Eye Movements:

a Window on Sensory and Motor Deficits

Inger Montfoort

The research presented in this thesis is conducted by the Department of Neuroscience, Erasmus Medical Center, Rotterdam, partly in collaboration with the Department of General Practice and the Department of Surgery and Traumatology.

This research was sponsored by the Revolving Fund of the Erasmus MC, the Dutch NWO-VIDI-program, the NWO-MW-program, the Prinses Beatrix Fonds, and the Erasmus Fellowship.

ISBN: 978-90-361-0108-0

Layout and printing:
Haveka BV | De Grafische Partner, Alblasserdam, the Netherlands.
Picture cover:
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Eye Movements: a Window on Sensory and Motor Deficits

Oogbewegingen: inzicht in sensorische en motorische aandoeningen

Proefschrift

ter verkrijgen van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de
rector magnificus

Prof.dr. S.W.J. Lamberts

en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op
Woensdag 4 februari 2009 om 9:45 uur

door

Inger Montfoort

geboren te Rotterdam

PROMOTIECOMMISSIE

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Ter nagedachtenis aan mijn vader

Do what you can, and the task will rest lightly in your hand, so lightly that you will be able to look forward to the more difficult tests which may be awaiting you.

Dag Hammarskjöld

(A. Montfoort, Analyses and some metabolic studies on lecithin from lung and other mammalian tissues (thesis), Rotterdam, 1970)

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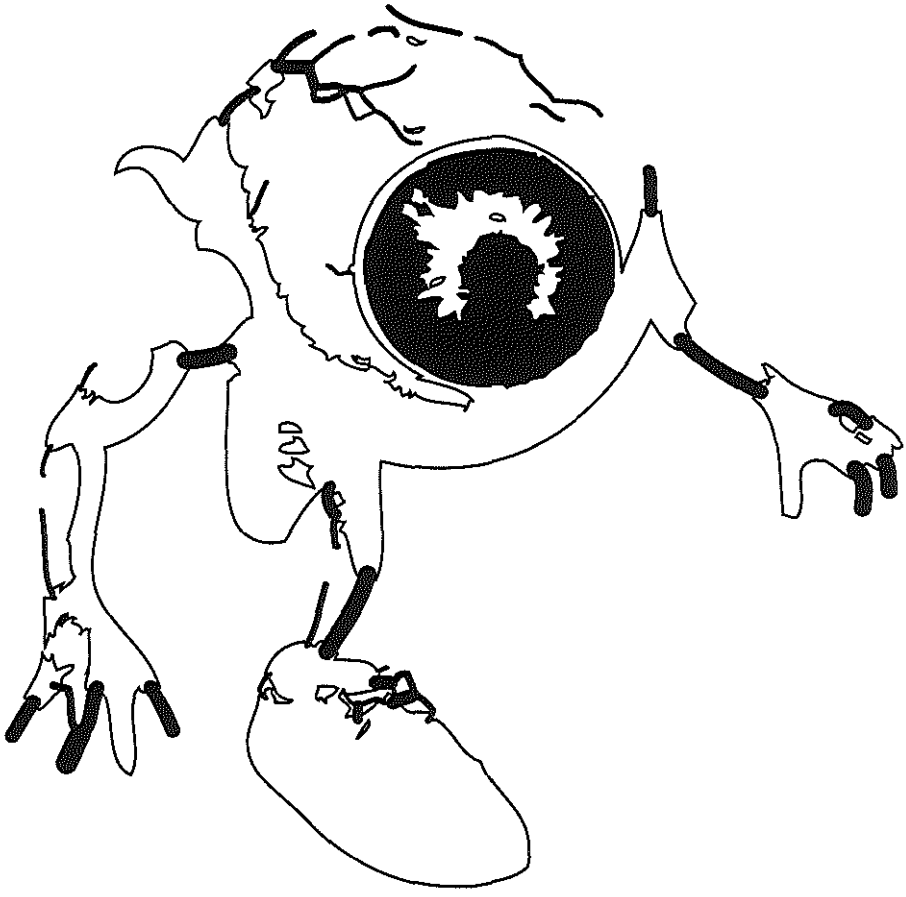
Preface



Becoming a scientist? Never! In high school my mind was very clear about my future career plans. From childhood I yearly spent one or two days looking around at my father's biochemistry lab during school breaks. Despite the high levels of enthusiasm both my parents (my mother was a laboratory assistant) exhibited for working with blood, phospholipids or fatty acids, lab work gave me the chills. Although at that time I did not knew what to become, it was beyond all doubt that the only chemical liquid inside the lab I was interested in was the hot chocolate coming out of the vending machine (though the working mechanism of the rotating fleas in the liquid containing Erlenmeyer flasks had a bizarre attraction). It was not until the first years of my medical training at the university that I came in touch with the field of Physiology and scientific research slowly changed from the status of a dusty profession into an attractive activity. A Master of Science project at the department of Neuroscience on eye movement behavior persuaded me to look further into the world of science....

C H A P T E R 1

General introduction

INTRODUCTION

Eye movements can be used as a tool for investigating neural mechanisms of both sensory and motor deficits. Not only does the oculomotor system comprise the entire transformation from sensory input to the generation of movement, also its accessibility, its ability to learn and remember, and the exhibition of both voluntary and reflexive behavior, make the oculomotor system a good diagnostic aid in understanding sensory-motor pathologies. Furthermore, recording eye movements generates data that are suitable for quantative analysis.

Eye movement behavior can be investigated in different ways. Obviously, movement control can be analysed by looking at factors such as the timing, metrics and dynamics of the movement. A more general high-level view is provided when the planning of the movement is examined. Likewise, testing reflexive behavior in response to sensory stimuli can offer information about how the sensory information is being processed. Therefore, looking at eye movement behavior gives insight into various aspects of the human mind. In this thesis we study visual search behavior in subjects with Williams-Beuren syndrome and we analyse ocular reflexive behavior in both whiplash injury patients and healthy controls.

1. STABILIZING GAZE - HOW TO GET A STABLE RETINAL INPUT

Eye movements play a leading role in our interaction with the world and are generally used to inspect the environment. The human eye has been designed to have both a high visual acuity and a large field of view. Some animals such as hawks, owls and other birds of prey restrict their field of vision, but a great density of light receptors in their eyes allows them to see small mice while soaring high above the ground. Others give up high resolution in favor of a larger range. Rabbits for instance have laterally placed eyes and a nearly 360 degrees visual field which allows them to see a predator approaching from every direction. However, with a smaller number of light receptors they have a limited visual acuity.

Despite the perception of a large field of view and the illusion of a high resolution scene, only a small part of the visual field is being processed in detail. Humans observe details of the outside world with a small high-resolution part of the retina, the fovea. This central region, in which photoreceptors are densely packed, has to be kept directed at an object of interest. The periphery is perceived with a much lower resolution. If we want to view more of the outside world than the tiny fraction we observe through the fovea or if we want to prevent the images slipping across the retina, the eyes must be moved.

Eye movements can be divided into two different categories: voluntary eye movements and eye stabilisation reflexes. Each category can be subdivided into smaller classes, each controlled by separate neuronal pathways. The first category, goal directed eye movements, contains ocular motions in which the fovea is aimed onto the region of interest: these are saccadic eye movements, smooth pursuit movements and vergence movements. The second category is compensatory eye movements, which prevent visual slip over the retina during head motion: the optokinetic reflex (OKR), vestibulo-ocular reflex (VOR) and cervico-ocular reflex (COR).

Being a predator or a prey results in different oculomotor parameters. The repertoire of these movements varies from a visuo-motor system lacking a fovea that is mainly focussed on gaze stability, in which the voluntary gaze directing eye movements play a limited role, to the more complex system in humans, where a whole range of volitional and reflexive eye movements accounts for optimizing vision.

Eye stabilisation reflexes

Movements of the head will change the position of the eyes. If uncorrected, this results in blurred vision, due to the slippage of the visual world across the retina. In order to see the target, the brain compensates by rotating the eyes to correct the head motion. Three stabilisation reflexes can be defined. These reflexes work in conjunction to reduce the error between the eye velocity and the moving image. Each stabilization reflex is based on one of three sensory systems (visus, vestibular system, proprioception of the cervical spine). Each system has its own dynamic properties.

In daily life all systems collaborate and hardly ever work independently. In an experimental setting however, the ocular stabilisation reflexes can be examined by stimulating one of the sensory systems seperately.

OKR

The optokinetic reflex (OKR) uses visual motion input at low to mid velocities to induce eye movements in the same direction and at the same velocity as the moving object. This reflex can therefore be considered as a negative closed loop feedback system. In contrast with smooth pursuit movements, the OKR is involuntary and consists of a slow compensatory phase in which the eyes track the motion of the object followed by a fast resetting one, the optokinetic nystagmus (OKN) (Simons and Büttner, 1985), in which the eyes are driven back involuntary rapidly when the element moves out of sight due to anatomical limitations of the rotating eyes. This reflex can be observed as to and fro movement of the eyes (alternating fast and slow phases) when passengers stare out of a driving car. During smooth pursuit eye movements the OKR is suppressed to prevent a reflexive eye movement in the opposite direction while tracking a moving object (Lindner and Ilg, 2006).

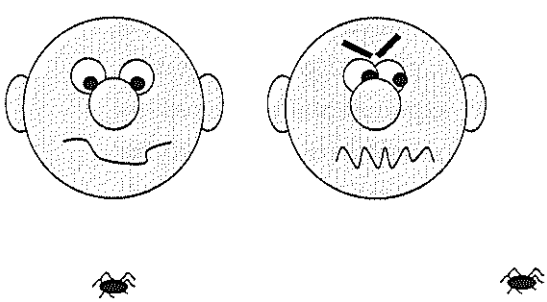


Figure 1: OKR: the eyes follow a moving object (spider), while the head remains stationary.

1

VOR

If the head is moved another reflex, the vestibulo-ocular reflex (VOR) rotates the eyes to compensate for this head motion and consequently keeps the eye orientation fixed in space. In contrast to the visually guided optokinetic reflex, the VOR is generated by vestibular information and responds optimally at high frequencies (Tabak et al., 1997). Receptors in the otolith organs and semicircular canals respectively detect rotational and linear acceleration (including gravity). As a result the VOR can be subdivided into rotational and translational components. The rotational VOR responds to high frequency input, whereas the translational VOR has a much broader tuning. Since the vestibular signal is not affected by the eye movements that this reflex has generated, the VOR works as an open loop reflex.

The loss of one labyrinth results in oculomotor and postural disorders, such as deviation of the eyes and alteration of reflexes depending upon vestibular input (Smith and Curthoys, 1989). The VOR gain (eye velocity devided by visual stimulus velocity) is reduced and the phase lead is increased (Baarsma and Collewijn, 1975; Maioli et al., 1983; Fetter and Zee, 1988; Vibert et al.,1993). Although it is impossible for the labyrinthine receptors to regenerate, over time recovery of some oculomotor and postural symptoms occurs through vestibular compensation (Smith and Curthoys, 1989). A long-term altered relationship between visual and vestibular information results in adaptation of the VOR gain. While at low stimulus velocities the VOR gain approaches normal values, at higher frequencies the recovery is less complete (Allum et al.,1988; Fetter and Zee, 1988; Curthoys and Halmagyi, 1995). The average time needed for adaptation is about one hour (Zee, 1989; Koizuka et al., 2000; Shelhamer et al., 2002; Watanabe et al.,2003). Adaptation can be experimentally evoked by wearing miniaturizing, magnifying or reversing spectacles or by altering the visual information that coincides the rotation of the head. Depending on the relation between the visual and vestibular stimulus adaptation of the VOR can either be an increase or decrease of gain.

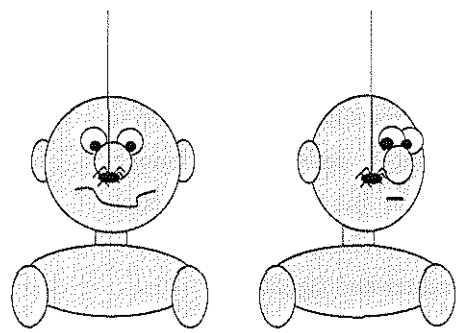


Figure 2: VOR: a rotation of the head induces eye movements in opposite direction of the head movement.

COR

Both OKR and VOR work in conjunction with the cervico-ocular reflex (COR), which is elicited by proprioceptive information of the cervical spine. Rotation of the neck stimulates proprioceptive afferents from deep neck muscles and joint capsula from C1-C3 to the vestibular nucleus (Hikosaka and Maeda, 1973), resulting in eye movements opposite to the direction of the head movement. Like the optokinetic reflex, the COR performs best at low velocities (Van Die and Collewijn, 1986; Mergner et al., 1998, Kelders et al., 2003). Like the VOR, also the COR has an open loop design: the oculomotor output does not change the sensory input.

Since the inception of eye movement research many studies on gaze stability have focussed on the vestibulo-ocular reflex. Especially investigation of vestibulopathy has contributed to expansion of understanding its neural mechanisms. The last few decades also the COR has become a more popular focus. For a long time, the existence of the COR has been a matter of debate. Possibly, technical problems going with the testing of this reflex fed this controversy (Bronstein and Hood, 1986).

Normally, all three stabilisation reflexes operate concurrently. In order to ensure an optimal response the relative strengths of the open loop components should be correlated. In patients with absent vestibular function, not only the VOR gain is reduced, also the COR gain is increased (Bronstein and Hood, 1986; Huygen et al., 1991; Bronstein et al., 1995; Bouyer and Watt, 1999) and partially takes over the role of the VOR (Bronstein and Hood, 1986; Bronstein et al., 1995). This reverses when the vestibular input recovers (Bronstein, 1995). Also in whiplash injury patients an elevated COR gain has been found (Kelders et al., 2005). In elderly persons the gain of the cervico-ocular reflex is augmented too (Kelders et al., 2003), whilst the OKR and VOR gains are decreased (Mulch and Petermann, 1979; Aust, 1991; Paige, 1994). Kelders et al. (2003) reported a covariation between the gains of the COR and VOR in healthy humans: i.e., when the VOR is relatively high, the COR is low and vice versa. The basis for this correlation is likely to be plasticity of both reflexes.
In analogy to VOR adaptation, also the COR can be modified on the basis of visual stimulation. Rijkaart et al. (2004) reported a reduction in COR gain in healthy subjects after ten minutes of concurrent mismatched visual and cervical stimulation.

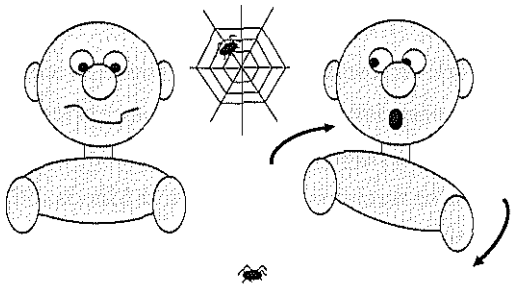


Figure 3: COR: movement of the neck induces eye movements in the same direction as the trunk motion.

Neural pathways

The cerebellum plays an important role in the coordination of the oculomotor reflexes (Leigh and Zee, 1999). Visual information from the retina, vestibular information from the labyrinth and proprioceptive information from the neck muscle spindles (Hikosaka and Maeda, 1973; Sato et al, 1997, Gdowksi et al., 2001) are projected to the vestibular nuclei. The vestibular nuclei project this information to the cerebellar cortex, in particular to the cerebellar flocculus, which in turn projects inhibitory signals back onto neurons in the vestibular nuclei. The latter commands the oculomotor nuclei, which controls most of the extraocular muscles. Although the cervico-ocular reflex pathways are not exactly known, generation and modification of the COR partly passes the VOR pathways (Gdowski et al., 2001). Motion or torsion information from the neck is forwarded to the central cervical nucleus as well as to area X in the vestibular nucleus. Analogous to the VOR this information is projected from the vestibular nuclei to the cerebellar flocculus and back again (Gdowski and McCrea, 2000; Gdowski et al., 2001).

In response to sensory input cells the vestibular nuclei also directly command the oculomotor nuclei. Furthermore, at the same time visual information is indirectly projected (via both the inferior olive and the nucleus reticularis tegmentum pontis) to the flocculus. Retinal slip induces by this means an error signal in the flocculus. Based on the discrepancy between the optimal and actual eye movement, the cerebellum modifies its inhibitory output signal to the vestibular nuclei in order to reduce the retinal error. Damage to the flocculus affects adaptive changes of the VOR (Robinson, 1976; Zee et al., 1981; Ito et al., 1982; Nagao, 1983; Lisberger et al., 1984; Schairer and Bennett, 1986; McElligott et al., 1998).

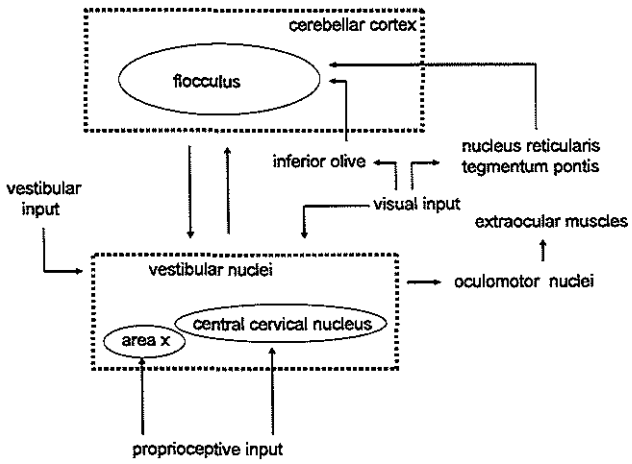


Figure 4: Oculomotor reflex pathways.

2. OPTIMIZING VISUAL PROCESSING - HOW TO GET DETAILED VISUAL INFORMATION

Voluntary eye movements

If an observed object stands still we are able to keep our eyes directed at it. This maintenance of gaze in a constant direction is called fixation. During a fixation, details of the watched object can be thoroughly analyzed and meanwhile sampling of the peripheral field takes place. If the information of the object has been gathered sufficiently the oculomotor system moves the fovea quickly to a new position. This latter transfer of the eyes is called a saccade. Saccades can reach peak velocities over 500 deg/s (Collewijn et al., 1988). During this ballistic eye movement vision is blurred because of suppression of the visual information (Matin, 1974; Bridgeman et al., 1975; Thiele et al., 2002) either by way of suppressing vision actively (Holt, 1903; Von Holst and Mittelstaedt, 1950; Thiele et al., 2002) or by insensitivity of the visual system to fast slips across the retina (Mackay, 1970; Matin et al., 1972; Matin 1974; Campbell and Wurtz, 1978). In order to gather reliable information of a large part of the visual scene, multiple eye movements are needed. In daily life we make about three saccades per second.

When a fixated object moves (with a velocity up to 100 deg/s; Simons and Büttner, 1985), i.e. a flying bird, the smooth pursuit system calculates its speed from the movement of the image on the retina ('retinal slip') and determines the velocity of the eyes to keep the projection on the fovea. Vergence eye movements keep the projection of an object aligned on both foveae at any distance from the observer.

Saccades are part of visual search. (Serial) visual search is defined as looking with saccadic eye movements (or attention shifts) for potentially interesting parts of the visual environment, one item after another, until the object of interest has been found. These kind of serial search tasks often occur in ordinary life (Land et al., 1999), i.e., when one is looking for a pencil on a desk. In-between the saccadic eye movements, people observe the outside world by foveal fixation, during which detailed information about an object can be extracted. When this information has been gathered sufficiently, a new saccade can be made to another part of the visual scene. The consecutive movements follow a certain path, the so-called scan-path (Noton and Stark, 1971) that consists of a more or less organized plan for an entire sequence of saccades.

