation for the diversity of whiplash disorders, such as oculomotor disturbances, is tissue damage of diverse structures due to the traumatic origin of complaints [27]. However, we recently observed that eye reflex alterations are also found in non-traumatic neck pain patients [25,26], making a lesion based explanation for eye reflex alterations in whiplash patients less likely. This, however, needs to be further explored.

Another finding in the current study is that excessive movement of the neck did not change the gain of the reflexes. However, we have to keep in mind that there is a timing difference between the hypokinesia and hyperkinesia condition. Possibly, twenty minutes was not enough for reflex adaptation. The result of the hyperkinesia condition implies that an increase of afferent somatosensory input of proprioceptors does not affect a properly functioning system. This is confirmed by a study of Peterka et al. who found saturation behavior to increased proprioceptive stimuli in subjects with normal sensory function [19]. The conclusion for the clinical practice is that with respect to eye reflexes, proprioceptive training of a properly working system may have little surplus value.

In the present study, the COR and VOR altered after an intervention. However, the gain was highly variable. Due to the complex nature of the measurement equipment not all data could be recorded and analyzed in this study, resulting in missing data. To elucidate this variability, replication of this experiment in a bigger population can be considered.

Conclusion

The amount of cervical movement influenced the gain of the eye stabilization reflexes as a part of the oculomotor system. The gain of the reflexes increased after temporary immobilization. However, the opposite strategy, intensification of movement, did not affect the oculomotor system. These findings suggest that neck immobility may indeed play a role in the oculomotor disturbances observed in patients with neck complaints.

REFERENCES

1. Heikkilä H V, Wenngren BI. Cervicocephalic kinesthetic sensibility, active range of cervical motion, and oculomotor function in patients with whiplash injury. *Arch Phys Med Rehabil*. 1998;79(9):1089-1094. http://www.ncbi.nlm.nih.gov/pubmed/9749689.

2. Kelders WP a, Kleinrensink GJ, van der Geest JN, et al. The cervico-ocular reflex is increased in whiplash injury patients. *J Neurotrauma*. 2005;22(1):133-137. doi:10.1089/neu.2005.22.133.

3. Storaci R, Manelli A, Schiavone N, Mangia L, Prigione G, Sangiorgi S. Whiplash injury and oculomotor dysfunctions: Clinical-posturographic correlations. *Eur Spine J*. 2006;15:1811-1816. doi:10.1007/s00586-006-0085-0.

4. Treleaven J, Jull G, Grip H. Head eye co-ordination and gaze stability in subjects with persistent whiplash associated disorders. *Man Ther*. 2011;16:252-257. doi:10.1016/j.math.2010.11.002.

5. Montfoort I, Kelders WP a, van der Geest JN, et al. Interaction between ocular stabilization reflexes in patients with whiplash injury. *Invest Ophthalmol Vis Sci*. 2006;47(7):2881-2884. doi:10.1167/iovs.05-1561.

6. Montfoort I, Van Der Geest JN, Slijper HP, De Zeeuw CI, Frens MA. Adaptation of the cervico- and vestibulo-ocular reflex in whiplash injury patients. *J Neurotrauma*. 2008;25:687-693. doi:10.1089/neu.2007.0314.

7. Ischebeck BK, de Vries J, Van der Geest JN, et al. Eye movements in patients with Whiplash Associated Disorders: a systematic review. *BMC Musculoskelet Disord*. 2016;17(1):441. doi:10.1186/s12891-016-1284-4.

8. Falla D, Farina D. Neural and muscular factors associated with motor impairment in neck pain. *Curr Rheumatol Rep*. 2007;9(6):497-502. http://www.ncbi.nlm.nih.gov/pubmed/18177604.

9. Hodges PW. Pain and motor control: From the laboratory to rehabilitation. *J Electromyogr Kinesiol*. 2011;21(2):220-228. doi:10.1016/j.jelekin.2011.01.002.

10. Kristjansson E, Treleaven J. Sensorimotor function and dizziness in neck pain: Implications for assessment and management. *J Orthop Sport Phys Ther*. 2009;39(5):364-377. doi:10.2519/jospt.2009.2834.

11. Treleaven J, Jull G, LowChoy N. The relationship of cervical joint position error to balance and eye movement disturbances in persistent whiplash. *Man Ther*. 2006;11:99-106. doi:10.1016/j.math.2005.04.003.

12. Hikosaka O, Maeda M. Cervical effects on abducens motoneurons and their interaction with vestibulo-ocular reflex. *Exp Brain Res*. 1973;18(5):512-530. http://www.ncbi.nlm.nih.gov/pubmed/4794882.

13. Schweigart G, Chien R-D, Mergner T. Neck proprioception compensates for age-related deterioration of vestibular self-motion perception. *Exp Brain Res*. 2002;147(1):89-97. doi:10.1007/s00221-002-1218-2.

14. Rijkaart DC, van der Geest JN, Kelders WP, de Zeeuw CI, Frens M a. Short-term adaptation of the cervico-ocular reflex. *Exp Brain Res*. 2004;156(1):124-128. doi:10.1007/s00221-004-1878-1.

15. Yakushin SB, Kolesnikova O V, Cohen B, et al. Complementary gain modifications of the cervico-ocular (COR) and angular vestibulo-ocular (aVOR) reflexes after canal plugging. *Exp Brain Res*. 2011;210(3-4):549-560. doi:10.1007/s00221-011-2558-6.

16. van der Geest JN, Frens M a. Recording eye movements with video-oculography and scleral search coils: a direct comparison of two methods. *J Neurosci Methods*. 2002;114(2):185-195. http://www.ncbi.nlm.nih.gov/pubmed/11856570.

17. Williams MA, Williamson E, Gates S, Cooke MW. Reproducibility of the cervical range of motion (CROM) device for individuals with sub-acute whiplash associated disorders. *Eur Spine J*. 2012;21(5):872-878. doi:10.1007/s00586-011-2096-8.

18. Jeka JJ, Oie KS, Kiemel T. Asymmetric adaptation with functional advantage in human sensorimotor control. *Exp Brain Res*. 2008;191(4):453-463. doi:10.1007/s00221-008-1539-x.

19. Peterka RJ. Sensorimotor integration in human postural control. *J Neurophysiol*. 2002;88(3):1097-1118. doi:10.1152/jn.00605.2001.

20. Treleaven J. Sensorimotor disturbances in neck disorders affecting postural stability, head and eye movement control. *Man Ther*. 2008;13:2-11. doi:10.1016/j.math.2007.06.003.

21. Bexander CSM, Hodges PW. Cervico-ocular coordination during neck rotation is distorted in people with whiplash-associated disorders. *Exp Brain Res*. 2012;217(1):67-77. doi:10.1007/s00221-011-2973-8.

22. Kristjansson E, Björnsdottir SV, Oddsdottir GL. The long-term course of deficient cervical kinaesthesia following a whiplash injury has a tendency to seek a physiological homeostasis. A prospective study. *Man Ther*. 2016;22:196-201. doi:10.1016/j.math.2015.12.008.

