Sensorimotor Disturbances in People with Non-Specific Neck Pain

Sensomotorische Verstoringen bij Mensen bij A-Specifieke Nekpijn

Jurryt de Vries

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Foar de wyn is elts in hurdryder

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Chapter 1:

General introduction

Neck pain

Neck pain is the fourth leading cause of global disability, and its annual prevalence rate exceeds 30%.[1,2] Disability as a result of neck pain is common and poses considerable physical, psychological, and economic consequences to individuals and society.[3,4] In the majority of people with neck pain, a specific pathophysiological cause for neck pain and associated symptoms cannot be found, and hence the term 'non-specific' (or 'a-specific') neck pain is used.'[5] The definition of neck pain, used in this thesis is the definition by '*The Bone and Joint Decade 2000–2010 Task Force on Neck Pain and its Associated Disorders*', reading: 'activity-limiting neck pain (± pain referred to the upper limb(s) that lasts for at least one day').[6] The anatomical region for neck pain is defined as ' the posterior region of the cervical spine, from the superior nuchal line to the first thoracic spinous process.'

Although mostly harmless in origin, the course of neck pain is characterized by exacerbations and remissions, and only a small part of people with neck pain experience full recovery of their symptoms within one year.[3]

In about 40% of the cases usual care for people with neck pain consists of giving advice about self-care combined with medication and/or referral for physiotherapy.[7]

Physiotherapy has positive effects in people with non-specific neck pain and consists mainly of combinations of patient education,[8] exercise therapy,[9] massage therapy[10] or spinal manipulation therapy.[11] Nevertheless, the overall effects of physiotherapy are only small to moderate, and recurrence rates for non-specific neck pain are high.[12]

A strategy to improve the effectiveness of physiotherapy in general, and neck pain in particular, is to examine the underlying bio-psycho-social mechanisms of neck pain and to align physiotherapy treatment strategies with these mechanisms. It can be hypothesized that the population of people with non-specific neck pain is very heterogeneous regarding signs and symptoms, prognosis, psychosocial determinants, quality of life et cetera and that different (combinations) of mechanisms can play a dominant role. For that reason, a ´one size fits all´ intervention strategy will have only limited success. It seems logical that people with non-specific neck pain will respond differently to standardized treatments. So, instead of the usual approach of treating people with neck pain with a combination of different modalities (with its limited effectiveness and efficiency), it might be useful to look at the bio-psycho-social characteristics of subgroups of people with neck pain, to define specific patient profiles and to align treatment according to the mechanistic determinants

of these subgroups. This is no minor task since countless factors can play a role in experiencing neck pain. This yields both for the `biological` factors (e.g., biomechanical, neurophysiological, pathological) as for the `psychosocial` factors (e.g., cognitions, emotions, behavior), let alone the interactions between these factors.

Nonetheless, for the advancement of the effectiveness of physiotherapy as a clinical practice, it is essential to examine which factors play a role in non-specific neck pain as this knowledge enables physiotherapists to design specific, mechanism-based, treatments for subgroups of people with non-specific neck pain. This implicates a focus on identifying factors which play a role in neck pain. The biological and anatomical factors related to specific neck pain have been studied extensively.[13-16]

However, a factor that has not been studied yet in people with non-specific neck pain is the role of oculomotor motor reflexes as part of sensorimotor control. Research has shown that in a subgroup of patients with non-specific neck pain, people complain about dizziness, blurred vision, and tired eyes.[17] It has been suggested that disturbed oculomotor reflexes have a relation with these clinical symptoms.[18] It is currently known that these reflexes can be altered in people with traumatic neck pain.[19] Oculomotor reflexes are essential for keeping clear vision while moving around in daily life and requires centrally orchestrated integration of peripheral and central visual and proprioceptive information. About 30% of the people with non-specific neck pain report visual disturbances as part of their complaints.[20] Therefore, it seems plausible that sensorimotor disturbances could be underlying these complaints.

Sensorimotor control

The central neurophysiological integration of afferent and efferent information involved in maintaining stability in the postural control system by intrinsic motor-control properties is described as sensorimotor control.[21] Sensorimotor control of head and eye movement relies on the integration of afferent information from the cervical spine, the vestibular system, and the visual system. The highly developed sensorimotor system of the cervical spine provides neuromuscular control to the mobile cervical spine via unique connections to the vestibular and visual systems.[22,23]

Besides pain, visual disturbances are commonly reported in people with neck pain.[20,24] Both visual disturbances and eye-movement disturbances are conceptually explained by altered cervical afferent input and/or the altered integration of visual and proprioceptive

information.[21,24,25] This concept is empirically supported by the fact that healthy asymptomatic individuals report visual disturbances when cervical afferents are artificially disturbed.[26-28] Research into the relationship between visual disturbances and altered eye stabilization reflexes in people with whiplash-associated disorders has shown that these reflexes are indeed altered when compared to healthy controls.[19,29]

Disturbances of peripheral proprioceptive information from the cervical spine in people with non-specific neck pain is hypothesized to be a possible cause for symptoms as dizziness, visual disturbances, and impaired head and eye movement control. Clinical experience[18] and research indicate that significant sensorimotor proprioceptive disturbances in the cervical spine can be an essential factor in the maintenance, recurrence, or progression of various symptoms in people with neck pain.[30,31] Thus, in clinical practice (i.e., the therapeutic context), addressing these deficits is essential.[32]

Proprioception

The interaction between afferent and efferent receptors that control the position and movement of the body (or body parts) in space is described as proprioception.[33] The orientation of the position of the head in relation to the world or in relation to the trunk demands not only the contribution of vestibular and visual information but also proprioceptive information from the cervical spine.[34] Many structures around the cervical spine provide this information by specific propiosensors in muscles, joints, tendons, capsules, and the skin.[35,36] These propriosensors function as transducers converting mechanical energy into the electrical energy of a nerve action potential.[35] Fast adapting receptors (such as Pacinian corpuscles) are associated with detection of deceleration and acceleration.[37] Slow adapting receptors (such as Golgi organs and Ruffini end organs) are sensitive to slow changes in position.[38] Afferent information from tendon organs contribute to proprioception under active conditions.[39] Muscle spindles also have a crucial role in joint position sense (JPS) and joint movement sense respectively.[40-42] In comparison to the limbs, a high concentration of muscle spindles in the intertransverse muscle system has been noted.[43-46] High densities also have been found in the small occipital muscles.[47] This finding suggests that these cervical muscles act as sensors and/or 'monitors' of craniovertebral motion.

Joint position error

Joint position sense/error (JPS or JPE) of the cervical spine is one's ability to relocate the head back to a predetermined position after a neck movement and is used to evaluate the proprioceptive ability of people[16]. The JPE has its neurological basis mostly in muscle spindles of the cervical spine.[48] Cervical muscles provide information to and receive information from the central nervous system.[49,50] Afferent information from the cervical muscles converges to the vestibular nuclei, where head movement-related information from the visual and vestibular system also converges.[51]

Eye stabilization reflexes

Eye stabilization reflexes guarantee stable vision on the retina during head movements. The absence of correct reflexes will result in blurred vision, and therefore, these eye reflexes play an essential role in our interaction with the world. Three eye stabilization reflexes are distinguished based on their sensory input: the cervico-ocular Reflex (COR), the vestibulo-ocular Reflex (VOR) and the optokinetic reflex (OKR). The OKR will not be addressed here because it was not a subject of investigation in this study. These eye stabilization reflexes work together to prevent slip of the visual input on the retina, all with their dynamic properties and based on their own afferent input from different systems. Their gains and phases can describe these eye reflexes. The gain is the magnitude of the movement of the eye relative to the movement stimulus. (See figure 1).

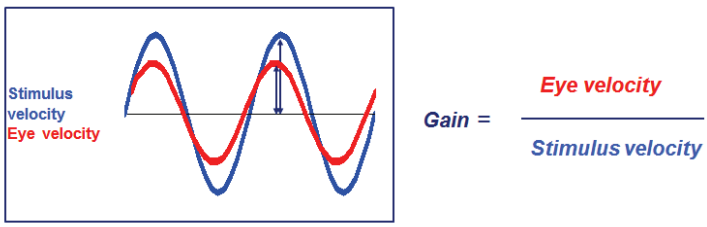

Figure 1 Calculation of the gain.

The COR is elicited by afferent information stemming from structures of the (upper) neck and results in a specific eye reflex. Hence it forms the principal object of investigation of this thesis. The COR receives its input from muscle spindles in the cervical spine, especially from the deep upper cervical muscles and joint capsules of C1 to C3.[44,52]

The COR is mainly responsive at low velocities[53,54] during trunk-to-head movement. The afferent information from the cervical spine results in eye movements opposite to the direction of the head movement. In daily life, the COR works in conjunction with the other eye stabilization reflexes. Therefore the COR was measured in isolation in an experimental setting. (See figure 2). To elicit the isolated COR, a rotating chair was used, and the head was fixated to the external world. In this chair, the body was rotated sinusoidally (trunk-to-head rotation) without visual input (complete darkness) or vestibular input (fixating the head with a biteboard). In assessing the COR all contrubitaries to the eye stabilizing reflex (vestibulum, visual information), except for the proprioception were blocked. Disturbances in this reflex could, therefore, be contributed exclusively to a proprioceptive deficit.

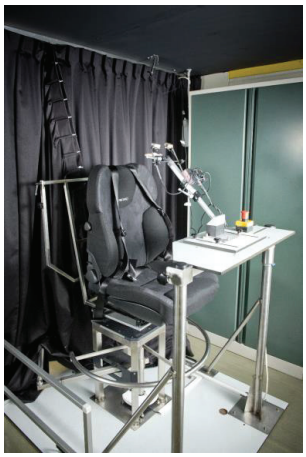

Figure 2 The COR setup with the bite board fixation.

The other reflexive eye movement, which was measured, was the vestibulo-ocular Reflex (VOR). The VOR stabilizes the retinal image by rotating the eyes to compensate for movements of the head. The VOR is elicited by vestibular information and compensates for any movement of the head in space. Resulting in the eye, remaining fixed in space during head motion, enabling clear vision. In contrast to the COR, the VOR is mainly responsive at high velocities.[55] The VOR is measured in the same experimental setup as the COR, with the difference being that the head is fixated to the chair. The consequence of this alteration is that the head is rotated in space, providing vestibular input. In people with a loss of vestibular function, the COR gain is increased,[56] and partially can take over the role of the VOR.[51,57]

In people with a Whiplash Associated Disorder, Kelders[19] found an increased COR and an unchanged VOR. This shows the COR is an adaptive eye stabilization reflex. Afferent information from the cervical region 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.[51] The central pathways of the VOR

and the COR are the same. Both reflexes converge at the vestibular nuclei.[52] Generally, the eye stabilization reflexes work in conjunction and hardly ever function isolated.

Smooth pursuit eye movements

In contrast to eye stabilization reflexes, smooth pursuit eye movements are essential to look at a moving object by keeping the retinal image steady within the foveal area. Smooth pursuit velocity matches the velocity of the moving object. Performing smooth pursuit eye movements requires the correct integration of visual, vestibular, and cervical information.[58] An earlier study of Tjell and Rosenhall[59] reported that smooth pursuit eye movements were altered in 75 people with a whiplash associated disorder compared to healthy controls by making use of the Smooth Pursuit Neck Torsion Test (SPNT). In this thesis, we investigate the fundamental concept of the SPNT. It is not yet entirely clear whether static neck position influences smooth pursuit eye movements differently in people without neck pain compared to people with pain. This assumption is the basis for the SPNT test. We performed this test with an experimental procedure, superior to the procedure used by Tjell and Rosenhall.[59] In the procedure, we used a setup in which eye movements were recorded with video-oculography (VOG) instead of electro-oculography (EOG). The latter is known to be limited in its accuracy and reliability.[60]

In measuring eye movements, a disadvantage of VOG for the clinical setting of is the technical complexity of the measurements. Especially the infrared eye-tracking method we used in this study is a complicated technical procedure. For the clinical setting, some oculomotor control tests are described. However, the reliability and validity of these tests are unknown.[31] Another often used measure to clinically operationalize cervical afferent information is the JPE of the cervical spine. [22,44,61,62] Cervical proprioception is defined as the sense of the position of the head or neck in space, describing the complex interaction between afferent and efferent receptors to monitor the position and movement.[33]

Outline of the thesis

This thesis aims to contribute to the body of knowledge about the relation between non-specific neck pain and sensorimotor disturbances. The results of the studies give a picture of the form and shape of these disturbances and, by comparing people with neck pain with healthy controls, of the potential relevance of these disturbances. More specifically

this thesis focusses on the specific relation between non-specific neck pain and eye stabilization reflexes, smooth pursuit movements and the joint position sense of the cervical spine

In order to summarize current knowledge about the relation between non-specific neck pain and the JPE, we conducted a systematic review to create an overview of the current evidence regarding the JPE in this group. In **chapter two,** we describe the outcomes of this systematic review. In **chapter three**, we report the results of our study into whether the cervico-ocular reflex is altered in people with non-specific neck pain compared to people without neck pain. After the description of the COR, we investigated if there was a relation between the COR and the JPE. The results of this investigation are reported in **chapter five**. The following **chapters six and seven** describe smooth pursuit eye movements in people without neck pain, people with non-traumatic neck pain, and people with traumatic neck pain. A general discussion concludes this thesis.

References

1. Fejer R, Kyvik KO, Hartvigsen J. The prevalence of neck pain in the world population: a systematic critical review of the literature. *European Spine Journal.* 2006;15(6):834-848.
2. Collaborators USBoD. The state of us health, 1990-2010: Burden of diseases, injuries, and risk factors. *JAMA.* 2013;310(6):591-606.
3. Vasseljen O, Woodhouse A, Bjrngaard JH, Leivseth L. Natural course of acute neck and low back pain in the general population: The HUNT study. *PAIN.* 2013;154(8):1237-1244.
4. Cohen SP. Epidemiology, Diagnosis, and Treatment of Neck Pain. *Mayo Clinic Proceedings.* 2015;90(2):284-299.
5. Borghouts JAJ, Koes BW, Bouter LM. The clinical course and prognostic factors of non-specific neck pain: a systematic review. *Pain.* 1998;77(1):1-13.
6. Guzman J, Hurwitz EL, Carroll LJ, et al. A New Conceptual Model of Neck Pain: Linking Onset, Course, and Care: The Bone and Joint Decade 2000–2010 Task Force on Neck Pain and Its Associated Disorders. *Spine.* 2008;33(4S):S14-S23.
7. Vos C, Verhagen A, Passchier J, Koes B. Management of acute neck pain in general practice: a prospective study. *British Journal of General Practice.* 2007;57(534):23-28.
8. Gross AR, Kaplan F, Huang S, et al. Psychological Care, Patient Education, Orthotics, Ergonomics and Prevention Strategies for Neck Pain: An Systematic Overview Update as Part of the ICON Project. *The Open Orthopaedics Journal.* 2013;7:530-561.
9. Gross A, Kay TM, Paquin JP, et al. Exercises for mechanical neck disorders. *Cochrane Database of Systematic Reviews.* 2015(1).
10. Patel KC, Gross A, Graham N, et al. Massage for mechanical neck disorders. *Cochrane Database of Systematic Reviews.* 2012(9).
11. Gross A, Langevin P, Burnie SJ, et al. Manipulation and mobilisation for neck pain contrasted against an inactive control or another active treatment. *Cochrane Database of Systematic Reviews.* 2015(9).
12. Vos CJ, Verhagen AP, Passchier J, Koes BW. Clinical Course and Prognostic Factors in Acute Neck Pain: An Inception Cohort Study in General Practice. *Pain Medicine.* 2008;9(5):572-580.
13. 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;157(1):43-48.
14. 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.

15. Strimpakos N. The assessment of the cervical spine. Part 1: Range of motion and proprioception. *Journal of Bodywork and Movement Therapies*.15(1):114-124.
16. Armstrong B MP, Taylor D. Head and neck position sense. *Sports Medicine*. 2008;38(2):101-117.
17. 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. *Archives of Physical Medicine and Rehabilitation*. 2008;89(3):522-530.
18. Treleaven J. Sensorimotor disturbances in neck disorders affecting postural stability, head and eye movement control; Part 2: Case studies. *Manual Therapy*. 2008;13(3):266-275.
19. 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.
20. Treleaven J, Takasaki H. Characteristics of visual disturbances reported by subjects with neck pain. *Manual Therapy*. 2014;19(3):203-207.
21. Kristjansson T. Sensorimotor function and dizziness in neck pain: implications for assessment and management. *Journal of Orthopaedic Sports and Physical Therapy*. 2009;39(5).
22. 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*. 2003;51(2):175-186.
23. McLain RF. Mechanoreceptor endings in human cervical facet joints. *Spine*. 1994;19(5):495-501.
24. Heikkilä HV, Wenngren B-I. Cervicocephalic kinesthetic sensibility, active range of cervical motion, and oculomotor function in patients with whiplash injury. *Archives of Physical Medicine and Rehabilitation*. 1998;79(9):1089-1094.
25. Treleaven J, Jull G, Grip H. Head eye co-ordination and gaze stability in subjects with persistent whiplash associated disorders. *Manual Therapy*. 2011;16(3):252-257.
26. Karnath H-O, Reich E, Rorden C, Fetter M, Driver J. The perception of body orientation after neck-proprioceptive stimulation. *Experimental Brain Research*. 2002;143(3):350-358.
27. Pettorossi VE, Panichi R, Botti FM, Biscarini A, Filippi GM, Schieppati M. Long-lasting effects of neck muscle vibration and contraction on self-motion perception of vestibular origin. *Clinical Neurophysiology*. 2015;126(10):1886-1900.
28. Beinert K, Englert V, Taube W. After-effects of neck muscle vibration on sensorimotor function and pain in neck pain patients and healthy controls – a case-control study. *Disability and Rehabilitation*. 2018:1-8.