3. DEFICITS IN GAZE STABILIZATION AND VISUAL PROCESSING

Whiplash

Historical overview and Definition

For years whiplash injuries take centre stage with common injuries seen in motor vehicle crashes. The American orthopaedic surgeon Dr. Harald E. Crowe first suggested the term 'whiplash' at a scientific meeting in San Fransisco in 1928 (Crowe, 1928). It was used to describe the effects when a victim's head suddenly bends backward relative to the body (hyperextension of the neck) and then forward (hyperflexion). Before that, the controversial diagnosis 'railway spine' was attributed to similar outcomes following train accidents (Harrington, 1996). In 1945, Davis first mentioned the term whiplash in literature (Davis, 1945), while in 1953 Gay and Abbott indicated rear-end collisions as common divider in the majority of injuries (Gay and Abbott, 1953). Since the early 1950s, there has been much debate about the diagnosis and description of the injury process. More than 10.000 studies have been published (Borchgrevink et al., 1998). In order to terminate the lack of consensus, in 1995 the Quebec Task Force introduced the definition:"whiplash is an acceleration-deceleration mechanism of energy transfer to the neck. It may result from rear end or side-impact motor vehicle collision, but can also occur during diving or other mishaps. The impact may result in bony or soft tissue injuries which in turn may lead to a variety of clinical manifestations (whiplash associated disorders (WAD))" (Spitzer et al., 1995). Furthermore, they also developed a five graded clinical classification system based upon the severity of signs and symptoms.

Grade 0 means no complaints about the neck or physical signs. Grade 1 indicates neck complaints (such as pain, tenderness and stiffness) without physical signs, while patients in grade 2 not only suffer from neck complaints but also from musculoskeletal signs (e.g. decrease range of motion). Patients with both neck complaints and neurological signs constitute grade 3 and finally grade 4 encompasses patients with neck complaints and fracture or dislocation of the cervical spine. Although this definition ceased the ambiguous descriptions, the condition remained contentious, to a large extent because of the absence of visible signs from the injury together with the high rate of litigation.

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

Table 1: WAD clinical classification system (Quebec Task Force (Spitzer et al., 1995)).

Epidemiology

Whiplash injuries constitute a significant public health problem in terms of medical care and socio-economical consequences in industrialised nations. The annual incidence varies amongst different parts of the world (Holm et al., 2008), but appears to be 3.2 per 1000 inhabitants for WAD grades 1-3 (Björnstig et al., 1990; Sterner et al., 2003). The last two decades of the twentieth century the incidence has risen dramatically in many Western countries. Galasko reports an increase from 7,7% up to 20,5% in the United Kingdom (Galasko et al., 2002). Traffic density, car design, increased litigation, but also cultural and sociopsychological factors account for this pattern (Galasko et al., 2002). However, since the turn of the last century the number of patients with WAD has levelled off (Galasko et al., 2002).

Symptoms and Diagnosis

Whether from a car accident, sporting activities, falls or a roller coaster ride, whiplash injuries are mostly characterized by neck pain, headache and stiffness of the neck with or without restricted cervical range of motion (CROM) (Stovner, 1996; Eck et al., 2001). Also shoulder/arm pain, hand paresthesia, back pain, vertigo, dizziness, visual disturbances, photophobia, fatigue, anxiety, depression, irritability,

concentration problems and insomnia are examples of the long list of reported symptoms by whiplash patients who consult a pshysician (Stovner, 1996; Eck et al., 2001). Diagnosing WAD grade 1 and 2 is generally based upon the patients' symptoms. An accurate reliable test is not available unfortunately. Even current sophisticated imaging techniques are usually not capable of confirming lesions in cervical muscles, ligaments, nerves, discs and vertebrae (Borchgrevink et al., 1995; Ronnen et al., 1996; Van Goethem et al., 1996; Bogduk and Teasell, 2000).

Restricted cervical range of motion

In order to estimate the efficacy of various therapeutic interventions for patients with WAD, assessment of the cervical range of motion (CROM) is commonly used. While the patient moves his head to and fro three magnetic angle meters mounted on the subjects head determine the amount of cervical rotation about three axes. Although the largest part of studies report ordinairy (Alaranta et al., 1994; Lind et al., 1989; Mayer et al., 1993; McClure et al., 1998; Mimura et al., 1989; Ordway et al., 1997; Penning and Wilmink, 1987; Tucci et al., 1986; Walmsley et al., 1996; Youdas et al., 1992) or less prominent CROM data (Drottning, 2003), the few that compare the results to an asymptotic control group have found notable results (Dall'Alba et al., 2001). Both in acute (Kasch et al., 2001) and chronic (Hagström and Carlsson, 1996; Dall'Alba et al., 2001; Madeleine et al., 2004, Prushansky et al., 2006) (symptoms/disabilities more than 6 months (Spitzer et al., 1995; Stovner, 1996)) WAD a reduced neck mobility has been shown, suggesting whiplash injury patients to be hypokinetic. Several studies even found the CROM to be able to discriminate between patients with persistent WAD and asypmtotic persons (Dall'Alba et al., 2001; Antonaci et al., 2002). Olson (2000) reported an association between higher disability and decreased neck rotation, and neck retraction. However, the relationship between subjective neck pain and reduced cervical spine mobility seems to be weak (Hagen et al., 1997).

Balance and coordination disturbances

Besides pain complaints whiplash injury patients often report vertigo and balancing problems (Oosterveld et al., 1991; Rubin et al., 1995). Posturographic studies have demonstrated impairment of balance control (El-Kahky et al., 2000; Kogler et al., 2000; Madeleine et al., 2004; Treleaven et al., 2005a; Treleaven et al., 2005b). Sjöström (2003) reported an increased trunk sway in WAD patients in order to stabilise gaze in tasks were head movement was limited and specific gaze control

was needed, such as walking up and down stairs. Trunk sway was diminished compared to healthy controls when large head movements were required. Stapley (2006) found that fatigability of the cervical muscles was accompanied by an increase in body sway. Facet joint pathologies and intervertebral disc lesions have been suggested causal for the postural disturbances (Loudon et al., 1997; Gimse et al., 1997). However also chronic pain and psychological factors could affect proprioceptive cervical information (Gamsa and Vikis-Freibergs, 1991; Field et al., 2008). Furthermore, patients who recently have experienced a whiplash trauma display incorrect perception of their head position (Uremović et al., 2007) and the ability to reproduce headposition seems to be affected (Heikkila and Aström, 1996; Heikkila and Wenngren, 1998; Kristjansson et al., 2003; Loudon et al., 1997; Treleaven et al., 2003). It is unclear whether central or peripheral damage, a mixture of both or other factors account for the vestibulo-postural disturbances.

Cervical Muscle dysfunction

Nederhand et al. (2000) reported a decreased relaxation ability of the cervical upper trapezoid muscles in whiplash injury patients. Since in patients with chronic neck pain without prior traumatic incidents comparable muscle relaxation patterns where found, the demonstrated cervical dysfunction displayed a general sign in chronic neck pain syndromes (Nederhand et al., 2002). However, in contrast to the relaxation pattern seen in persons with non specific chronic neck pain despite the lack of significance, WAD patients grade 2 inclined towards muscle activation (Nederhand et al., 2002). Furthermore, in a follow-up cohort study no hyper-reactivity of the cervical upper trapezoid muscles was found. Instead, six months after the motor vehicle collision a decreased muscle activation was seen during physical exercise oppositely associated with both the reported level of neck pain disability (Nederhand et al., 2003; Nederhand et al., 2006) and an increased level of fear of movement (Nederhand et al., 2006).

Aetiology

Many studies on the biomechanics of the cervical spine during rear-end collisions have lead to a relatively good understanding of the kinematics of the spinal elements (Spitzer et al., 1995; Kaneoka et al., 2002). During a rear-end collision the patients trunk and shoulders are accelerated forward relative to the stationary head, resulting in a forced extension of the neck. The cervical spine forms an S-shape (extension of the lower cervical segments and flexion of the upper segments) (Grauer et al.,

1997). Next, the head also accelerates forward and the neck is forced into flexion. However, despite the numerous experiments with dummies, kadavers and volunteers (Cholewicki et al., 1998; Siegmund et al., 2001; Tencer et al., 2002) the exact pathofysiology and if the reported symptoms directly result from the injury mechanism itself are still unclear.

Prognosis

Despite the clinical variability, usually most whiplash injury patients fully recover (Spitzer et al., 1995). However, a substantial proportion (incidence ranging from 19% to 60% (Barnsley et al., 1994; Stovner, 1996; Freeman et al., 1998) develops chronic complaints. Half of the population experiencing WAD report neck pain symptoms one year after the traumatic event (Carroll et al., 2008). Although many factors, such as direction of collision, coping style, depressed mood and fear of movement affect the course of WAD, particularly the extent of the severity of the symptoms seems to be prognostic for a slower recovery (Carroll et al., 2008).

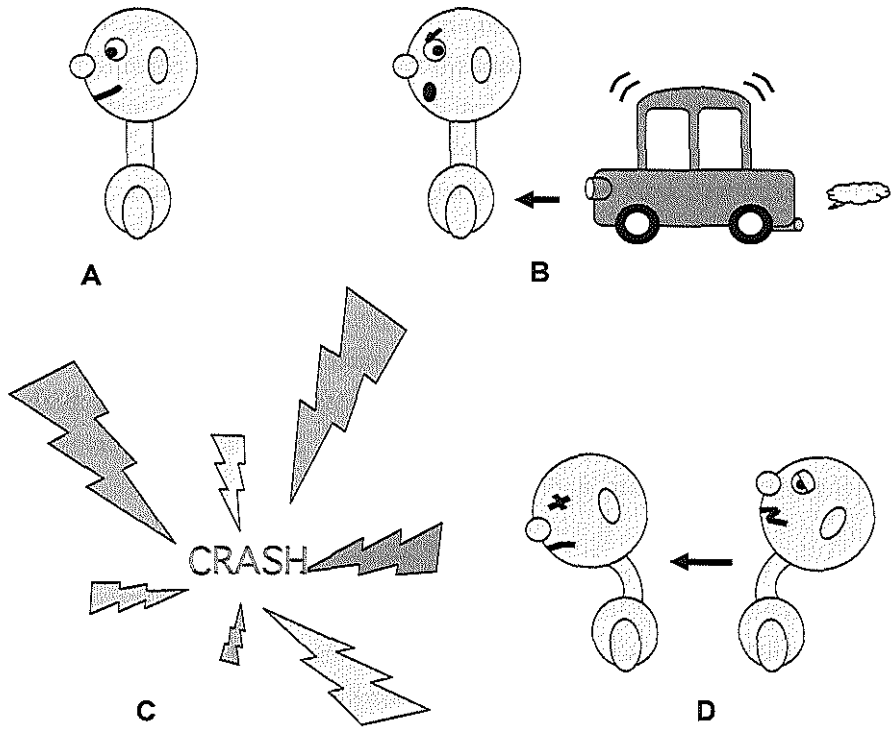


Figure 5: After a rear-end motor vehicle collision the head is forced to bend backwards and forwards successively, which may result in whiplash injury complaints.

Treatment

Much controversy exists about the benefit of the wide range of offered treatments in patients with WAD (Verhagen et al., 2007). Several reviews of the literature have evaluated the efficacy of conservative interventions. Active interventions (such as education, manual therapy, mobilization and excercises) and continuation of normal preinjury activities are recommended (Peeters et al., 2001; Hurwitz et al., 2008). Intensive use of health-care and wearing of cervical collars may affect recovery in a negative way (Hurwitz et al., 2008).

Williams-Beuren syndrome

Williams-Beuren syndrome (WBS), or Williams syndrome, is a sporadic congenital neurodevelopmental disorder. The syndrome is characterized by several features, such as congenital heart disease, mental retardation (mean IQ from 40 to79), cardiovascular anomalies (supravalvular aortic and pulmonary arterial stenosis), growth deficiency, idiopatic infantile hypercalcemia, hyperacusis, dental abnormalities, overfriendlyness, visual-spatial and visual motor impairments, attention deficits, relatively preserved expressive language skills and a peculiar feature: their facial dysmorphology, an elfin-like facies, which created the naming "Elfin Facies syndrome" (Trauner et al., 1989; Bellugi et al., 1990; Bellugi et al., 1999; Chapman et al., 1996; Gosch and Pankau, 1996; Withers, 1996; Mervis et al., 2001; Van der Geest et al., 2004; Van der Geest et al., 2005). The prevalence of WBS ranges from 1 per 20.000 (Morris et al., 2003) to 1 in 7.500 (Greenberg, 1990; Strømme et al., 2002) of the population. It occurs troughout the world and affects males and females equally.

Genetically, in 95% of the patients with WBS a 1.55-1.84 Mb deletion, containing 25-30 genes, on the long arm of chromosome 7, band 7q11.23 is observed (Van Hagen et al., 2007; Lowery et al., 1995; Korenberg et al., 2000; Osborne and Pober, 2001; Makeyev et al., 2004). This deletion includes, among others, the genes ELN (encoding elastin, codes for elastic protein in connective tissue, including large bloodvessels (i.e. aorta) (Ewart et al., 1994; Lowery et al., 1995; Tassabehji et al., 1999), CYLN2 (cytoplasmic linker-2 gene encoding the protein CLIP-115) and GTF2I (involved in mental retardation (Morris et al., 2003), encoding the proteins BAP-135 and TFII-I). Both CYLN2 and GTF21 should be responsible for deficits in motor coordination and memory formation (Van Hagen et al., 2007). Furthermore, the deletion encompasses the gene GTF2IRD1 (encode proteins of the TFII-I family (Makeyev et al., 2004), which is held to be responsible for craniofacial abnor-

malities (Tassabehji et al., 2005) and should together with GTF21 and of LIMK1 (encoding Lim Kinase-1 (Frangiskakis et al., 1996) be involved in visual spatial functioning (Hirota et al., 2003). However, the exact role of the various genes mentioned to the contribution of the Williams-Beuren syndrome is yet unclear.

It has been reported that the impaired visuo-spatial processing in WBS subjects appears especially in processing the global visual information relative to local information (Bihrle et al., 1989). This impairment is seen as the incapability to process the spatial relations between several local elements in a scene (Bellugi et al., 2000; Bihrle et al., 1989; Georgopoulos et al, 2004). For instance, when asked to reproduce a drawing, WBS subjects often copy local elements without a global coherence. In other words, these drawings consist of a rich collection of fragmented details that are not always in the right position relative to each other (Bihrle et al., 1989). Furthermore, subjects with WBS show specific deficits in visual spatial working memory. In a visual spatial learning test WBS subjects were less able to recognize the location of a previously seen object positioned in one out of four quadrants (Vicari et al., 2005). Also mild motor activity problems, in which visual spatial information is needed, such as walking down steps, are commonly observed in individuals with Williams-Beuren syndrome (Van der Geest et al., 2005; Withers, 1996). The deficits of visuo-spatial functioning in WBS have been attributed to functional deficits in the fronto-parietal circuits within the dorsal stream of spatial processing (Atkinson et al., 2003). Both visual spatial processing and working memory are likely to be critically involved in (serial) visual search. During which saccadic eye movements and fixations are alternated. Processing and remembering the relative spatial locations of the objects within a scene can eliminate ineffective saccades toward already fixated objects during visual search (McCarley et al., 2003). So, in serial visual search perceptual processes, working memory and the oculomotor system act in conjunction. Moreover, visual search induces ample activation of parietal and frontal areas within the dorsal stream (Gitelman et al., 2002). Hence, the impairments within the dorsal stream, as suggested by the deficits in visual-spatial processing and working memory, may hamper the effectiveness of visual search in WBS.

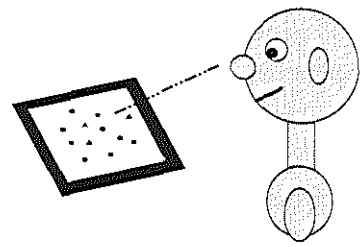


Figure 6: An example of the visual search task presented to WBS subjects and control subjects, with the instruction to find a target out of several stimulus elements (Chapter 5).

4. OVERVIEW OF THE THESIS

The general aim of this thesis is to investigate mechanisms underlying oculomotor coordination. Studying eye movement behaviour not only helps to increase our insight in cerebellar motor coordination and motor learning, it also gives us a better understanding of mechanisms underlying sensory-motor pathologies, such as whiplash associated disorders and Williams-Beuren syndrome.

In order to establish the effect of additional proprioceptive training (given by physiotherapists) on the development of chronic whiplash complaints, we started a randomized clinical trial. Unfortunately, due to failure to recruit sufficient numbers of patients, we were forced to abort the trial early. This is not an isolated case. Also other researchers report problematic recruitment of patients with WAD (Scholten-Peeters et al, 2006, Van der Windt et al., 2000). In chapter 2, we discuss difficulties concerning patient recruitment of subjects with WAD.
Kelders et al. (2005) hypothesized that in whiplash injury patients the found increase in COR gain could be partly compensatory for a reduced VOR gain analogous to the higher COR and lower VOR gain values found in elderly. Hypo caloric responses in both WAD patients and elderly should support this theory (Chester, 1991; Claussen and Claussen, 1995; Vibert and Hausler, 2003). In chapter 3, we investigate whether the reported raise in COR gain in WAD patients (Kelders et al., 2005) is accompanied by changes in OKR, VOR or both. Neckstiffness could be another explanation for the increased COR gain. A reduced mobility of the neck induced by pain could increase the sensitivity of the neck proprioceptors (Kelders et al., 2005).
In chapter 4, we examine in healthy controls whether the COR gain can be influenced by a reduced neck mobility. In this chapter, we also look further into the plasticity of the ocular stabilisation reflexes and we test the adaptive abilities of COR and VOR eye movements in both whiplash injury patients and healthy controls. Furthermore, we study the relationship between muscle activities and COR gain in healthy individuals and we question if an increase in superficial cervical muscle activity may lead to a higher COR gain.
In chapter 5, we focus on the planning of eye movements. We investigate how subjects with Williams-Beuren syndrome scan and search their environment compared to healthy controls. This thesis is concluded by a general discussion in chapter 6.

REFERENCES

Alaranta H, Hurri H, Heliövaara M, Soukka A, Harju R (1994). Flexibility of the spine: normative values of goniometric and tape measurements. Scand J Rehabil Med 26(3):147-154.

Allum JH, Yamane M, Pfaltz CR (1988). Long-term modifications of vertical and horizontal vestibulo-ocular reflex dynamics in man. I. After acute unilateral peripheral vestibular paralysis. Acta Otolaryngol 105(3-4):328-337.

Antonaci F, Bulgheroni M, Ghirmai S, Lanfranchi S, Dalla Toffola E, Sandrini G, Nappi G (2002). 3D kinematic analysis and clinical evaluation of neck movements in patients with whiplash injury. Cephalalgia 22(7):533-542.

Atkinson J, Braddick O, Anker S, Curran W, Andrew R, Wattam-Bell J, Braddick F (2003). Neurobiological models of visuospatial cognition in children with Williams syndrome: measures of dorsal-stream and frontal function. Dev Neuropsychol 23(1-2):139-172.