23. Stenneberg MS, Rood M, de Bie R, Schmitt MA, Cattrysse E, Scholten-Peeters GG. To What Degree Does Active Cervical Range of Motion Differ Between Patients With Neck Pain, Patients With Whiplash, and Those Without Neck Pain? A Systematic Review and Meta-Analysis. *Arch Phys Med Rehabil*. October 2016. doi:10.1016/j.apmr.2016.10.003.

24. Treleaven J, Takasaki H. Characteristics of visual disturbances reported by subjects with neck pain. *Man Ther*. 2014;19(3):203-207. doi:10.1016/j.math.2014.01.005.

25. de Vries J, Ischebeck BK, Voogt LP, et al. Cervico-ocular Reflex Is Increased in People With Nonspecific Neck Pain. *Phys Ther*. 2016;96(8):1190-1195. doi:10.2522/ptj.20150211.

26. Ischebeck BK, de Vries J, Janssen M, et al. Eye stabilization reflexes in traumatic and non-traumatic chronic neck pain patients. *Musculoskelet Sci Pract*. 2017;29:72-77. doi:10.1016/j.msksp.2017.03.004.

27. Curatolo M, Bogduk N, Ivancic PC, McLean S a, Siegmund GP, Winkelstein B a. The role of tissue damage in whiplash-associated disorders: discussion paper 1. *Spine (Phila Pa 1976)*. 2011;36(25 Suppl):S309-15. doi:10.1097/BRS.0b013e318238842a.

Chapter 10:

General discussion

GENERAL DISCUSSION

The main goal of the research described in this thesis is to improve understanding of oculomotor disorders in neck pain patients. This final chapter discusses to what extent this goal is achieved, and will discuss the clinical implications.

Patients with neck pain experience a wide range of complaints. In addition to pain and a diminished range of motion they may also experience dizziness and report cognitive complaints [1–3]. Previous studies suggest that oculomotor disturbances are present in patients with neck pain, which are a cause of many complaints [4–6]. In this thesis we have investigated disturbances in the oculomotor function of patients with neck pain in some detail. The investigation contributes to improved diagnostics and therapy in neck pain patients with oculomotor disorders.

Chapter 2 shows in a systematic review that oculomotor problems occur significantly more frequently in patients with WAD compared to healthy subjects, a finding which confirms the idea that further study in this area is desirable. The other important result of this study is that very diverse methods are used to record oculomotor disturbances. This variety of methods is likely to reflect distinct underlying concepts with respect to oculomotor disturbances. Three different eye movement types were used to assess oculomotor problems in patients with WAD: eye stabilization reflexes, smooth pursuit eye movements and head-eye coordination. Methods applied primarily in fundamental research (measurement of eye stabilization reflexes) are reliable and valid, but very time-consuming and unfit for clinical application, while methods that are predominantly applied in clinical practice (head-eye coordination tests and SPNT test) have not yet been extensively studied. Moreover, these clinical methods do not allow for discrimination concerning which part of the oculomotor system is causing the disturbance. We conclude that there is no currently available clinical test which has sufficient construct validity. This is an important limitation in the diagnostics of neck pain patients with oculomotor disorders.

This thesis aims at improving understanding of oculomotor disorders in neck pain patients in order to enhance assessment and therapy. Therefore we chose from the existing measurement methods for the experimental studies, measurement of eye stabilization reflexes with state-of-the-art video-oculography. This measurement system was primarily developed for fundamental neuroscience research, but was, with some exceptions [5,7–9] rarely used in clinical studies involving neck pain patients. Video-oculography is capable of detecting small changes in the performance of eye stabilization reflexes. Our measurement setup also allows for the quantifying of oculomotor disorders of neck pain patients in detail by measuring eye stabilization reflexes in isolation.

The experimental studies described in Chapters 3 to 5 focus on the quantification of altered eye stabilization reflexes in chronic neck pain patients. Two of these studies (**Chapters 3 and 5**) are performed on chronic, unsuccessfully treated neck pain patients. One study (**Chapter 4**) is performed on less severely impaired chronic neck pain patients. These three studies show that altered eye reflexes occur far more commonly than is generally suspected in all neck pain patients. Altered eye stabilization reflexes are not only present in patients with acute WAD, but also in chronic, traumatic and non-traumatic

patients with neck pain (Chapters 3 and 5). Even in a group of patients with less impairments and shorter-term complaints, the eye stabilization reflexes are altered (Chapter 4). In these non-traumatic neck pain patients applying for physical therapy and experiencing low-to-moderate neck pain and disability levels, the COR is elevated.
Based on the results of these studies, it was argued that changes in eye stabilization reflexes are not predominantly caused by a traumatic physical impact, but have other, currently unknown causes. COR alterations do not diminish spontaneously in chronic neck pain patients over time. Despite suggestions from earlier studies, this outcome shows that the trauma and the duration of complaints are not the dominant causes of eye reflex disturbances [5,7]. The question then remains: 'what does cause eye reflex disturbances?'

In order to assess the factors that may be associated with the cause of oculomotor dysfunctions a broad spectrum of mechanical, behavioral and personal factors, and their possible relationship with eye reflexes, are studied (**Chapter 5**). In previous studies concerning eye stabilization reflexes only demographic characteristics, i.e. age and gender, were included into the analyses [7,10,11]. This made it impossible to rule out the possible influence of other factors, such as the cervical function, as well as personal factors and personality traits, on eye stabilization reflexes. Such an understanding is necessary in order to learn more about why some neck pain patients experience oculomotor problems, while others do not. It also helps to eliminate confounding in forthcoming studies, and could contribute, at a later date, to improvements in therapies for neck pain patients.

Thus we have deliberately chosen factors from different domains in Chapter 5, and have studied their relationship with eye stabilization reflexes. None of the factors included in this study showed any strong relationship with altered eye reflexes. This lack of effect might be related to the admittedly large number of factors (21) tested in the study that required statistical corrections. Nonetheless, this result enables us to exclude many studied factors and to focus on a small number of remaining parameters which might possibly influence eye reflexes. The relationship between the amount of pain and eye reflexes does seem to be worth examining.

The results of this study form an important step towards ruling out specific factors for further research, and later also for the therapy of neck pain patients.

Parallel to the studies already mentioned, four other experimental studies were also in progress. The studies in Chapters 6 and 9 address the question of why neck pain patients have oculomotor problems. Chapters 7 and 8 focus on what might be the best way to test these patients.

The first of these four studies (**Chapter 6**) focused on the relationship between cervical proprioception and eye stabilization reflexes, similar to the study in Chapter 5. There are two relevant differences between the two studies: first, the study in Chapter 6 was undertaken using another patient population than that of Chapter 5. While in Chapter 5 severe, chronic neck pain patients are included, Chapter 6 concerns non-traumatic short-term neck pain patients having less severe neck pain. The second and probably more important difference is the measurement protocol of the JPE. In contrast to Chapter 5, in

Chapter 6 the JPE is measured more extensively. Separate JPEs are calculated for rotations in both the vertical and horizontal planes and the absolute error is presented with a higher accuracy.