29. 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.
30. Sterling M, Jull G, Vicenzino B, Kenardy J, Darnell R. Development of motor system dysfunction following whiplash injury. *PAIN®.* 2003;103(1):65-73.
31. Treleaven. Sensorimotor disturbances in neck disorders affecting postural stability, head and eye movement control. *Manual Therapy.* 2008;13(1):2-11.
32. Treleaven. A tailored sensorimotor approach for management of whiplash associated disorders. A single case study. *Manual Therapy.* 2010;15(2):206-209.
33. Newcomer L, Yu, Larson, An. Repositioning Error in Low Back Pain: Comparing Trunk Repositioning Error in Subjects With Chronic Low Back Pain and Control Subjects. *Spine.* 2000;25(2):245.
34. Taylor JL, McCloskey DI. Proprioception in the neck. *Experimental Brain Research.* 1988;70(2):351-360.
35. Hogervorst T, Brand RA. Mechanoreceptors in joint function. *Journal of Bone and Joint Surgery - Series A.* 1998;80(9):1365-1378.
36. McCloskey DI. Kinesthetic sensibility. *Physiological Reviews.* 1978;58(4):763-820.
37. Lephart SM, Pincivero DM, Giraldo JL, Fu FH. The role of proprioception in the management and rehabilitation of athletic injuries. *American Journal of Sports Medicine.* 1997;25(1):130-137.
38. Riemann BL, Lephart SM. The Sensorimotor System, Part I: The Physiologic Basis of Functional Joint Stability. *Journal of Athletic Training.* 2002;37(1):71-79.
39. Colebatch JG, McCloskey DI. Maintenance of constant arm position or force: reflex and volitional components in man. *The Journal of physiology.* 1987;386(1):247-261.
40. Proske U, Wise AK, Gregory JE. The role of muscle receptors in the detection of movements. *Progress in Neurobiology.* 2000;60(1):85-96.
41. P R Burgess, J Y Wei, F J Clark a, Simon J. Signaling of Kinesthetic Information by Peripheral Sensory Receptors. *Annual Review of Neuroscience.* 1982;5(1):171-188.
42. Gandevia SC, Burke D. Does the nervous system depend on kinesthetic information to control natural limb movements? *Behavioral and Brain Sciences.* 1992;15:614-614.
43. Abrahams VC. The physiology of neck muscles; their role in head movement and maintenance of posture. *Canadian journal of physiology and pharmacology.* 1977;55(3):332-338.

44. Richmond FJ, Bakker DA. Anatomical organization and sensory receptor content of soft tissues surrounding upper cervical vertebrae in the cat. *Journal of Neurophysiology*. 1982;48(1):49-61.
45. Boyd-Clark LC, Briggs CA, Galea MP. Muscle Spindle Distribution, Morphology, and Density in Longus Colli and Multifidus Muscles of the Cervical Spine. *Spine*. 2002;27(7):694-701.
46. Amonoo-Kuofi HS. The density of muscle spindles in the medial, intermediate and lateral columns of human intrinsic postvertebral muscles. *Journal of Anatomy*. 1983;136(Pt 3):509-519.
47. Kulkarni V CM, Babu K S Quantitative study of muscle spindles in suboccipital muscles of human foetuses. *Neurology India*. 2001 49(4):355-359.
48. Proske U, Gandevia SC. The Proprioceptive Senses: Their Roles in Signaling Body Shape, Body Position and Movement, and Muscle Force. *Physiological Reviews*. 2012;92(4):1651-1697.
49. 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.
50. 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.
51. 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*. 2002;88(4):2000-2018.
52. Hikosaka O MM. Cervical effects on abducens motoneurons and their interaction with vestibulo-ocular reflex. *Experimental brain research Experimentelle Hirnforschung Experimentation cerebrale*. 1973;18(5):521-530.
53. Mergner T, Schweigart G, Botti F, Lehmann A. Eye movements evoked by proprioceptive stimulation along the body axis in humans. *Experimental Brain Research*. 1998;120(4):450-460.
54. 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.
55. Tabak S CH, Boumans LJ, van der Steen J. Gain and delay of human vestibulo-ocular reflexes to oscillation and steps of the head by a reactive torque helmet. I. Normal subjects. *Acta oto-laryngologica*. 1997;117(6):785-795.

56. Bouyer LJ, Watt DG. "Torso Rotation" experiments. 4: the role of vision and the cervico-ocular reflex in compensation for a deficient VOR. *Journal of vestibular research : equilibrium & orientation*. 1999;9(2):89-101.
57. Bronstein AM, Morland AB, Ruddock KH, Gresty MA. Recovery from bilateral vestibular failure: implications for visual and cervico-ocular function. *Acta oto-laryngologica Supplementum*. 1995;520 Pt 2:405-407.
58. Lencer R, Trillenberg P. Neurophysiology and neuroanatomy of smooth pursuit in humans. *Brain and Cognition*. 2008;68(3):219-228.
59. Tjell R. Smooth pursuit neck torsion test: a specific test for cervical dizziness. *American Journal of Otology*. 1998;19(1):76-81.
60. 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.
61. Strimpakos N. The assessment of the cervical spine. Part 2: Strength and endurance/fatigue. *Journal of Bodywork and Movement Therapies*. 2011;15(4):417-430.
62. Stanton TR, Leake HB, Chalmers KJ, Moseley GL. Evidence of Impaired Proprioception in Chronic, Idiopathic Neck Pain: Systematic Review and Meta-Analysis. *Physical Therapy*. 2015.

Chapter 2:

Joint position sense error in people with neck pain: A systematic review

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Abstract

Background

Several studies in recent decades have examined the relationship between proprioceptive deficits and neck pain. However, there is no uniform conclusion on the relationship between the two. Clinically, proprioception is evaluated using the Joint Position Sense Error (JPSE), which reflects a person's ability to accurately return his head to a predefined target after a cervical movement.

Objectives

We focused to differentiate between JPSE in people with neck pain compared to healthy controls.

Study design

Systematic review according to the PRISMA guidelines.

Method

Our data sources were Embase, Medline OvidSP, Web of Science, Cochrane Central, CINAHL and Pubmed Publisher. To be included, studies had to compare JPSE of the neck (O) in people with neck pain (P) with JPSE of the neck in healthy controls (C).

Results/findings

Fourteen studies were included. Four studies reported that participants with traumatic neck pain had a significantly higher JPSE than healthy controls. Of the eight studies involving people with non-traumatic neck pain, four reported significant differences between the groups. The JPSE did not vary between neck-pain groups.

Conclusions

Current literature shows the JPSE to be a relevant measure when it is used correctly. All studies which calculated the JPSE over at least six trials showed a significantly increased JPSE in the neck pain group. This strongly suggests that 'number of repetitions' is a major element in correctly performing the JPSE test.

Introduction

The primary measure to clinically operationalize cervical proprioception is the Joint Position Sense Error (JPSE) (Strimpakos, 2011 Armstrong and Taylor, 2008). Joint position sense, an individual's ability to reproduce and perceive previous predetermined positions or ranges of motion of a joint, is a major component of proprioception. The error people make whilst reproducing the predefined position is defined as the JPSE. Recently, several studies on the relation between neck pain and JPSE have been published (Chen and Treleaven, 2013, Woodhouse and Vasseljen, 2008, Cheng et al., 2010).

Cervical proprioception is the sense of position of the head or neck in space, describing the complex interaction between afferent and efferent receptors to monitor the position and movement [1]. In the cervical spine, this sense has its neurological basis in muscle spindles (Proske and Gandevia, 2012) and, to a lesser extent, in tendon organs (Golgi receptors) (Hogervorst and Brand, 1998), cutaneous receptors, and joint receptors [2-7]. The cervical muscles provide information to (Bolton et al., 1998) and receive information from the central nervous system [8-10]. Afferent information from the cervical muscles converges in the vestibular nuclei, where the head movement-related information from the visual and vestibular system also converges [11]. Malmström et al. [12] showed that accurate head-on-trunk orientation can be achieved without vestibular information. This suggests that proprioceptive information of the cervical spine is important for head-on-trunk orientation. The cervical JPSE is assessed by testing the ability of a blindfolded participant to accurately relocate their head to the trunk relative to a predefined target (often the neutral position of the head) after a cervical movement. Other examples of joint regions in which JPSE has been used for testing proprioception are the shoulder [13], the knee [14], and the ankle [15].

People with neck pain originating from trauma and people whose neck pain has developed more gradually both seem to have a higher JPSE than people without neck pain [16,17]. This implies that an increase in JPSE may not be caused solely by soft tissue damage or neurological impairments following trauma [18,19].

Narrative reviews of the literature on cervical JPSE have been published [20,21]. Both reviews give conflicting conclusions concerning the presence of a higher JPSE in people with neck

pain. The present study is a comprehensive, systematic overview according the PRISMA guidelines of the literature. It presents the data of the JPSE of the cervical spine caused by neck pain of traumatic and non-traumatic origin in comparison of the JPSE in healthy controls.

Methods

The PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [22] were used in this systematic literature review to report the method of literature search, appraisal, and presentation of evidence.

Eligibility criteria

To be included in this systematic review, studies had to report on joint position sense error of the neck (O); and, include participants with neck pain (P), compared to healthy controls (C). It is important to compare the JPSE of people with neck pain with the JPSE of healthy controls because it is assumed that a higher JPSE test reflects aberrant afferent input from the neck (Revel et al., 1991, Heikkila and Wenngren, 1998, Treleaven et al.,2003, Malmström et al., 2009). Therefor a reference score form healthy controls is a necessity.

Information sources and search parameters

In order to be as comprehensive as possible, the following databases were searched on December 17th 2014: Embase, Medline OvidSP, Web of Science, Cochrane Central, CINAHL and Pubmed Publisher.

Keywords were derived from the research question and transformed to associated "Emtree" terms and free-text words. For Embase, the following Emtree terms were used: sensorimotor integration, sensorimotor function, somatosensory system, somatosensory cortex, balance impairment, motor control, proprioception, body equilibrium, eye movement, proprioceptive feedback, cornea reflex, neck pain, and whiplash injury.

The free-text words were as follows: deep sensitivity, kinesthe*, propriorecep*, propriocep*, kinesio NEXT/1 percept*, cornea*, eye* OR ocular OR cervicoocul* NEAR/3 reflex*, movement*,body, musculoskelet*, postural, NEAR/3 balanc*, equilibr*, sway, control, joint position, head position, neck position, NEAR/3 error*, sense*, reproduc*, abilit*, inaccura*, accura*, replicat*, head NEAR/3 steadiness, balance NEAR/3 impair*, difficult*, neck, cervic* NEAR/6 pain*, hyperextension*, ache, neckache*, Cervicalgia*,

Cervicodynia*, whiplash.
In addition, Medline, OvidSP, Web of Science, Cochrane Central, CINAHL and Pubmed Publisher were similarly searched with their own thesaurus used for indexing studies and free entries, in order to be as comprehensive as possible.

Study selection

In order to be included, studies had to meet the following criteria: (1) Participants in the study had to be over 18 years old; (2) Participants had to suffer from neck pain; (3) The outcome measures in the study had to be the JPSE; (4) Control subjects had to be healthy individuals; and (5) The study had to be written in English. Initially, the search results were screened based on title and abstract. The studies that fulfilled all inclusion criteria were evaluated in full-text, and included in the systematic review.

Data items and collection

Information was extracted from the included studies and presented in three evidence tables (Tables 1, 2, and 3). This information is presented in the evidence table regarding (1) study, (2) sample size, (3) characteristics of the paarticipantss, (4) JPSE testing instrument, (5) JPSE testing protocol, and (6) results. Data extraction was executed by author JV and checked by author LV.

Risk of bias in individual studies

The validity and risk of bias of the remaining studies was checked by using the "Methodology Checklist 4: Case-control studies" version 2.0, provided by the *Scottish Intercollegiate Guidelines Network* (SIGN) (www.sign.ac.uk). The SIGN-group develops evidence-based clinical practice guidelines in order to translate new knowledge into clinical action. One aspect of the work of this group is the development of critical appraisal checklists. Studies were scored on a clearly focused research question, 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), to "Acceptable" (+), to "High quality" (++). In the present review, only studies graded as "Acceptable" (+) or "High quality" (++) were included. This criterion was set a priori.

Methodological quality of the included studies was assessed blindly and independently by authors JV and LV. After both researchers had appraised the selected studies, results were compared and any differences discussed after screening the studies a second time. In the event of disagreement a third opinion was provided by author GK.

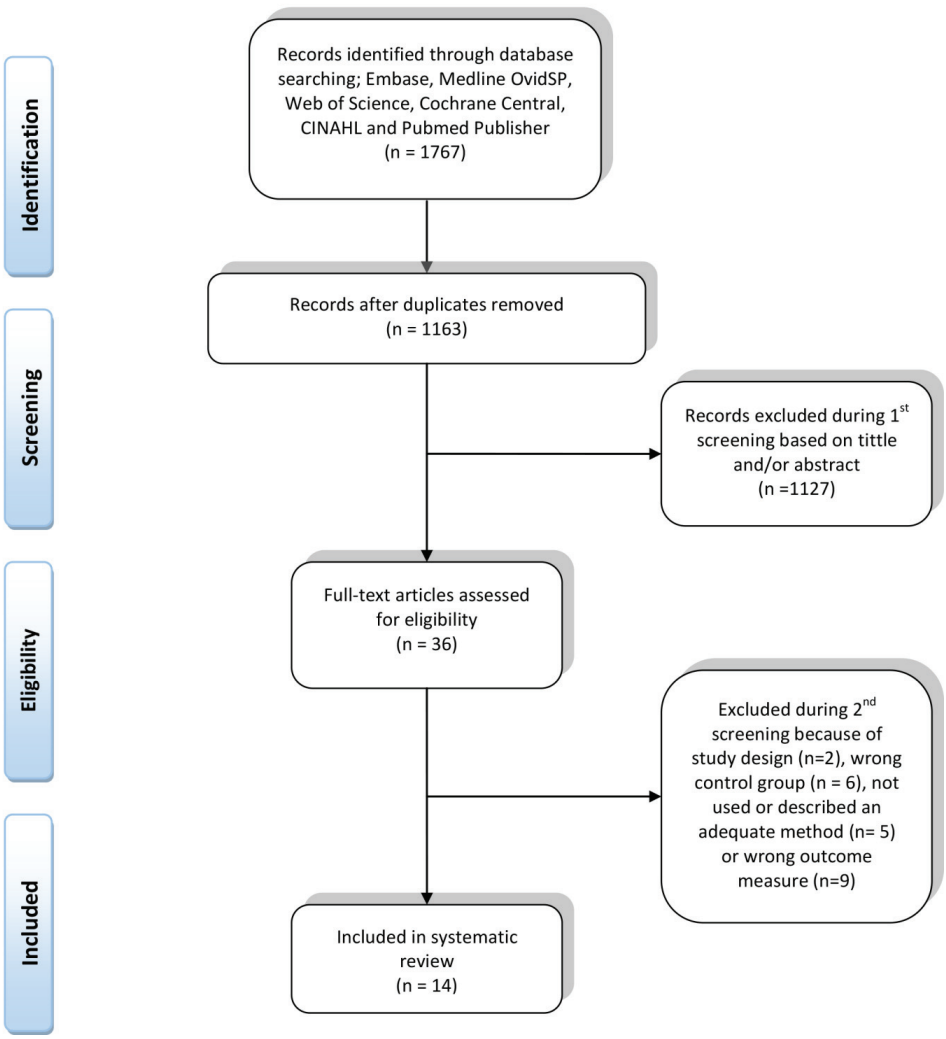

Figure 1. Flowchart of the literature search and the selection of the studies

Summary measures

The principal outcome measure of this review was the JPSE, which was the main issue to be researched in the included studies. In 9 of the 14 included studies, JPSE was defined as "the ability to reposition the head to the starting position after a maximal active movement of the head in a vertical or horizontal plane with occluded vision" (Woodhouse and Vasseljen, 2008, Sjolander et al., 2008, Treleaven et al., 2003, Revel et al., 1991, Sterling et al., 2003, Feipel et al., 2006, Cheng et al., 2010, Uthaikhup et al., 2012, Armstrong et al., 2005, Chen and Treleaven, 2013). The outcome measure was given in degrees or centimeters.

Results

Study selection

A total of 1163 studies were identified. As shown in Figure 1, 14 studies remained after two screening phases.

Study characteristics

The characteristics of the data that were extracted from the included studies (study, sample size, characteristics of the participants, JPSE testing instrument, JPSE testing protocol, and results) are presented in Tables 1, 2, and 3.