Aust G (1991). [The effect of age on vestibulo-ocular reactions]. Der Einfluss des Lebensalters auf vestibulo-okulare Reaktionen. Laryngorhinootologie 70(3):132-137.

Baarsma EA, Collewijn H (1975). Changes in compensatory eye movements after unilateral labyrinthectomy in the rabbit. Arch Otorhinolaryngol 211(4):219-230.

Barnsley L, Lord S, Bogduk N (1994). Whiplash injury. Pain 58(3):283-307.

Bellugi U, Bihrle A, Jernigan T, Trauner D, Doherty S (1990). Neuropsychological, neurological, and neuroanatomical profile of Williams syndrome. Am J Med Genet Suppl 6:115–125. Bellugi U, Lichtenberger L, Mills D, Galaburda A, Korenberg JR (1999). Bridging cognition, the brain and molecular genetics: evidence from Williams syndrome. Trends Neurosci 22(5):197–207.

Bellugi U, Lichtenberger L, Jones W, Lai Z, St George MI (2000). The neurocognitive profile of Williams Syndrome: a complex pattern of strengths and weaknesses. J Cogn Neurosci 12 Suppl 1:7-29.

Bihrle AM, Bellugi U, Delis D, Marks S (1989). Seeing either the forest or the trees: dissociation in visuospatial processing. Brain and Cognition 11(1):37-49.

Björnstig U, Hildingsson C, Toolanen G (1990). Soft-tissue injury of the neck in a hospital based material. Scand J Soc Med 18(4):263-267.

Bogduk N, Teasell R (2000). Whiplash: the evidence for an organic etiology. Arch Neurol 57(4):590-591.

Borchgrevink GE, Smevik O, Nordby A, Rinck PA, Stiles TC, Lereim I (1995). MR imaging and radiography of patients with cervical hyperextension-flexion injuries after car accidents. Acta Radiol 36(4):425-428.

Borchgrevink GE, Kaasa A, McDonagh D, Stiles TC, Haraldseth O, Lereim I (1998). Acute treatment of whiplash neck sprain injuries. A randomized trial of treatment during the first 14 days after a car accident. Spine 23(1):25-31.

Bouyer LJ, Watt DG (1999). "Torso Rotation" experiments. 4: the role of vision and the cervico-ocular reflex in compensation for a deficient VOR. J Vestib Res 9(2):89-101.

Bridgeman B, Hendry D, Stark L (1975). Failure to detect displacement of the visual world during saccadic eye movements. Vision Res 15(6):719-722.

Bronstein AM, Hood JD (1986). The cervico-ocular reflex in normal subjects and patients with absent vestibular function. Brain Res 373(1-2):399-408.

Bronstein AM, Morland AB, Ruddock KH, Gresty MA (1995). Recovery from bilateral vestibular failure: implications for visual and cervico-ocular function. Acta Otolaryngol Suppl 520 Pt 2:405-407.

Campbell FW, Wurtz RH (1978). Saccadic omission: why we do not see a grey-out during a saccadic eye movement. Vision Res 18(10):1297-1303.

Carroll LJ, Holm LW, Hogg-Johnson S, Côté P, Cassidy JD, Haldeman S, Nordin M, Hurwitz EL, Carragee EJ, van der Velde G, Peloso PM, Guzman J (2008). Bone and Joint Decade 2000-2010 Task Force on Neck Pain and Its Associated Disorders. Course and prognostic factors for neck pain in whiplash associated disorders (WAD): results of the Bone and Joint Decade 2000-2010 Task Force on Neck Pain and Its Associated Disorders. Spine 33(4 Suppl):S83-92.

Chapman CA, du Plessis A, Pober BR (1996). Neurologic findings in children and adults with Williams syndrome. J. Child Neurol 11(1):63–65.

Chester JB Jr (1991). Whiplash, postural control, and the inner ear. Spine 16(7):716-720.

Cholewicki J, Panjabi MM, Nibu K, Babat LB, Grauer JN, Dvorak J (1998). Head kinematics during in vitro whiplash simulation. Accid Anal Prev 30(4):469–479.

Claussen CF, Claussen E (1995). Neurootological contributions to the diagnostic follow-up after whiplash injuries. Acta Otolaryngol Suppl 520 Pt 1:53-56.

Collewijn H, Erkelens CJ, Steinman RM (1988). Binocular co-ordination of human horizontal saccadic eye movements. Journal of Physiology 404:157-182.

Crowe HE (1928). Injuries to the cervical spine. Paper presented at the meeting of the Western Orthopaedic Association. San Francisco, USA.

Curthoys IS, Halmagyi GM (1995). Vestibular compensation: a review of the oculomotor, neural, and clinical consequences of unilateral vestibular loss. J Vestib Res 5(2):67-107.

Dall'Alba PT, Sterling MM, Treleaven JM, Edwards SL, Jull GA (2001). Cervical range of motion discriminates between asymptomatic persons and those with whiplash. Spine 26(19):2090-2094.

Davis AG (1945). Injuries of the cervical spine. J Am Med Assoc 127:149-156.

Drottning M (2003). Cervicogenic headache after whiplash injury. Curr Pain Headache Rep 7(5):384-386.

Eck JC, Hodges SD, Humphreys SC (2001). Whiplash: a review of a commonly misunderstood injury. Am J Med 110(8):651-656.

El-Kahky AM, Kingma H, Dolmans M, De Jong I (2000). Balance control near the limit of stability in various sensory conditions in healthy subjects and patients suffering from vertigo or balance disorders: impact of sensory input on balance control. Acta Otolaryngol 120(4):508–516.

Ewart AK, Jin W, Atkinson D, Morris CA, Keating MT (1994). Supravalvular aortic stenosis associated with a deletion disrupting the elastin gene. J Clin Invest 93(3):1071–1077.

Fetter M, Zee DS (1988). Recovery from unilateral labyrinthectomy in rhesus monkey. J Neurophysiol 59(2):370-393.

Field S, Treleaven J, Jull G (2008). Standing balance: A comparison between idiopathic and whiplash-induced neck pain. Man Ther 13(3):183-191.

Frangiskakis JM, Ewart AK, Morris CA, Mervis CB, Bertrand J, Robinson BF, Klein BP, Ensing GJ, Everett LA, Green ED, Pröschel C, Gutowski NJ, Noble M, Atkinson DL, Odelberg SJ, Keating MT (1996). LIM-kinase1 hemizygosity implicated in impaired visuospatial constructive cognition. Cell 86(1):59–69.

Freeman MD, Croft AC, Rossignol AM (1998). 'Whiplash associated disorders: redefining whiplash and its management' by the Quebec Task Force. A critical evaluation. Spine 23(9):1043-1049.

Galasko C, Murray P, Stephenson W (2002). Incidence of whiplash associated disorder. BC Medical Journal 44(5):237-240.

Gamsa A, Vikis-Freibergs V (1991). Psychological events are both risk factors in, and consequences of, chronic pain. Pain 44(3):271–277.

Gay JR, Abbott KH (1953). Common whiplash injuries of the neck. J Am Med Assoc 152(18):1698-1704.

Gdowski GT, McCrea RA (2000). Neck proprioceptive inputs to primate vestibular nucleus neurons. Exp Brain Res 135(4):511-526.

Gdowski GT, Belton T, McCrea RA (2001). Neurophysiological substrate for the cervical-ocular reflex in the squirrel monkey. Exp Brain Res 140(3):253-264.

Georgopoulos MA, Georgopoulos AP, Kurz N, Landau B (2004). Figure copying in Williams syndrome and normal subjects. Exp Brain Res 157(2):137-146.

Gimse R, Björgen IA, Tjell C, Tyssedal JS, Bø K (1997). Reduced cognitive functions in a group of whiplash patients with demonstrated disturbances in the posture control system. J Clin Exp Neuropsychol 19(6):838–849.

Gitelman DR, Parrish TB, Friston KJ, Mesulam MM (2002). Functional Anatomy of Visual Search: Regional Segregations within the Frontal Eye Fields and Effective Connectivity of the Superior Colliculus. NeuroImage 15(4): 970-982.

Gosch A, Pankau R (1996). Longitudinal study of the cognitive development in children with Williams–Beuren syndrome. Am J Med Genet 61(1):26–29.

Grauer JN, Panjabi MM, Cholewicki J, Nibu K, Dvorak J (1997). Whiplash produces an S-shaped curvature of the neck with hyperextension at lower levels. Spine 22(21):2489-2494.

Greenberg F(1990). Williams syndrome professional symposium. Am J Med Genet Suppl 6:85-88.

Hagen KB, Harms-Ringdahl K, Enger NO, Hedenstad R, Morten H (1997). Relationship between subjective neck disorders and cervical spine mobility and motion-related pain in male machine operators. Spine 22(13):1501-1507.

Hagström Y, Carlsson J (1996). Prolonged functional impairments after whiplash injury. Scand J Rehabil Med 28(3):139-146.

Harrington R (1996). The "railway spine" diagnosis and Victorian responses to PTSD. J Psychosom Res 40(1):11-14.

Heikkilä H, Aström PG (1996). Cervicocephalic kinesthetic sensibility in patients with whiplash injury. Scand J Rehabil Med 28(3):133–138.

Heikkilä HV, Wenngren BI (1998). Cervicocephalic kinesthetic sensibility, active range of cervical motion, and oculomotor function in patients with whiplash injury. Arch Phys Med Rehabil 79(9):1089–1094.

Hikosaka O, Maeda M (1973). Cervical effects on abducens motoneurons and their interaction with vestibulo-ocular reflex. Exp Brain Res 18(5):512-530.

Hirota H, Matsuoka R, Chen XN, Salandanan LS, Lincoln A, Rose FE, Sunahara M, Osawa M, Bellugi U, Korenberg JR (2003). Williams syndrome deficits in visual spatial processing linked to GTF2IRD1 and GTF2I on chromosome 7q11.23. Genet Med 5(4):311–321.

Holm LW, Carroll LJ, Cassidy JD, Hogg-Johnson S, Côté P, Guzman J, Peloso P, Nordin M, Hurwitz E, van der Velde G, Carragee E, Haldeman S (2008). Bone and Joint Decade 2000-2010 Task Force on Neck Pain and Its Associated Disorders. The burden and determinants of neck pain in whiplash associated disorders after traffic collisions: results of the Bone and Joint Decade 2000-2010 Task Force on Neck Pain and Its Associated Disorders. Spine 33(4 Suppl):S52-59.

Holt EB (1903). Eye-movement and central anaesthesia. Harvard psychol Stud 1, 3-45.

Hurwitz EL, Carragee EJ, van der Velde G, Carroll LJ, Nordin M, Guzman J, Peloso PM, Holm LW, Côté P, Hogg-Johnson S, Cassidy JD, Haldeman S (2008). Bone and Joint Decade 2000-2010 Task Force on Neck Pain and Its Associated Disorders. Treatment of neck pain: noninvasive interventions: results of the Bone and Joint Decade 2000-2010 Task Force on Neck Pain and Its Associated Disorders. Spine 33(4 Suppl):S123-152.

Huygen PL, Verhagen WI, Nicolasen MG (1991). Cervico-ocular reflex enhancement in labyrinthine-defective and normal subjects. Exp Brain Res 87(2):457-464.

Ito M, Jastreboff PJ, Miyashita Y (1982). Specific effects of unilateral lesions in the flocculus upon eye movements in albino rabbits. Exp Brain Res 45(1-2):233-242.

Kaneoka K, Ono K, Inami S , Ochiai N, Hayashi K (2002). The human cervical spine motion during rear-impact collisions: a proposed cervical facet injury mechanism during whiplash trauma. J Whiplash Rel Dis 1(1):85-97.

Kasch H, Stengaard-Pedersen K, Arendt-Nielsen L, Staehelin Jensen T (2001). Headache, neck pain, and neck mobility after acute whiplash injury: a prospective study. Spine 26(11):1246-1251.

Kelders WP, Kleinrensink GJ, van der Geest JN, Feenstra L, de Zeeuw CI, Frens MA (2003). Compensatory increase of the cervico-ocular reflex with age in healthy humans. J Physiol 553(Pt 1):311-317.

Kelders WP, Kleinrensink GJ, van der Geest JN, Schipper IB, Feenstra L, de Zeeuw CI, Frens MA (2005). The cervico-ocular reflex is increased in whiplash injury patients. J Neurotrauma 22(1):133-137.

Kogler A, Lindfors J, Odkvist LM, Ledin T (2000). Postural stability using different neck positions in normal subjects and patients with neck trauma. Acta Otolaryngol 120(2):151-155.

Korenberg JR, Chen XN, Hirota H, Lai Z, Bellugi U, Burian D, Roe B, Matsuoka R (2000). Genome structure and cognitive map of Williams syndrome. J Cogn Neurosci 12(Suppl 1):89-107.

Koizuka I, Katsumi N, Hattori K, Okada T, Kato I (2000). Effect of adaptive plasticity of linear vestibulo-ocular reflex upon angular vestibulo-ocular reflex. Auris Nasus Larynx 27(2):89-93.

Kristjansson E, Dall'Alba P, Jull G (2003). A study of five cervicocephalic relocation tests in three different subject groups. Clin Rehabil 17(7):768-774.

Land M, Mennie N, Rusted J (1999). The roles of vision and eye movements in the control of activities of daily living. Perception 28(11):1311-1328.

Leigh RJ, Zee DS (1999). The neurology of eye movements, 3rd Edition. Oxford University Press.

Lind B, Sihlbom H, Nordwall A, Malchau H (1989). Normal range of motion of the cervical spine. Arch Phys Med Rehabil 70(9): 692–5.

Lindner A, Ilg UJ (2006). Suppression of optokinesis during smooth pursuit eye movements revisited: the role of extra-retinal information. Vision Res 46(6-7):761-767.

Lisberger SG, Miles FA, Zee DS (1984). Signals used to compute errors in monkey vestibuloocular reflex: possible role of flocculus. J Neurophysiol 52(6):1140-1153.

Loudon JK, Ruhl M, Field E (1997). Ability to reproduce head position after whiplash injury. Spine 22(8):865–868.

Lowery MC, Morris CA, Ewart A, Brothman LJ, Zhu XL, Leonard CO, Carey JC, Keating M, Brothman AR (1995). Strong correlation of elastin deletions, detected by FISH, with Williams syndrome: evaluation of 235 patients. Am J Hum Genet 57(1):49-53.

Mackay, D (1970). Elevation of Visual Threshold by Displacement of Retinal Image. Nature 225(5227):90-92.

Madeleine P, Prietzel H, Svarrer H, Arendt-Nielsen L (2004). Quantitative posturography in altered sensory conditions: a way to assess balance instability in patients with chronic whiplash injury. Arch Phys Med Rehabil 85(3):432–438.

Maioli C, Precht W, Ried S (1983). Short- and long-term modification of vestibulo-ocular response dynamics following unilateral vestibular nerve lesions in the cat. Exp Brain Res 50(2-3):259-274.

Makeyev AV, Erdenechimeg L, Mungunsukh O, Roth JJ, Enkhmandakh B, Ruddle FH, Bayarsaihan D (2004). GTF2IRD2 is located in the Williams-Beuren syndrome critical region 7q11.23 and encodes a protein with two TFII-I-like helix-loop-helix repeats. Proc Natl Acad Sci USA 101(30):11052-11057.

Matin E, Clymer AB, Matin L (1972). Metacontrast and saccadic suppression. Science 178(57):179-182.

Matin, E (1974). Saccadic suppression: a review and an analysis. Psychol Bull 81(12):899-917.

Mayer T, Brady S, Bovasso E, Pope P, Gatchel RJ (1993). Noninvasive measurement of cervical triplanar motion in normal subjects. Spine 18(15): 2191–2195.

McCarley JS, Wang RF, Kramer AF, Irwin DE, Peterson MS (2003). How much memory does oculomotor search have? Psychol Sci 14(5):422-426.

McClure P, Siegler S, Nobilini R (1998). Three-dimensional flexibility characteristics of the human cervical spine in vivo. Spine 23(2): 216–223.

McElligott JG, Beeton P, Polk J (1998). Effect of cerebellar inactivation by lidocaine microdialysis on the vestibuloocular reflex in goldfish. J. Neurophysiol 79(3):1286-1294.

Mergner T, Schweigart G, Botti F, Lehmann A (1998). Eye movements evoked by proprioceptive stimulation along the body axis in humans. Exp Brain Res 120(4):450-460.

Mervis CB, Klein-Tasman BP, Mastin ME (2001). Adaptive behavior of 4- through 8-year-old children with Williams syndrome. Am J Ment Retard 106(1):82–93.

Mimura M, Moriya H, Watanabe T, Takahashi K, Yamagata M, Tamaki T (1989). Three-dimensional motion analysis of the cervical spine with special reference to the axial rotation. Spine 14(11):1135–1139.

Morris CA, Mervis CB, Hobart HH, Gregg RG, Bertrand J, Ensing GJ, Sommer A, Moore CA, Hopkin RJ, Spallone PA, Keating MT, Osborne L, Kimberley KW, Stock AD (2003). GTF2I hemizygosity implicated in mental retardation in Williams syndrome: genotype-phenotype analysis of five families with deletions in the Williams syndrome region. Am J Med Genet A 123A(1):45-59.

Mulch G, Petermann W (1979). Influence of age on results of vestibular function tests. Review of literature and presentation of caloric test results. Ann Otol Rhinol Laryngol Suppl 88(2 Pt 2 Suppl 56):1-17.

Nagao S (1983). Effects of vestibulocerebellar lesions upon dynamic characteristics and adaptation of vestibulo-ocular and optokinetic responses in pigmented rabbits. Exp Brain Res 53(1):36-46.

Nederhand MJ, IJzerman MJ, Hermens HJ, Baten CTM, Zilvold G (2000). Cervical muscle dysfunction in the chronic whiplash associated disorder grade II (WAD-II). Spine. 25(15), 1938-1943.

Nederhand MJ, Hermens HJ, IJzerman MJ, Turk DC, Zilvold G (2002). Cervical muscle dysfunction in chronic whiplash associated disorder grade II: the relevance of the trauma. Spine 27(10):1056-1061.

Nederhand MJ, Hermens HJ, IJzerman MJ, Turk DC, Zilvold G (2003). Chronic neck pain disability due to an acute whiplash injury. Pain 102(1-2):63-71.

Nederhand MJ, Hermens HJ, IJzerman MJ, Groothuis KG, Turk DC (2006). The effect of fear of movement on muscle activation in posttraumatic neck pain disability. Clin J Pain 22(6):519-525.

Noton D, Stark L (1971). Scanpaths in saccadic eye movements while viewing and recognizing patterns. Vision Res. 11(9):929-942.

Olson SL, O'Connor DP, Birmingham G, Broman P, Herrera L (2000). Tender point sensitivity, range of motion, and perceived disability in subjects with neck pain. J Orthop Sports Phys Ther 30(1):13-20.

Oosterveld WJ, Kortschot HW, Kingma GG, de Jong HA, Saatci MR (1991). Electronystagmographic findings following cervical whiplash injuries. Acta Otolaryngol 111(2): 201–205.

Ordway NR, Seymour R, Donelson RG, Hojnowski L, Lee E, Edwards WT (1997). Cervical sagittal range-of-motion analysis using three methods: cervical range-of-motion device, 3space and radiography. Spine 22(5): 501–508.