The results of the study in Chapter 6 show that, in contrast to that of Chapter 5, JPE as a parameter of cervical proprioception is weakly correlated with the COR test in non-specific neck pain patients. This result suggests a connection between the COR and the cervical JPE, as both tests receive afferent information from the (upper) cervical spine. The rather weak correlation between the COR and the JPE might be due to the fact that the result of the JPE test depends on multiple factors. While the COR test measures purely cervical induced eye movements, the JPE test is also influenced by the vestibular function. Since the two tests represent different aspects of sensorimotor function it could be argued that in order to obtain adequate insight into neck reflex function, both tests should be used complementarily. Treleaven and co-workers already support the idea that the JPE reflects a general disturbance to postural control rather than a solitary altered cervical afferent input and emphasize that solitary use of the JPE test as a representative for cervical afferent information and eye movement control is an oversimplification[12].

To gain more insight into how eye movement control could be tested in neck pain patients, one clinical test was examined. One of the conclusions of the systematic review in Chapter 2 was that the fundamental concept and methodology of the Smooth Pursuit Neck Torsion (SPNT) test should be evaluated. Therefore, **Chapters 7 and 8** focus on the SPNT test. The setup of these two studies is rather complex, because two different items are simultaneously tested:

1. The fundamental concept of the test that only in neck pain patients and not in the healthy controls smooth pursuit eye movements are influenced by the neck position.
2. The methodology of the test regarding the degree of cervical rotation and the kind of stimulus (predictable or unpredictable).

The fundamental concept of the SPNT test must be evaluated, because it is unclear whether the neck position influences smooth pursuit eye movements differently in healthy controls compared to neck pain patients. The assumption of this different relationship is prerequisite for the SPNT test. However, it seems plausible that the neck position of healthy controls does influence eye movements [12–14], and this questions the validity of the test.

In order to clarify the fundamental concept of the SPNT test, in **Chapter 7** the interaction between neck torsion and two aspects of the oculomotor system (saccadic eye movements and smooth pursuit eye movements) are explored in healthy controls. In this study a clear confirmation of the relationship between neck position and eye movements cannot be found. Neck torsion has a small but significant influence on the performance of both smooth pursuit and saccadic eye movements. In order to assess this small effect, the gain change of healthy controls needs to be compared with the gain change of neck pain patients, which has been performed in Chapter 8. Another result of the study is the influence of target predictability on the outcome of the test. As expected, healthy controls perform better with predictable targets compared to unpredictable targets. The reaction of target predictability might be an indicator of the cognitive performance of the participant

The results of the study with healthy controls (Chapter 7) become more significant when compared to the results of neck pain patients (**Chapter 8**), resulting in three major observations. First, as expected, neck pain patients generally perform worse than healthy controls. Under all conditions smooth pursuit gains are lower. Secondly, and unexpectedly, the influence of neck rotation is as small in neck pain patients as in healthy controls. Neck pain patients perform slightly worse in rotated neck positions, but the differences in smooth pursuit gains between most eccentric neck rotations and neutral rotations are the same in patients with neck pain as in the controls. This result might suggest that the effect of neck torsion is not a decisive factor in the differentiation between patients with neck pain and healthy controls and therefore questions the applicability of the SNPT test in a clinical setting. In addition, it must be asked what other factors, besides neck torsion, influence the outcome of the test.

Thirdly, the performance of neck pain patients is not influenced by the type of stimulus (predictable or unpredictable). This contrasts with the results obtained in healthy controls. The apparently easier task when target movement is predictable does not lead to better performance. It is unclear why predictability influences in different ways patients with neck pain and healthy controls. Cognitive factors such as distraction due to pain might offer an explanation, but we can only speculate about this, as we did not study those factors. Cognitive factors could certainly play a role, since, in general, neck pain patients experience cognitive impairments. Alterations in the central nervous system are also found[15–17]. The influence of cognitive impairments on the execution of the SPNT test should therefore be evaluated more thoroughly. This information is essential in order to determine whether the SPNT is a suitable (clinical) test for the diagnosis of neck pain patients.

The results of these two studies lead to questions concerning the suitability of the SPNT test in the diagnostic process of neck pain patients. More factors than were suspected seem to influence the outcome of the test. Thus, we can now already conclude that the outcome of the SPNT seems unlikely to be influenced by impaired neck proprioception alone, as was previously suggested [12,14,18,19].

The proposed relationship between cervical function and oculomotor control is further explored in **Chapter 9**. The existence of a relationship between cervical function and oculomotor control was confirmed in the previous studies. This study focusses on the influence of cervical motion on eye stabilization reflexes. The exact relationship between cervical movement behavior and eye reflexes in neck pain patients has not yet been studied. As a first step the current study concentrated on the effect of quantity of neck movement on eye reflexes in healthy controls. In particular, dynamic neck movements might influence reflexive eye movements. This is the first study that has entirely focused on the relationship between amount of movement and eye stabilization reflexes.

Eye stabilization reflexes can indeed be manipulated by altered movement behavior: the COR increases after two hours of hypokinesia and does not change after the hyperkinesia condition. Remarkably, even in healthy controls the reflex system instantly reacts to altered movement behavior. Thus, the reflexive system is so sensitive that a short disturbance of movement already has rather large effects. Many neck pain patients move their neck less due to pain than to cognitions such as fear avoidance behavior. Could it be that patients have reflex alterations because they move their neck less, regardless of the underlying reason?

In summary, the studies described in this thesis support the notion that oculomotor disorders are important in the study and assessment of neck pain patients. We have shown that oculomotor disorders are a widespread problem in neck pain patients, and that far more patients than suspected have oculomotor problems that could have a substantial impact on their daily functioning. In addition to patients with WAD, many non-traumatic patients and those who have already received physiotherapy still have oculomotor disorders. Given the diversity of this patient group, traumatic impact as the sole cause of oculomotor disturbances can be ruled out and other possible causes need have to be examined. The relationship between neck function and oculomotor function has been extensively explored in this heterogeneous, severely impaired patient group. Different parts of the oculomotor system are influenced by cervical dysfunction; in particular, the influence of neck motion on eye reflexes.

In addition, various personal, physical and behavioral factors can be practically ruled out as an explanation for oculomotor alterations. Nevertheless it remains challenging to explain what exactly happens and what the causes and consequences are. The interactions between oculomotor function, cervical function, cognitive function and pain does need to be further investigated. Such understanding is necessary for the optimal assessment and therapy of neck pain patients. We suggest that dysfunction of the neck causes pain and alters oculomotor function and that, subsequently, pain and oculomotor dysfunction lead to cognitive impairments.

Future research

Oculomotor disorders are a widespread problem in chronic neck pain patients. We now understand a little more about the possible reasons for these persistent disorders and the associations with other complaints, but there is still much more to achieve.

In order to improve diagnostics in neck pain patients with respect to oculomotor disturbances, both fundamental research and clinical development are essential. In general, fundamental research is needed to comprehend the pathophysiology of oculomotor disturbances. Meanwhile, patient and user-friendly tests need to be developed for daily clinical practice. One measure would be to compare the outcome of a fundamental and a clinical measurement method of eye movement control (eye stabilization reflexes and head-eye coordination) in the same patient group. Such a comparison would help us to know whether the two tests measure the same part of the oculomotor system, and would be a long-term help in developing a valid clinical test.

With testing eye stabilization reflexes in a large patient group, we gained more insights into who suffers from altered eye reflexes and whether the alteration is associated with cervical function, personal factors, personality traits and/or patients' impairments. It was thus possible to rule out many factors. However, we still do not know exactly which factor most influences oculomotor dysfunction. Therefore, in order to offer optimal therapy, more insight into the factors that cause and prolong reflex alterations is essential. It is not sufficient to simply wait until the reflex alterations diminish automatically; the way that patients function in this respect needs to be changed through therapy.