In nine out of 14 included studies JPSE was assessed in participants with traumatic neck pain [17,18,23-29]. Seven of those nine studies used the classification of the Quebec Task Force on Whiplash-Associated Disorders (WAD) [30,31]. In this classification system, WAD grade 1 corresponds to complaints of neck pain, stiffness or tenderness only without physical signs that are noted by an examining physician; WAD grade 2 corresponds to complaints of neck pain and musculoskeletal signs, such as a decreased range of motion and point tenderness in the neck; and WAD grade 3 includes additional signs (decreased or absent deep tendon reflexes, weakness, and sensory deficits). Of these nine studies, four also included a group of people with non-traumatic neck pain [23,25-27]. The studies that reported both on participants with traumatic and with non-traumatic neck pain are presented in tables 1 and 2. Another study, described in Table 3, had a combined group consisting of both participants with traumatic and idiopathic neck pain [32].

Risk of bias

Thirty-six of the included studies remained after the first screening. These 36 studies fulfilled all of the inclusion criteria, based on title and abstract. After the first full-text reading, two researchers agreed on twelve studies. On two studies, the researchers disagreed regarding the validity of the measurement protocol. Another study was subject of discussion with regard to the outcome measure. After a second reading and comparison of the differences, the researchers reached consensus for the three studies. Both conflicting studies regarding the validity of the measurement protocol were included. The study that was subject of discussion with regard to the outcome measure was excluded, resulting in 14 included studies.

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 of the studies lost points on "sample size" or "not blinding the assessor".

Outcome measures

The included studies in this review used JPSE as an outcome measure to reflect proprioception of the cervical spine. The JPSE was described in angular units (degrees) or centimeters to measure the error.

Traumatic neck-pain

As shown in Table 1, four studies [18,24,25,28] reported that participants with traumatic neck pain had a significantly higher JPSE than healthy controls. Of these four studies, Sterling et al. [18] reported a significant difference compared to healthy controls on rotation to the right. Rotation to the left and extension were not significantly different from the healthy controls. In the studies of Kristjansson et al. [25] (rotation), and [28] (rotation and flexion-extension), all the investigated directions of movement regarding the JPSE were significantly higher in participants with traumatic neck pain. In the study of Treleaven et al. [24], JPSE in all the investigated directions of movement (right rotation, left rotation, and extension) was significantly higher compared to healthy controls, but only after results from the two different neck pain groups were pooled. Five studies that included participants with neck-pain of a traumatic origin did not show a significantly altered JPSE compared to healthy controls [17,23,26,27,29]

vidence table of the included studies which researched traumatic neck pain patients.

	Sample	Inclusion criteria	JPSE testing instrument	JPSE testing protocol	Results
et	23 WAD (8M, 15W) 41.2±11.9 23 CON (10M, 13W) 33.9±12.1	WAD: grade 2 or 3 not <3 Mo or >5Yr CON: Healthy WAD and CON matched; age gender and anthropometrically	3 Space Fastrak (model 3SF0002, Polhemus, Navigation Science Division, Kaiser Aerospace,Colchester, Vermont, USA) 1 sensor centered on the forehead, 1 sensor on the spinous of c3 and 1 sensor on the spinous of T1	Flexion, extension, rotation. Mean of 3 trials Self selected neutral position Self selected pace	WAD: Global abs. error ± SD (°), all movements combined Neutral = 3.55 ± 1.72, Mid range = 2.97 ± 1.15 CON: Global abs. error ± SD (°), all movements combined Neutral = 3.25 ± 2.32, Mid range = 2.43 ± 0.62
e	56 WAD (34W, 22M) 57 CON (28W, 29M) 38.2±10.9	WAD: grade 1 or 2 not <6 Mo or >10Yr CON: Healthy	3 Space Fastrak (Polhemus, Inc, Colchester, Vermont, USA) 1 sensor centered on the forehead, 1 sensor placed on the upper part of the wooden backrest above the subjects head.	Rotation Mean of 4 trials Absolute error (largest error was selected) Selected neutral position Self selected pace. Examiner was not blinded	WAD: Global abs. error ± SD (°) Left-right rotation = 3.35 ± 1.6 CON: Global abs. error ± SD (°) Left-right rotation = 2.86 ± 1.2
t	76 WAD Dizzy (71%W) 39.11(1.3SE) 26 WAD Not Dizzy (73%W) 40.23 (1,9 SE) 102 WAD combined 44 CON (66% W) 34.1(1.8 SE)	WAD Dizzy: grade 2 or 3 not < 3Mo with dizziness WAD Not Dizzy: grade 2 or 3 not < 3Mo without dizziness WAD combined: grade 2 or 3 CON: Healthy	3 Space Fastrak (Polhemus, Inc, Colchester, Vermont, USA) 1 sensor centered on the forehead, 1 sensor on the spinous of C7	Rotation, extension Mean of 3 trials Absolute errors Selected neutral position Self selected pace	WAD Dizzy: Global abs. error ± SE (°) Right rotation = 4.5 ± 0.3, Left rotation = 3.9 ± 0.3, Extensio WAD Not Dizzy: Global abs. error ± SE (°) Right rotation = 2.9 ± 0.4, Left rotation = 2.8 ± 0.4, Extensio WAD Combined: Global abs. error ± SE (°) Right rotation = 4.1 ± 1.6*, Left rotation = 3.6 ± 0.3*, Extens 0.3* CON: Global abs. error ± SE (°) Right rotation = 2.5 ± 0.2, Left rotation = 2.0 ± 0.2, Extensio
al.	27 WAD (13W,14M) 39 CON (24W, 15M)	WAD Dizzy: grade 2 or 3 CON: Healthy	Laser pointer	Rotation, flexion/extension Mean of 10 trials maximal end range	WAD: Global abs. error ± SD (cm) Right rotation = 4.05 ± 3.4*, Left rotation = 3.36 ± 2.41*, Fle ±3.75*, Extension =3.80 ± 2.,86* CON: Global abs. error ± SD (cm) Right rotation = 2.85 ± 2.00 Left rotation = 2.73± 1.78, Flexi ±2.08, Extension =2.85 ± 1.88
n	22 WAD (11W, 11M) 33.4±10.6 21 CON (11W, 10M) 26.9±6.4	WAD Whiplash injury not < 3 Mo or > 48Mo, no previous history of NP CON: Healthy	3 Space Fastrak (Polhemus, Inc, Colchester, Vermont, USA) 1 sensor centered on the forehead, 1 sensor on the spinous of C7	Rotation Mean of 3 trials Error in degrees Full active rotation within comfortable limits Selected neutral position	Trauma: Global abs. error ± SD (°) Rotation = 4.14 ± 1.58* CON: Global abs. error ± SD (°) Rotation = 2.48 ± 1.12

	Sample	Inclusion criteria	JPSE testing instrument	JPSE testing protocol	Results
al.	19 Moderate/severe pain and disability after WAD (84%W) 41.3±13.6 22 Mild pain and disability after WAD (64%W) 34.7± 12.6 25 Recovered after WAD (60%W) 33.5±10.2 20 CON (60%W) 40.1±13.6	Mod/Sev pain and dis: WAD grade 2 or 3, NDI score of >30 after 3 Mo post injury Mild pain and dis: WAD grade 2 or 3, NDI score of 10-28 after 3 Mo post injury Recovered: WAD grade 2 or 3, NDI score of <8 after 3 Mo post injury CON: Healthy	3 Space Fastrak (Polhemus, Inc, Colchester, Vermont, USA) sensor placement unclear	Rotation, extension Mean of 3 trials Absolute errors Selected neutral position Movement within comfortable limits	Moderate/severe pain and disability after WAD: Marginal n Left rotation = 3.2 ± 0.3, Right rotation = 4.8* ± 0.3, Extensi Mild pain and disability after WAD: Marginal means ± SEM Left rotation = 2.7 ± 0.2, Right rotation = 2.7 ± 0.3, Extensio Recovered after WAD: Marginal means ± SEM (°) Left rotation = 3.0 ± 0.2, Right rotation = 3.6 ± 0.3, Extensio CON: Marginal means ± SEM (°) Left rotation = 2.6 ± 0.3, Right rotation = 2.7 ± 0.3, Extensio
	29 WAD (62%W) 37± 14 26 CON (54%W) 35±11	WAD: Grade 1, 2 or 3 CON: Healthy	Electrogoniometer (CA 6000 Spine Motion Analyzer, O.S.I., Union City, CA) mounted using a harness on the spinous process of the first thoracic vertebra and a helmet on top of the head	Rotation, flexion, extension, lateral bending. Mean of 4 trials	WAD: Global abs. error ± SD (°) Rotation = 1.1 ± 1.1 Flexion/extension = 3.5 ± 2.4 Lateral bending = 0.8 ± 0.6 CON: abs. error ± SD (°) Rotation = 0.6 ± 0.5 Flexion/extension = 2.1 ± 2.0 Lateral bending = 0.4 ± 0.3
	22 WAD (17W, 5M) 49±15 24 CON (16W, 8M) 50±18	WAD: grade 1, 2 not <3 Mo of symptoms Con: Healthy	ProReflex System (Qualisys Medical AB, Gothenburg, Sweden) 13 markers were placed on the head and upper torso	Rotation, flexion, extension Mean of 5 trials Error in degrees Self selected neutral position Self selected pace Only moving back to neutral with closed eyes	WAD: Global abs. error ± SD (°) Right rotation = 3.7 ± 1.9. Left rotation = 4.0 ± 2.1 Flexion 3.4 ± 1.6, Extension = 3.5 ± 1.8 CON: Global abs. error ± SD (°) Right rotation = 3.1 ± 1.3, Left rotation = 3.5 ± 1.3 Flexion 2.9 ± 0.9, Extension = 2.7 ± 1.0
t	7 WAD (2M, 5W) 45±11 16 CON (3M, 13W) 40±9	WAD: grade 2 or 3 not < 6 Mo CON: Healthy	3 Space Fastrak (Polhemus, Inc, Colchester, Vermont, USA) 1 sensor centered on the forehead, 1 sensor on the spinous of T1	Rotation Mean of trials unclear Move the head as fast and far as possible Self selected neutral position Patients were standing. Examiner was blinded	WAD: Over/under shooting ± SD (°) Right rotation = -0.4 ± 0.8, Left rotation = 0.7 ± 1.1 CON: Over/under shooting ± SD (°) Right rotation = 0.1 ± 0.5, Left rotation = 0.1 ± 0.6

position sense error, WAD = Whiplash associated disorder; WAD grade 1 = neck complaints of pain, stiffness or tenderness only but no physical signs are noted by the examining physician; W
aints and musculoskeletal signs as decreased range of motion and point tenderness in the neck; WAD grade 3 includes additional signs (decreased or absent deep tendon reflexes, weaknes
)N: Healthy controls; SD = Standard Deviation; SE= Standard Error, SEM = Standard Error of the Mean; M= Men; W= Women; Abs.= Absolute; Mod= Moderate; Sev= Severe; NDI= Neck Disabi
o=Month *= indicates statistically significant differences between groups

vidence table of the included studies which researched non-traumatic neck pain patients.

	Sample	Inclusion criteria	JPSE testing instrument	JPSE testing protocol	Results
	11 Non Traumatic NP (6M,5W) 41.1±13.3 11 CON (5M,6W) 39.3±10.3	Non traumatic NP: Continuous neck pain > 7Wk, No history of cervical injury or WAD CON: Healthy Non traumatic neck pain and CON matched; age and gender	Laser pointer	Flexion, extension, rotation. Mean of 10 trials Absolute errors Self selected neutral position Self selected pace Examiner was not blinded	Non Traumatic NP: Global abs. error median (°) Right rotation = 6.1, Left rotation = 3.7, Flexion = 5.7*, Exte CON: Global abs. error median (°) Right rotation = 6.0, Left rotation = 4.0, Flexion = 4.2, Exten
so 3)	20 Non Traumatic NP (9W, 11M) 30.0±9.1 21 CON (11W, 10M) 26.9±6.4	Non Traumatic NP : Insidious onset of neck pain not < 3 Mo or > 48Mo CON: Healthy	3 Space Fastrak (Polhemus, Inc, Colchester, Vermont, USA) 1 sensor centered on the forehead, 1 sensor on the spinous of C7	Rotation Mean of 3 trials Error in degrees Full active rotation within comfortable limits Selected neutral position	Non traumatic NP : Global abs. error ± SD (°) Rotation = 3.33 ± 1.42* CON: Global abs. error ± SD (°) Rotation = 2.48 ± 1.12
e	57 Chronic NP (38W, 19M) 43.7±12.6 57 CON (28W, 29M) 38.2±10.9	Chronic NP: not <6 Mo or >10 Yr CON: Healthy	3 Space Fastrak (Polhemus, Inc, Colchester, Vermont, USA) 1 sensor centered on the forehead, 1 sensor placed on the upper part of the wooden backrest above the subjects head.	Rotation Mean of 4 trials Absolute error (largest error was selected) Selected neutral position Self selected pace Examiner was not blinded	Chronic NP: Global abs. error ± SD (°) Rotation = 3.17 ± 1.1 CON: Global abs. error ± SD (°) Rotation = 2.86 ± 1.2
t	9 Insidious NP (0M, 9W) 40±9 16 CON (3M, 13W) 40±9	Insidious NP: Idiopathic neck pain of insidious onset CON: Healthy	3 Space Fastrak (Polhemus, Inc, Colchester, Vermont, USA) 1 sensor centered on the forehead, 1 sensor on the spinous of T1	Rotation Mean of trials unclear Move the head as fast and far as possible Self selected neutral position Patients were standing. Examiner was blinded	Insidious NP: Over/under shooting ± SD (°) Right rotation = 0.4 ± 0.5, Left rotation = 0.4 ± 0.8 CON: Over/under shooting ± SD (°) Right rotation = 0.1 ± 0.5, Left rotation = 0.1 ± 0.6
	21 NP (14W, 7M) 49±16 24 CON (16W, 8M) 50±18	NP: not <3 Mo Neck Pain Con: Healthy	ProReflex System (Qualisys Medical AB, Gothenburg, Sweden) 13 markers were placed on the head and upper torso	Rotation, flexion, extension Mean of 5 trials Error in degrees Self selected neutral position Self selected pace Only moving back to neutral with closed eyes	NP: Global abs. error ± SD (°) Right rotation = 3.7 ± 1.6, Left rotation = 3.6 ± 3.0 Flexion 2.8 ± 1.2, Extension = 2.9 ± 1.3 CON: Global abs. error ± SD (°) Right rotation = 3.1 ± 1.3, Left rotation = 3.5 ± 1.3 Flexion 2.9 ± 0.9, Extension = 2.7 ± 1.0

	Sample	Inclusion criteria	JPS testing instrument	JPS testing protocol	Results
	30 Chronic NP (10M, 20W) 45 (25-73) 30 CON (10M, 20W) 44 (21-72)	Chronic NP: Cervical pain. CON: Healthy	Laser pointer	Flexion, extension, rotation. Mean of 10 trials Absolute errors Self selected neutral position Self selected pace. Examiner was not blinded	Chronic NP: Global abs. error ± SD (°) Left-right rotation = 6.11 ± 1.59*, Flexion-extension = 5.47 CON: Global abs. error ± SD (°) Left-right rotation = 3.50 ± 0.82, Flexion-extension = 3.37 ±
.	12 Non traumatic NP (6W,6M) 25.4 ± 2.1 12 CON (7W,5M)24.9 ± 1.8	Non traumatic NP: not <2 Yr Neck Pain CON: Healthy Non traumatic neck pain and CON matched; age	Electrogoniometer CXTLA02, Crossbow, Inc., San Jose, CA, USA	Flexion, extension Mean of 3 trials Constant error Selected neutral position Self selected pace	Non traumatic NP: Constant error ± SD (°) Flexion = 7.1 ± 3.5*, Extension = 6.3 ± 4.7* CON: Constant error ± SD (°) Flexion = 3.5 ± 1.8, Extension = 4.2 ± 3.3
et	20 NP (70%W) 73.2±6.2 20 CON (60%W) 69.6±4.2	NP: >3 Mo neck pain, at least a score 10 or more on the NDI and older than 65Yr CON: Healthy and older than 65Yr	3 Space Fastrak (Polhemus, Inc, Colchester, Vermont, USA) 1 sensor centered on the forehead, 1 sensor on the spinous of C7	Rotation, extension Mean of 3 trials Absolute error Selected neutral position Self selected pace	NP: Global abs. error ± SD (°) Right rotation = 5.5 ± 3.1, Left rotation = 5.1 ± 4.0, Extensio CON: Global abs. error ± SD (°) Right rotation = 4.2 ± 2.2, Left rotation = 2.8 ± 1.8, Extensio

position sense error, NP= Neck Pain; CON: Healthy controls; SD = Standard Deviation; M= Men; W= Women; Abs.= Absolute; NDI= Neck Disability Index; Yr=Year; Mo=Month; *= indicates sta
differences between groups.

ɪidence table of the included study with a combined patient group.