Osborne L, Pober B (2001). Genetics of childhood disorders: XXVII. Genes and cognition in Williams syndrome. J Am Acad Child Adolesc Psychiatry 40(6):732-735.

Paige GD (1994). Senescence of human visual-vestibular interactions: smooth pursuit, optokinetic, and vestibular control of eye movements with aging. Exp Brain Res 98(2):355-372.

Peeters GG, Verhagen AP, de Bie RA, Oostendorp RA (2001). The efficacy of conservative treatment in patients with whiplash injury: a systematic review of clinical trials. Spine 26(4):E64-73.

Penning L, Wilmink J (1987). Rotation of the cervical spine: a CT study in normal subjects. Spine 12(8):732–739.

Prushansky T, Pevzner E, Gordon C, Dvir Z (2006). Performance of cervical motion in chronic whiplash patients and healthy subjects: the case of atypical patients. Spine 31(1):37-43.

Rijkaart DC, van der Geest JN, Kelders WP, de Zeeuw CI, Frens MA (2004). Short-term adaptation of the cervico-ocular reflex. Exp Brain Res 156(1):124-128.

Robinson DA (1976). Adaptive gain control of vestibuloocular reflex by the cerebellum. J Neurophysiol 39(5):954-969.

Ronnen HR, de Korte PJ, Brink PR, van der Bijl HJ, Tonino AJ, Franke CL (1996). Acute whiplash injury: is there a role for MR imaging?--a prospective study of 100 patients. Radiology 201(1):93-96.

Rubin AM, Woolley SM, Dailey VM, Goebel JA (1995). Postural stability following mild head or whiplash injuries. Am J Otol 16(2): 216–221.

Sato H, Ohkawa T, Uchino Y, Wilson VJ (1997). Excitatory connections between neurons of the central cervical nucleus and vestibular neurons in the cat. Exp Brain Res 115(3):381-386.

Schairer JO, Bennett MV (1986). Changes in gain of the vestibulo-ocular reflex induced by combined visual and vestibular stimulation in goldfish. Brain Res 373(1-2):164-176.

Scholten-Peeters GGM, Neeleman-van der Steen CWM, van der Windt DAWN, Hendriks EJM, Verhagen AP, Oostendorp RAB (2006). Education by general practitioners or education and exercises by physiotherapists for patients with whiplash associated disorders? A randomized clinical trial. Spine 31(7):723-731.

Siegmund GP, Myers BS, Davis MB, Bohnet HF, Winkelstein BA (2001). Mechanical evidence of cervical facet capsule injury during whiplash: a cadaveric study using combined shear, compression, and extension loading. Spine 26(19):2095–2101.

Shelhamer M, Peng GC, Ramat S, Patel V (2002). Context-specific adaptation of the gain of the oculomotor response to lateral translation using roll and pitch head tilts as contexts. Exp Brain Res 146(3):388-393.

Simons B, Büttner U (1985). The influence of age on optokinetic nystagmus. Eur Arch Psychiatry Neurol Sci 234(6):369-373.

Sjöström H, Allum JH, Carpenter MG, Adkin AL, Honegger F, Ettlin T (2003). Trunk sway measures of postural stability during clinical balance tests in patients with chronic whiplash injury symptoms. Spine 28(15):1725-1734.

Smith PF, Curthoys IS (1989). Mechanisms of recovery following unilateral labyrinthectomy: a review. Brain Res Brain Res Rev 14(2):155-180.

Spitzer WO, Skovron ML, Salmi LR, Cassidy JD, Duranceau J, Suissa S, Zeiss E (1995). Scientific monograph of the Quebec Task Force on whiplash associated disorders: redefining "whiplash" and its management. Spine 20(8 Suppl):1S-73S.

Stapley PJ, Beretta MV, Toffola ED, Schieppati M (2006). Neck muscle fatigue and postural control in patients with whiplash injury. Clinical Neurophysiol 117(3):610-622.

Sterner Y, Toolanen G, Gerdle B, Hildingsson C (2003). The incidence of whiplash trauma and the effects of different factors on recovery. J Spinal Disord Tech 16(2):195-199.

Stovner LJ (1996). The nosologic status of the whiplash syndrome: a critical review based on a methodological approach. Spine 21(23):2735-2746.

Strømme P, Bjørnstad PG, Ramstad K (2002). Prevalence estimation of Williams syndrome. J Child Neurol 17(4):269-271.

Tabak S, Collewijn H, Boumans LJ, van der Steen J (1997). Gain and delay of human vestibulo-ocular reflexes to oscillation and steps of the head by a reactive torque helmet. I. Normal subjects. Acta Otolaryngol 117(6):785-795.

Tassabehji M, Metcalfe K, Karmiloff-Smith A, Carette MJ, Grant J, Dennis N, Reardon W, Splitt M, Read AP, Donnai D (1999). Williams syndrome: Use of chromosomal microdeletions as a tool to dissect cognitive and physical phenotypes. Am J Hum Genet 64(1):118–125.

Tassabehji M, Hammond P, Karmiloff-Smith A, Thompson P, Thorgeirsson SS, Durkin ME, Popescu NC, Hutton T, Metcalfe K, Rucka A, Stewart H, Read AP, Maconochie M, Donnai D (2005). GTF2IRD1 in craniofacial development of humans and mice. Science 310(5751):1184–1187.

Tencer F, Mirza S, Bensel K (2002). Internal loads in the cervical spine during motor vehicle rear-end impacts: the effect of acceleration and head-to-head restraint proximity. Spine 27(1):34–42.

Thiele A, Henning P, Kubischik M, Hoffmann KP (2002). Neural mechanisms of saccadic suppression. Science 295(5564):2460-2462.

Tucci SM, Hicks JE, Gross EG, Campbell W, Danoff J (1986). Cervical motion assessment: a new, simple and accurate method. Arch Phys Med Rehabil 67(4):225–230.

Trauner DA, Bellugi U, Chase C (1989). Neurologic features of Williams and Down syndromes. Pediatr Neurol 5(3):166–168.

Treleaven J, Jull G, Sterling M (2003). Dizziness and unsteadiness following whiplash injury: characteristic features and relationship with cervical joint position error. J Rehabil Med 35(1): 36–43.

Treleaven J, Jull G, Lowchoy N (2005a). Standing balance in persistent whiplash: a comparison between subjects with and without dizziness. J Rehabil Med 37(4):224–229.

Treleaven J, Murison R, Jull G, LowChoy N, Brauer S (2005b). Is the method of signal analysis and test selection important for measuring standing balance in subjects with persistent whiplash? Gait Posture 21(4):395–402.

Uremović M, Cvijetić S, Pasić MB, Serić V, Vidrih B, Demarin V (2007). Impairment of proprioception after whiplash injury. Coll Antropol 31(3):823-827.

Van der Geest JN, Lagers-van Haselen GC, van Hagen JM, Govaerts LC, de Coo IF, de Zeeuw CI, Frens MA (2004). Saccade dysmetria in Williams-Beuren syndrome. Neuropsychologia 42(5):569–576.

Van der Geest JN, Lagers-van Haselen GC, van Hagen JM, Brenner E, Govaerts LC, de Coo IF, Frens MA (2005). Visual depth processing in Williams–Beuren syndrome. Exp Brain Res 166(2):200–209.

Van der Windt DA, Koes BW, van Aarst M, Heemskerk MA, Bouter LM (2000). Practical aspects of conducting a pragmatic randomised trial in primary care: patient recruitment and outcome assessment. Br J Gen Pract 50(454):371-374.

Van Die GC, Collewijn H (1986). Control of human optokinetic nystagmus by the central and peripheral retina: effects of partial visual field masking, scotopic vision and central retinal scotomata. Brain Res 383(1-2):185-194.

Van Goethem JW, Biltjes IGGM, van den Hauwe L, Parizel PM, de Schepper AM (1996). Whiplash injuries: is there a role for imaging? Eur J Radiol.22:30-37.

Van Hagen JM, van der Geest JN, van der Giessen RS, Lagers-van Haselen GC, Eussen HJ, Gille JJ, Govaerts LC, Wouters CH, de Coo IF, Hoogenraad CC, Koekkoek SK, Frens MA, van Camp N, van der Linden A, Jansweijer MC, Thorgeirsson SS, de Zeeuw CI (2007). Contribution of CYLN2 and GTF2IRD1 to neurological and cognitive symptoms in Williams Syndrome. Neurobiol Dis 26(1):112-24.

Verhagen AP, Scholten-Peeters GG, van Wijngaarden S, de Bie RA, Bierma-Zeinstra SM (2007). Conservative treatments for whiplash. Cochrane Database Syst Rev 2:CD003338.

Vibert N, de Waele C, Escudero M, Vidal PP (1993). The horizontal vestibulo-ocular reflex in the hemilabyrinthectomized guinea-pig. Exp Brain Res 97(2):263-273.

Vibert D, Häusler R (2003). Acute peripheral vestibular deficits after whiplash injuries. Ann Otol Rhinol Laryngol 112(3):246-251.

Vicari S, Bellucci S, Carlesimo GA (2005). Visual and spatial long-term memory: differential pattern of impairments in Williams and Down syndromes. Dev Med Child Neurol 47(5):305-311.

Von Holst E, Mittelstaedt H (1950). Das Reafferenzprinzip. Die Naturwissenschaften 20:464-476.

Walmsley R, Kimber P, Culham E (1996). The effect of initial head position on active cervical axial rotation range of motion in two age populations. Spine 21(21): 2435–2442.

Watanabe S, Hattori K, Koizuka I (2003). Flexibility of vestibulo-ocular reflex adaptation to modified visual input in human. Auris Nasus Larynx 30 Suppl:S29-34.

Withers S (1996). A new clinical sign in Williams syndrome. Arch Dis Child 75(1):89.

Youdas JW, Garrett TR, Suman VJ, Bogard CL, Hallman HO, Carey JR (1992). Normal range of motion of the cervical spine: an initial goniometric study. Phys Ther 72(11):770–781.

Zee DS, Yamazaki A, Butler PH, Gücer G (1981). Effects of ablation of flocculus and paraflocculus of eye movements in primate. J Neurophysiol 46(4):878-899.

Zee DS (1989). Adaptation and the ocular motor system. Bull Soc Belge Ophtalmol 237:191-207.

CHAPTER 2

Tragedy of conducting a clinical trial; Generic alert system needed

ABSTRACT

Stopping a clinical trial without reaching the final objective is not the ideal outcome any researcher wants; sometimes ceasing is inevitable. Due to marginal inclusion of patients we were forced to cease our randomized clinical trial on the effectiveness of proprioceptive training on the development of chronic whiplash complaints a year after the start. Although incidence figures demonstrate that recruitment of the planned number of whiplash patients would be easily feasible, we were unable to enroll the amount of subjects. Several motives can be proposed that would have prevented this obliged halting from happening. Other studies also report impracticability of the planned number of whiplash injury patients.

INTRODUCTION

In spite of preceding investigation of social relevance and feasibility, sometimes ending a clinical trial without achieving the aims is inevitable. Research about stopping clinical trials is often related to the likelihood of achieving statistical significant results at all (Snapinn et al., 2006) or stopping a trial early for benefit (Pocock, 2006; Armstrong and Granger, 2006). Sometimes other factors make ceasing inevitable. Although successful research endings generally result in publication, failures are usually sentenced to disappearance. Unfortunately, in this way it is not educational. Publication of such failures and their circumstances may increase our knowledge of the associated determinants, which may lead to better prevention of future failures.

Example

Last year, we started a randomized clinical trial in patients suffering from acute whiplash associated disorders (WAD (Spitzer et al., 1995)). The overall aim was to determine the effectiveness of proprioceptive training (performed by physiotherapists) which was specifically aimed at restoring cervical muscle stabilization, compared to usual care on the development of chronic complaints of WAD and to find out to what extent psychosocial indicators can influence the complaints of WAD patients.

We planned to include 120 WAD patients between 4 days and 12 weeks after the car collision to receive proprioceptive training plus usual care (intervention group) or usual care only (non-intervention group) during an eight week intervention period. 'Usual care' involved pain medication and information about the natural course of WAD. Three measurements were scheduled. Each measurement included a questionnaire and measurement of the optokinetic reflex (OKR), cervico-ocular reflex (COR), and vestibulo-ocular reflex (VOR). Randomization took place after the baseline measurement. We planned to measure again all patients of both groups at 9 (T2) and 26 (T3) weeks after randomisation. Additionally six weeks after the first measurement WAD patients were sent an extra questionnaire by mail (T1).

Patients were recruited by participating General Practitioners (GP) or at one of three Emergency Departments (ED) within Rotterdam and surroundings (6,61,887 persons (2005)(www.cbs.nl)). In order to recruit, 260 General Practitioners were

contacted by phone about ten days after receiving an informing letter to arouse their interest. In general on average four phone calls were needed to get an answer from a GP. Of all 260 contacted General Practitioners, 105 were willing to participate. The cooperating GPs received patient information brochures, an overview of the trial's inclusion criteria, a small poster and fax forms to fill in patients contact data.
Three out of five contacted EDs contributed in the trial. The two non-participating EDs treated their visiting whiplash patients in accordance with a neck collar immobilization protocol. The participating EDs received patient information forms and posters. The latter were placed on the wall in the emergency rooms to attract the physicians' and patients' attention.
Of all 56 contacted physiotherapy practices in the same region, 25 physiotherapists (PT) were willing to participate in the trial. Two meetings were needed to train the PTs in the intervention.

After 12 months, 79 probably eligible whiplash patients were referred to us (21 by their GP, 25 by the EDs, 17 subjects contacted us themselves after an advertisement in the local newspapers, 1 phoned after an interview and call for participants on a local radio station and 15 subjects entered by way of oral publicity). Within a week after receiving the address, subjects were contacted by telephone and, if wanted, they received an appointment notification.
Finally, only 11 whiplash patients meeting the selection criteria were included in the study. Every patient gave a written informed consent. In accordance with the ethical standards laid down in the 1964 Declaration of Helsinki the experiments were approved by the medical ethical committee of the Erasmus MC.

Major reasons for exclusion were: collision appeared more than 3 months ago (n=8), subjects already received physiotherapy (n=29) and no rear-end collision but frontally or sideways (n=20). Reasons for withdrawal were: recovery (n=2), unknown (n=1). Two patients did not show up for the baseline measurement even after three subsequent appointments were made.

What can go wrong in conducting a trial?

Although randomized controlled trials are a widely used design in medical research, often recruitment problems give rise to bringing the trial to a standstill. According to the literature most studies suffer from Lasagna's Law, meaning that as soon as a study starts to recruit participants, 90% of the eligible participants disappear to return only after the end of the recruitment period (Gorringe, 1970; Huibers et al., 2004). Failure to recruit sufficient numbers of patients frequently threatens a successful completion of research projects (Van der Wouden et al., 2007). Often reported unfavourable factors for patient enrolment are recruitment by GPs during routine consultations (incident cases), strong resistance or preference of patients for one of the interventions, and GPs time restraints (Van der Wouden et al., 2007). In a survey of 78 studies, an extension of the recruitment period in almost 40% of the projects is reported by at least 50% (Van der Wouden et al., 2007). It appeared that studies that focussed on incident cases were less successful, probably because the GP had to be alert during consultations. When the GP or practice assistant was the first to inform the patient about the study, patient recruitment was also less successful than when the patient received a letter by mail (Van der Wouden et al., 2007).

Ross et al. (1999) mentioned several recruitment barriers, such as lack of time and lack of support staff. However, worries in participating clinicians about the doctor - patient relationship, treatment toxicity, or side effects affected the decision for trial admittance as well as loss of clinical autonomy and difficulties in the consent procedure. Furthermore, additional procedures and appointments, travel problems and costs, and preference for a specific treatment may hamper patients' recruitment (Ross et al., 1999). Haidich and Ioannidis (2001) reported a relationship between patient enrollment during the first two months of the trial and finally, the achieved sample size.

Patient recruitment in other WAD studies

A few years ago Scholten-Peeters et al. (2006) started a comparable clinical trial in patients with WAD in the Netherlands. They also were unable to enroll the planned number of whiplash patients. A series of extra effort in recruiting whiplash patients, such as periodic newsletters, clinical meetings, telephone calls and small incentives did not lead to the desirable outcome. They finally included 80 patients over a 3-year period, whereas the initial planned number of patients was 150 within a shorter time frame. Likewise, Van der Windt et al. (2000) reported problematic patient enrolment via participating GPs despite careful preparation, although the intended study population was 120 patients within 18 months. After 20 months, when 109 patients had been admitted to the trial, recruitment was halted.

However, also fortunate recruitments have been reported. Borchrevink et al. (1998) included 201 car accident neck sprain injury patients, who had been admitting the Emergency Clinic in Trondheim between September 1994 and December 1995 in a randomized trial with a 6-month follow-up period. Also Rosenfeld et al. (2000) found 97 whiplash patients within 12 months, starting in March 1995, recruited by physicians in primary care units, emergency wards, and private clinics willing to participate in a 3-year follow-up prospective intervention trial. Strikingly, both 1-year lasting fortunate recruitments occurred halfway the nineties.

What can be done?

There are many interventions that could potentially improve clinician and patient participation in trials. Finding which ones are effective would be of benefit to the research community and society. A Cochrane review was published on strategies to improve recruitment (Mapstone et al., 2002). The authors found only strategies aimed at patients, none was aimed at research collaborators (e.g., doctors), whereas factors mentioned in literature mainly focus on factors associated to the clinician (Van der Wouden et al., 2007). Besides using a clear and simple protocol, demanding minimum effort of participating clinicians and carefully planning and monitoring recruitment process, according to Ross et al. (1999) extra support should be given to patients in their decision to participate. Furthermore, restrictive entry criteria and attractiveness of the protocol may influence the number of enrolling patients (Haidich and Ioannidis, 2001).

What did we do?

We have tried to overcome Lasagna's Law preliminary by basing our calculation of needed number of participating GPs and EDs on conservative estimations of whiplash incidence. Preparatory, social relevance was examined and affirmed, and we estimated that the number of patients with recent whiplash injury complaints after a rear-end collision would be sufficiently. Also, a feasibility analysis based on a cohort study resulted in well achievable aims (Vos et al., 2007). On the basis of the (inter)national incidence figures we calculated, a recruitment of 120 patients in an 18-month period would be easily feasible.

During the course of the trial, we tried to increase patient recruitment by different methods. An advertisement was published three times in different local newspapers. This resulted in 17 extra subjects of whom none could be included in the study because of long term morbidity and an extensive history of therapy. Also, a live interview on a local radio station and a call on the Internet from the whiplash injury patient association did not increase the amount of eligible patients. Likewise, we regularly contacted physicians at the EDs as well as sending newsletters to the GPs and reminders to the subjects for their appointment at the research center. This extra endeavor did not lead to a rise in patient inflow. Overall, the participation of 105 GPs, physicians at 3 EDs, and some local advertisement resulted in the inclusion of 11 WAD patients in one year. This disappointing number was just 12% of calculated patient recruitment, and not enough to be able to continue the study.

More manpower (i.e., recruiting more GPs and/or EDs) could be put forward as only a partial solution to the low attendance.

General learning points and recommendations

Recently, an international trial register has been created, in which clinical trials are registered prospectively to prevent double studies and positive publication bias. In the future, such a register can also determine the number of ceased trials (www.controlled-trial.com, 2007). Reasons for cessation will be recorded and a better overview of these reasons can be provided. Also, strategies to improve patient recruitment can be retrieved.