The possible relationship between oculomotor disorders and pain, as suggested by the outcome of the study described in Chapter 5, also warrants further investigation. It would be interesting to understand whether COR changes due to central processes, such as sensitization, or is rather due to local processes, such as altered cervical motor control. Even a combination of these two processes is conceivable. Pain is currently considered to be multidimensional [20–23]. Measuring those dimensions of pain in eye reflex studies might help to understand their relationship to COR change. For example, measuring pressure pain thresholds and conditioned pain modulation efficacy could become parameters for sensitization of the central nervous system[16,17]. A study of eye stabilization reflexes in patients with musculoskeletal pain, but without neck pain, would be endorsed.

We have hypothesized that patients with chronic neck pain have altered eye stabilization reflexes because they move their neck differently. Based on this idea, we recommend measuring the voluntary amount of daily neck movement in future clinical studies, not only the maximum range of motion, as is now commonly performed.

Another, more biomechanical option for future studies would be to compare the cervical muscle morphology with the eye stabilization reflexes. Patients with neck pain, and in particular patients with WAD, have altered morphology of neck muscles[24]. These changes are most prominent in the upper cervical region, which has the highest density of muscle spindles[25]. The cause of these morphology changes are currently still debated. There are indications that muscle changes are associated with pain intensity and with post-traumatic stress[26]. We believe that pain, caused by sensorimotor changes and post-traumatic stress, influences cervical movement behavior. Over the long term dysfunctional cervical movement leads to altered morphology of the neck muscles and could cause altered eye stabilization reflexes.

A clinical study that tests the eye reflexes both before and after suitable sensorimotor training programs could answer the question of whether these alterations are reversible by therapy. Recently, more studies have focused on the benefits of virtual reality tools for the training of neck pain patients. The first results were positive [27,28]; this therapy does seem to be suitable, especially for neck pain patients with oculomotor problems.

Whether improvement of oculomotor function can diminish the perceived cognitive problems of neck pain patients is an issue that still awaits focused research. The new ‘Dutch modified perceived deficits questionnaire’ [29] seems to have additional benefits in the registration of cognitive problems and should be added to the suggested clinical trial on the effect of specific sensorimotor training on eye stabilization reflexes.

CLINICAL IMPLICATIONS

This thesis draws attention to oculomotor disorders as a widespread problem in neck pain patients and argues that these disorders require special attention in clinical assessment. These disorders do not diminish spontaneously, and affected functions need to be restored through suitable therapy. Therefore, to offer optimal assessment and therapy, greater insight into the particular factors that cause and maintain reflex alterations is essential.

Currently no valid test is available to measure oculomotor problems in neck pain patients. The suitability of the existing clinical SPNT test has been placed under question by the results of Chapters 7 and 8. It seems likely that more factors than have been assumed influence the outcome of the test. The need for reliable assessment is confirmed by the fact that the group of patients with altered eye stabilization reflexes is larger than was suspected.

In this group differentiation between traumatic and non-traumatic patients seems less important regarding eye reflexes. Over the last decades the prevalence of patients diagnosed with Whiplash Associated Disorders has increased. Research on this group of patients, as well as a specific guideline, has been developed (KNGF Richtlijn Whiplash)[30]. Remarkably, in 2016 the ‘Guideline Whiplash’ of the Dutch Physiotherapy Association was replaced by a general guideline on neck pain[31]. Patients with WAD were no longer seen as specific types of neck pain patients but were incorporated as one subgroup of patients, namely those with neck pain related to trauma. This shows that patients with WAD are to be regarded as ‘normal’ neck pain patients, although they often experience more impairments [32,33]. As discovered in this thesis, patients with WAD do not differ from patients with non-traumatic neck pain regarding eye stabilization reflexes. It would no doubt be better to differentiate patients by the severity of their complaints rather than by their origin.

In clinical practice it should be borne in mind that different complaints and dysfunctions are associated with each other. For instance: oculomotor disorders seem to develop through altered cervical sensorimotor function and could cause dizziness and cognitive disorders. Structural damage is less likely to be the cause of these alterations. In order to diminish oculomotor disorders, evaluation of both the oculomotor and cervical sensorimotor function seems useful.

In recent years evidence has been growing that isolated treatment of one complaint is not as successful as an integrated approach[34,35]. Sensorimotor training[36–38], oculomotor training[36], pain education[23] and self-management education[23] should ideally all be combined.

Based on the study in Chapter 6, it can be suggested that diminishing pain should be a main therapeutic goal. This may prevent deterioration of eye reflexes, although it is unknown whether less pain might even contribute to an improvement in eye reflexes. In general, pain reduction through functional recovery rather than solitary pain treatment is preferable.

In Chapter 9 we gained important knowledge of the influence of the cervical movement on eye reflexes. It is also crucial to learn whether theses alterations are reversible. Therapy should focus on improvement of sensorimotor neck function and the reduction of sensitization. It should also be evaluated whether the oculomotor function improves. It is currently unknown whether these reflex alterations are reversible in patients; in healthy controls the temporary increase of the COR as a result of the neck immobilization is reversible[39]. For the development of therapy it will be essential to understand how patients with disturbed eye reflexes, i.e., an increased COR gain, will react to augmented neck motion. It would certainly be exciting if improved quality and increased neck motion helped to normalize COR gain and reduce long-term visual and cognitive problems for neck pain patients. In particular, patients with sensorimotor disorders in the upper cervical spine might benefit from specific oculomotor training.

The second valuable finding of the randomized trial is that an adequately working oculomotor system in healthy controls does not improve through extensive and active neck movements. The conclusion for clinical practice is that whereas proprioceptive training for patients with oculomotor problems seems highly desirable, proprioceptive training of a properly working system may have little additional value.

In conclusion, the studies described in this thesis have improved our understanding of oculomotor disorders in patients with neck pain. For the clinical practice the five most important take home messages are:

1. Oculomotor disorders occur far more often than previously suspected and needs attention during the standard diagnostic process of neck pain patients. Beside common factors like pain and range of motion, also the possible presence of oculomotor disorders should always be kept in mind.
2. The occurrence of oculomotor disorders is not dependent of origin or severity of cervical spine complaints.
3. Despite the lack of one optimal clinical test for the diagnosis of oculomotor disorders, a combination of the existing tests should be used during the diagnostic process.
4. Particular attention is needed for the amount and quality of cervical motion.
5. Sensorimotor training of the upper cervical spine can potentially diminish oculomotor disorders.

REFERENCES

1. Curatolo M, Bogduk N, Ivancic PC, McLean S a, Siegmund GP, Winkelstein B a. The role of tissue damage in whiplash-associated disorders: discussion paper 1. *Spine (Phila Pa 1976)*. 2011;36(25 Suppl):S309-15. doi:10.1097/BRS.0b013e318238842a.

2. Treleaven J, Jull G, Sterling M. Dizziness and unsteadiness following whiplash injury: characteristic features and relationship with cervical joint position error. *J Rehabil Med*. 2003;35(1):36-43. http://www.ncbi.nlm.nih.gov/pubmed/12610847.