	Sample	Inclusion criteria	JPSE testing instrument	JPSE testing protocol	Results
	25 NP (10M, 15W) 39.4±12.8 26 CON (11M, 12W) 31.0±11.9	NP: chronic NP of traumatic or idiopatic origin, not <3 Mo Neck Pain and at least a score 10 or more on the NDI CON: Healthy Av. age of the NP group significantly differs from the CON group (p=0.02)	3 Space Fastrak (Polhemus, Inc, Colchester, Vermont, USA) 1 sensor centered on the forehead, 1 sensor on the spinous of C7 and one sensor at the mid sternum region Laser Pointer	Rotation Mean of 6 trials Absolute errors Examiner was not blinded "Conventional JPS (conv)" in this protocol the subjects actively move their heads. "JPS trunk to head rotation (tors)" in this protocol the subjects actively move their trunk whilst their head does not move.	NP: Global abs. error ± SD (°) Conv R Fastr 2.79 ± 1.3, Conv L Fastr 3.00 ± 1.1, Conv RL Fas Conv R Laser 3.08 ± 1.3, Conv L Laser 3.25 ± 1.1, Conv RL La Tors R Fastr 2.66 ± 1.3, Tors L Fastr 2.81 ± 0.8*, Tors RL Fast Tors R Laser 3.31 ± 1.4, Tors L Laser 3.07 ± 1.1*, Tors RL Lase CON: Global abs. error ± SD (°) Conv R Fastr 2.36 ± 0.9, Conv L Fastr 2.83 ± 1.0, Conv RL Fas Conv R Laser 2.37 ±1 0, Conv L Laser 2.77 ± 1.1, Conv RL La Tors R Fastr 2.17 ± 0.9, Tors L Fastr 2.22 ± 0.9, Tors RL Fastr Tors R Laser 2.81 ± 1.2, Tors L Laser 2.56 ± 1.0, Tors RL Laser

ɔosition sense error, NP= Neck Pain; CON: Healthy controls; SD = Standard Deviation; M= Men; W= Women; Abs.= Absolute; NDI= Neck Disability Index; Yr=Year; Mo=Month; Fast= Fastrak *= significant differences between groups.

Non-traumatic neck pain

Eight studies were included, involving participants with non-traumatic neck pain [16,19,23,25-27,33,34] as can be seen in Table 2. Of these eight studies, four [16,19,25,33] reported a significantly higher JPSE in people with non-traumatic neck pain than in controls. Joint position sense error in the investigated directions of movement was significantly higher in the studies of Kristjansson et al. [25] (rotation), Revel et al. [19] (rotation and flexion-extension) and Cheng et al. [16] (flexion and extension). For the study of [33], this was not the case. In this study only, the flexion movement was significantly higher than in healthy controls. With respect to right rotation, left rotation and extension, JPSE in participants with neck pain was not significantly different. The studies of [23], Sjolander et al. [27], Grip et al. [26], and Uthaikhup et al. [34], did not report any significant differences in JPSE between participants with non-traumatic neck pain and healthy controls.

Combined group consisting of traumatic and non-traumatic neck pains

As shown in Table 3, Chen and Treleaven [32] included participants with chronic neck pain with either a traumatic or idiopathic origin. This study used a laser pointer as well as the "Fastrak™" instrument to measure the JPSE. The authors also used two different measurement protocols for measuring the JPSE. In the conventional protocol, participants were asked to actively rotate their heads (left or right) as far as was comfortable, and then had to return to the starting position as accurately as possible. In the alternative protocol, participants had to actively rotate the trunk (instead of the head) and return to the starting position. The chest sensor and the chest laser were used to obtain data on trunk rotation error. As can be seen in Table 3, for the conventional measurement protocol only the pooled JPSE (left/right rotation) significantly differed between participants with neck pain and controls when measured with the laser pointer. The JPSE measured with the "Fastrak™" did not show any significant differences when measured with the conventional protocol.

For the trunk-to-head measurement protocol, left rotation and the pooled left/right rotation significantly differed from the healthy controls. This held for the laser pointer measurement instrument as well as for the "Fastrak™" measurement instrument. Rotation to the right was not significantly altered, regardless of measurement instrument or protocol.

Discussion

The main goal of this systematic review was to differentiate between JPSE of the cervical spine in participants with neck pain of a traumatic or a non-traumatic origin, compared to healthy controls. The results of this review suggest that when the JPSE is measured over 6 trials or more, the JPSE is generally higher in the neck pain group than in the control group.

Various factors might influence the outcome of the JPSE measurement. The first is the influence of the vestibular system. As the peripheral and central vestibular systems provide and integrate information essential for establishing the position of the head in space, they indirectly influence the head-to-body position sense. Deficits in any of the vestibular mediated pathways may thus affect JPSE [32,35]. However, Pinsault et al.[36] and Malmström et al. [37] did not find an increased JPSE in people with vestibular loss when compared to healthy controls. Because the vestibulum is particularly sensitive to fast, jerky head movements [38], the velocity of head motion during measurement of the JPSE is important. When participants move their heads faster than 2.1°/s, cervical input decreases and vestibular input increases [39]. Thus, the faster the head moves, the more JPSE represents vestibular afferention rather than cervical afferention. It is not clear whether all the included studies tried to rule out as much afferention from the vestibulum as possible, by having the subjects move slowly. A study by Chen and Treleaven[32] showed interestingly that trunk-to-head rotation, excluding input of the vestibulum, gave different results compared to the conventional measurement protocol of head-to-trunk rotation. However, as the differences were small, this measurement protocol should be examined further to see whether possible vestibular input plays a role in the conventional measurement protocol.

A second factor that may affect the conclusion is the anatomy of the cervical spine. Large quantities of muscle spindles in the cervical spine muscles provide (Bolton et al., 1998) and receive information from the central nervous system[8-10]. In the cervical spine, the information from muscles (muscle afferention) is a dominant source of information [2,5]. A study using Magnetic Resonance Imaging has shown a widespread presence of fatty infiltrates in the neck muscles of people with persisting moderate to severe levels of pain

following a whiplash injury [40,41]. This implies that the intensity of the perceived pain may influence proprioception. For the traumatic group, the duration of complaints or severity of the WAD did not seem to influence JPSE significantly. In the non-traumatic group, there was no correlation between the duration of the neck pain and an altered JPSE. Likewise, the intensity of perceived pain, which was described in all studies, did not seem to influence the JPSE. In some of the included studies, relatively low perceived pain levels were correlated with significantly altered JPSE, and *vice versa*.

A third factor is the variety of measurement devices used. Some researchers used a laser pointer, where others used either the electromagnetic tracking system 3 Space "Fastrak™" (Polhemus Inc, USA), a ProReflex System (Qualisys Medical AB, Gothenburg, Sweden), or different types of electrogoniometers. This made it difficult to compare the various study results. The 3 Space "Fastrak™" was the most commonly used instrument, employed in eight out of fourteen studies [18,23-25,27,29,32,34]. The ' Fastrak™ 'system is an electromagnetic measuring instrument that tracks the positions of sensors relative to a source in three dimensions. Previously Jordan et al., [42]. demonstrated that it is a reliable and valid measurement system with an accuracy of up to ±0.2°. The nine studies using it produced contrasting results regarding the JPSE in people with neck pain.

The sensor placement is another possible source of measurement bias. Not all studies used the same placement, or described the placement of the sensors precisely. This inconsistency could have consequences for the validity of the measurements and the ability to compare the different study results.

The laser method, which is also commonly used to assess the JPSE (four out of fourteen studies), has a good test-retest reliability and a strong correlation with an ultrasound technique for measuring JPSE [43]. It is remarkable that all four studies [19,28,32,33] using a laser pointer showed significantly higher cervical joint reposition errors in people with neck pain than in controls. However, in none of these four studies were the examiners blinded for "controls" or "participants with neck-pain ". The results in these studies may, therefore, have been influenced by expectation bias. Revel et al. [19] compared the inter-observer reliability of the laser pointer instrument in 11 controls. This test showed no significant difference between the examiners.

The application of various testing protocols and data-analysis software is a fourth possible factor influencing the conclusion. Swait et al. [44] reported that at least six trials were needed to optimize the stability and reliability of the cervical JPSE measurement. Nonetheless, in only four of the fourteen studies did the researchers use six or more trials to calculate the mean JPSE. All four studies [19,28,32,33], in which the mean JPSE was calculated over six or more trials, showed significantly higher joint position errors in people with neck pain than in controls. These studies used a laser pointer as a JPSE testing device. An explanation for this could lie in the applied statistics. It might be that the vulnerability to outliers is less when the mean JPSE is calculated over more trials hereby reducing the standard error of the mean. This stresses the importance of calculating the joint position error over at least six trials. Further research needs to be performed on the effect on learning curves in the presence of pain and/or after (traumatic) damage to the joints of the cervical spine.

The studies with an electronic testing device used custom-made analysis software [17,18,23-25,27,29,32,34]. As only a general description of the algorithms of this software was given, the reproducibility of these experiments are low. Absence of the presentation of raw data in most studies is in line with the previous point. Only when both the data-analysis protocol and the (raw) data are presented, readers can interpret results and conclusions of the studies. Another threat to the validity and reliability of the included studies is the small number of participants that some of them included [16,27,33]. However, studies which have included a relative high number of participants do not show other or more robust results than the studies with a smaller amount of participants.

In general, data cannot be compared without harmonization of testing protocols and data analysis systems. Therefore, it was not possible to conduct a meta-analysis of the included studies. This pooling of data would help to resolve the problem of the small number of participants included in some of the studies. Besides improving the current study designs, it is also important to correlate JPSE with other specific variables (i.e. age, gender, location of perceived pain, anxiety levels, perceived disability, and cervical range of motion).

Conclusion

In general, the results of the included studies give an equivocal answer to the question of whether the JPSE is higher in people with cervical spine lesions caused by trauma and/or non-traumatic neck complaints than in controls. The JPSE is overall higher in the neck pain group when measured over at least 6 trials.

References

1. Newcomer L, Yu, Larson, An. Repositioning Error in Low Back Pain: Comparing Trunk Repositioning Error in Subjects With Chronic Low Back Pain and Control Subjects. *Spine.* 2000;25(2):245.
2. Proske U, Gandevia SC. The Proprioceptive Senses: Their Roles in Signaling Body Shape, Body Position and Movement, and Muscle Force. *Physiological Reviews.* 2012;92(4):1651-1697.
3. P. G. Peripheral neural mechanisms in proprioception. *Journal of Sport Rehabilitation.* 1994;3:1 2-17.
4. McCloskey DI. Kinesthetic sensibility. *Physiological Reviews.* 1978;58(4):763-820.
5. Hogervorst T, Brand RA. Mechanoreceptors in joint function. *Journal of Bone and Joint Surgery - Series A.* 1998;80(9):1365-1378.
6. Lephart SM, Pincivero DM, Giraldo JL, Fu FH. The role of proprioception in the management and rehabilitation of athletic injuries. *American Journal of Sports Medicine.* 1997;25(1):130-137.
7. Proske U, Wise AK, Gregory JE. The role of muscle receptors in the detection of movements. *Progress in Neurobiology.* 2000;60(1):85-96.
8. 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.
9. 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.
10. Kalaska. Central neural mechanisms of touch and proprioception. *Canadian journal of physiology and pharmacology.* 1994;72(5):542-545.
11. 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.* 2002;88(4):2000-2018.
12. Malmström E-M, Karlberg M, Fransson P-A, Lindbladh J, Magnusson M. Cervical proprioception is sufficient for head orientation after bilateral vestibular loss. *Eur J Appl Physiol.* 2009;107(1):73-81.
13. Anderson VB, Wee E. Impaired Joint Proprioception at Higher Shoulder Elevations in Chronic Rotator Cuff Pathology. *Archives of Physical Medicine and Rehabilitation.* 2011;92(7):1146-1151.

14. van der Esch M, Knoop J, Hunter DJ, et al. The association between reduced knee joint proprioception and medial meniscal abnormalities using MRI in knee osteoarthritis: results from the Amsterdam osteoarthritis cohort. *Osteoarthritis and Cartilage*. 2013;21(5):676-681.
15. Nakasa T, Fukuhara K, Adachi N, Ochi M. The deficit of joint position sense in the chronic unstable ankle as measured by inversion angle replication error. *Arch Orthop Trauma Surg*. 2008;128(5):445-449.
16. Cheng CH, Wang JL, Lin JJ, Wang SF, Lin KH. Position accuracy and electromyographic responses during head reposition in young adults with chronic neck pain. *J Electromyogr Kinesiology*. 2010;20(5):1014-1020.
17. Feipel V, Salvia P, Klein H, Rooze M. Head repositioning accuracy in patients with whiplash-associated disorders. *Spine*. 2006;31(2):E51-E58.
18. 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.
19. Revel M, Andre-Deshays C, Minguet M. Cervicocephalic kinesthetic sensibility in patients with cervical pain. *ARCH PHYS MED REHABIL*. 1991;72(5):288-291.
20. Armstrong B MP, Taylor D. Head and neck position sense. *Sports Medicine*. 2008;38(2):101-117.
21. Strimpakos N. The assessment of the cervical spine. Part 1: Range of motion and proprioception. *J Bodywork Mov Ther*. 2011;15(1):114-124.
22. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *Journal of Clinical Epidemiology*. 2009;62(10):1006-1012.
23. Woodhouse A, Vasseljen O. Altered motor control patterns in whiplash and chronic neck pain. *BMC Musculoskelet Disord*. 2008;9.
24. 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.
25. 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.
26. Grip H, Sundelin G, Gerdle B, Karlsson JS. Variations in the axis of motion during head repositioning - A comparison of subjects with whiplash-associated disorders or non-specific neck pain and healthy controls. *Clin Biomech*. 2007;22(8):865-873.
27. Sjolander P, Michaelson P, Jaric S, Djupsjobacka 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.

28. Heikkilä HV, Wenngren B-I. Cervicocephalic kinesthetic sensibility, active range of cervical motion, and oculomotor function in patients with whiplash injury. *Archives of Physical Medicine and Rehabilitation*. 1998;79(9):1089-1094.
29. Armstrong BS, McNair PJ, Williams M. Head and neck position sense in whiplash patients and healthy individuals and the effect of the cranio-cervical flexion action. *Clinical Biomechanics*. 2005;20(7):675-684.
30. Spitzer WO SM, Salmi LR, Cassidy JD, Duranceau J, Suissa S, Zeiss E. Scientific monograph of the Quebec Task Force on Whiplash-Associated Disorders: redefining "whiplash" and its management. *Spine*. 1995;20:2S–73S.
31. Rydevik B, Szpalski M, Aebi M, Gunzburg R. Whiplash injuries and associated disorders: new insights into an old problem. *European Spine Journal*. 2008;17(3):359-416.
32. 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.
33. Rix GD, Bagust J. Cervicocephalic kinesthetic sensibility in patients with chronic, nontraumatic cervical spine pain. *Arch Phys Med Rehabil*. 2001;82(7):911-919.
34. Uthaikhup S, Jull G, Sungkarat S, Treleaven J. The influence of neck pain on sensorimotor function in the elderly. *Archives of Gerontology and Geriatrics*. 2012(0).
35. Treleaven. Sensorimotor disturbances in neck disorders affecting postural stability, head and eye movement control. *Manual Therapy*. 2008;13(1):2-11.
36. Pinsault N, Vuillerme N, Pavan P. Cervicocephalic Relocation Test to the Neutral Head Position: Assessment in Bilateral Labyrinthine-Defective and Chronic, Nontraumatic Neck Pain Patients. *Arch Phys Med Rehabil*. 2008;89(12):2375-2378.
37. Malmstrom EM, Karlberg M, Fransson PA, Lindbladh J, Magnusson M. Cervical proprioception is sufficient for head orientation after bilateral vestibular loss. *European Journal of Applied Physiology*. 2009;107(1):73-81.
38. Day BL, Fitzpatrick RC. The vestibular system. *Current Biology*. 2005;15(15):R583-R586.
39. 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.
40. Elliott JM. Are There Implications for Morphological Changes in Neck Muscles After Whiplash Injury? *Spine*. 2011;36:S205-S210.
41. 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.

42. Jordan K, Dziedzic K, Jones PW, Ong BN, Dawes PT. The reliability of the three-dimensional FASTRAK measurement system in measuring cervical spine and shoulder range of motion in healthy subjects. *Rheumatology*. 2000;39(4):382-388.
43. Roren A, Mayoux-Benhamou M-A, Fayad F, Poiraudeau S, Lantz D, Revel M. Comparison of visual and ultrasound based techniques to measure head repositioning in healthy and neck-pain subjects. *Manual Therapy*. 2009;14(3):270-277.
44. Swait G, Rushton AB, Miall RC, Newell D. Evaluation of Cervical Proprioceptive Function: Optimizing Protocols and Comparison Between Tests in Normal Subjects. *Spine*. 2007;32(24):E692-E701 610.1097/BRS.1090b1013e31815a31815a31811b.

Chapter 3:

The Cervico-Ocular Reflex is increased in people with non-specific neck pain.

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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.