Randomized controlled trials are a valid method to determine the effectiveness of interventions in medical care objectively and are an excellent way of following groups of patients over time.

Possibly, Lasagna's Law has struck us to a major extent. In a large study in the Netherlands evaluating the influence of Lasagna's Law in studies in primary care, one of the main factors found was the inclusion of incident cases, especially when they were not very frequently seen (Van der Wouden et al., 2007). A real-time computerized doctor reminder (or clinical trial alert) system could take care of the familiar problem that the trial has slipped the doctors' mind until the patient has left the consulting room (Embi et al., 2005). Unfortunately, GPs in the Netherlands make use of several different software programs, which makes the implementation of such alert system for trial purposes difficult.

Although we have not been able to assess the cause of the recruitment problems, the findings of the trial are of clinical interest. For future researchers, planning on doing a comparable trial this may serve as a learning point.

Learning points

1. Researchers do many things to increase patient recruitment.
2. Patient recruitment strategies should be evaluated better for incident cases.
3. A trial alert system can improve patient recruitment.

REFERENCES

Armstrong PW, Granger CB (2006). Reflections on early stopping of a clinical trial. Am Heart J 152(3):407-409.

Blankenstein AH, van der Wouden JC, Huibers MJH, Verhagen AP, Boek AJP, van der Windt DAWM, Stalman WAB. Why is Lasagna's Law so prevalent in primary care? A literature and focus group study on determinants of patient recruitment for research in general practice. Submitted.

Borchgrevink GE, Kaasa A, McDonagh D, Stiles TC, Haraldseth O, Lereim I (1998). Acute treatment of whiplash neck sprain injuries. A randomized trial of treatment during the first 14 days after a car accident. Spine 23(1):25-31.

Cbs.nl [homepage on the Internet]. Voorburg/Heerlen: Centraal Bureau voor de Statistiek; 2006 [updated 2006 Aug 15]. Available from http://www.cbs.nl

Controlled-trials [homepage on the Internet]. London: Current Controlled Trials, Ltd.; [updated 2006 Aug 15]. Available from http://www.controlled-trials.com

Embi PJ, Jain A, Clark J, Bizjack S, Hornung R, Harris CM (2005). Effect of a clinical trial alert system on physician participation in trial recruitment. Arch Intern Med 165(19):2272-2277.

Gorringe JAL (1970). Initial preparation for clinical trials. In: Harris EL, Fitzgerald JD, editors. The principles and practice of clinical trials. Edinburgh/London: Livingstone.

Haidich AB, Ioannidis JP (2001). Patterns of patient enrollment in randomized controlled trials. J Clin Epidemiol 54(9):877-883.

Huibers MJ, Bleijenberg G, Beurskens AJ, Kant IJ, Knottnerus JA, van der Windt DA, Bazelmans E, van Schayck CP (2004). An alternative trial design to overcome validity and recruitment problems in primary care research. Fam Pract 21(2): 213-218.

Mapstone J, Elbourne D, Roberts I (2002). Strategies to improve recruitment to research studies. Cochrane Database Syst Rev 2:MR000013.

Pocock SJ (2006). Current controversies in datamonitoring for clinical trials. Clin Trials 3(6):513-521.

Rosenfeld M, Gunnarson R, Borenstein P (2000). Early intervention in whiplash associated disorders. A comparison of two treatment protocols. Spine 25(14):1782-1787.

Ross S, Grant A, Counsell C, Gillespie W, Russell I, Prescott R (1999). Barriers to participation in randomised controlled trials: a systematic review. J Clin Epidemiol 52(12):1143-1156.

Scholten-Peeters GG, Neeleman-van der Steen CW, van der Windt DA, Hendriks EJ, Verhagen AP, Oostendorp RA (2006). Education by general practitioners or education and exercises by physiotherapists for patients with whiplash associated disorders? A randomized clinical trial. Spine 31(7):723-731.

Snapinn S, Cheng MC, Jiang Q, Koutsoukos T (2006). Assessment of futility in clinical trials. Pharm Stat 5(4):273-81.

Spitzer WO, Skovron ML, Salmi LR, Cassidy JD, Duranceau J, Suissa S, Zeiss E (1995). Scientific monograph of the Quebec Task Force on whiplash associated disorders: redefining "whiplash" and its management. Spine 20(8 Suppl):1S-73S.

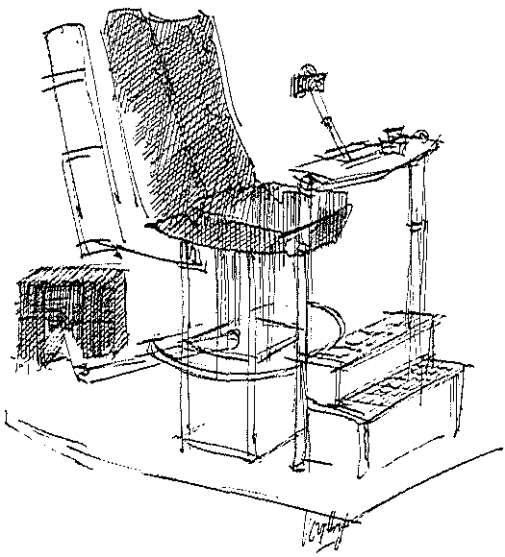
Van der Windt DA, Koes BW, van Aarts M, Heemskerk MA, Bouter LM (2000). Practical aspects of conducting a pragmatic randomised trial in primary care: patient recruitment and outcome assessment. Br J Gen Pract 50(454):371-374.

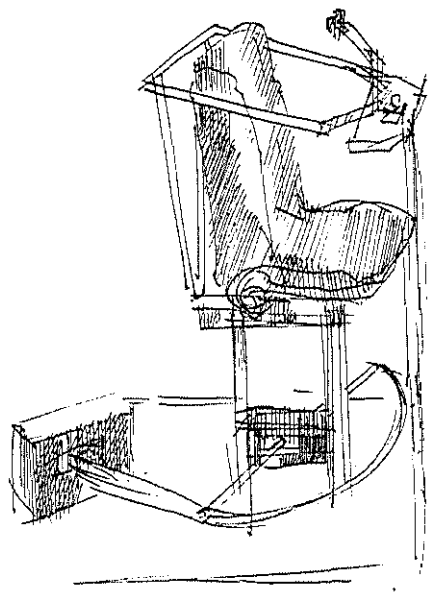
Van der Wouden JC, Blankenstein AH, Huibers MJ, van der Windt DA, Stalman WA, Verhagen AP (2007). Survey among 78 studies showed that Lasagna's law holds in Dutch primary care research. J Clin Epidemiol 60(8):819-24.

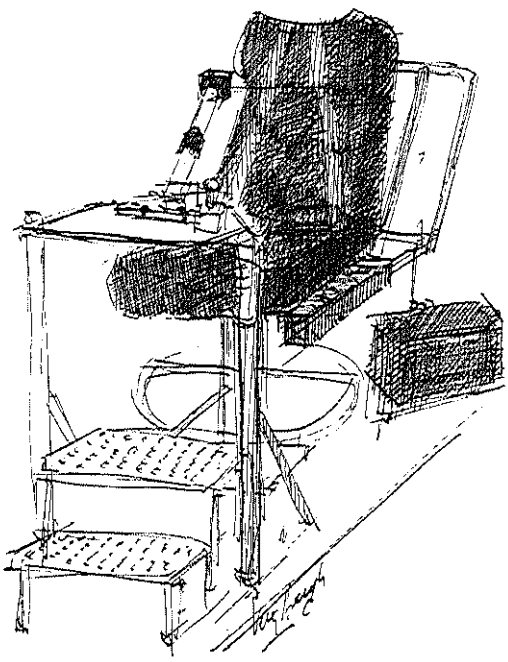
Vos CJ, Verhagen AP, Passchier J, Koes BW (2007). Management of Acute Neck Pain in general practice; A prospective study. Br J Gen Pract 57(534):23-28.

C H A P T E R 3

Interaction between ocular stabilisation reflexes in patients with whiplash injury







ABSTRACT

In the past few decades, the automobile has become an increasingly more popular means of transport, which has led to an increasing number of rear-end collisions and consequently has resulted in more patients with whiplash associated disorders (WAD). Recently, it was found that the gain of one of the ocular stabilization reflexes - the cervico-ocular reflex (COR) - is elevated in patients with whiplash injury. The COR responds to proprioceptive signals from the neck and acts in conjunction with the vestibulo-ocular reflex (VOR) and the optokinetic reflex (OKR) to preserve stable vision on the retina during head motion. Therefore, an investigation was conducted to determine whether the reported elevation of the COR in WAD is accompanied by changes in VOR or OKR. Eye movements of 13 patients and 18 age-matched healthy controls were recorded with an infrared eye-tracking device. Analysis confirmed a significant increase in COR gain in whiplash patients. Meanwhile the VOR and OKR gains remained the same. No correlation was found between the gains of the reflexes in individual patients. This is in contrast to earlier observations in elderly subjects and subjects with labyrinthine defects, who showed increases in COR gain and decreases in VOR gain. Impaired neck motion, altered proprioception of the neck, or disorganization in the process of VOR plasticity could explain the lack of change in VOR gain.

INTRODUCTION

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

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

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

The VOR can be subdivided into rotational and translational components induced by stimulation of the semicircular canals and the otolith organs, respectively. When the head is turned, the VOR moves the eyes in the opposite direction, responding optimally to high frequencies (Tabak et al., 1997). The OKR is stimulated by visual motion and uses the relative velocity of the image on the peripheral retina to generate eye movements in the same direction. Both OKR and COR reflexes respond best at

low head movement velocities (Van Die and Collewijn, 1986; Mergner et al., 1998; Kelders et al., 2003). The gain values of the COR are increased over a broad range of velocities (ranging from 1.2 deg/s to 12.8 deg/s) in whiplash injury patients, although the largest difference was found at lower velocities (Kelders et al., 2005).

In healthy persons, the COR gain can be modified after 10 minutes of concurrent visual and cervical stimulation (Rijkaart et al., 2004). In patients with absent vestibular function, the COR gain is also increased (Bronstein and Hood, 1986; Bronstein et al., 1995; Huygen et al., 1991; Bouyer and Watt, 1999) as it is with age (older than 60 years (Kelders et al., 2003)). Meanwhile, in elderly persons, the gains of the VOR and OKR are decreased (Mulch and Petermann, 1979; Aust, 1991; Paige, 1994). Earlier, Kelders et al. (2003) reported a covariation between the gains of the COR and VOR in healthy persons: i.e., when the VOR is relatively high, the COR is low and vice versa.

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

MATERIALS AND METHODS

Subjects

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

In accordance with the ethical standards laid down in the 1964 Declaration of Helsinki the experiments were approved by the medical ethical committee of the Erasmus MC.

Experimental setup

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

COR recordings

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

VOR recordings

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

OKR recordings

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

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

Stimulus Paradigms

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

Analysis

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

RESULTS

Gain values were independent of stimulus frequencies within the range that we presented, as was also described in Kelders et al. (2003). Therefore, data were pooled at all frequencies. Analysis of the average data per subject, rather than on individual data points, gave qualitatively similar results.

The three reflex gain values of the age-matched subjects at all frequencies are plotted in figure 1 (controls A,C,E; patients B,D,F).

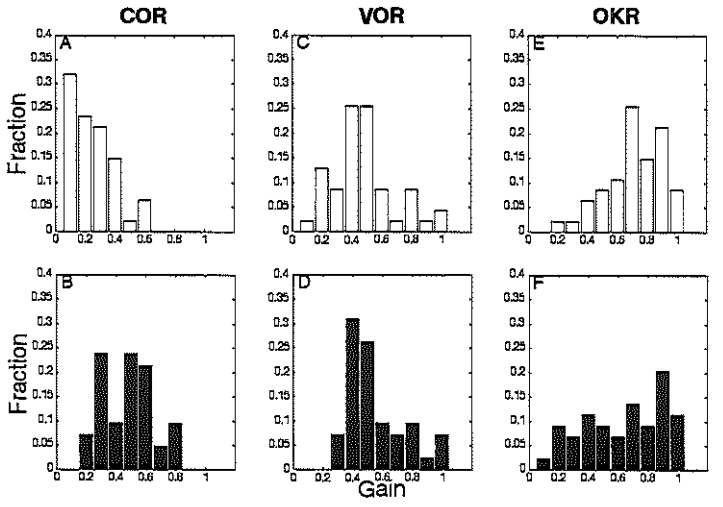


Figure 1. Fractions of COR, VOR, and OKR gains pooled for the whole range of stimulus peak velocities. Results of the age-matched healthy controls and whiplash patients are plotted in panels A,C, E and B,D,F respectively.

Recently, Kelders et al. (2003; 2005) found an increased COR gain in elderly (> 60 years) and in whiplash injury patients. Also in this study, a higher COR gain was found in WAD patients as compared to healthy controls (Figures 1A, B, KS-test, $p = 2.9 * 10^{-6}$). The gains of the OKR and VOR do not show a significant change (VOR gain, $p = 0.27$; OKR gain, $p = 0.25$). The gain values of patients remained consistent with those of healthy controls. (Figures 1C - F). Previously, Kelders et al. (2003) also found a negative correlation between the COR gain and VOR gain in normal controls. Figure 2A shows a similar correlation for healthy participants ($r = -0.38$, $p = 0.01$), but not for patients ($r = 0.01$, $p = 0.95$). The correlation in the control group was significantly higher than in the patient group ($p = 0.01$).

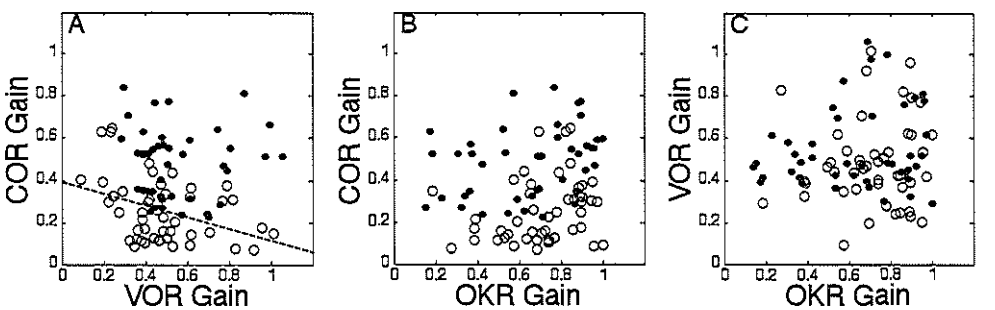


Figure 2. Correlations between the reflex gains (A-C). Different symbols indicate the whiplash patients (closed circles, •) and controls (open circles, ○). In A the dotted line is a orthogonal fit through the data of the healthy subjects (slope = - 0.4581). In the remaining data, no significant correlation could be found; therefore, no fitting line is shown.

Furthermore, neither reflex was significantly correlated with the OKR in controls ($r=0.26$, $p=0.08$, $r=-0.02$, $p=0.9$ respectively, Figure 2B), or patients ($r=0.09$, $p=0.05$, $r=0.16$, $p=0.31$ respectively, Figure 2C). Although the COR gain increases with age in controls ($r=0.32$, $p<0.02$), such a difference does not appear in patients ($r=-0.05$, $p>0.7$; Figure 3).

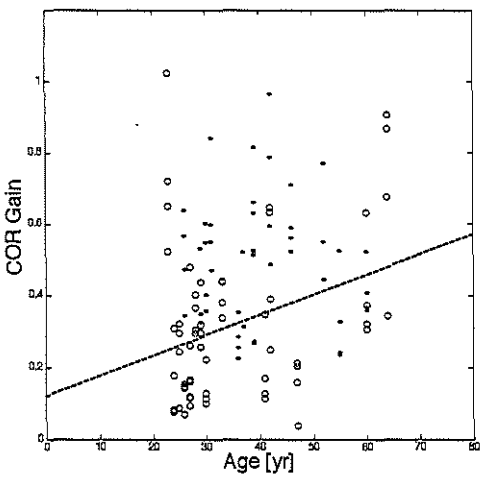


Figure 3. Correlation between the COR gain and age. Different symbols indicate the whiplash patients (closed circles, •) and controls (open circles, ○). The dotted line is fitted trough the data of the healthy subjects by means of linear regression (slope = 0.0057 yr^{-1})

DISCUSSION

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

A decrease in VOR gain might have been responsible for an increase in COR gain in our whiplash patients, as seen in elderly subjects (Kelders et al., 2003) and in those with labyrinthine deficits (Bronstein and Hood, 1986; Bronstein et al., 1995; Huygen et al., 1991; Bouyer and Watt, 1999). However, a higher COR gain could also be the cause of a decline in VOR gain. Earlier experiments showed that the VOR gain can be adapted in one hour by noncorresponding vestibular and visual information (Zee, 1989; Koizuka et al., 2000; Shelhamer et al., 2002; Watanabe et al., 2003). Contrary to the latter theory, the COR gain was elevated with no decline in the VOR gain in WAD patients.

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

First, it may be that decreased mobility of the neck leads to alteration in proprioception of the neck, which in turn results in an augmented gain of the COR without any problems in the VOR pathway.

Second, it may be that adaptation of the VOR requires sufficient head motion, and, because of impaired neck motion, the patient has too little adaptive input for the VOR to induce a negative adaptation in VOR gain. It is known that the VOR responds best at high frequencies, whereas the COR is most responsive at low velocities (Kelders et al., 2003). This could explain the lack of decrease in VOR gain.

Third, it may be that there is a disorganization in the process of VOR plasticity because of microtrauma in the VOR pathway, such as in the flocculonodular area of the cerebellum. The latter hypothesis will be subject to more research in the near future when we perform VOR adaptation experiments in patients with whiplash injury.

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

REFERENCES

Aust G (1991). [The effect of age on vestibulo-ocular reactions]. Der Einfluss des Lebensalters auf vestibulo-okulare Reaktionen. Laryngorhinootologie 70(3):132-137.

Bouyer LJ, Watt DG (1999). "Torso Rotation" experiments. 4: the role of vision and the cervico-ocular reflex in compensation for a deficient VOR. J Vestib Res 9(2):89-101.

Bronstein AM, Hood JD (1986). The cervico-ocular reflex in normal subjects and patients with absent vestibular function. Brain Res 373(1-2):399-408.

Bronstein AM, Morland AB, Ruddock KH, Gresty MA (1995). Recovery from bilateral vestibular failure: implications for visual and cervico-ocular function. Acta Otolaryngol Suppl 520 Pt 2:405-407.

Eck JC, Hodges SD, Humphreys SC (2001). Whiplash: a review of a commonly misunderstood injury. Am J Med 110(8):651-656.

Heimbrand S, Bronstein AM, Gresty MA, Faldon ME (1996). Optically induced plasticity of the cervico-ocular reflex in patients with bilateral absence of vestibular function. Exp Brain Res 112(3):372-380.

Hikosaka O, Maeda M (1973). Cervical effects on abducens motoneurons and their interaction with vestibulo-ocular reflex. Exp Brain Res 18(5):512-530.

Huygen PL, Verhagen WI, Nicolasen MG (1991). Cervico-ocular reflex enhancement in labyrinthine-defective and normal subjects. Exp Brain Res 87(2):457-464.

Kelders WP, Kleinrensink GJ, van der Geest JN, Feenstra L, de Zeeuw CI, Frens MA (2003). Compensatory increase of the cervico-ocular reflex with age in healthy humans. J Physiol 553(Pt 1):311-317.