3. Rodriquez AA, Barr KP, Burns SP. Whiplash: pathophysiology, diagnosis, treatment, and prognosis. *Muscle Nerve*. 2004;29(6):768-781. doi:10.1002/mus.20060.

4. Montfoort I, Kelders WP a, van der Geest JN, et al. Interaction between ocular stabilization reflexes in patients with whiplash injury. *Invest Ophthalmol Vis Sci*. 2006;47(7):2881-2884. doi:10.1167/iovs.05-1561.

5. Kelders WP a, Kleinrensink GJ, van der Geest JN, et al. The cervico-ocular reflex is increased in whiplash injury patients. *J Neurotrauma*. 2005;22(1):133-137. doi:10.1089/neu.2005.22.133.

6. Treleaven J, Takasaki H. Characteristics of visual disturbances reported by subjects with neck pain. *Man Ther*. 2014;19:203-207. doi:10.1016/j.math.2014.01.005.

7. Montfoort I, Kelders WPA, Van Der Geest JN, et al. Interaction between ocular stabilization reflexes in patients with whiplash injury. *Invest Ophthalmol Vis Sci*. 2006;47:2881-2884. doi:10.1167/iovs.05-1561.

8. Montfoort I, Geest JNVANDER, Slijper HP, Zeeuw CIDE, Frens MA. Adaptation of the Cervico- and Vestibulo-Ocular Reflex. *J Neurotrauma*. 2008;693(June):687-693. doi:10.1089/neu.2007.0314.

9. Rijkaart DC, van der Geest JN, Kelders WP, de Zeeuw CI, Frens M a. Short-term adaptation of the cervico-ocular reflex. *Exp Brain Res*. 2004;156(1):124-128. doi:10.1007/s00221-004-1878-1.

10. Montfoort I, Van Der Geest JN, Slijper HP, De Zeeuw CI, Frens MA. Adaptation of the cervico- and vestibulo-ocular reflex in whiplash injury patients. *J Neurotrauma*. 2008;25:687-693. doi:10.1089/neu.2007.0314.

11. Kelders WP a, Kleinrensink GJ, van der Geest JN, et al. The cervico-ocular reflex is increased in whiplash injury patients. *J Neurotrauma*. 2005;22(1):133-137. doi:10.1089/neu.2005.22.133.

12. Treleaven J, Jull G, LowChoy N. The relationship of cervical joint position error to balance and eye movement disturbances in persistent whiplash. *Man Ther*. 2006;11(2):99-106. doi:10.1016/j.math.2005.04.003.

13. Corneil BD, Elsley JK, Nagy B, Cushing SL. Motor output evoked by subsaccadic stimulation of primate frontal eye fields. *Proc Natl Acad Sci*. 2010;107(13):6070-6075. doi:10.1073/pnas.0911902107.

14. Treleaven J, LowChoy N, Darnell R, Panizza B, Brown-Rothwell D, Jull G. Comparison of sensorimotor disturbance between subjects with persistent whiplash-associated disorder and subjects with vestibular pathology associated with acoustic neuroma. *Arch Phys Med Rehabil*. 2008;89(3):522-530. doi:10.1016/j.apmr.2007.11.002.

15. Coppieters I, De Pauw R, Caeyenberghs K, et al. Differences in white matter structure and cortical thickness between patients with traumatic and idiopathic chronic neck pain: Associations with cognition and pain modulation? *Hum Brain Mapp*. January 2018. doi:10.1002/hbm.23947.

16. Coppieters I, De Pauw R, Kregel J, et al. Differences Between Women With Traumatic and Idiopathic Chronic Neck Pain and Women Without Neck Pain: Interrelationships Among Disability, Cognitive Deficits, and Central Sensitization. *Phys Ther*. 2017;97(3):338-353. doi:10.2522/ptj.20160259.

17. Coppieters I, Pauw R De, Caeyenberghs K, et al. Decreased Regional Grey Matter Volume in Women with Chronic Whiplash-Associated Disorders: Relationships with Cognitive Deficits and Disturbed Pain Processing. *Pain Physician*. 2017;20:E1025-E1051.

18. Tjell C, Tenenbaum A, Sandstrom S. Smooth pursuit neck torsion test - A specific test for whiplash associated disorders? *J Whiplash Rel Disord*. 2002;1:9-24. doi:10.1300/J180v01n02_02.

19. Treleaven J, Jull G, LowChoy N. Smooth pursuit neck torsion test in whiplash-associated disorders: Relationship to self-reports of neck pain and disability, dizziness and anxiety. *J Rehabil Med*. 2005;37:219-223. doi:10.1080/16501970410024299.

20. Bunketorp L, Lindh M, Carlsson J, Stener-Victorin E. The perception of pain and pain-related cognitions in subacute whiplash-associated disorders: Its influence on prolonged disability. *Disabil Rehabil*. 2006;28:271-279.

21. Nijs J, Van Houdenhove B. From acute musculoskeletal pain to chronic widespread pain and fibromyalgia: application of pain neurophysiology in manual therapy practice. *Man Ther*. 2009;14(1):3-12. doi:10.1016/j.math.2008.03.001.

22. Van Oosterwijck J, Nijs J, Meeus M, Paul L. Evidence for central sensitization in chronic whiplash: a systematic literature review. *Eur J Pain*. 2013;17(3):299-312. doi:10.1002/j.1532-2149.2012.00193.x.

23. Nijs J, Van Oosterwijck J, De Hertogh W. Rehabilitation of chronic whiplash: treatment of cervical dysfunctions or chronic pain syndrome? *Clin Rheumatol*. 2009;28(3):243-251. doi:10.1007/s10067-008-1083-x.

24. De Pauw R, Coppieters I, Kregel J, De Meulemeester K, Danneels L, Cagnie B. Does muscle morphology change in chronic neck pain patients? - A systematic review. *Man Ther*. 2016;22:42-49. doi:10.1016/j.math.2015.11.006.

25. Liu JX, Thornell LE, Pedrosa-Domellöf F. Muscle spindles in the deep muscles of the human neck: A morphological and immunocytochemical study. *J Histochem Cytochem*. 2003;51(2):175-186. doi:10.1177/002215540305100206.

26. Elliott J, Pedler A, Kenardy J, Galloway G, Jull G, Sterling M. The temporal development of fatty infiltrates in the neck muscles following whiplash injury: an association with pain and posttraumatic stress. *PLoS One*. 2011;6(6):e21194. doi:10.1371/journal.pone.0021194.

27. Sarig Bahat H, Croft K, Carter C, Hoddinott A, Sprecher E, Treleaven J. Remote kinematic training for patients with chronic neck pain: a randomised controlled trial. *Eur Spine J*. October 2017. doi:10.1007/s00586-017-5323-0.

28. Treleaven J, Chen X, Sarig Bahat H. Factors associated with cervical kinematic impairments in patients with neck pain. *Man Ther*. 2016;22:109-115. doi:10.1016/j.math.2015.10.015.

29. Lenoir D, De Pauw R, Ickmans K, et al. Validity and test-retest reliability of the Dutch modified Perceived Deficits Questionnaire to examine cognitive symptoms in women with chronic whiplash, chronic idiopathic neck pain and fibromyalgia. *Pain Pract*. 2018;12(10):3218-3221. doi:10.1111/papr.12683.