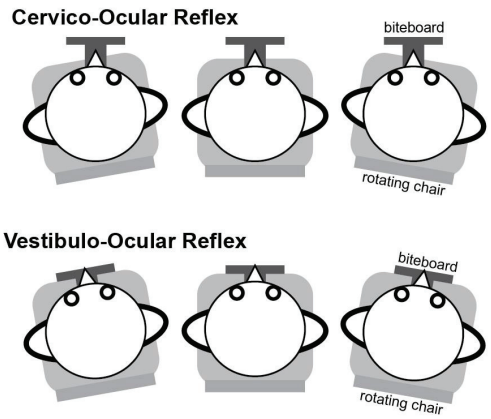

Figure 1. A schematic representation of the experimental set-up. In both paradigms the participants had to look at a position directly in front of the set-up. For the COR, the body of the subjects was rotated while the head of the participants was held fixed relative to the floor to fixate the position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

TABLE 1

Comparison of demographic and questionnaire data between asymptomatic controls and participants with neck pain.

	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

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).

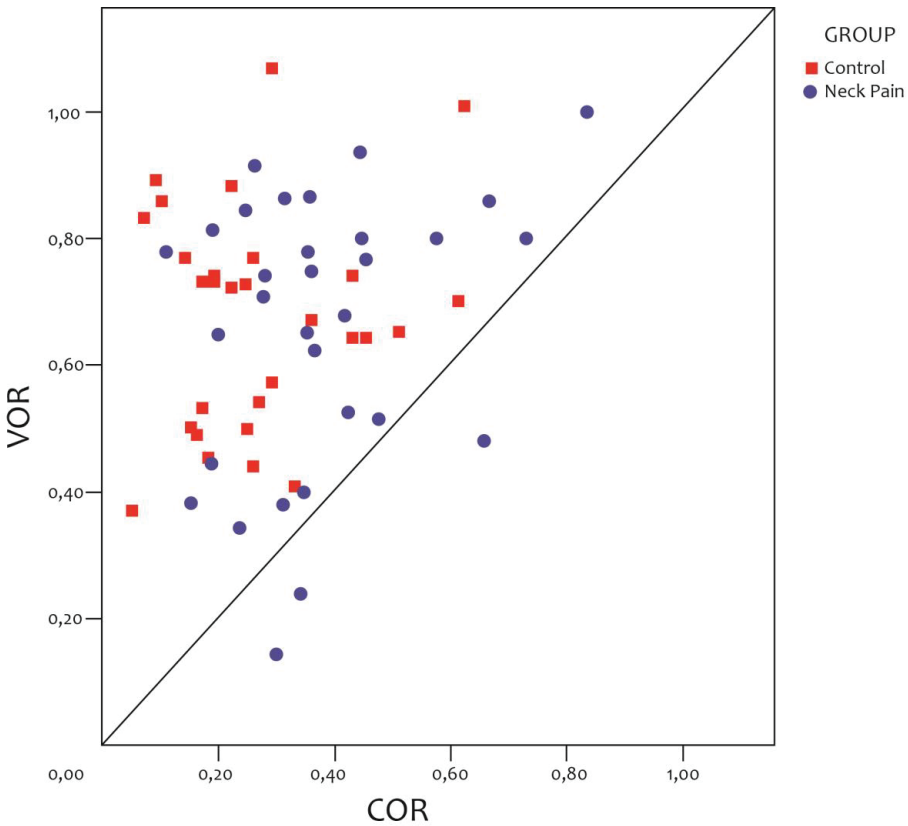

Figure 2. Scatterplot of the COR and VOR for all participants.

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]

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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*. 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*. 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*. 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;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*. 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.* 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.* 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.* 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.* 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.* 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*. 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;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*. 2014:1-6.
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*. 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*. 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*. 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*. 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*. 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*. 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*. 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.

Chapter 4:

On de Vries J, Ischebeck BK, Voogt LP. "Cervico-ocular Reflex Is Increased in People With Nonspecific Neck Pain. "*Phys Ther*. 2016;96:1190–1195.

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We read the salient research report by de Vries and colleagues,[1] unraveling an important clinical issue on nonspecific neck pain. Indeed, nonspecific neck pain is a common musculoskeletal disease affecting a multitude of people globally. It is reported that 48.5% of adults might experience neck pain during their lifetime.[2] The study by de Vries and colleagues provides novel insights for the scientific community on increased Cervico-ocular Reflex in people with nonspecific neck pain. We have several comments. First, participants with neck pain in the study experienced neck pain for less than 1 year. They might omit the minimal duration of neck pain. In fact, patients with neck pain for longer than 6 months are considered to have chronic neck pain with various risk factors, including female sex, older age, and high job demands.[3,4] The underlying mechanisms of acute and chronic neck pain might be different and thus have an impact that cannot be ignored. Therefore, it might be more convincing to use stratified patient groups in terms of the duration of neck pain. Second, Lee et al[5] noted that cervicothoracic junctional structure is a reliable method predicting chronic neck pain in young adults. Moreover, the anteroposterior diameter of the thoracic cage is significantly smaller in patients with chronic neck pain in comparison with controls, in particular for women. It should be stressed that the thoracic cage acts as a fixed base for head and neck motion. Therefore, specific anatomic structures might contribute to the increase of Cervico-ocular Reflex in patients with neck pain. Third, the authors drew the conclusion that people with nonspecific neck pain have an increased Cervico-ocular Reflex. We would raise the issue of the clinical significance of the conclusions. Given the prevalence of nonspecific neck pain, spinal surgeons might see a number of such patients in their outpatient clinics. Bearing the conclusions in mind, we would like to consult the expert authors: What should we instruct patients during doctor-patient interactive counseling? The issue might be important for both spinal surgeons and patients with neck pain.

Author Response

We would like to thank Lan and colleagues for providing feedback on our recent publication in *Physical Therapy*.[1] They raise some interesting points, which we address below. The first point deals with the duration of neck pain in our patient group. We agree that it would indeed be very interesting to make use of stratified patient groups for factors such as duration of neck pain, age, pain levels, levels of dizziness, levels of disability, or, as

mentioned, job demands. However, for this stratification, a larger number of people with neck pain is needed, including patients with chronic pain, as central mechanisms become disturbed in this group of patients in particular.[6] This is likely to apply to the Cervico-ocular Reflex (COR) as well. We would like to mention an upcoming study from our research group in which we report differences in COR between people with chronic neck pain and traumatic neck pain. The focus of our present study was only to investigate possible differences in eye movement reflexes between people with nonspecific neck and controls. As we observed an altered COR, stratification of neck pain duration or a longitudinal design would be recommended in a future study to investigate a causal relationship between neck pain and altered COR. In our present study, patients had a minimum duration of neck pain of at least 3 weeks, as all participants were recruited via physical therapist practices in Rotterdam, the Netherlands. This recruitment procedure meant that patients with neck pain were seen by a general practitioner and a physical therapist before they were referred to our research group. This minimum duration, therefore, was due to logistical reasons, which we could not control. We did control for age and sex as possible confounders. The study by Lee et al[5] showed that the anatomical aspects of the cervicothoracic junctional structure are related to chronic neck pain in young adults. Although they did not show a causal relationship between anatomical aspects of the thoracic cage and neck pain, we believe that the suggestion of specific anatomic structures affecting the COR changes in patients with neck pain is indeed quite interesting. Another interesting anatomical factor is the density of the muscle spindles of the neck muscles situated close to the spine (eg, longus colli and longus capitis muscles). Magnetic resonance imaging has shown that a widespread presence of fatty infiltrates in neck muscles is present in people with neck pain.[7] These factors might be worthwhile to take into account. Finally, our study did not primarily focus on clinical relevance but rather on changes in neurophysiological parameters such as the COR in patients with neck pain. Indeed, the functional effects of an altered COR in these patients need to be assessed. Moreover, as we observed a group effect, more research is needed before we can introduce individual tests, similar to, for instance, the gaze stability test, the eye-head coordination test, and the saccadic eye movement test described by Treleaven.[8] When individual tests research shows positive results, this could become a part of the diagnosis

and therapy in patients with neck pain, in particular for patients with concomitant symptoms such as cervical dizziness and decreased postural control.

References

1. de Vries J, Ischebeck BK, Voogt LP, et al. Cervico-ocular Reflex Is Increased in People With Nonspecific Neck Pain. *Physical Therapy*. 2016.
2. Fejer R, Kyvik KO, Hartvigsen J. The prevalence of neck pain in the world population: a systematic critical review of the literature. *European Spine Journal*. 2006;15(6):834-848.
3. Lau KT, Cheung KY, Chan kB, Chan MH, Lo KY, Wing Chiu TT. Relationships between sagittal postures of thoracic and cervical spine, presence of neck pain, neck pain severity and disability. *Manual Therapy*. 2010;15(5):457-462.
4. Silva AG, Punt TD, Sharples P, Vilas-Boas JP, Johnson MI. Head Posture and Neck Pain of Chronic Nontraumatic Origin: A Comparison Between Patients and Pain-Free Persons. *Archives of Physical Medicine and Rehabilitation*. 2009;90(4):669-674.
5. Lee J-H, Park Y-K, Kim J-H. Chronic neck pain in young adults: perspectives on anatomic differences. *The Spine Journal*. 2014;14(11):2628-2638.
6. Herren-Gerber R, Weiss S, Arendt-Nielsen L, et al. Modulation of Central Hypersensitivity by Nociceptive Input in Chronic Pain After Whiplash Injury. *Pain Medicine*. 2004;5(4):366-376.
7. 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.
8. Treleaven. Sensorimotor disturbances in neck disorders affecting postural stability, head and eye movement control. *Manual Therapy*. 2008;13(1):2-11.

Chapter 5:

The relation between Joint Position Error and Cervico-Ocular Reflex in people with non-specific neck pain.

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Submitted

Abstract

Question

Is there a relation between the joint position error (JPE) and the cervico-ocular reflex (COR) in people with non-specific neck pain?

Design

This study had a cross-sectional design involving participants with neck pain and asymptomatic controls.

Participants

Thirty-seven participants with non-specific neck pain and 30 asymptomatic controls participated in the study.

Outcome measures

The primary outcome measures of this study were the JPE and the gains of COR, and vestibulo-ocular reflex (VOR). Secondary outcomes were perceived pain, cervical range of motion, disability, and dizziness.

Results

Participants with neck pain showed an increased JPE for rotation and flexion-extension. They showed an increased COR after controlling for age and gender, compared to asymptomatic controls, whereas the VOR was unaltered. The relation between the gain of the COR and the JPE flexion/extension was significantly correlated, the COR and the JPE rotation was not significantly correlated. In the control group, there were no significant correlations.

Conclusion

This study showed that on a group level, there is a difference between people with non-specific neck pain on JPE and COR than people without neck pain. On an individual level, the COR gain or JPE alone do not seem to classify people with neck pain readily. The only correlation between COR and JPE was in the vertical plane outcome measures, which was weak. This implicates that the group of people with neck pain is a heterogeneous group.

Introduction

Neck pain affects 10 to 20% of the world population.[1] The majority of neck pain does not have an apparent cause and is therefore considered idiopathic[2]. Practice guidelines for neck pain recommend conservative treatment.[3] People with neck pain often complain about other symptoms besides their neck pain, including lightheadedness, dizziness, unsteadiness, and/or visual complaints.[4]

It is known that neck pain affects the activity in muscle spindle afferents,[5,6], and that people with neck pain show altered timing patterns in the contraction of cervical muscles such as m. longus colli, the m. longus capitis, and the m. sternocleidomastoid during a neck flexion movement.[7,8] These changes could lead to altered afferent proprioceptive information stemming from the cervical muscles. This afferent information converges within the vestibular nuclei and integrates with the afferent input from head movement-related information stemming from the visual[9] and vestibular system.[10]

This altered cervical afferent information can be assessed by measuring the Joint Position Error (JPE) of the cervical spine, which is often used as a clinical measure of cervical afferent dysfunction.[11] A recent systematic review and meta-analysis showed that people with neck pain had a larger JPE than people without neck pain.[12] Evidence from randomized controlled trials suggests that targeted proprioceptive exercises can result in both pain reduction and reduction of JPE.[13,14] However, the required head movements during the JPE test may be affected by the vestibular system[15] and/or be influenced consciously or subconsciously by the participants.

Cervical afferents are not only crucial for controlling head movements but are also playing a role in the cervico-ocular reflex (COR), which stabilizes the eye in response to trunk-to-head movements.[16-18] The COR is a non-voluntary eye reflex that stabilizes the eye in response to afferent information from the neck.[19] The COR is elicited in response to trunk-to-head movements, so there is no afferent information of the vestibulum. There is also no (subconscious) influence of pain behavior processes in the COR because this is a non-voluntary eye-reflex.[20] Earlier research showed that people with traumatic neck pain[21] and people with non-specific neck pain[22] have an increased COR compared to asymptomatic controls. The COR and VOR function both serve to stabilize the visual image on the retina

during head and trunk movements. Previous studies showed that the synergy between COR and VOR could be disturbed in neck pain patients from an idiopathic or traumatic origin, due to altered cervical sensory input.[21-23] This afferent input 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[9].

Clinically, direct measurement of the COR is not feasible, as it requires a specific setup involving a rotating chair and an accurate eye movement recording device. This is in contrast to measuring the JPE, which is uncomplicated and reliable.[24] Based on previous studies, we expect that both the COR and the JPE are affected in patients with neck pain. In the present study, we aim to investigate the relationship between these two measures of cervical afferent dysfunction. Therefore, the research questions for this study is:
- Is there a relation between the joint position error and the cervico-ocular reflex in people with non-specific neck pain?

Method

Design

This study had a cross-sectional design involving participants with non-specific neck pain and asymptomatic controls.

Participants and centre

Participants with neck pain were recruited via physiotherapy practices in Rotterdam, The Netherlands. Asymptomatic controls were recruited using an information letter distributed among people 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. Participants gave written informed consent prior to the start of the study.

Inclusion criteria for participants with neck pain were: being aged between 18 and 65 years, having non-specific neck pain continuously for less than one year, and being physically able to undergo COR and VOR measurements. Inclusion criteria for asymptomatic controls were overlapping with the inclusion criteria for participants with neck pain with the exception that they had not experienced any complaints of the cervical

spine (including cervicogenic headache and dizziness) in the last 5 years. Participants were excluded if they used medication that influenced alertness or balance; suffered from any neurological disorder; had vestibular or visual problems, or had a history of neck trauma.

Outcome measures

All participants filled in a standard demographic questionnaire. For 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 NPRS, NDI, and DHI have shown good psychometric properties in people with neck pain.[25-27] All participants underwent measurements of maximal cervical range of motion (CROM) in the sagittal and the horizontal plane. This was measured with a CROM device that has shown good reproducibility.[28]

Cervical JPE testing

For each participant, the accuracy in relocating the natural head posture (cervical JPE) was tested after active cervical movements into left and right rotation, flexion, and extension. The methodology is previously described for the lower back and pelvic girdle[29] and adapted from Revel et al.[30] Participants were equipped with four infrared LEDs. Two markers were placed on the head, and two markers were placed on the thoracic spine. For the sagittal plane, the one head marker was placed at the height of C1, and one marker was rigidly connected to this marker 3 cm up. The thoracic markers were placed on Th 1, and one marker was rigidly connected to this marker 3 cm down.

For the horizontal JPE one head marker was placed centrally on top of the head in line with the rotational axis of the neck, and one marker was rigidly connected to this marker 3 cm to the front. The thoracic markers were placed on Th 1, and one marker was rigidly connected to this marker 3 cm down. Marker positions were recorded using a CCD video-camera (Javelin JE7642) equipped with a black filter. Accuracy, inter- and intraobserver reliability, and reproducibility showed good properties.[29] At the beginning of the recording, the subject sat upright in a chair with a backrest. Next, subjects were asked to rotate left, rotate right, or bend their neck or extend their neck as far as possible in a moderate pace without forcing or jerking and then return to the initial position. Each motion was repeated three times. The two pairs of coordinates obtained from each video

image were converted into an angle in the sagittal plane or the rotational plane representing the JPE in degrees. The JPE is presented as an absolute error calculated over three repetitions. For rotation and flexion-extension, six repetitions were averaged into one JPE.

Recording of Reflexive Eye Movements

The exact procedure of recording reflexive eye movements are described elsewhere. [22] In short, monocular (left) eye positions were recorded by infrared video-oculography (Eyelink 1, SMI, Germany[31]) during either cervical or vestibular stimulation in complete darkness by rotating a chair. The chair was attached to a motor that ensured sinusoidal chair rotation without any backlash. Eye movements were recorded during either cervical or vestibular stimulation. In both stimulation paradigms (COR and VOR), participants were instructed to look at a position directly in front of the set-up. Head position was fixed in both conditions via a biteboard.

During the COR stimulation, rotation of the chair induced pure cervical stimulation by fixating the position of the head in space, 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. degrees/s. During the VOR stimulation, the biteboard was mounted to the chair, so that rotation of the chair induced pure vestibular stimulation. 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.

Reflexive eye movements were analyzed by taking the first 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. All data processing was done with Matlab R2013a (The MathWorks Inc., Natick, MA).

Data analysis

Descriptive statistics were computed for the entire sample for the gains of the COR, VOR, and JPE (outcome parameters), NDI, DHI, perceived pain, CROM (outcome variables), and

age and gender. Since the COR, VOR, NDI, DHI, perceived pain, and CROM data were 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 asymptomatic controls and participants with neck pain with age and gender as covariates. JPE data was not normally distributed (Kolmogorov-Smirnov test). Differences in JPE between people with neck pain and asymptomatic controls were statistically assessed using Mann-Whitney tests. Correlations between the gains, JPE (outcome parameters), and outcome variables were assessed using Spearman's correlations. Cross-tabulations were made of the highest and lowest half of the scores of JPE and COR. A two-tailed alpha level of $P < 0.05$ was considered significant for all statistical tests.