Kelders WP, Kleinrensink GJ, van der Geest JN, Schipper IB, Feenstra L, de Zeeuw CI, Frens MA (2005). The cervico-ocular reflex is increased in whiplash injury patients. J Neurotrauma 22(1):133-137.

Koizuka I, Katsumi N, Hattori K, Okada T, Kato I (2000). Effect of adaptive plasticity of linear vestibulo-ocular reflex upon angular vestibulo-ocular reflex. Auris Nasus Larynx 27(2):89-93.

Lovell ME, Galasko CS (2002). Whiplash disorders--a review. Injury 33(2):97-101.

Mergner T, Schweigart G, Botti F, Lehmann A (1998). Eye movements evoked by proprioceptive stimulation along the body axis in humans. Exp Brain Res 120(4):450-460.

Mulch G, Petermann W (1979). Influence of age on results of vestibular function tests. Review of literature and presentation of caloric test results. Ann Otol Rhinol Laryngol Suppl 88(2 Pt 2 Suppl 56):1-17.

Nederhand MJ, IJzerman MJ, Hermens HJ, Baten CTM, Zilvold G (2000). Cervical muscle dysfunction in the chronic whiplash associated disorder grade II (WAD-II). Spine. 25(15), 1938-1943.

Paige GD (1994). Senescence of human visual-vestibular interactions: smooth pursuit, optokinetic, and vestibular control of eye movements with aging. Exp Brain Res 98(2):355-372.

Rijkaart DC, van der Geest JN, Kelders WP, de Zeeuw CI, Frens MA (2004). Short-term adaptation of the cervico-ocular reflex. Exp Brain Res 156(1):124-128.

Shelhamer M, Peng GC, Ramat S, Patel V (2002). Context-specific adaptation of the gain of the oculomotor response to lateral translation using roll and pitch head tilts as contexts. Exp Brain Res 146(3):388-393.

Spitzer WO, Skovron ML, Salmi LR, Cassidy JD, Duranceau J, Suissa S, Zeiss E (1995). Scientific monograph of the Quebec Task Force on whiplash associated disorders: redefining "whiplash" and its management. Spine 20(8 Suppl):1S-73S.

Tabak S, Collewijn H, Boumans LJ, van der Steen J (1997). Gain and delay of human vestibulo-ocular reflexes to oscillation and steps of the head by a reactive torque helmet. I. Normal subjects. Acta Otolaryngol 117(6):785-795.

Thomas J (1990). Road traffic accidents before and after seatbelt legislation--study in a district general hospital. J R Soc Med 83(2):79-81.

Van der Geest JN, Frens MA (2002). Recording eye movements with video-oculography and scleral search coils: a direct comparison of two methods. J Neurosci Methods 114(2):185-195.

Van Die GC, Collewijn H (1986). Control of human optokinetic nystagmus by the central and peripheral retina: effects of partial visual field masking, scotopic vision and central retinal scotomata. Brain Res 383(1-2):185-194.

Watanabe S, Hattori K, Koizuka I (2003). Flexibility of vestibulo-ocular reflex adaptation to modified visual input in human. Auris Nasus Larynx 30 Suppl:S29-34.

Zee DS (1989). Adaptation and the ocular motor system. Bull Soc Belge Ophtalmol 237:191-207.

C H A P T E R 4

Adaptation of cervico- and vestibulo-ocular reflex in whiplash injury patients

ABSTRACT

The aim of this study was to investigate the underlying mechanisms of the increased gains of the cervico-ocular reflex (COR) and the lack of synergy between the COR and the vestibulo-ocular reflex (VOR) that have been previously observed in patients with whiplash associated disorders (WAD). Eye movements during COR or VOR stimulation were recorded in four different experiments. The effect of restricted neck motion and the relationship between muscle activity and COR gain was examined in healthy controls. The adaptive ability of the COR and the VOR was tested in WAD patients and healthy controls. Reduced neck mobility yielded an increase in COR gain. No correlation between COR gain and muscle activity was observed. Adaptation of both the COR and VOR was observed in healthy controls, but not in WAD patients. The increased COR gain of WAD patients may stem from a reduced neck mobility. The lack of adaptation of the two stabilization reflexes may result in a lack of synergy between them. These abnormalities may underlie several of the symptoms frequently observed in WAD, such as vertigo and dizziness.

INTRODUCTION

In order to prevent blur of the visual image during self-motion, several ocular stabilization reflexes exist. These reflexes move the eyes with respect to the head in order to keep them fixed relative to the outside world. Two of these reflexes, the cervico-ocular reflex (COR) and the vestibulo-ocular reflex (VOR), work as open loop reflexes: the oculomotor output does not change the sensory input. Their inputs are proprioception of the neck for the COR and vestibular signals for the VOR. A third reflex, the optokinetic reflex (OKR), responds to visual motion information and can therefore be considered to be a closed loop negative feedback system.

Since all three stabilization reflexes normally operate concurrently, the relative strengths of the open loop components should be correlated, in order to ensure an optimal response. Indeed, Kelders et al. (2003) showed that in healthy subjects a negative correlation can be found between the gains of the COR and the VOR. The basis for this correlation is likely to be the plasticity of both reflexes. Both the COR and the VOR can be modified on the basis of visual stimulation. Rijkaart et al. (2004) reported a reduction in COR gain in healthy subjects after ten minutes of concurrent mismatched visual and cervical stimulation. A long-term altered relationship for about one hour between visual and vestibular information results in adaptation of the VOR gain. Depending on the relation between the visual and vestibular stimulus, this adaptation can either be an increase or a decrease of gain (Zee, 1989; Koizuka et al., 2000; Shelhamer et al., 2002; Watanabe et al., 2003).

Kelders et al. (2003; 2005) reported an elevated COR gain in both elderly subjects and in patients with whiplash associated disorders (WAD). Whiplash is an acceleration-deceleration mechanism of energy transfer to the neck, which may result from rear end or side-impact motor vehicle collision, but can also occur during diving or other mishaps. The impact may result in bony or soft tissue injuries (Spitzer et al., 1995) and can cause numerous varieties of signs and symptoms, which include headache, neck pain and stiffness, visual disturbances, fatigue, vertigo and dizziness (Eck et al., 2001).

However, while the higher COR gain is accompanied by a lower VOR gain in the elderly (Kelders et al., 2003), recent data from our laboratory show that this synergy between the eye movement reflexes is not present in WAD patients; that is, the COR is enhanced, but this is not accompanied by a lower VOR (Montfoort et al., 2006 (see chapter 3)). The lack of synergy could be related to disturbances in the plasticity of the COR and/or the VOR.

In the present study, we investigated possible mechanisms for the elevated COR gains and the adaptive abilities of the two eye movement reflexes in WAD patients. Dall'Alba et al. (2001) reported a reduced cervical range of motion in patients with persistent WAD, suggesting that WAD patients are hypokinetic. As a consequence, the strength of the neck proprioceptors may be upregulated, in analogy to, for instance, dark adaptation of the retina. We examined whether the COR gain can be influenced by a reduced neck mobility.

Furthermore, Nederhand et al. (2000) reported a decreased relaxation ability of the cervical trapezoid muscles in patients with whiplash injury complaints. Earlier, in chapter 3, we hypothesized that an increased muscle tension may lead to an increased COR gain (Montfoort et al., 2006). Here we examined the relationship between muscle activity and COR gain in asymptotic individuals. In two other experiments, we tested the plasticity of COR and VOR eye movements in WAD patients and healthy controls. This study is the first to examine the mechanism behind the elevated COR response in WAD, and the lack of compensation for this increase.

MATERIALS AND METHODS

Subjects

In total, 28 healthy subjects and 20 WAD patients participated in four experiments, which are described below. These experiments were approved by the medical ethical committee of the Erasmus MC in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. All subjects gave informed consent after explanation of the nature and the possible consequences of the study.

All 28 healthy subjects had no known history of any neurological or vestibular disorder. The 20 patients with whiplash injury symptoms (WAD grade 1 and 2 according to Spitzer et al. (1995); all having neck complaints of pain, stiffness or tenderness, without neurological signs, such as sensory deficits) following a head-to-tail car collision participated in one of the two experiments on COR or VOR adaptation. We excluded patients without clear vision as well as those with fractures or dislocations of cervical or thoracical bones, recent use of tranquilizing or vestibular sedative medication, cervical arthrosis, or a history of vestibular problems.

Table 1 describes the subjects participating in each of the four experiments. Some healthy subjects participated in more than one experiment (one in all four, four in three, and seven subjects in two experiments). These subjects participated in the various experiments on different days. All subjects (both patients and controls)

were of an age that no age-dependent decrease or increase in their reflexes is to be expected (Kelders et al., 2003). The age distributions of patienst and healthy controls did not differ significantly (Kolmogorov-Smirnov, $p > 0.1$).

Table 1: Number of healthy subjects and WAD patients, and their age range for each of the four experiments of the present study.

	Healthy subjects		*WAD patients*	
	N	*Age*	*N*	*Age*
Experiment				
Neck mobility	16 (5 females, 11 males)	21–40 (mean 30) years	—	—
Muscle activity	10 (4 females, 6 males)	22–39 (mean 29) years	—	—
COR adaptation	10 (3 females, 7 males)	18–54 (mean 31) years	10 (8 females, 2 males)	22–52 (mean 42) years
VOR adaptation	10 (4 females, 6 males)	24–39 (mean 30) years	10[a] (7 females, 3 males)	19–56 (mean 39) years

[a] *One subject was excluded due to recording failure, leaving 9 WAD patients in the VOR adaptation experiment. WAD, whiplash associated disorders; COR, cervico-ocular reflex; VOR, vestibulo-ocular reflex.*

Stimulation

COR stimulation

The COR was evoked by moving the trunk while the head was kept stationary. In this way, COR stimulation could be given in the absence of vestibular signals. Subjects were seated on a custom-built rotating chair, with a double belt system at shoulder level fastening their trunk. While the subject's head was fixated by means of a custom-made bite board (Dental Techno Benelux, Rotterdam, the Netherlands), the body could be passively rotated. A cervical range of motion (CROM) device showed that the chair motion induced a negligibly small head movement. Further details of the experimental setup can be found in Kelders et al. (2003). The angular orientation of the chair was stored on hard disk for off-line analysis. For COR stimulation the chair was rotated sinusoidally at a frequency of 0.04 Hz with a peak-to-peak amplitude of 10 degrees about the vertical axis (maximum angular velocity:1.26 deg/s). The subjects were positioned on the chair so that the axis of rotation was aligned with the neck.

VOR stimulation

In the same setup, the bite board could be attached to the chair for VOR stimulation. In this way, both the trunk and the head could be passively rotated together. For VOR stimulation, the chair was rotated sinusoidally with a peak-to-peak amplitude of 10 degrees at a frequency of 0.08 Hz about the vertical axis (maximum angular velocity: 2.52 deg/s).

Visual stimulation

Visual stimuli were projected by a data projector (Infocus LP 335; GroupComm Systems, Newton, MA) on a wide translucent screen (235 cm broad and 170 cm high) located 160 cm in front of the subject. The projector back-projected the stimulus on the screen via a rotatable mirror, which could be moved by a stepping motor (model number 6900; Cambridge Technology, Cambridge, MA). The visual stimuli for the eye movement calibration and the COR adaptation experiments were generated by a personal computer using Matlab 6.1 (Mathworks Inc., Natick, MA). The visual stimulation for the VOR adaptation experiment was generated by a DVD-player.

Recordings

Eye movements

Eye movements during COR or VOR stimulation were recorded with an infrared eye-tracking device (EyeLink 2.04, SensoMotoric Instruments, Berlin, Germany) with a resolution of 20 sec of arc and a sampling frequency of 250 Hz (Van der Geest and Frens, 2002).

Eye position was calibrated using a built-in automatic routine, based on a 3x3 array of fixation positions. The position of the eyes relative to the cameras was continuously monitored to ensure that the subject's head remained well stabilized.

Eye velocity was calculated by derivation of the horizontal eye position signal as described in Kelders et al. (2003). After removal of blinks, saccades, and fast phases using a 20 deg/s threshold, a sine was fitted through the velocity signal, discarding the first cycle of stimulus. The gain of the response was defined as the amplitude of the fitted sine divided by the peak velocity of the rotating chair.

EMG of the neck muscles

Surface electromyography (EMG) activity was recorded of both sternocleidomastoid muscles and upper trapezoid muscles via disposable self-adhesive electrodes placed on the muscle bellies (centers approximately three centimeters apart) during COR registration. The ground electrode was placed on the bony part of the right forehead of the subject. Before recording the signals at 1024 Hz, the signals were amplified (x 3000) and band-pass filtered (60–500 Hz). EMG signals were rectified and filtered off-line with a 50 Hz low-pass, fourth-order, zero-lag Butterworth filter.

Experimental paradigms

In all four experiments, the measurements were performed in total darkness, and all visual stimulation was turned off. Only during COR and VOR adaptation trials was the visual stimulus used, but no recordings were made during these adapatation periods. The subject was asked to look in the direction of an imaginary target straight ahead throughout the recording trials, in order to reduce the number of spontaneous voluntary saccades. Prior to each measurement, this location was briefly indicated by a laser dot.

Neck mobility

In 16 healthy subjects, the eye movements were recorded in response to COR stimulation on three different time points: before, immediately after, and two hours after wearing a rigid cervical collar (Laerdal Stifneck® SelectTM, 4 Size) for two hours.

Analogous to Rijkaart et al. (2004), we normalized the change in gain (ΔG) by dividing the difference in gain between the two conditions by the gain in the first condition, in order to compare between subjects:

$$\Delta G_{AB} = \frac{Gain_B - Gain_A}{Gain_A}$$

The changes between COR gains between the three conditions were statistically compared using two-tailed Students' t-tests.

Muscle activity

In 8 healthy subjects, we recorded eye movements in response to COR stimulation simultaneously with neck EMG in two subsequent conditions. In the first condition (relax) subjects were instructed to relax their neck muscles while the chair was rotated for 120 s. Immediately thereafter, they were instructed to contract their neck muscles as much as possible by resisting neck movement while their body was again rotated by the chair for 120 s (tense condition). After a short period of rest for about 5 min, these two conditions were repeated.

For the time window, starting 5 s after the onset of chair rotation until 5 s before the end, the area under the curve was determined to represent the level of EMG activity during the condition. Across all subjects, we found a more than threefold increase in EMG activity in the tense condition.

For each muscle and every repetition separately, EMG values were subsequently normalized by dividing through the highest value found across the condition. The normalized changes in EMG activity (ΔEMG) for each muscle was calculated as follows:

$$\Delta EMG = \frac{EMG_{tense} - EMG_{relax}}{EMG_{max}}$$

We calculated the normalized changes in COR gains (ΔG) between the relax and the tense condition:

$$\Delta G = \frac{Gain_{tense} - Gain_{relax}}{Gain_{relax}}$$

The average normalized changes in EMG and in COR gain across the two repetitions were correlated across subjects.

COR adaptation

In 10 healthy subjects and 10 WAD patients eye movements in response to COR stimulation were recorded at two moments: before and immediately after presentation of the adaptation stimulus.

The adaptation stimulus consisted of a static visual target (white cross on a black screen, 0.7-by-0.7 degrees in size). Subjects were instructed to look at it continuously for 10 min while their body was passively rotated. In this way, a mismatch was created between the COR stimulation, which induced an eye movement reflex while the head was fixed, and the static visual stimulation, which induced no eye movements. Just below the cross a digital clock (1.2-by-3.8 degrees in size) was presented, counting down in seconds from 10 min, in order to motivate the subject. The normalized changes in COR gain between the two conditions were statistically analyzed using a two-tailed Students' t-test.

VOR adaptation

In 10 healthy subjects and 10 WAD patients eye movements in response to VOR stimulation were recorded before and after 45 min presentation of the adaptation stimulus. The adaptation stimulus consisted of a large projection of a movie ("Babe", © 2004 Universal Studios, without subtitles and with acoustics). We chose to project a movie rather than a static pattern in order to encourage subjects to attend to the visual stimulus for the full 45 min. The size of the movie display was

35.5-by-26.6 deg. The whole visual display oscillated with an amplitude of 5 degrees in phase with the chair movement using the mirror and stepping motor used for the visual projection. In this way, a mismatch is created between the VOR stimulation, which induces an eye movement reflex in the opposite direction of the head movements, and the visual stimulus that moves in the same direction as the head. Post-hoc, one WAD patient was excluded from analyses, due to technical failures during eye movement recordings.

RESULTS

Neck mobility

The gain values for healthy subjects before applying and after removal of the collar are plotted in figure 1A. A reduced neck mobility for two hours produced an increase in COR gain ($\Delta G = 0.99 \pm 0.27$ SEM, $p = 0.002$). Two hours after removal of the rigid collar, the COR gain showed a significant decrease when compared to the gain immediately after removal of the collar ($\Delta G = -0.23 \pm 0.079$, $p = 0.011$, Figure 1B) and was not significantly different from the baseline COR gain ($\Delta G = 0.39 \pm 0.19$, $p = 0.057$).

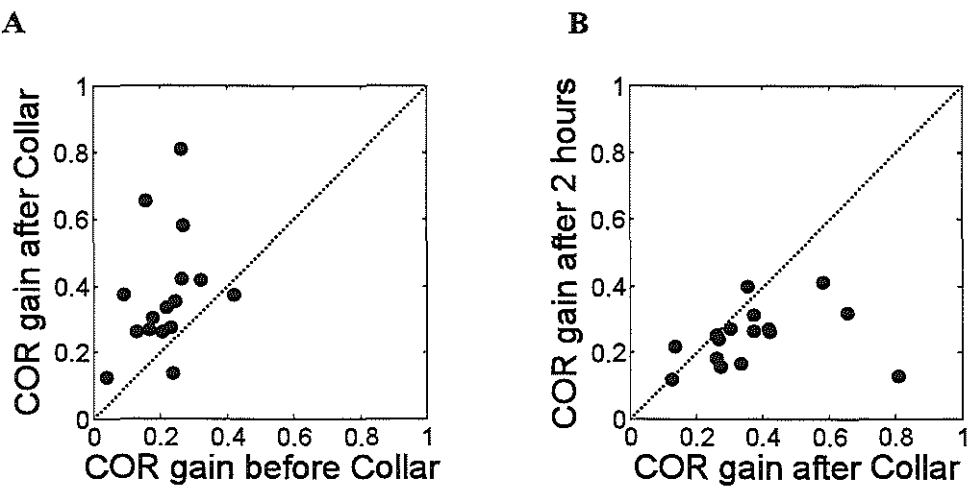


Figure 1. The cervico-ocular reflex (COR) gain values before wearing the cervical collar for two hours versus immediately after removal of the collar (A) and immediately after removal of the collar versus two hours later (B). Each dot represents one healthy subject. The dashed line is the unity line.