30. Bekkering GE, Hendriks HJM, Lanser K, Oostendorp RAB, G.G.M. PeetersV APV, Windt DAWM van der. KNGF-richtlijn Whiplash. *Ned Tijdschr voor Fysiother*. 2001;3(111):1-25. http://www.ohcbv.nl/hulppagina/documenten/kngfrichtlijn whiplash.pdf. Accessed September 11, 2013.

31. Bier J, Scholten-Peeters G, Staal J, et al. KNGF richtlijn nekpijn. 2016. www.kngfrichtlijnen.nl.

32. De Pauw R, Coppieters I, Palmans T, Danneels L, Meeus M, Cagnie B. Motor impairment in patients with chronic neck pain: does the traumatic event play a significant role? – a case control study. *Spine J*. January 2018. doi:10.1016/j.spinee.2018.01.009.

33. Verhagen AP, Lewis M, Schellingerhout JM, et al. Do whiplash patients differ from other patients with non-specific neck pain regarding pain, function or prognosis? *Man Ther*. 2011;16(5):456-462. doi:10.1016/j.math.2011.02.009.

34. Hansen IR, Søgaard K, Christensen R, Thomsen B, Manniche C, Juul-Kristensen B. Neck exercises, physical and cognitive behavioural-graded activity as a treatment for adult whiplash patients with chronic neck pain: design of a randomised controlled trial. *BMC Musculoskelet Disord*. 2011;12:274. doi:10.1186/1471-2474-12-274.

35. Treleaven J, Peterson G, Ludvigsson ML, Kammerlind AS, Peolsson A. Balance, dizziness and proprioception in patients with chronic whiplash associated disorders complaining of dizziness: A prospective randomized study comparing three exercise programs. *Man Ther*. 2016;22(December):122-130. doi:10.1016/j.math.2015.10.017.

36. Kristjansson E, Treleaven J. Sensorimotor function and dizziness in neck pain: implications for assessment and management. *J Orthop Sports Phys Ther*. 2009;39(5):364-377. doi:10.2519/jospt.2009.2834.

37. Treleaven J. A tailored sensorimotor approach for management of whiplash associated disorders. A single case study. *Man Ther*. 2010;15(2):206-209. doi:10.1016/j.math.2009.05.001.

38. Clark NC, Röijezon U, Treleaven J. Proprioception in musculoskeletal rehabilitation. Part 2: Clinical assessment and intervention. *Man Ther*. 2015;20(3):378-387. doi:10.1016/j.math.2015.01.009.

39. Montfoort I, Van Der Geest JN, Slijper HP, De Zeeuw CI, Frens M a. Adaptation of the cervico- and vestibulo-ocular reflex in whiplash injury patients. *J Neurotrauma*. 2008;25(6):687-693. doi:10.1089/neu.2007.0314.

Chapter 11:

Summary

SUMMARY

The aim of the research described in this thesis was to gain knowledge about oculomotor disorders in (traumatic and non-traumatic) neck pain patients. This knowledge is certainly needed to improve the understanding of the complex entity of disorders in neck pain patients and to integrate oculomotor complaints in diagnostics and therapy of these patients.

In the first article of this thesis we conducted a systematic review about eye movement control in patients with ‘Whiplash Associated Disorders’ (WAD) to get on overview of the magnitude of the problem **(chapter 2)**. In general, it can be concluded that eye movements are disturbed in patients with WAD. At present, three different methods are in use to test the disorders which challenges a straightforward comparison of the different studies. There is not one single test that provides all required information. The included studies focused on respectively the measurement of eye stabilization reflexes, smooth pursuit eye movements or head-eye coordination. A specific combination of tests may be more suitable to properly determine eye motion. Currently, head-eye coordination measurements seem the most suitable for clinical use. Particularly when training oculomotor coordination as therapeutic intervention. However, the clinician has to keep in mind that when a test comprises multiple (sub-) systems, like the head-coordination measurements do, it remains difficult to determine the most important factor in the observed change. This knowledge is necessary for successful treatment of the patient.

In the second article of this thesis we investigated if oculomotor problems are only present in patients with WAD or also in non-traumatic neck pain patients **(chapter 3)**. The results of this study show that chronic, severely impaired neck pain patients have an elevated cervico-ocular reflex (COR) and an unchanged vestibulo-ocular reflex (VOR) compared with healthy controls. Seemingly, COR does not diminish automatically in chronic neck pain patients even when they receive paramedical treatment. It appears that in this severely impaired patient group the persistence of altered reflexes depends on other -non temporary- factors.

The second result of this study is that in a rather large group of chronic neck pain patients with traumatic (WAD and non-WAD) and non-traumatic origin of complaints, the patients have comparable gains of the eye stabilization reflexes. Thus, in the studied population, the origin of complaints, whether traumatic or non-traumatic, do not determine alteration of reflexes and can no longer be seen as a negative predictive factor for the development of altered eye stabilization reflexes. This implies that the alteration is dependent on other, presently unknown, factors which can possibly be changed by treatment.

Even patients who experience nonspecific neck pain for less than one year and who had less impairments, had altered eye stabilization reflexes **(chapter 4)**. Their COR was elevated by an unchanged VOR gain.

To get more insight into the reasons why eye stabilization reflexes are altered in chronic neck pain patients, we investigated the relationship between eye stabilization reflexes and cervical function, personality traits, impairments in daily life and cognitive complaints **(chapter 5)**. In all patients, no

significant associations between the eye stabilization reflexes and the studied parameters were found. We did observe indications for a moderate association between COR gain and level of pain. It suggests that in neck pain patients the, normally almost absent, COR is elevated and patients with more neck pain have a higher COR. This relationship seems stronger in the group with traumatic neck pain patients, who also experience more neck pain. Why or how pain and COR are related is obscure and needs further study.

In **chapter 6,** the relationship between the eye stabilization reflexes and the joint position error (JPE) was tested. The cervical JPE is a clinical test to measure cervical proprioception. Patients with non-specific neck pain have a higher JPE and also a higher COR than people without neck pain. However, these two outcome measures of cervical dysfunction only seem to correlate weakly, and only between the COR and the JPE in the flexion/extension direction in the neck pain group. No correlations between eye movement reflexes and the JPE were present in the control group.

Chapter 7 and 8 focused on the fundamental concept and methodology of the clinical Smooth Pursuit Neck Torsion (SPNT). The SPNT test is designed for clinical use to measure oculomotor disorders in neck pain patients. However, it can be doubted if the test in its current form only tests the influence of cervical proprioception on smooth pursuit eye movements or is influenced by other factors. The effect of neck torsion and target predictability on smooth pursuit eye movements and saccadic eye movements in patients with neck pain was investigated. As was expected on the basis of previous studies, patients with neck pain showed lower smooth pursuit gains than healthy controls. Moreover, smooth pursuit gains in patients decreased with increasing torsion of the neck, which is in line with several previous studies. However, this decrease in gain was not different between patients and controls. Target predictability, affected smooth pursuit gains differently in healthy controls and patients. Smooth pursuit performance of healthy controls decreased when targets moved unpredictably, which might be explained by the fact that these subjects are adequately able to predict the movement of the target when the target moved in a simple fashion. In contrast, the performance of patients with neck pain was the same for both conditions.