Results

Forty-one participants with neck pain and 30 asymptomatic controls participated in the study. Eye movement recordings were successful in 37 participants with neck pain. In four participants, the data was discarded due to technical problems. For the 37 participants with neck pain, the JPE was measured correctly, for the control group in 3 measurements were not stored properly on the hard disk. The group characteristics concerning the demographics and eye reflexes are shown in table 1.

TABLE 1

Comparison of demographic and questionnaire data between asymptomatic controls and participants with neck pain.

	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]

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, ($F(1,62) = 4.15$, $p= 0.046$, $\eta^2=0.063$) compared to asymptomatic controls. Table 2 shows the median and the interquartile range (IQR) of the JPE for the neck pain group and the control group.

TABLE 2

Comparison of the Joint Position Error in degrees (median and IQR) between asymptomatic controls and participants with neck pain.

	Control (n = 27)	Neck pain (n = 37)
	Median (IQR)	Median (IQR)
Rotation*	3.6 (1.5)	5.2 (4.4)
Flexion/extension*	3.6 (2.3)	6.3 (3.3)

* Significant difference between control and neck pain group at $p < 0.05$.

People with neck pain showed an increased JPE for rotation (U=343.5, Z=-2.313, p=0.021), right rotation (U=343.0, Z=-2.321, p=0.020), flexion extension (U=239.5 Z=-3.691, p=0.000), extension (U=315.0 Z=-2.509, p=0.012), and flexion (U=216.0 Z=-4.005, p=0.000) compared to asymptomatic controls. Left rotation showed no significant difference between people with neck pain and asymptomatic controls (U=359.0, Z=-1.912, p=0.056). The relation between the gain of the COR and the JPE flexion/extension was significantly correlated for all participants (r = 0.335, p=0.007), the COR and the JPE rotation was not significantly correlated (r= -0.028, p=0.825). For the participants with neck pain relation between the gain of the COR and the JPE flexion/extension was significantly correlated (r = 0.358, p=0.032), the COR and the JPE rotation was not significantly correlated (r= -0.172, p=0.317). In the control group there were no significant correlations between the COR and the JPE (COR and flexion/extension, r=0.032, p=0.870 and COR and JPE rotation, r=-0.012, p=0.950).

We observed a large proportion of participants with neck pain scoring in the highest 50% of COR and in the highest 50% of the JPE flexion/extension, whereas the controls scored mostly in the lowest 50% of the COR and JPE flexion/extension (table 3). For the COR and JPE rotation, this distinction between neck patients and controls was less clear (table 4).

TABLE 3

Cross tabulation describing the highest and lowest half of the scores of JPE flexion/extension and COR.

			JPE flexion/extension	
			Lowest 50%	Highest 50%
COR	Lowest 50%	Control	14	8
		Neck pain	7	4
	Highest 50%	Control	5	3
		Neck pain	6	20

TABLE 4

Cross tabulation the highest and lowest half of the scores of JPE rotation and COR.

			JPE rotation	
			Lowest 50%	Highest 50%
COR	Lowest 50%	Control	13	9
		Neck pain	3	8
	Highest 50%	Control	6	2
		Neck pain	11	15

Discussion

The current study aimed to determine if there was a relationship between the joint position error in the cervical spine and the cervico-ocular reflex in people with non-specific neck pain. The results do suggest that people 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. In the control group there, were no correlations between eye movement reflexes and the JPE.

Similar to numerous other studies[12,21,22,32,33] we did observe effects on a group level in the COR and JPE between people with neck pain and without neck pain. On an individual level, however, the COR gain or JPE alone do not seem to readily classify people with neck

pain. The same yields for other outcome measures regarding neck pain such as range of motion[34] or motor control.[35] However, it is conceivable that a (weighted) combination of these objective measures can improve individual classifications. Such a classification could give direction to a specifically targeted intervention towards people with neck pain. Such an approach showed promising results in people with low back pain.[36,37]

It is somewhat surprising that we found a correlation between the COR and the JPE in the flexion/extension direction, whereas the COR was measured in a rotational plane. An explanation could be related to the fact that the CROM was more restricted in this plane than in the rotational plane, leading to a more pronounced JPE in this plane in particular.

A limitation of quantifying objective ocular reflexes with video-oculography is the technical difficulty of the measurement. Electro-oculography (EOG) could be an alternative measurement method which is widely used in clinical settings, but it is less suitable for recording COR eye movements due to its limited accuracy and reliability.[38,39] A possible limitation in regard to measuring protocol for the JPE was the amount of repetitions participants made to calculate the JPE, which was three. Swait et al.[40] reported that at least six trials were needed to optimize stability and reliability of the cervical JPE measurement. However, another study[24] showed that three repetitions also gives a moderate to almost perfect agreement for joint position error a recent review[32] concluded that all studies which calculated the JPE over at least six trials showed a significantly increased JPE in the neck pain group. Therefore the applied measurement protocol regarding the JPE in this study could be possibly underestimating the difference in JPE between controls and people with neck pain.

We conclude that people suffering from non-specific neck pain present a deficit in JPE and COR but that these representations of cervical afferent information only seem to correlate weakly. Evaluation of different components of sensorimotor control in patients with neck pain might be worthwhile in clinical settings.[41] We advocate from a clinical point of view that intervention programs should target those functional disorders that are present in the heterogeneous group of people with non-specific neck pain. These multi-modal programs, therefore, should also address the important links between the cervical, vestibular and ocular systems in those where this relation is disturbed.[42]

Acknowledgments

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References

1. Hoy DG, Protani M, De R, Buchbinder R. The epidemiology of neck pain. *Best Practice & Research Clinical Rheumatology*. 2010;24(6):783-792.
2. Borghouts JAJ, Koes BW, Bouter LM. The clinical course and prognostic factors of non-specific neck pain: a systematic review. *Pain*. 1998;77(1):1-13.
3. Childs JD, Cleland JA, Elliott JM, et al. Neck Pain. *Journal of Orthopaedic & Sports Physical Therapy*. 2008;38(9):A1-A34.
4. Treleaven J, Takasaki H. Characteristics of visual disturbances reported by subjects with neck pain. *Manual Therapy*. 2014;19(3):203-207.
5. 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*. 1995;22(3):325-333.
6. 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*. 2001;91(1–2):15-22.
7. 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;157(1):43-48.
8. Falla D, Jull G, Edwards S, Koh K, Rainoldi A. Neuromuscular efficiency of the sternocleidomastoid and anterior scalene muscles in patients with chronic neck pain. *Disability and Rehabilitation*. 2004;26(12):712-717.
9. 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*. 2002;88(4):2000-2018.
10. Corneil BD, Olivier E, Munoz DP. Neck Muscle Responses to Stimulation of Monkey Superior Colliculus. I. Topography and Manipulation of Stimulation Parameters. *Journal of Neurophysiology*. 2002;88(4):1980-1999.
11. Strimpakos N. The assessment of the cervical spine. Part 1: Range of motion and proprioception. *Journal of Bodywork and Movement Therapies*.15(1):114-124.
12. Stanton TR, Leake HB, Chalmers KJ, Moseley GL. Evidence of Impaired Proprioception in Chronic, Idiopathic Neck Pain: Systematic Review and Meta-Analysis. *Physical Therapy*. 2015.

13. Jull G, Falla D, Treleaven J, Hodges P, Vicenzino B. Retraining cervical joint position sense: The effect of two exercise regimes. *Journal of Orthopaedic Research.* 2007;25(3):404-412.
14. Revel M, Minguet M, Gergoy P, Vaillant J, Manuel JL. Changes in Cervicocephalic Kinesthesia After a Proprioceptive. *Arch Phys Med Rehabil.* 1994;75.
15. 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.
16. Barany. Augenbewgungen durch Thoraxbewegungen ausgelost. *Zentralbl Physiol.* 1906;20:298-302.
17. Barany. Uber enige Augen- Und Halsmuskelreflexe beei Neugeborene. *Acta Otolaryngol (Stockh).* 1918/1919;1:97-102.
18. Reisman JE, Anderson JH. Compensatory eye movements during head and body rotation in infants. *Brain research.* 1989;484(1-2):119-129.
19. Reisman JE, Anderson JH. Compensatory eye movements during head and body rotation in infants. *Brain research.* 1989;484(1–2):119-129.
20. 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.
21. 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.
22. de Vries J, Ischebeck BK, Voogt LP, et al. Cervico-ocular Reflex Is Increased in People With Nonspecific Neck Pain. *Physical Therapy.* 2016.
23. Montfoort I, Kelders WP, 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.
24. Juul T, Langberg H, Enoch F, Sogaard K. The intra- and inter-rater reliability of five clinical muscle performance tests in patients with and without neck pain. *BMC Musculoskeletal Disorders.* 2013;14(1):339.
25. 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.
26. 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.* 2014:1-6.
27. 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.* 2008;89(1):69-74.

28. 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.
29. van Wingerden J-P, Vleeming A, Ronchetti I. Differences in Standing and Forward Bending in Women With Chronic Low Back or Pelvic Girdle Pain: Indications for Physical Compensation Strategies. *Spine.* 2008;33(11):E334-E341.
30. Revel M, Andre-Deshays C, Minguet M. Cervicocephalic kinesthetic sensibility in patients with cervical pain. *ARCH PHYS MED REHABIL.* 1991;72(5):288-291.
31. 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.* 2002;114(2):185-195.
32. de Vries J, Ischebeck BK, Voogt LP, et al. Joint position sense error in people with neck pain: A systematic review. *Manual Therapy.* 2015;20(6):736-744.
33. 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.
34. Snodgrass SJ, Cleland JA, Haskins R, Rivett DA. The clinical utility of cervical range of motion in diagnosis, prognosis, and evaluating the effects of manipulation: a systematic review. *Physiotherapy.*100(4):290-304.
35. Röijezon U, Clark NC, Treleaven J. Proprioception in Musculoskeletal Rehabilitation. Part 1: Basic Science and Principles of Assessment and Clinical Interventions. *Manual Therapy.*
36. Hill JC, Whitehurst DGT, Lewis M, et al. Comparison of stratified primary care management for low back pain with current best practice (STarT Back): a randomised controlled trial. *The Lancet.* 2011;378(9802):1560-1571.
37. O'Sullivan K, O'Sullivan P, Vibe Fersum K, Kent P. Better targeting care for individuals with low back pain: opportunities and obstacles. *British Journal of Sports Medicine.* 2017;51(6):489-490.
38. 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.
39. Collewijn. *Eye movement recording.* Oxford: Oxford University Press; 1999.
40. Swait G, Rushton AB, Miall RC, Newell D. Evaluation of Cervical Proprioceptive Function: Optimizing Protocols and Comparison Between Tests in Normal Subjects. *Spine.* 2007;32(24):E692-E701 610.1097/BRS.1090b1013e31815a31815a31811b.

41. Treleaven. Sensorimotor disturbances in neck disorders affecting postural stability, head and eye movement control. *Manual Therapy*. 2008;13(1):2-11.
42. Treleaven J. Sensorimotor disturbances in neck disorders affecting postural stability, head and eye movement control; Part 2: Case studies. *Manual Therapy*. 2008;13(3):266-275.

Chapter 6:

Small effects of neck torsion on healthy human voluntary eye movements

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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.

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]).

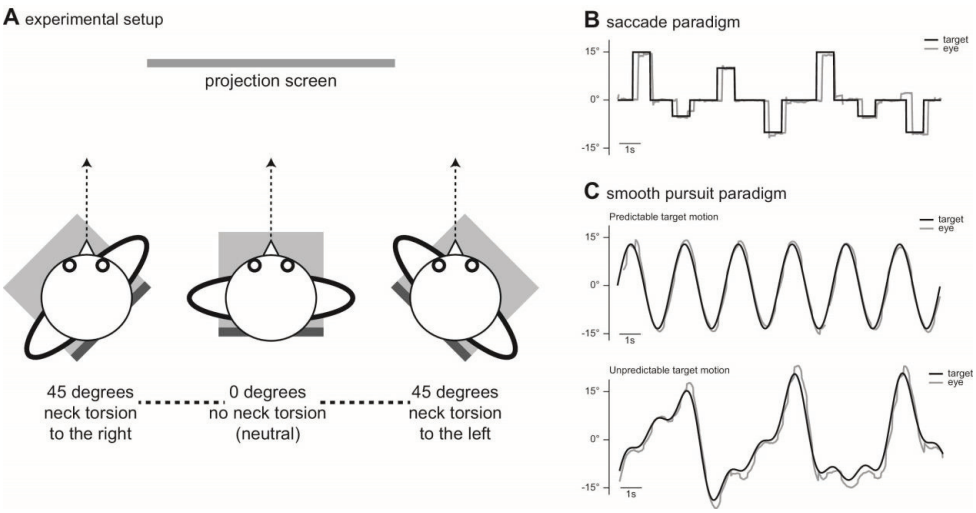

Figure 1. Experimental setup and paradigms. Panel A shows a schematic representation of the experimental setup: the body of the subjects could rotated to a static position while the head faced forwards toward the screen on which the target was presented. Panel B shows an example of the saccade paradigm: 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.

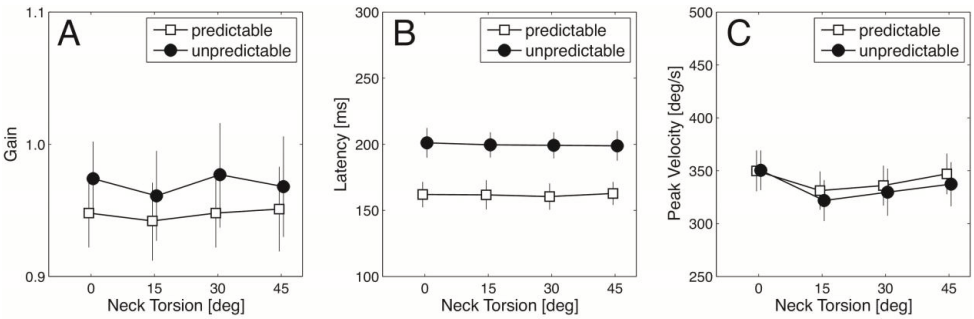

Figure 2: Saccadic gains (panel A), latencies (panel B) and peak velocities (panel C) for each of the four eccentricities of chair rotation, for predictable centripetal saccades (closed circles) and unpredictable centrifugal saccades (open squares). Error bars represent 95% confidence interval.

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 $\eta 2 = .71$), whereas the gains of predictable centripetal saccades did not ($0.92 \pm$

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 $\eta 2 = .53$). 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 $\eta 2 = .55$). 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 $\eta 2 = .86$) 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 $\eta 2 = .98$), 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 $\eta 2 = .97$). 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 $\eta 2 = .98$). 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.

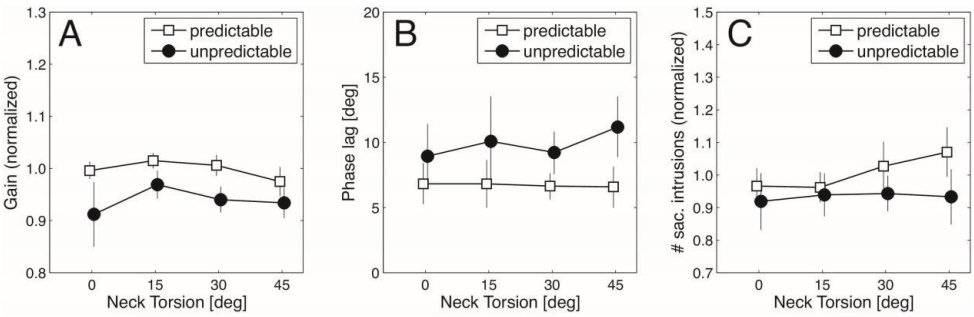

Figure 3: Normalized smooth pursuit gain (panel A), phase lags (panel B) and normalized number of saccadic intrusions (panel C) for each of the four eccentricities of chair rotation, for predictably moving targets (closed circles) and unpredictably moving targets (open squares). Error bars represent 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 t he 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&Li nkReadableName=Related Articles&IdsFromResult=417959&ordinalpos=3&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubme d_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&Li nkReadableName=Related Articles&IdsFromResult=9455954&ordinalpos=3&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubm ed_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&Li nkReadableName=Related Articles&IdsFromResult=3681722&ordinalpos=3&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubm ed_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&Li nkReadableName=Related Articles&IdsFromResult=11834598&ordinalpos=3&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pub med_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_predic table_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&Li nkReadableName=Related Articles&IdsFromResult=9746145&ordinalpos=3&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum.

Chapter 7:

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

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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.

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.