Muscle activity

The instruction to actively contract the neck muscles led on average to a more than threefold increase of EMG activity ($p < 0.001$). The results of the accompanying changes in the COR were variable, with the COR gain increasing in two subjects and decreasing in six (ΔG ranging between - 0.6 and 2.1). As an example, figure 2 shows the changes in EMG activity for the left sternocleidomastoid muscle and the changes in COR gain for all subjects. A higher muscle activity (ΔEMG) did not correspond with higher COR gain value (ΔG) in this particular muscle ($r = -0.21$, $p = 0.6$), nor in any of the other muscles (all p-values > 0.3)

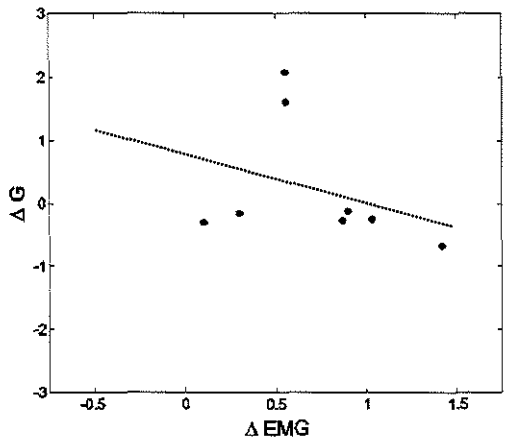


Figure 2.

The normalized changes in cervico-ocular reflex (COR) gain (ΔG) versus the normalized changes in electromyography (EMG) of the left sternocleidomastoid muscle between the two conditions of tense and relax (ΔEMG). Each dot represents one healthy subject.

COR adaptation

Ten minutes of concurrent visual and cervical simulation resulted in a significant decrease of COR gains in 10 healthy controls ($\Delta G = -0.19 \pm 0.06$, $p = 0.011$), but not in 10 WAD patients ($\Delta G = 0.13 \pm 0.24$, $p = 0.59$, Figure 3A). ΔG in the control group was significantly larger than in the patient group ($p < 0.05$).

VOR adaptation

Forty-five minutes of concurrent visual and vestibular stimulation resulted in a significant decrease in VOR gain in 10 healthy controls ($\Delta G = -0.20 \pm 0.072$, $p = 0.021$), but not in 9 patients ($\Delta G = 0.037 \pm 0.062$, $p = 0.57$, Figure 3B).

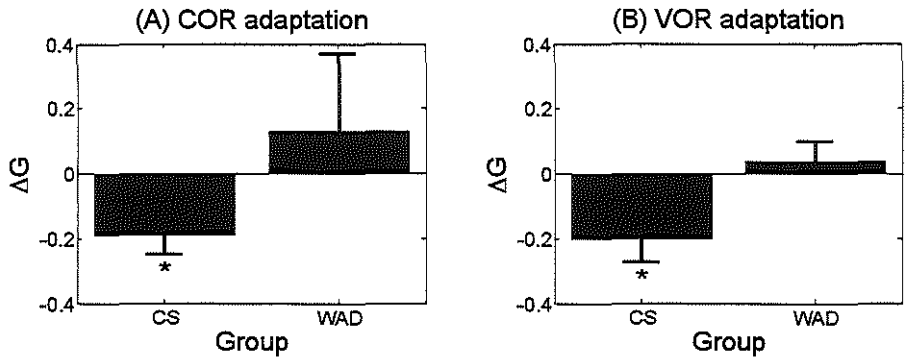


*Figure 3. The average changes in normalized gain (ΔG) after 10 min of cervico-ocular reflex (COR) adaptation (A) and after 45 min of vestibulo-ocular reflex (VOR) adaptation (B) of the two groups of subjects (healthy subjects and whiplash associated disorders (WAD) patients). Error bars represent standard deviations. Bars marked with a * represent significant changes in gain ($p < 0.025$).*

DISCUSSION

The aim of the experiments described here was to investigate the underlying mechanisms of the increased gains of the COR and the lack of synergy between the VOR and the COR in patients with WAD (Kelders et al., 2005).

One of the major complaints in WAD is neck pain, which may cause the commonly observed reduced neck mobility (Dall'Alba et al., 2001). We observed that such a reduced neck mobility, induced by a cervical collar for two hours, yielded an acute increase in COR gain. This acute effect was effectively abolished after two hours. The increase in COR gain may also be related to the increase in muscle activity, reflected by the decreased relaxation ability of the cervical trapezoid muscles in patients with whiplash injury complaints (Nederhand et al., 2000). This increased muscle activity could alter the proprioception of the neck. In our experiment, we did not observe any correlation between (superficial) muscle activity and COR gain. However, both the superficial and deep neck muscles contribute to rotation of the neck, both of which may be affected in WAD. The absence of a correlation between muscle activity and COR gain observed here does not rule out the possibility that the deep neck muscles are the major proprioceptive input for the COR, rather than the superficial sternocleidomastoid and upper trapezoid muscles we recorded from. Clearly, more sophisticated experiments are needed to fully address this issue. Nonetheless, in our opinion, these two experiments suggest that the increased COR

gain of WAD patients may be related to the reduced neck mobility of these patients, rather than an upregulation of the superficial neck muscle proprioceptors.

In healthy subjects, such an increase in COR gain is compensated for by a decrease in VOR gain, in order to maintain an optimal response to head and trunk movements. This negative correlation between COR and VOR can be observed in elderly subjects (Kelders et al., 2003) and in subjects with labyrinthine deficits (Bronstein and Hood, 1986, Huygen et al., 1991 Heimbrand et al., 1996), who both show increased COR gains that arguably compensate for the decline in VOR function. In the present data, we could not obtain a correlation between COR and VOR gain, since different subjects participated in the experiments.

It is likely that plasticity of the COR and/or the VOR is at the basis of this correlation. It has been shown that both the COR (Rijkaart et al., 2004) and the VOR (Zee, 1989; Koizuka et al., 2000; Shelhamer et al., 2002; Watanabe et al., 2003) can be modified after visual stimulation that is presented concurrently with cervical and vestibular stimulation, respectively. However, we observed that WAD patients were unable to modify both the COR and the VOR eye movement responses, in contrast to healthy control subjects. It might be that the adaptation processes of the COR and the VOR take more time than 10 and 45 min, respectively, to operate adequately in WAD patients.

The absence of VOR adaptation may be a result from the limited neck motion in WAD patients. In order to adapt, the VOR system must be confronted with mismatches between the intended reflex and the actual reflex. The VOR is most effective at high movement speeds, and VOR plasticity is most readily observed at high frequencies (Tabak et al., 1997). Therefore, a limited neck motion of WAD patients may not provide optimal stimulation for the VOR adaptation process. So far, no data exist as to whether WAD patients actually move their neck less in normal life. However, the limited range of motion (Dall'Alba et al., 2001) and neck pain (Spitzer et al., 1995) make this a likely option.

It has to be noted that the stimulation velocities for the two eye movement reflexes were quite low. Such low velocities might not provide the optimal stimulus conditions for VOR adaptation in WAD. However, in both controls and patients, significant eye movement reflexes were observed, and the stimulus protocols induced adaptation for both reflexes in the control group.

We can only speculate about the neurophysiological underpinnings of the absence of COR and VOR adaptation in WAD patients. The COR shares most of its neural pathways with the VOR, including the cerebellar cortex which is essential for VOR

adaptation (Blazquez et al., 2004). Therefore, it could be that a cerebellar disturbance underlies the absence of adaptation of both the COR and VOR. However, cerebellar disturbances, such as ataxia, are not commonly observed in WAD.

Our data suggest that the elevated COR gains observed may be induced by a reduced neck mobility in WAD patients. However, their change in COR function is not compensated for by a change in VOR function. The lack of adaptation can lead to a reduced synergy between the two stabilization reflexes, which may underlie several of the symptoms observed in WAD, such as visual disturbances, vertigo, and dizziness (Eck et al., 2001).

REFERENCES

Blazquez, PM, Hirata Y, Highstein SM (2004). The vestibulo-ocular reflex as a model system for motor learning: what is the role of the cerebellum? Cerebellum 3(3):188-192.

Bronstein AM, Hood JD (1986). The cervico-ocular reflex in normal subjects and patients with absent vestibular function. Brain Res 373(1-2):399-408.

Dall'Alba PT, Sterling MM, Treleaven JM, Edwards SL, Jull GA (2001). Cervical range of motion discriminates between asymptomatic persons and those with whiplash. Spine 26(19):2090-2094.

Eck JC, Hodges SD, Humphreys SC (2001). Whiplash: a review of a commonly misunderstood injury. Am J Med 110(8):651-656.

Heimbrand S, Bronstein AM, Gresty MA, Faldon ME (1996). Optically induced plasticity of the cervico-ocular reflex in patients with bilateral absence of vestibular function. Exp Brain Res 112(3):372-380.

Huygen PL, Verhagen WI, Nicolasen MG (1991). Cervico-ocular reflex enhancement in labyrinthine-defective and normal subjects. Exp Brain Res 87(2):457-464.

Kelders WP, Kleinrensink GJ, van der Geest JN, Feenstra L, de Zeeuw CI, Frens MA (2003). Compensatory increase of the cervico-ocular reflex with age in healthy humans. J Physiol 553(Pt 1):311-317.

Kelders WP, Kleinrensink GJ, van der Geest JN, Schipper IB, Feenstra L, de Zeeuw CI, Frens MA (2005). The cervico-ocular reflex is increased in whiplash injury patients. J Neurotrauma 22(1):133-137.

Koizuka I, Katsumi N, Hattori K, Okada T, Kato I (2000). Effect of adaptive plasticity of linear vestibulo-ocular reflex upon angular vestibulo-ocular reflex. Auris Nasus Larynx 27(2):89-93.

Montfoort I, Kelders WP, van der Geest JN, Schipper IB, Feenstra L, de Zeeuw CI, Frens MA (2006). Interaction between ocular stabilization reflexes in patients with whiplash injury. Invest Ophthalmol Vis Sci. 47(7),2881-2884.

Nederhand MJ, IJzerman MJ, Hermens HJ, Baten CTM, Zilvold G (2000). Cervical muscle dysfunction in the chronic whiplash associated disorder grade II (WAD-II). Spine. 25(15), 1938-1943.

Rijkaart DC, van der Geest JN, Kelders WP, de Zeeuw CI, Frens MA (2004). Short-term adaptation of the cervico-ocular reflex. Exp Brain Res 156(1):124-128.

Shelhamer M, Peng GC, Ramat S, Patel V (2002). Context-specific adaptation of the gain of the oculomotor response to lateral translation using roll and pitch head tilts as contexts. Exp Brain Res 146(3):388-393.

Spitzer WO, Skovron ML, Salmi LR, Cassidy JD, Duranceau J, Suissa S, Zeiss E (1995). Scientific monograph of the Quebec Task Force on whiplash associated disorders: redefining "whiplash" and its management. Spine 20(8 Suppl):1S-73S.

Tabak S, Collewijn H, Boumans LJ, van der Steen J (1997). Gain and delay of human vestibulo-ocular reflexes to oscillation and steps of the head by a reactive torque helmet. I. Normal subjects. Acta Otolaryngol 117(6):785-795.

Van der Geest JN, Frens MA (2002). Recording eye movements with video-oculography and scleral search coils: a direct comparison of two methods. J Neurosci Methods 114(2):185-195.

Watanabe S, Hattori K, Koizuka I (2003). Flexibility of vestibulo-ocular reflex adaptation to modified visual input in human. Auris Nasus Larynx 30 Suppl:S29-34.

Zee DS (1989). Adaptation and the ocular motor system. Bull Soc Belge Ophtalmol 237:191-207.

CHAPTER 5

Visual search deficits in Williams-Beuren syndrome

ABSTRACT

Williams-Beuren syndrome (WBS) is a rare genetic condition characterized by several physical and mental traits, such as a poor visuo-spatial processing and a relative strength in language. In this study we investigated how WBS subjects search and scan their visual environment.

We presented 10 search displays on a computer screen to WBS subjects as well as control subjects, with the instruction to find a target out of several stimulus elements. We analyzed the eye movement patterns for fixation characteristics and systematicy of search. Fixations generally lasted longer in WBS subjects than in control subjects. WBS subjects made more fixations at a stimulus element they had already looked at and more fixations that were not aimed at a stimulus element at all, decreasing the efficiency of search. These outcomes lead to the conclusion that visual search of individuals with Williams-Beuren syndrome is less effective than in control subjects. This finding may be related to their motor deficits, an impaired processing of global visual information and/or deficits in working memory and could reflect impairments within the dorsal stream.

INTRODUCTION

Williams-Beuren syndrome (WBS) is characterized by several features, such as a facial dysmorphology, congenital heart disease, a general mental retardation with a poor visuo-spatial processing and a relative strength in language (Bellugi et al., 2000; Mervis et al., 2000; Meyer-Lindenberg et al., 2006). Genetically, a 1-2 Mb deletion on the long arm of chromosome 7, band 7q11.23 is observed in 95% of the subjects with WBS (Korenberg et al., 2000; Osborne and Pober, 2001). This deletion includes, among others, the genes ELN (encoding elastin), CYLN2 (cytoplasmic linker-2 gene encoding the protein CLIP-115), LIMK1 (encoding Lim-1 Kinase) and GTF2I (encoding the proteins BAP-135 and TFII-I).

It has been reported that the impaired visuo-spatial processing in WBS subjects appears especially in processing the global visual information relative to local information (Bihrle et al., 1989). This impairment is seen as the incapability to process the spatial relations between several local elements in a scene (Bellugi et al., 2000; Bihrle et al., 1989; Georgopoulos et al., 2004). For instance, when asked to reproduce a drawing, WBS subjects often copy local elements without a global coherence. In other words, these drawings consist of a rich collection of fragmented details that are not always in the right position relative to each other (Bihrle et al., 1989). Furthermore, subjects with WBS show specific deficits in visual spatial working memory. In a visual spatial learning test WBS subjects were less able to recognize the location of a previously seen object positioned in one out of four quadrants (Vicari et al., 2005). Also mild motor activity problems in which visual spatial information is needed, such as walking down steps, are commonly observed in individuals with Williams-Beuren syndrome (Van der Geest et al., 2005; Withers, 1996). The deficits of visuo-spatial functioning in WBS have been attributed to functional deficits in the fronto-parietal circuits within the dorsal stream of spatial processing (Atkinson et al., 2003).

Both visual spatial processing and working memory are likely to be critically involved in (serial) visual search. Serial search is defined as looking with saccadic eye movements (or attention shifts) for potentially interesting parts of the visual environment, one item after another, until the object of interest has been found. These kind of serial search tasks often occur in ordinary life (Land et al., 1999), i.e., when one is looking for a pencil on a desk. In-between the saccadic eye movements, people observe the outside world by foveal fixation, during which detailed information about an object can be extracted. When this information has been

gathered sufficiently, a new saccade can be made to another part of the visual scene. The consecutive movements follow a certain path, the so-called scan-path (Noton and Stark, 1971) that consists of a more or less organized plan for an entire sequence of saccades. Processing and remembering the relative spatial locations of the objects within a scene can eliminate ineffective saccades toward already fixated objects during visual search (McCarley et al., 2003).

So, in serial visual search perceptual processes, working memory and the oculomotor system act in conjunction. Moreover, visual search induces ample activation of parietal and frontal areas within the dorsal stream (Gitelman et al., 2002). Hence, the impairments within the dorsal stream, as suggested by the deficits in visual-spatial processing and working memory, may hamper the effectiveness of visual search in WBS.

In this chapter we investigated how WBS subjects search and scan their visual environment. Since saccadic search behavior is readily quantifiable by means of an eye-tracking device, it can be used to map the search behavior of WBS subjects quantitatively. This approach has the advantage that putative differences in search efficiency can be attributed to specific quantitative factors in the search behavior such as the number, the spatial distribution and the duration of fixations. We hypothesized that visual search in WBS will be less efficient than in normal controls.

METHODS

Subjects

Informed consent was obtained from 58 subjects. This study was approved by the Ethical committee of the Erasmus MC, according to standards laid down in the declaration of Helsinki (1964).

The 32 individuals with Williams-Beuren Syndrome (WBS; 8-41 years of age, 15 subjects below 18 years of age) all showed a submicroscopic deletion on chromosome 7, band 7q11.23 using FISH (fluorescence in situ hybridization). The subjects were contacted through the Dutch Williams subjects Association. The 21 control subjects (CS; 18-44 years of age) were recruited from the Erasmus MC. Because WBS subjects have a lower IQ (Bellugi et al., 2000) compared to our control subjects, we included a small control group of 5 extra subjects (QL) with a lower IQ (16-19 years of age, IQ-range: 66-85) with an unknown aetiology. These five subjects were recruited from a special ability clinic.

The visual acuity of all subjects was estimated using the Landolt-C test and was

good enough to perform the task (WBS: 0.79 ± 0.29 SD, versus 0.86 ± 0.28 SD in controls, $p = 0.2$). All subjects could reliably make saccadic eye movements toward visual targets (van der Geest et al., 2004).

Apparatus

Subjects were seated with their head in a chinrest to restrain head movements. Vision was monocular with the dominant eye. The other eye was patched. Eye position was calibrated using a built-in automatic routine, based on a 3x3 array of fixation positions. The search displays were presented on a 1024 x 768 pixel resolution 21-inch computer screen at a distance of 70 cm from the subjects. Monocular gaze positions were recorded using infrared video-oculography (EyeLink 2.04, SensoMotoric Instruments, Berlin, Germany (Van der Geest and Frens, 2002)) at a sample rate of 250 Hz.

Stimuli

A search display consisted of a number of differently shaped small stimulus elements (squares, triangles and circles; about 0.3 degrees of visual angle) placed against a homogeneous gray background. The distance between stimulus elements ranged from 3.8 to 28 degrees. Every search display was composed of 4 to 11 white stimulus elements and one red stimulus element. This red stimulus element functioned as a pop-out stimulus element and was only meant to attract the first saccade within a new stimulus (D'Zmura, 1991), in order to reduce the chance that the subject looked at the target straight away. The presence of the pop-out stimulus was not mentioned to the subjects explicitly, and served only to lengthen the average visual search patterns toward the target. The target which the subject had to find was one white stimulus element that had a black spot in the middle. The black spot (size 0.03 degrees in diameter) was so small that foveal vision was required to identify it. In total there were ten different visual search displays (see figure 1 for an example).

Paradigm

The procedure of the experiment was explained to the subject. One exemplary search display was shown and the subject had to point manually toward the target. If this was done correctly the experiment itself was started.

The experiment consisted of ten trials. Preceding every trial a small black circle was shown in the center of the screen. This small circle was shown for drift correction purposes, and ensured that every trial started from the center of the screen. Note

that there were no stimulus elements at this location in any of the search displays. When the subject fixated this circle properly, the circle was removed and one of the ten search displays was shown for five seconds. In every display the subject was asked to look for the target and he or she was instructed to keep fixating at it after reaching it. The same ten displays in the same order were shown to each subject. Due to the short concentration span of WBS subjects, only a limited number of search displays could be shown (although the alleged problems of sustained attention in WBS was not reflected by a decrease in performance during the experiment).