To judge the immobilization theory, we studied the effect of temporary hypokinesia versus hyperkinesia on eye stabilization reflexes in healthy controls **(chapter 9)**. We wanted to elucidate the role of neck movements in the adaptive mechanisms of the COR and the VOR. Thereto we temporarily immobilized the neck (hypokinesia) or asked participants to move their neck extensively (hyperkinesia). While COR gain does not adapt after one hour hypokinesia or after hyperkinesia, it increases after two hours of hypokinesia. VOR gain increases slightly after one hour hypokinesia but was not changed after two hours hypokinesia nor after hyperkinesia.

Finally, in **chapter 10 and 11** we summarized and discussed the main results as well as some limitations of our studies. Recommendations for further research and implications for clinical practice were mentioned.

We strongly suggest to continue both fundamental and clinical research on oculomotor disorders. Fundamental research is needed to comprehend the pathophysiology of oculomotor disturbances. One measure would be to compare the outcome of a fundamental and a clinical measurement method of eye movement control (eye stabilization reflexes and head-eye coordination) in the same patient group.

A clinical study that tests the eye reflexes both before and after suitable sensorimotor training programs could answer the question whether these alterations are reversible by therapy.

For the clinical practice the five most important recommendations are:

1. Oculomotor disorders occur far more often than previously suspected and need attention during the standard diagnostic process of neck pain patients. Beside common factors like pain and range of motion, the possible presence of oculomotor disorders should also always be kept in mind.
2. The occurrence of oculomotor disorders is not dependent on origin or severity of cervical spine complaints.
3. Despite the lack of one optimal clinical test for the diagnosis of oculomotor disorders, a combination of the existing tests should be used during the diagnostic process.
4. Particular attention is needed for the amount and quality of cervical motion.
5. Sensorimotor training of the upper cervical spine can potentially diminish oculomotor disorders.

Chapter 12:

Samenvatting

SAMENVATTING

Het doel van dit promotieonderzoek was meer inzicht te krijgen in de oculomotorische (dis)functie bij (traumatische en niet-traumatische) nekpijnpatiënten. Deze kennis is noodzakelijk om het complexe klachtenbeeld van nekpijnpatiënten beter te begrijpen en om oculomotorische functie te integreren in de diagnostiek en therapie van deze patiënten.

In het eerste deel van dit proefschrift werd een systematische review uitgevoerd. Doel van deze review was om een overzicht te krijgen van de omvang van het probleem van oogbewegingscontrole bij patiënten met 'Whiplash Associated Disorders' (WAD) **(hoofdstuk 2)**. Over het algemeen kan geconcludeerd worden dat veel patiënten met WAD verstoorde oogbewegingen hebben. De bestaande 3 testen meten echter allen een ander aspect van verstoorde oogreflex (oogstabilisatiereflexen, oogvolgbewegingen, de oog-hoofdcoördinatie) Dit maakt vergelijk van deze testen lastig. Momenteel lijken de metingen van de hoofd-oogcoördinatie het meest geschikt voor klinisch gebruik omdat zij heel gebruiksvriendelijk zijn. De clinicus moet echter in gedachten houden dat wanneer een test meerdere (sub)systemen omvat, zoals de metingen van de oog- hoofdcoördinatie, het moeilijk is om de belangrijkste factor in de waargenomen verstoring te bepalen. Weten welke factor de verstoring veroorzaakt is echter noodzakelijk voor een succesvolle behandeling van de patiënt. Oogreflexen zijn afhankelijk van verschillende neurologische (sub-) systemen. Daarom blijft het lastig te bepalen welke neurologische aspecten de verstoringen in oogreflexen veroorzaken.

In het tweede hoofdstuk van dit proefschrift werd onderzocht of het hebben van oculomotorische problemen beperkt is tot een specifieke patiëntengroep of dat deze problemen diffuser aanwezig zijn in een grotere populatie **(hoofdstuk 3)**. Het blijkt dat bij chronische nekpatiënten zowel traumatische als niet-traumatische nekpatiënten een verhoogde cervico-oculaire reflex (COR) en een ongewijzigde vestibulo-oculaire reflex (VOR) hebben. Chronische nekpijnpatiënten die al langer dan zes maanden nekpijn hebben, vertonen nog steeds een verhoogde COR en een ongewijzigde VOR. Klaarblijkelijk neemt de COR niet automatisch af bij chronische nekpijnpatiënten, zelfs niet na een paramedische behandeling. Het lijkt erop dat in deze ernstig gestoorde patiëntengroep de persistentie van veranderde reflexen afhankelijk is van andere - niet tijdelijke - factoren.

Het tweede resultaat van deze studie was dat zowel traumatische als niet-traumatische nekpijnpatiënten vergelijkbare COR en VOR-waardes hebben. Een traumatisch ontstaan van de klachten lijkt dus geen vereiste te zijn voor de ontwikkeling van oculomotorische disfuncties. In de bestudeerde populatie wordt de verandering van reflexen niet bepaalt door de ontstaanswijze van de klachten (traumatisch of niet-traumatisch). De ontstaanswijze kan daarmee niet langer worden gezien als negatief voorspellende factor voor de ontwikkeling van veranderde oogstabilisatiereflexen. Dit resultaat impliceert tevens dat de verandering afhankelijk is van andere, momenteel onbekende, factoren die mogelijk door behandeling kunnen worden veranderd.

Ook bij patiënten met korter dan een jaar aanwezige niet-specifieke nekpijn, worden afwijkende oogstabilisatiereflexen gevonden **(hoofdstuk 4)**. Hun COR is verhoogd bij een onveranderde VORwaarde. Deze groep patiënten ervaart wel minder klachten dan de groep patiënten die in hoofdstuk 3 bestudeerd werd.

Om meer inzicht te krijgen in de oorzaken waarom oogstabilisatiereflexen bij chronische nekpijnpatiënten veranderen, werd de relatie tussen oogstabilisatiereflexen en cervicale functie, persoonlijkheidskenmerken, beperkingen in het dagelijks leven en cognitieve klachten onderzocht **(hoofdstuk 5)**. Bij geen van de patiënten werden een significante correlatie gevonden tussen de oogstabilisatiereflexen en de bestudeerde parameters. Mogelijk is er sprake van een associatie tussen de cervico-oculaire reflex en de ervaren hoeveelheid pijn. Deze correlatie was echter niet significant. Het resultaat suggereert dat bij nekpijnpatiënten de doorgaans bijna afwezige, COR verhoogd is en dat patiënten met meer nekpijn een hogere COR hebben. Er waren aanwijzingen dat deze relatie sterker is in de groep met traumatische nekpijnpatiënten, die ook meer nekpijn ervaren. Waarom of hoe pijn en COR gerelateerd zijn, is onduidelijk en moet verder worden bestudeerd.

In **hoofdstuk 6** werd de relatie tussen oogstabilisatiereflexen en de 'Joint Position Error' (JPE) getest. De cervicale JPE is een klinische test om cervicale proprioceptie te meten. Patiënten met aspecifieke nekpijn hebben een hogere JPE en een hogere COR dan mensen zonder nekpijn. Deze twee uitkomstmaten van cervicale disfunctie lijken echter slechts zwak te correleren, en alleen tussen de COR en de JPE in de flexie/ extensie richting in de nekpijngroep. In de controlegroep waren er geen correlaties tussen oogbewegingsreflexen en de JPE.