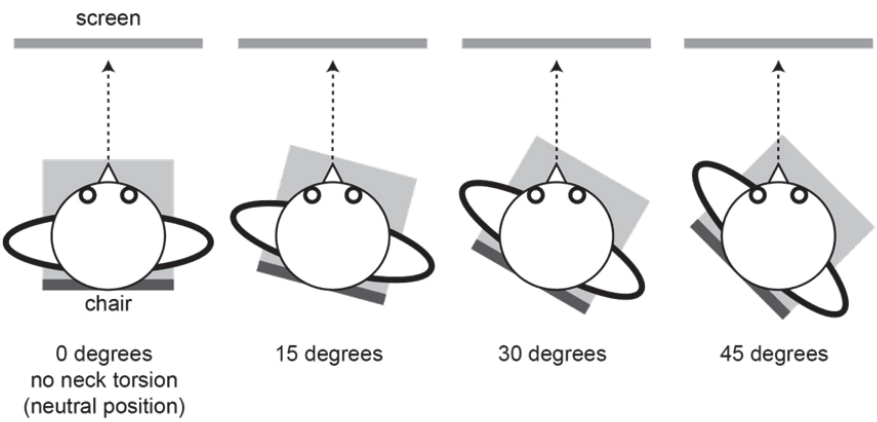

Figure1: Schematic representation of the chair rotation conditions. While the head was fixated by means of a bite board, the torso was held in a fixed rotation to the right or to the left, which induced static neck torsion. The subject was asked to follow a single moving dot that was projected on the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

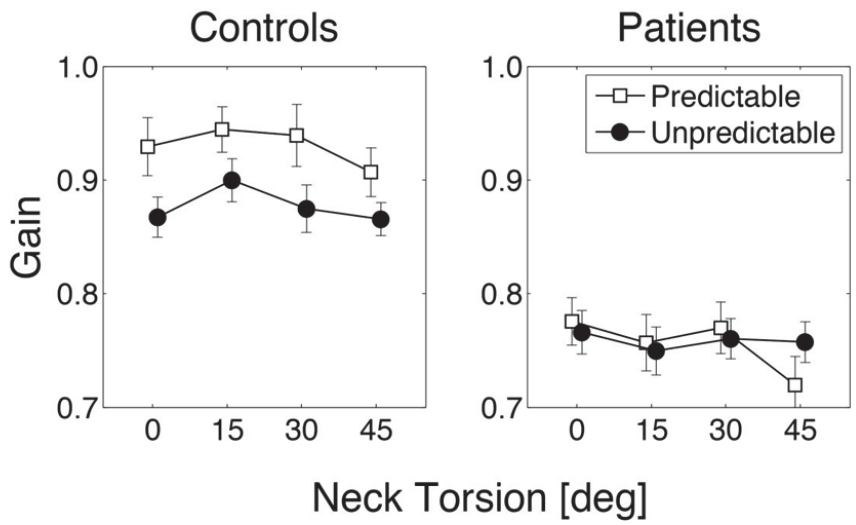

Figure 2: Smooth pursuit gains per group (20 Controls and 45 Patients), for each of the four eccentricities of chair rotation (Neck Torsion), and for predictably moving targets (open squares) and unpredictably moving targets (closed circles). Error bars represent Standard Error of the Mean.

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 ($p = 0.38$).

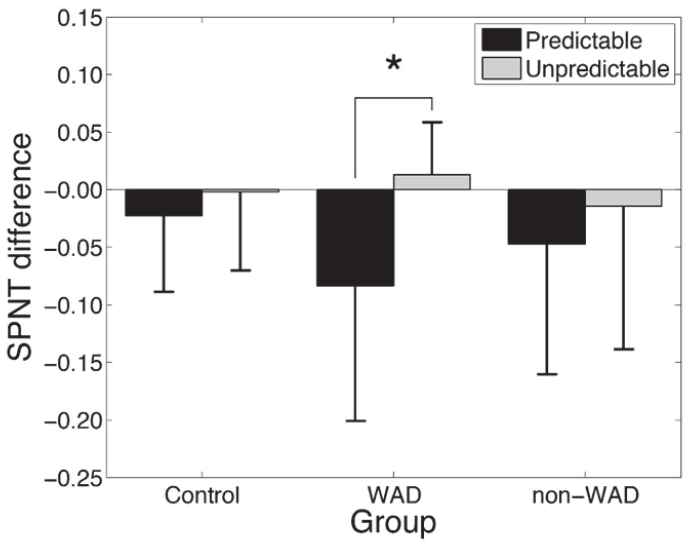

Figure 3: Smooth Pursuit Neck Torsion (SPNT) differences for each of the three groups (Controls, WAD patients and non-WAD patients) and the two stimulus conditions (predictably moving targets and unpredictably moving targets). Error bars represent Standard Deviations. * $p < 0.05$

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-)fron tal 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.
25. 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.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 8:

General discussion

Neck pain is highly prevalent, hard to treat health problem with substantial consequences for individuals and society. [1-4] People with neck pain experience a wide range of complaints leading in many cases to some form of disability. However, a less well-known aspect of neck pain is that these people may also experience visual disturbances, dizziness, and/or unsteadiness as part of their complaints.[5,6] This thesis describes the interactions between head and eye movement systems in people with neck pain. Overall, these studies provide insight into oculomotor (stabilizing) reflex disturbances and proprioceptive deficit in people with neck pain.

This thesis is the reflection of a series of experiments and a review in which the relation between neck proprioception and eye stabilizing reflexes were studied in people with neck pain. The link between the clinical representation of complaints and the level of disability is subject of an ongoing debate. In this final chapter, results will be discussed in light of existing research with sometimes methodological inconsistencies but also sometimes with strong arguments. In addition, general considerations are posed regarding oculomotor disturbances and proprioceptive disturbances in people with neck pain. Furthermore, the description and direction of future research based on this thesis are presented. In this thesis, the results from laboratory studies are discussed in light of their practical significance. Although this is a complicated task, new hypotheses and ideas can be delineated from these studies and can potentially improve clinical practice.

Joint position sense error in patients with neck pain (and healthy controls)

We hypothesized that the 'Joint Positioning Sense Error' (JPSE) would be (negatively) influenced by the (altered) cervical afferent information of people with neck pain. The first step to verify this hypothesis was to make an inventory of the existing literature on this subject and summarize the results in, a systematic review. The main finding of our systematic review regarding the JPSE in people with neck pain (presented in chapter 2) showed an increased JPSE in people with neck pain compared with healthy controls. Results of the review also showed that the JPSE did not differ between people with traumatic and non-traumatic neck pain and that pain duration or neck pain intensity did not influence JPSE.

Interestingly, all studies in which the mean JPSE was calculated over at least six trials, showed significantly higher joint position error in people with neck pain than in controls.

Studies which measured the JPSE over less than six trials did not show a consequent difference between people with neck pain and people without neck pain — suggesting that applied statistics play a role. It might be that the vulnerability to outliers is less when the mean JPSE is calculated over more trials, as a result of this, reducing the standard error of the mean. Another explanation could be that in the first trials a kind of learning curve was experienced in both groups, but after three trials, the group of participants without pain increased their performance while people with neck pain did not further learn or adapt.

For an adequate interpretation of JPSE-tests of the cervical spine, it is essential to realize that we cannot move our heads without stimulating proprioceptors of the (upper) cervical spine and our vestibular systems; head repositioning tests always stimulate both systems at the same time.[7,8] However, differentiation between these systems to determine which system is dysfunctional may be needed for effective treatment choices. Chen and Treleaven[7] showed that trunk-to-head rotation (thereby excluding input of the vestibulum) showed a different JPSE compared to the JPSE of the conventional measurement protocol of head-to-trunk rotation in the same sample. From a clinical perspective, it is essential to know which system (proprioceptive or vestibular) should be targeted in therapeutic interventions. For this reason, modifications of the traditional JPSE tests have been suggested that are more likely to stimulate cervical afferent information. A case-control study[9] showed that people with non-specific neck pain have impairments in implicit motor imagery performance. People without neck pain in this study were more accurate than people with non-specific neck pain in making left/right judgments of images of head rotation.[10,11] Other research has shown improvements in JPSE in people with neck pain during mental imagery and action observation.[12,13] Cervical JPSE was also declined in people without neck pain and improved in people with neck pain after neck muscle vibration (this effect lasted up to 24 hours).[13] This vibration is thought to stimulate muscle spindle afferents.[14,15] Based on the results stated above, it is essential to realize that JPSE results cannot always be attributed explicitly to proprioceptive dysfunction but can include vestibular involvement or supraspinal involvement. Suggesting that changes in proprioceptive input is not a prerequisite for an altered position sense but plays a part in it. The solitary use of the JPSE test as a representative for cervical afferent information is thus an oversimplification.[16]

Besides, the difficulties regarding the separate roles of the proprioceptive and vestibular subsystems in JPSE it is not (yet) clear what the minimal clinically important difference is of the JPSE which is necessary to use the JPSE as an evaluative instrument.[17] The precision of many of the JPSE testing instruments ranges from 0.1 degrees to 0.5 degrees.[18-20] Such a minimal difference would not be reliably detectable using clinical methods such as universal goniometry or visual estimation.[21] A study by Basteris et al.,[22] demonstrated a method for measuring JPSE that does not require the participant to wear any equipment. Based on a webcam with available head tracking software, they developed a system that allows assessment of the JPSE. This system, however, should be validated before it could be used in clinical practice. This development would also make it possible to measure more people with neck pain all with their specific properties. Creating an opportunity to investigate the possible relationship between, pain, disability, cervical range of motion (CROM) and other properties which could relate to the JPSE.

Cervico-ocular reflex

The results of the study presented in chapter three showed that the cervico-ocular Reflex (COR) is increased in people with non-specific neck pain compared to people without neck pain, whereas the vestibulo-ocular Reflex (VOR) did not differ between these groups. The studied population showed no correlation between cervical range of motion, dizziness, pain levels, and COR gain. In contrast to the neck pain group, adaption between COR and VOR was seen in people without neck pain.[23] Ischebeck[24] and Kelders[25] showed similar results in people with Whiplash Associated Disorders (WAD), people with traumatic neck pain, and people with chronic neck pain. This implicates that an increased COR is a general feature of oculomotor control in patients with neck pain and is not limited to specific subgroups. Despite suggestions from earlier studies, this outcome shows that trauma and duration of complaints are not the dominant reason for an altered oculomotor control.[25,26]

A probable explanation for an increased COR could be altered afferent information from the cervical spine, as this is a dominant source of information regarding the COR.[27]Additionally, altered movement patterns of the neck and/or avoiding end range of motion could also influence the afferent information of the cervical spine. Possibly resulting in a lack of adaption between the COR and VOR in people with neck pain which

could be associated with visual disturbances[5], dizziness[28], and disturbances in postural control.[29] As mentioned before there was no correlation between the gain of the COR and dizziness. The properties of the study population could explain the absence of correlations in our study described in chapter three between the COR, pain level, dizziness, or disability. The participants with neck pain scored reasonably low on pain levels, dizziness and also the cervical range of motion (CROM) only differed in the vertical plane when the participants with neck pain were compared with the control group.

Since we only observed group effects and results were quite variable in both groups, it is not yet possible to identify a person as a sufferer from neck pain solely based on an altered COR. The same yields for the studies of Ischebeck[24] and Kelders[25] concerning other subgroups like WAD, traumatic neck pain, or chronic neck pain. This also holds for other outcome measures regarding neck pain. Group differences are also known to be present in outcome measures like a decreased cervical range of motion[30] and/or irregular cervical movement strategies like jerky and irregular cervical movements.[31] In order to conclude that a person feels neck pain solely based on the fact that there is a reduced cervical range of motion compared to the group norm, does not stand. However, to define a therapeutic baseline situation and be able to evaluate results of therapeutic interventions, possibly a combination of weighed factors could build up to an individual patient profile which could be the starting point of a patient-centered, personalized intervention.

The relation between the JPSE and COR

The relation between the JPSE and COR was investigated in an experimental set-up (chapter four) and showed a correlation between the COR and the JPSE in the vertical plane in people with neck pain. This result suggests a relation between the COR and the cervical JPSE, as both tests receive afferent information from the (upper) cervical spine. The rather weak correlation between the COR and the JPSE might be caused by the fact that the result of the JPSE test depends on multiple factors. While the COR is a derivative of cervical afferent information, the JPE test is also influenced by other factors like vestibular function, as described earlier. Since the two tests represent different aspects of sensorimotor function, it can be argued that to obtain adequate insight into neck reflex function, both tests should be used as an additive to each other also resulting in a specific patient profile.

There was no correlation between the COR and the JPSE in the horizontal plane in people with neck pain, while the COR was measured in the rotational plane. A possible explanation for this result is that the CROM was more restricted in the vertical plane in people with neck pain. The correlation between the COR and the JPSE in the vertical plane should be described as weak. It has been described earlier in this general discussion that sensorimotor control is a complex concept with its afferent, efferent, and central integration and processing components. Therefore, it was expected that only a small part of the variance of the COR could be explained by the variance of the JPSE and vice versa. In the group of people without neck pain, there were no correlations between eye movement reflexes and the JPE. It could be argued that JPSE has to be assessed in other planes. Alternatively, even in multiple planes at the same time, i.e., in a three-dimensional setting. Using an experimental set-up in which movements in 3-D can be generated, these aspects can be studied further.

Smooth pursuit eye movements

In chapters six and seven, the interaction between head and eye movement systems are described. Chapter six describes the effect of static neck rotation on smooth pursuit and saccadic eye movement behavior in participants without neck pain. It is yet not utterly evident whether static neck torsion influences smooth pursuit eye movements in healthy controls compared to people with neck pain. This is a prerequisite for the Smooth Pursuit Neck Torsion (SPNT) test. However, it seems plausible that the neck position of healthy controls influences eye movements.[16,32,33] In chapter six, we found that both smooth pursuit, as well as saccadic eye movement performance, were indeed mildly affected by static rotation of the trunk relative to the head. The effect, although small, was most prominent for smooth pursuit eye movements. Remarkably, optimal performance (i.e., by high gains) was not always reached when the head and trunk were aligned. An adaptive process might explain the small effect of neck torsion. 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 cervical afferent input caused by increased neck torsion. Healthy controls perform better with predictable targets compared to unpredictable targets when looking at smooth pursuit gains; they show higher gains. It was expected that people without neck pain would show higher gains with predictable targets, as a possible indicator of cognitive performance of the participant. In order to interpret these

results, the change in gain in people without neck pain should be compared to the change in gain in of people with neck pain.

In chapter 7, we described that, as expected, people with neck pain showed lower smooth pursuit gains than people without neck pain.[34,35] Less expected was that the influence of neck rotation was as small in people with neck pain as in people without neck pain. People with neck pain had a slightly lower smooth pursuit gain in rotated neck positions, but the differences in smooth pursuit gains between most eccentric neck rotations and neutral rotations were the same in people with neck pain when compared to people without neck pain. The type of stimulus (predictable or unpredictable), which we also investigated in this chapter, affected smooth pursuit gains differently between people with neck pain and people without neck pain. It is not yet clear why predictability of the stimulus has a different effect on people with neck pain, compared to people without neck pain. It can be suggested that neck pain inhibited adequate prediction of the straightforward trajectory of a target. Another explanation is that people with neck pain are distracted by their pain and therefore perform not optimally with an easier task.

Recommendations for further research

If we want to improve the understanding of the underlying mechanisms of neck pain, it is encouraged to conduct more fundamental research concerning people with neck pain. It is essential to comprehend the pathophysiology in people with neck pain in general and (in the light of this thesis) regarding oculomotor disturbances in particular. Only when we can unravel the black box of neck pain step by step, we can improve and personalize our diagnostics and therapeutical interventions substantially. Furthermore, it is essential to investigate what the Minimal Clinical Important Difference of the JPSE is, to further explore the possibility of measuring the JPSE with a webcam reliably and validly. However, the first step is to understand people with neck pain. If we do so, it is possible to construct a ratio for using a reliable and valid diagnostic instrument in order to make it possible to choose the most appropriate therapeutic intervention.

Regarding the JPSE, we suggest that learning and/or habituation effects can be an explanation for the result that JPSE between people with neck pain and healthy controls was significantly different after at least six trials. It would be of interest to investigate a

possible effect of neck pain concerning proprioception of the neck and/or motor learning. Another opportunity for further research would be to investigate the possible relationship between, pain, disability, cervical range of motion (CROM) and other properties which could relate to the JPSE. This would be possible when a sizeable heterogenic group of people with neck pain is included in a study. In respect to the therapeutic point of view, it would be interesting to determine if an increased proprioceptive acuity could be accomplished by targeting cortical areas using tasks such as left/right judgments or by conservative proprioceptive training.

The present set-up to assess the COR is an expensive, inflexible laboratory setting. In order to make it worthwhile to measure the COR in a clinical setting, it is indispensable that it is possible to test the COR in a way that is reliable and valid, however easy to use and cheap. Only if these requirements are met, this outcome measure can make its way to clinical practice. Research and means should be concentrated on the implementation of easy measurements set-ups. Besides studies which investigate the psychometrical properties of these oculomotor tests, it also needs the connection to technicians engaged in industrially redesign the COR set-up. Treleaven described these tests, such as gaze stability and eye/head coordination,[36] are based on construct validity. Besides researching the COR and the JPSE in an isolated manner in different groups of people with neck pain, it would also be recommended to further investigate the relationship between the COR and the JPSE in a larger study population with different outcome measures. Here, for example, one can think of people with dizziness, differences in duration of perceived pain, the degree of disability but also age. Moreover, experiments in 3-D should be introduced.

The results described in chapter six and chapter seven 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 question the applicability of the SNPT test in a clinical setting. The influence of cognitive impairments on the execution of the SPNT test should, therefore, be evaluated more thoroughly. This information is essential to determine whether the SPNT is a suitable (clinical) test for the diagnosis of people with neck pain. The same applies to research to evaluate the psychometric properties of the SPNT not with electrooculography as Daly and colleagues[37] but with video-oculography.

In conclusion, the studies described in this thesis have lifted the lid of the black box containing the underlying biological processes of non-specific neck pain. Taken together, the studies show to what extent proprioceptive and oculomotor reflexes are disturbed in these patients. People with non-specific neck pain have higher gains of the COR and a larger JPSE. Furthermore, we found that static rotation of the neck influences smooth pursuit eye movements. Sensorimotor disturbances are indeed part of the biology of neck pain and should be part of the considerations of physical therapists working with patients with non-specific neck pain. However, we did not find a significant relation between oculomotor disorders and/or JPSE, and the origin or severity of neck pain intensity further research into the relevance of the sensorimotor disturbances is required to determine the clinical implications of this type of disturbances. The black box regarding the biology of neck pain should be opened further to make a better understanding of the alignment between biological processes and physiotherapeutic interventions possible.

References

1. Fejer R, Kyvik KO, Hartvigsen J. The prevalence of neck pain in the world population: a systematic critical review of the literature. *European Spine Journal*. 2006;15(6):834-848.
2. Collaborators USBoD. The state of us health, 1990-2010: Burden of diseases, injuries, and risk factors. *JAMA*. 2013;310(6):591-606.
3. Vos CJ, Verhagen AP, Passchier J, Koes BW. Clinical Course and Prognostic Factors in Acute Neck Pain: An Inception Cohort Study in General Practice. *Pain Medicine*. 2008;9(5):572-580.
4. LCJ S, JM S, J G, MJJC P, GJ K. Kosten van Ziekten in Nederland 2007 : Trends in de Nederlandse zorguitgaven 1999-2010. *Cost of Illness in the Netherlands 2007 : Trends in healthcare expenditure 1999-2010*: Rijksinstituut voor Volksgezondheid en Milieu RIVM

   Centraal Bureau voor de Statistiek CBS.
5. Treleaven J, Takasaki H. Characteristics of visual disturbances reported by subjects with neck pain. *Manual Therapy*. 2014;19(3):203-207.
6. Leaver AM, Maher CG, McAuley JH, Jull GA, Refshauge KM. Characteristics of a new episode of neck pain. *Manual Therapy*. 2012(0).
7. 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.
8. Karnath HO, Sievering D, Fetter M. The interactive contribution of neck muscle proprioception and vestibular stimulation to subjective "straight ahead" orientation in man. *Experimental Brain Research*. 1994;101(1):140-146.
9. Elsig S, Luomajoki H, Sattelmayer M, Taeymans J, Tal-Akabi A, Hilfiker R. Sensorimotor tests, such as movement control and laterality judgment accuracy, in persons with recurrent neck pain and controls. A case-control study. *Manual Therapy*. 2014;19(6):555-561.
10. Parsons LM. Integrating cognitive psychology, neurology and neuroimaging. *Acta Psychologica*. 2001;107(1):155-181.
11. Parsons LM, Fox PT. THE NEURAL BASIS OF IMPLICIT MOVEMENTS USED IN RECOGNISING HAND SHAPE. *Cognitive Neuropsychology*. 1998;15(6-8):583-615.
12. Beinert K, Preiss S, Huber M, Taube W. Cervical joint position sense in neck pain. Immediate effects of muscle vibration versus mental training interventions: a RCT. *Eur J Phys Rehabil Med*. 2015;51(6):825-832.
13. Beinert K, Englert V, Taube W. After-effects of neck muscle vibration on sensorimotor function and pain in neck pain patients and healthy controls – a case-control study. *Disability and Rehabilitation*. 2018:1-8.

14. Courtine GrCP, Charalambos; Laroche, Davy; Pozzo, Thierry. Gait-dependent integration of neck muscle afferent input. *Neuroreport*. 2003;14(18):2365-2368.
15. Lennerstrand G, Han Y, Velay JL. Properties of eye movements induced by activation of neck muscle proprioceptors. *Graefe's archive for clinical and experimental ophthalmology = Albrecht von Graefes Archiv fur klinische und experimentelle Ophthalmologie*. 1996;234(11):703-709.
16. 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(2):99-106.
17. Stanton TR, Leake HB, Chalmers KJ, Moseley GL. Evidence of Impaired Proprioception in Chronic, Idiopathic Neck Pain: Systematic Review and Meta-Analysis. *Physical Therapy*. 2015.
18. Cheng C-H, Wang J-L, Lin J-J, Wang S-F, Lin K-H. Position accuracy and electromyographic responses during head reposition in young adults with chronic neck pain. *Journal of Electromyography and Kinesiology*. 2010;20(5):1014-1020.
19. Roren A, Mayoux-Benhamou M-A, Fayad F, Poiraudeau S, Lantz D, Revel M. Comparison of visual and ultrasound based techniques to measure head repositioning in healthy and neck-pain subjects. *Manual Therapy*. 2009;14(3):270-277.
20. Jordan K, Dziedzic K, Jones PW, Ong BN, Dawes PT. The reliability of the three-dimensional FASTRAK measurement system in measuring cervical spine and shoulder range of motion in healthy subjects. *Rheumatology*. 2000;39(4):382-388.
21. de Koning CHP, van den Heuvel SP, Staal JB, Smits-Engelsman BCM, Hendriks EJM. Clinimetric evaluation of active range of motion measures in patients with non-specific neck pain: a systematic review. *European Spine Journal*. 2008;17(7):905-921.
22. Basteris A, Pedler A, Sterling M. Evaluating the neck joint position sense error with a standard computer and a webcam. *Manual Therapy*. 2016;26:231-234.
23. 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.
24. Ischebeck BK, de Vries J, Janssen M, et al. Eye stabilization reflexes in traumatic and non-traumatic chronic neck pain patients. *Musculoskeletal Science and Practice*. 2017;29:72-77.
25. 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.
26. Montfoort I, Kelders WP, 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.

27. Proske U, Gandevia SC. The Proprioceptive Senses: Their Roles in Signaling Body Shape, Body Position and Movement, and Muscle Force. *Physiological Reviews.* 2012;92(4):1651-1697.
28. Treleaven. Dizziness, Unsteadiness, Visual Disturbances, and Postural Control: Implications for the Transition to Chronic Symptoms After a Whiplash Trauma. *Spine.* 2011;36(25):211-217.
29. Silva AG CA. Standing balance in patients with whiplash-associated neck pain and idiopathic neck pain when compared with asymptomatic participants: A systematic review. *Physiotherapy Theory and Practice.* 2012;29:1/18.
30. 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. *Archives of Physical Medicine and Rehabilitation.* 2017;98(7):1407-1434.
31. 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. *Manual Therapy.* 2008;13(2):122-131.
32. Corneil BD, Elsley JK, Nagy B, Cushing SL. Motor output evoked by subsaccadic stimulation of primate frontal eye fields. *Proceedings of the National Academy of Sciences.* 2010:200911902.
33. 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. *Archives of Physical Medicine and Rehabilitation.* 2008;89(3):522-530.
34. Tjell R. Smooth pursuit neck torsion test: a specific test for cervical dizziness. *American Journal of Otology.* 1998;19(1):76-81.
35. 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 Musculoskeletal Disorders.* 2014;15(1):16.
36. Treleaven. Sensorimotor disturbances in neck disorders affecting postural stability, head and eye movement control. *Manual Therapy.* 2008;13(1):2-11.
37. Daly L, Giffard P, Thomas L, Treleaven J. Validity of clinical measures of smooth pursuit eye movement control in patients with idiopathic neck pain. *Musculoskeletal Science and Practice.* 2018;33:18-23.

Chapter 9:

Summary

This thesis aimed to describe the interactions between head and eye movement systems in people with neck pain. The first paper (chapter 2) of this thesis was a systematic review in which we described joint position sense error (JPSE) in people with neck pain. In general, it can be concluded that people with neck pain show a larger cervical JPSE error when it is measured over at least six trials. There was no difference between onset, pain intensity, or duration regarding the joint position sense error.

The paper concerning the cervico-ocular reflex (COR) in people with non-specific neck pain (chapter 3) showed an altered gain of the COR in non-specific neck pain in comparison to people without neck pain. The VOR did not differ between these two groups. The COR differed on a group level, and there was no correlation between cervical range of motion, pain intensity, dizziness, and the gain of the COR. This was the first study describing the COR in a study population of people with non-specific neck pain, which is by far the majority of people with neck pain.

Chapter 4 was a letter to the editor on 'the cervico-ocular reflex is increased in people with non-specific neck pain.'

In chapter 5 we described the relationship between the COR and the JPSE. Here we presented a correlation between the COR and the JPSE in a vertical plane. As both tests receive information from the cervical spine, this was expected. What was less expected was the result that there was no correlation between the COR and the JPSE in the horizontal because the COR was measured in a horizontal plane and not in a vertical plane. The fact that the JPSE is a representation of different aspects of sensorimotor function can explain this finding.

In chapters 6 and 7, we described the effect of static neck torsion and target predictability on smooth pursuit eye movements and saccadic eye movements in people without neck pain and people with neck pain. The Smooth Pursuit Neck Torsion test is used as a clinical measure for oculomotor disorders in people with neck pain. However, it is doubtful that the SPNT merely tests the influence of cervical proprioception on smooth pursuit eye movements. As was expected, people with neck pain showed lower smooth pursuit gains than people without neck pain. Smooth pursuit gains in people with neck pain decreased with increasing torsion of the neck. This decrease did not differ between people with neck

pain and people without neck pain.

Chapter 10:

Samenvatting

Dit proefschrift heeft als doel de interacties te beschrijven tussen oculomotore functie en hoofdbewegingen bij mensen met a specifieke nekpijn. De eerste paper (hoofdstuk 2) van dit proefschrift was een systematische review waarin we de Joint Position Sense Error (JPSE) beschreven bij mensen met nekpijn. In het algemeen kan worden geconcludeerd dat mensen met nekpijn een structureel grotere JPSE vertonen wanneer deze over ten minste zes herhalingen wordt gemeten. Er was geen verschil in JPSE wat betreft ontstaanswijze, pijnintensiteit of de duur van de klachten.

Hoofdstuk 3 beschrijft de cervico-oculaire reflex (COR) bij mensen met a-specifieke nekpijn. De resultaten laten zien dat in de groep van mensen met a-specifieke nekpijn een hogere gain van de COR had in vergelijking met mensen zonder nekpijn. De vestibulo-oculaire reflex (VOR) verschilde niet tussen deze twee groepen. De COR verschilde op groepsniveau en er was geen correlatie tussen de cervicale bewegingsuitslag, pijnintensiteit, duizeligheid en toename van de COR. Dit was de eerste studie die de COR beschrijft in een onderzoekspopulatie van mensen met niet-specifieke nekpijn.

Hoofdstuk 4 was een brief aan de redacteur met betrekking tot het artikel ´The Cervico-ocular Reflex is increased in people with non-specific neck pain.'

In hoofdstuk 5 hebben we de relatie tussen de COR en de JPSE beschreven. De resultaten laten zien dat er een correlatie was tussen de hoogte van de gain van de COR en de JPSE gemeten in het verticale vlak. Er was geen correlatie tussen de gain van de COR en de JPSE gemeten in het horizontale vlak. Dit resultaat viel op aangezien de COR enkel in het horizontale vlak gemeten is. Het feit dat de JPSE een weergave is van verschillende aspecten van de sensorimotorische functie, kan deze bevinding verklaren evenals dat de range of motion van de cervicale wervelkolom in de nekpijngroep kleiner was ten opzichte van de controle groep waar dit in het horizontale vlak niet het geval was.

In de hoofdstukken 6 en 7 beschreven we het effect van statische nekrotatie en de voorspelbaarheid van het te volgen doel op oogvolgbewegingen bij mensen zonder nekpijn en mensen met nekpijn. De smooth pursuit neck torsion-test (SPNT) wordt gebruikt als een klinische maat voor oculomotorische stoornissen bij mensen met nekpijn. Het is echter nog niet geheel duidelijk of de SPNT alleen de invloed van cervicale proprioceptie representeert. Er zijn namelijk verschillende andere factoren welke het

testresultaat lijken te beïnvloeden. De groep van mensen met nekpijn vertoonden minder goede oogvolgbewegingen dan de groep van mensen zonder nekpijn. De nauwkeurigheid van oogvolgbewegingen nam bij mensen met nekpijn af wanneer de statische rotatie van de nek toenam.

De verschillen in oogvolgbewegingen tussen maximale rotatie en de neutrale positie van het hoofd waren zowel bij mensen met nekpijn als mensen zonder nekpijn even groot. Overeenkomstig met eerdere onderzoeken, presteerden mensen met nekpijn bij voorspelbare stimuli slechter dan mensen zonder nekpijn. Bij onvoorspelbare stimuli hadden echter alleen mensen zonder nekpijn meer moeite met de taak. Mensen met nekpijn presteerden hetzelfde bij zowel voorspelbare als niet-voorspelbare stimuli.

Chapter 11:

About the author

Jurryt de Vries was born on July 16th, 1982 in Bernisse. After graduation from de Ring van Putten in Spijkenisse, he enrolled in the study physiotherapy at the University of Applied Science in Rotterdam. In 2005 he started the master Public Health at the Maastricht University. After obtaining his Master of Science, he started to study Manual Therapy at the Transfergroep Rotterdam.

After attaining his bachelor of physiotherapy, he worked in various physiotherapy practices. In 2008 he started combining his work as a physiotherapist with tutoring students manual therapy and sports physiotherapy the University of Applied Science in Rotterdam.

Jurryt is married to Kayung Cheung, father of Halina Sam-Yee (born in 2012) and Cato Suk-Yee (born in 2017).

Chapter 12:

List of publications

Janssen M, de Vries J, Ischebeck BK, Frens MA, van der Geest JN. Small effects of neck torsion on healthy human voluntary eye movements. *Eur J Appl Physiol.* 2013;113(12):3049-3057.

de Vries J, Ischebeck BK, Voogt LP, et al. Joint position sense error in people with neck pain: A systematic review. *Manual Therapy.* 2015;20(6):736-744.

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.* 2015;40(19):E1052-E1057.

Voogt L, de Vries J, Meeus M, Struyf F, Meuffels D, Nijs J. Analgesic effects of manual therapy in patients with musculoskeletal pain: A systematic review. *Manual Therapy.* 2015;20(2):250-256.

de Vries J, Ischebeck BK, Voogt LP, Frens MA, Kleinrensink G-J, van der Geest JN. Cervico-ocular Reflex Is Increased in People With Nonspecific Neck Pain. *Physical Therapy.* 2016.

Ischebeck BK, de Vries J, Van der Geest JN, et al. Eye movements in patients with Whiplash Associated Disorders: a systematic review. *BMC Musculoskeletal Disorders.* 2016;17(1):441.

Ischebeck BK, de Vries J, Janssen M, et al. Eye stabilization reflexes in traumatic and non-traumatic chronic neck pain patients. *Musculoskeletal Science and Practice.* 2017;29:72-77.

Ischebeck BK, de Vries J, van Wingerden JP, Kleinrensink GJ, Frens MA, van der Geest JN. The influence of cervical movement on eye stabilization reflexes: a randomized trial. *Experimental Brain Research.* 2018;236(1):297-304.

de Vries J, Ischebeck BK, Voogt LP, Frens MA, Kleinrensink G-J, van der Geest JN. The relation between Joint Position Error and Cervico-Ocular Reflex in people with non-specific neck pain. *Submitted*

Chapter 13:

PhD-portfolio

1. PhD training	Congresses. courses and skills	Year	Workload (Hours/ECTS)
	Data analysis with Matlab	2012	1.2 ECTS
	Biomedical English Writing and Communication	2013	2 ECTS
	Basic Principles of Endnote	2013	0.1 ECTS
	Systematic Literature research with PubMed	2013	0.1 ECTS
	Systematic Literature research with other databases	2013	0.1 ECTS
	Biostatistical Methods I: Basic Principles Part A Netherlands Institute for Health Sciences	2014	2 ECTS
	Presentations		
	Posterpresentation at Endo-Neuro-Psych meeting. Lunteren	2012	0.3 ECTS
	Posterpresentation at Helmholtz retrait. Bergen	2013	0.3 ECTS
	Presentation at Dutch anatomists association	2013	0.3 ECTS
	Labmeetings and labtalks SysFys group	2012-2018	5 ECTS
2. Teaching	**Supervising practicals and excursions. Tutoring**		
	Lecturing students of master's program of the Department of Physical Therapy. Rotterdam University of Applied Sciences	2011-2018	5 ECTS
	Lecturing students of bachelor's program of the Department of Physical Therapy. Rotterdam University of Applied Sciences	2006-2018	3 ECTS
	Supervising Master's theses Malou Janssen	2012	2 ECTS
	Supervising of master's program of the Department of Physical Therapy. Rotterdam University of Applied Sciences	2011-2018	5 ECTS
	Lecturing students for the Minor Cervical disorders	2016-2018	3 ECTS

Chapter 14:

Dankwoord

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