In de **hoofdstukken 7 en 8** werd het fundamentele concept en de methodologie van de 'Smooth Pursuit Neck Torsion' (SPNT) -test bestudeerd. De SPNT- test is een klinische test die ontwikkeld is om oculomotorische stoornissen bij nekpijnpatiënten te meten. Het is echter twijfelachtig of de test in zijn huidige vorm enkel de invloed van cervicale sensomotoriek op oogvolgbewegingen test omdat verschillende andere factoren het testresultaat lijken te beïnvloeden. Zoals verwacht op basis van eerdere onderzoeken, vertoonden patiënten met nekpijn minder goede oogvolgbewegingen dan gezonde controles. De nauwkeurigheid van oogvolgbewegingen nam bij patiënten met toenemende torsie van de nek af. De verschillen in oogvolgbewegingen tussen maximale rotaties en neutrale positie waren zowel bij patiënten als bij gezonden even groot. Het effect van voorspelbaarheid op oogvolgbewegingen was verschillend tussen patiënten en gezonde. Net zoals in eerdere onderzoeken, presteerden patiënten bij voorspelbare stimuli slechter dan gezonde controles. Bij onvoorspelbare stimuli hadden echter alleen gezonden meer moeite met de taak. Patiënten presteerden hetzelfde bij zowel voorspelbare als niet-voorspelbare stimuli. Mogelijk zijn gezonde proefpersonen beter in staat om bij een simpele taak de beweging te voorspellen.

In **hoofdstuk 9** werd de invloed van de mate van cervicale beweging op oogreflexen onderzocht door middel van tijdelijke hypokinesie versus hyperkinesie. De nek werd tijdelijk geïmmobiliseerd (hypokinesie) d.m.v. het dragen van een nekkraag. Een week later werd aan de deelnemers gevraagd hun nek juist intensief te bewegen (hyperkinesie). De COR veranderde niet na een uur hypokinesie of na hyperkinesie, maar nam wel toe na twéé uur hypokinesie. De VOR nam licht toe na een uur hypokinesie, maar bleef onveranderd na twee uur hypokinesie en na hyperkinesie.

In **hoofdstuk 10 en 11** worden de belangrijkste conclusies van deze thesis besproken. Er worden aanbevelingen voor verder onderzoek gedaan en implicaties voor de klinische praktijk worden toegelicht.

Het wordt sterk aanbevolen om zowel fundamenteel als klinisch onderzoek na oculomotorische stoornissen bij nekpatiënten uit te voeren. Met fundamenteel onderzoek kan meer inzicht in de verschillende meetsystemen en de onderliggende verklaringsmechanismen voor oogstoornissen verkregen worden. Tijdens klinisch onderzoek kan het effect van specifieke behandeling op oculomotorische stoornissen en de ervaren klachten gemeten worden.

De belangrijkste suggesties en aandachtspunten voor de klinische praktijk zijn:

1. Oculomorische disfuncties treden veel vaker op dan aangenomen. De clinicus moet daarom alert zijn op mogelijke afwijkingen tijdens de diagnostiek van nekpijn patiënten. Het registreren van oculomotorische disfuncties zou op den duur net zo normaal moeten zijn als het meten van de mate van pijn en de bewegelijkheid van de nek.
2. Het optreden van oculomotorische disfuncties is onafhankelijk van de ontstaanswijze van de klachten.
3. Zolang er nog geen optimale klinische test bestaat, adviseren wij de bestaande tests te combineren tijdens het diagnostisch proces.
4. Bij patiënten met oculomotorische disfuncties moet er extra aandacht zijn voor de mate en kwaliteit van de cervicale bewegingen.
5. Mogelijk kunnen oculomotorische disfuncties verminderen door sensomotorisch training van de hoogcervicale wervelkolom.

Chapter 13:

Curriculum vitae

CURRICULUM VITAE

Britta Castelijns Ischebeck was born in Ennepetal, Germany in 1980 as daughter of Ernst Friedrich and Ruth Ischebeck.

After graduating from secondary school at the Reichenbach Gymnasium in Ennepetal (Abitur) in 1999, she started to study Physical Therapy in at the University of Applied Science (‘Hogeschool van Utrecht’) in Utrecht, the Netherlands. In 2003 she graduated with a ‘Bachelor of Health’. In 2004 she started to study Manual Therapy at the Vrije Universiteit Brussel, Belgium and finished her study in 2007 with a ‘Master of science’.

After finishing her first study, she worked in 2004 as physiotherapist at the ‘Medical Centre’ in Bad Ragaz, Zwitserland and from 2004 to 2007 in a private clinic in Geel, Belgium. In 2007 she started working at the ‘Spine & Joint Centre’, a Dutch rehabilitation center, specialized in the treatment of chronic patients with pelvic, back and neck pain. As of 2010 she started combining her work as Manual therapist in the Spine & Joint Centre with a phD-project at the department of neuroscience at the Erasmus MC in Rotterdam. Sinds 2017 Britta reviews theses of Bachelor students at the Rotterdam University of applied Sciences, department of physiotherapy (Hogeschool of Rotterdam).

Britta is married to Joost Castelijns, mother of Tore (born in 2015) and Nena (born in 2017) and expecting their third child.

Chapter 14:

phD- portfolio

PHD PORTFOLIO

1. PhD training	General courses	Year	Workload (Hours/ECTS)
	Data analysis with Matlab	2011	1,2 ECTS
	Biomedical English Writing and Communication	2013	2 ECTS
	BROK (Basic course Rules and Organization for Clinical researchers)	2011, 2016	1,5 ECTS
	Werken met Endnote	2013	0,1 ECTS
	Systematisch Literatuuronderzoek in PubMed	2013	0,1 ECTS
	Systematisch Literatuuronderzoek in andere databases	2013	0,1 ECTS
	CPO-course (Patient Oriented Research: design, conductance, analysis and clinical implications)	2014	0,3 ECTS
	Seminars and workshops		
	Helmholtz retrait, Bergen	2013	0,6 ECTS
	Presentations		
	Posterpresentation at International Whiplash Trauma Congres, Lund, Sweden	2011	0,3 ECTS
	Posterpresentation at Endo-Neuro-Psych meeting, Lunteren	2012	0,3 ECTS
	Posterpresentation at Helmholtz retrait, Bergen	2013	0,3 ECTS
	Posterpresentation at Neural Control of Movement, Amsterdam	2014	0,3 ECTS
	(Inter)national conferences		
	International Whiplash Trauma Congres, Lund, Sweden	2011	1,2 ECTS
	Neural Control of Movement, Amsterdam	2014	1,2 ECTS
2. Teaching	**Supervising practicals and excursions, Tutoring**		
	Ba3.VO Centraal Visueel Systeem	2011-2015	1,5 ECTS
	intern teaching of colleagues of the Spine & Joint Centre	2011-2018	3 ECTS
	Supervising Master's theses		
	Malou Janssen	2011-2012	5 ECTS

Spine & Joint Centre
samen in beweging

ISBN 978-94-6332-439-7