ANALYSIS

Saccadic eye movements were marked in the data using a velocity criterion of 30 degrees per second. The data in between saccades after removal of blinks were considered as fixations. For the calculation of mean fixation time and number of fixations we included only fixations with a duration that was longer than 80 ms, to exclude fixations that occurred before a small correction saccade.
Fixations were considered to be on a stimulus element when they were within a radial distance of 3 degrees of that stimulus element. If more than one stimulus element was within 3 degrees of the fixation position, the closest stimulus element was considered to be fixated. A similar criterion was used to determine separate fixations. Fixations nearby each other in time or place were considered as one. Although subjects were asked to keep fixating on the target once it was found, we considered the target to be located, when it was fixated for the first time. Search time to find the target, fixation duration, number of fixations and type of fixations (mis- and refixations) were investigated.
Two subjects, one from the WBS and one from the CS group, were excluded from the analysis due to a calibration error in the eye position recording. The data of the remaining 31 WBS subjects were statistically compared with the remaining 20 control subjects (CS) using two-tailed Students' t-tests. Although considering different parameters per subject would be a more classical approach and would provide information about individual differences, in the analyses subjects were pooled for each search trial. Otherwise most results would be incomplete because of low statistical power. After all, because of the low concentration span in WBS subjects a limited number of experiments could be performed.

fixation in each search display. This is defined as the time from presentation of the search display until the onset of the first saccade. From the literature is known that this first fixation in a new search environment has a special status, because it is prolonged with respect to the subsequent fixations (Hooge et al., 1999; Van Loon et al., 2002; Zingale and Kowler, 1987). Both in the WBS group and in the control group the duration of this first fixation was indeed longer than the average duration of the subsequent fixations (363 ± 6 ms vs. 337 ± 5 ms, respectively; Figure 3B). The difference between the WBS group and the control group just failed to reach significance ($p = 0.06$).

In about half of all the trials (58% in both groups) the first saccade was directed to the red pop-out stimulus element. No significant differences in first fixation durations were observed between these types of trials and the remainder of the trials in which the first saccade was not directed to the red pop-out.

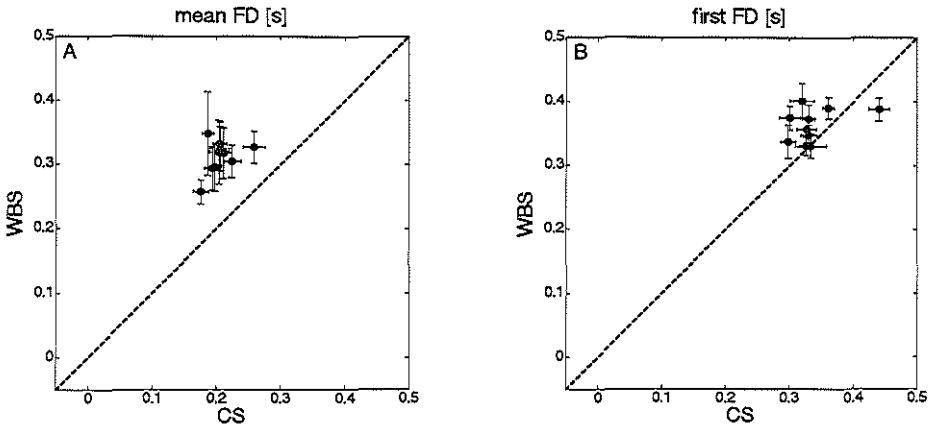


Figure 3. Fixation durations. Each point represents a search display. Errorbars indicate the SEM and the dotted line is the unity line. (A) Mean fixation duration of the subsequent fixations before the target is reached. (B) Duration of the first fixation.

Number of Fixations

We analyzed the number of fixations that were needed to find the target. In order to do so, we determined for each display the cumulative number (n) of fixations that were needed to find the target (Figure 4A) and the median value ($n_{0.5}$), similar to the analysis of the search time presented above. In all search displays the WBS group needed more fixations to find the target (Figure 4B). This value was on average 2.2 fixations higher for WBS subjects than for control subjects.

The finding that WBS subjects needed more fixations than controls can be attributed

to two factors. Firstly, they frequently fixated the same stimulus element more than once ('refixations'). Secondly, they fixated more often at locations where no potential target was shown ('misfixations'). Both types of fixation do not bring the eye to a possible target position and will therefore increase the search time and decrease systematicity.

The number of fixations needed increased with the number of display items in the search display (Figure 4C). The slopes of these relations were 1.4 (WBS) and 0.7 (CS) fixations/element, respectively. These values are noteworthy because they directly reflect search systematics. Assuming that observers process one stimulus element per fixation, systematic search (with perfect memory of visited locations) predicts a value of 0.5 whereas totally random search (without memory) predicts a value of 1 (Bloomfield, 1972; Gilchrist and Harvey, 2000). The slope of the relation in WBS subjects was significantly higher than 1 ($p = 0.03$). After removal of the misfixations no significant difference from 1 could be found ($p = 0.21$).

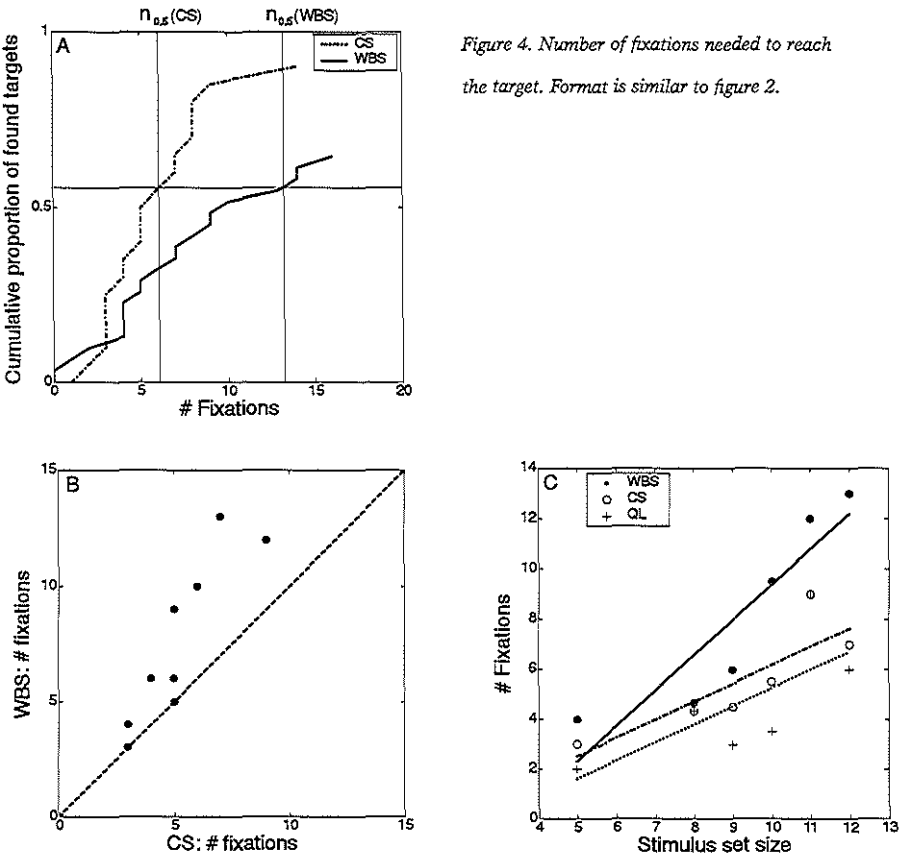


Figure 4. Number of fixations needed to reach the target. Format is similar to figure 2.

Figure 5 shows the frequency of occurrence of both types of fixations as a fraction of the total number of fixations. The average fraction of refixations in the WBS group was 0.13 (Figure 5A), which indicates that about one out of eight fixations was a refixation. The fraction of refixations was significantly higher in each individual search display (all $p < 0.0001$) compared to the control subjects (CS). Misfixations hardly occur in control subjects (Figure 5B), but constitute on average 13% of all fixations in the WBS group. This difference is significant in each individual search display for the whole group. So, one out of four fixations made by the WBS subjects were not directed to a possible target.
In order to determine the contribution of re- and misfixations we subtracted re- and misfixations from the total number of fixations. After removal WBS subjects do not need more fixations than healthy controls to find the target.

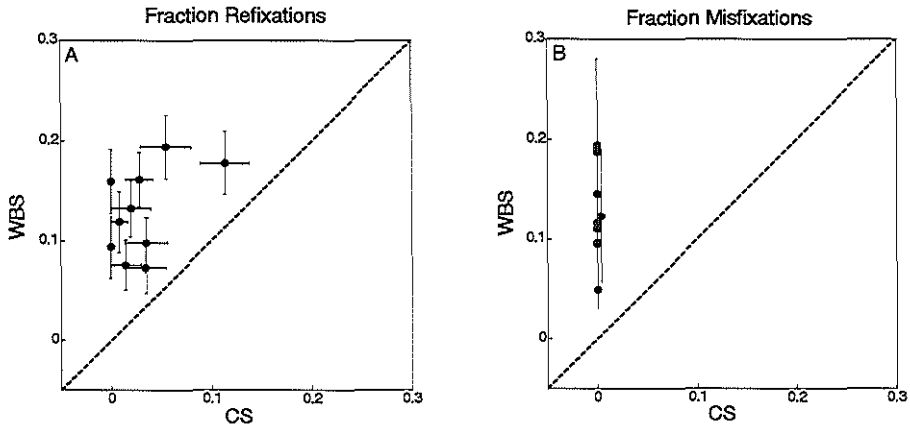


Figure 5. Re- and misfixations. (A) Fraction of refixations before the target is reached. (B) Fraction of misfixations before the target is reached. In both panels the format is similar to figure 3.

DISCUSSION

In this paper we investigated the visual search behavior of WBS subjects. Qualitatively, we clearly observed a difference in the scan-patterns between WBS subjects and controls in a visual search task. The scan-paths of the WBS subjects appeared less structured than those of controls (see figure 1). They often did not follow the logical pattern in which the complex stimulus display was laid out, they sometimes skipped stimulus elements and they looked at positions where there was no stimulus element at all. Furthermore, we compared WBS subjects and controls quantitatively with

respect to their fixation behavior. WBS subjects took on general longer to find the target, their individual fixations lasted longer, and they made more refixations and misfixations than controls. This also suggests that the visual search behavior was less systematic, since both refixations and misfixations direct the eyes to locations where there is no possible target.

The observed inefficient visual search behavior of WBS subjects may arise from inaccurate oculomotor control, and/or from impaired visual spatial processing and/or from deficits in visual spatial working memory.

Subjects with WBS indeed show mild inaccuracies in oculomotor control yielding some degree of saccadic dysmetria and a higher number of correction saccades before a saccadic target was reached (Van der Geest et al., 2004; Van der Geest et al., 2006). The saccadic behavior of WBS suggests a cerebellar component which is in line with molecular and morphological findings in WBS (Hoogenraad et al., 2002; Meyer-Lindenberg et al. 2006). However, the saccadic inaccuracies in WBS (estimated at maximum 2.5 degrees for the average saccades in the present experiment) are too mild to explain adequately the misfixations (more than 3 degrees off target) in the present experiment. Moreover, it cannot explain the less structured search behavior and the increase in number of saccades to already fixated targets.

To assess the contribution of impaired visual spatial processing on visual search behavior we looked at the durations of fixations. During a fixation at least two processes take place: a local inspection process and a global preparation process, which occur probably at least partly in parallel (Hooge et al., 1999; Viviani, 1990). During inspection the observer processes the local object of interest, i.e., the object on the fovea. During preparation the observer prepares the next saccadic eye movement to another part of the visual scene. The longer duration of fixations suggests that subjects with Williams-Beuren syndrome need more processing time during fixations. This is supported by the observation of the slightly increased saccadic reaction times towards single targets (Van der Geest, unpublished data). However, on the basis of our data it is impossible to distinguish between the two types of processing during a fixation.

It has been suggested that during the first fixation observers process the spatial properties of the whole scene, in order to plan (part of) the scan path in advance (Hooge et al., 1999; Motter and Belky, 1998; Van Loon et al., 2002; Zingale and Kowler, 1987). This is reflected by an elongated duration of the first fixation. Also in the Williams-Beuren group (as well as in the control groups) the duration of the first fixation was longer than the mean duration of the subsequent fixations. This

was independent of the total number of stimulus elements in the display and independent whether the first fixation was directed at the pop-out stimulus or not. However, the difference in duration between the first and other fixations seemed to be smaller in the WBS group than in the control group. This difference between the groups just failed to reach significance, which is probably caused by the low statistical power due to the limited number of trials. This trend might suggest that WBS subjects have problems in processing and remembering the spatial properties of the search display. This would be in good accordance with the abundant literature on visual spatial processing deficits in Williams-Beuren syndrome (Bellugi et al., 2000; Bihrle et al., 1989; Georgopoulos et al., 2004, Vicari et al., 2005).

Deficits in visual spatial working memory might contribute to the visual search anomalies in WBS, such as the observed increase in the number of refixations. Spatial working memory temporarily stores and processes small amounts of position information (Baddeley and Hitch, 1974) which can be used later on for the execution of a saccade. Working memory is thought to involve the frontal cortex and the parietal lobe. The first seems to play a part in dividing relevant from irrelevant object information (Soto et al., 2006). Within the parietal lobe, which is part of the dorsal processing stream, information about position of objects in relation to each other is encoded (Mishkin et al., 1983; Milner and Goodale, 1995).

It has been hypothesized that deficits within the dorsal stream contribute to the problems with visual spatial processing in WBS (Atkinson et al., 2003). Parietal lobe abnormalities have been reported in WBS, such as smaller superior parietal lobe gray matter volumes (Eckert et al., 2005) and isolated hypoactivation during fMRI of the parietal portion of the dorsal stream (Meyer-Lindenberg et al., 2004). Subjects with parietal damage showed deficits in remembering searched locations and, similar to our WBS subjects, frequently looked at locations that had already been searched (Husain et al., 2001). Deficits in parietal lobe functioning and spatial working memory might therefore account for the high number of refixations.

The occurrence of misfixations are rather suggestive of deficits on a more perceptual or visuo-motor level. These misfixations contribute to the apparently random scan path observed in our WBS group. In random search the assumption is made that every single fixation is aimed at a stimulus element, i.e., there are no misfixations during random search. Therefore, the ratio between number of fixations and number of stimulus elements will be about 1. However, the search behavior of WBS subjects was not better than would be expected on the basis of random search behavior without a memory, even after removal of the misfixations. Including these

misfixations, the performance of WBS subjects was even worse than random (see Figure 4C). In other words, their visual search behavior did not show clear signs of an adequate memory for already fixated stimulus elements.

One could argue that the differences in search behavior between WBS subjects and controls are not due to the specific deficits of Williams-Beuren syndrome, but rather to differences in IQ or mental age. We believe that this is not the case. Qualitively the search patterns in low-IQ controls looked similar to normal controls. In both groups hardly any misfixations or refixations were seen in contrast to the WBS group and most saccades went to the nearest adjacent distractor. Separate quantitative analysis of the low-IQ group did not show an impaired search performance. Moreover, in some aspects they performed even better than the normal control group (Table 1).

In conclusion, the efficiency of visual search is decreased in WBS subjects. They need almost three times as much time to process a visual scene and show a substantial increase in both fixation durations and number of fixations, when compared to controls. This reflects their known deficits in visual spatial processing and working memory. Their ineffective visual search may hamper the fast and detailed inspection of their visual environment.

REFERENCES

Atkinson J, Braddick O, Anker S, Curran W, Andrew R, Wattam-Bell J, Braddick F (2003). Neurobiological models of visuospatial cognition in children with Williams syndrome: measures of dorsal-stream and frontal function. Dev Neuropsychol 23(1-2):139-172.

Baddeley AD, Hitch G (1974). Working memory. In G.A. Bower (ed.), The Psychology of Learning and Motivation, Vol. 8, pp. 47-90. New York: Academic Press.

Bellugi U, Lichtenberger L, Jones W, Lai Z, St George MI (2000). The neurocognitive profile of Williams Syndrome: a complex pattern of strengths and weaknesses. J Cogn Neurosci 12 Suppl 1:7-29.

Bihrle AM, Bellugi U, Delis D, Marks S (1989). Seeing either the forest or the trees: dissociation in visuospatial processing. Brain and Cognition 11(1):37-49.

Bloomfield JR (1972). Visual search in complex fields: size differences between target disc and surrounding discs. Hum Factors 14(2):139-148.

D'Zmura M (1991). Color in visual search. Vision Res 31(6):951–966.

Eckert MA, Hu D, Eliez S, Bellugi U, Galaburda A, Korenberg J, Mills D, Reiss AL (2005). Evidence for superior parietal impairment in Williams syndrome. Neurology, 64(1):152-153.

Georgopoulos MA, Georgopoulos AP, Kurz N, Landau B (2004). Figure copying in Williams syndrome and normal subjects. Exp Brain Res 157(2):137-146.

Gilchrist ID, Harvey M (2000). Refixation frequency and memory mechanisms in visual search. Curr Biol, 10(19):1209-1212.

Gitelman DR, Parrish TB, Friston KJ, Mesulam MM (2002). Functional Anatomy of Visual Search: Regional Segregations within the Frontal Eye Fields and Effective Connectivity of the Superior Colliculus. NeuroImage 15(4): 970-982.

Hooge IT, Beintema JA, van den Berg AV (1999). Visual search of heading direction. Exp Brain Res 129(4): 615-628.

Hoogenraad CC, Koekkoek B, Akhmanova A, Krugers H, Dortland B, Miedema M, van Alphen A, Kistler WM, Jaegle M, Koutsourakis M, van Camp N, Verhoye M, van der Linden A, Kaverina I, Grosveld F, de Zeeuw CI, Galjart N (2002). Targeted mutation of Cyln2 in the Williams syndrome critical region links CLIP-115 haploinsufficiency to neurodevelopmental abnormalities in mice. Nat Genet 32(1): 116-127.

Husain M, Mannan S, Hodgson T, Wojciulik E, Driver J, Kennard C (2001). Impaired spatial working memory across saccades contributes to abnormal search in parietal neglect. Brain 124(Pt 5):941-52.

Korenberg JR, Chen XN, Hirota H, Lai Z, Bellugi U, Burian D, Roe B, Matsuoka R (2000). Genome structure and cognitive map of Williams syndrome. J Cogn Neurosci 12(Suppl 1):89-107.

Land M, Mennie N, Rusted J (1999). The roles of vision and eye movements in the control of activities of daily living. Perception 28(11):1311-1328.

McCarley JS, Wang RF, Kramer AF, Irwin DE, Peterson MS (2003). How much memory does oculomotor search have? Psychol Sci 14(5):422-426.

Mervis CB, Robinson BF, Bertrand J, Morris CA, Klein-Tasman BP, Armstrong SC (2000). The Williams syndrome cognitive profile. Brain and Cogn 44(3): 604-628.

Meyer-Lindenberg A, Kohn P, Mervis CB, Kippenhan JS, Olsen RK, Morris CA, Berman KF (2004). Neural basis of genetically determined visuospatial construction deficit in Williams syndrome. Neuron 43(5):623-631.

Meyer-Lindenberg A, Mervis CB, Berman KF (2006). Neural mechanisms in Williams syndrome: a unique window to genetic influences on cognition and behavior. Nat Rev Neurosci 7(5):380-393.

Milner AD, Goodale MA (1995). The visual Brain in Action. Oxford University Press.

Mishkin M, Ungerleider L, Macko KA (1983). Object vision and spatial vision: two cortical pathways. Trends Neurosci 6:414-417.

Motter BC, Belky EJ (1998). The guidance of eye movements during active visual search. Vision Res 38(12):1805-1815.

Noton D, Stark L (1971). Scanpaths in eye movements during pattern perception. Science 171(968):308-311.

Osborne L, Pober B (2001). Genetics of childhood disorders: XXVII. Genes and cognition in Williams syndrome. J Am Acad Child Adolesc Psychiatry 40(6):732-735.

Soto, D, Humphreys GW, Heinke D (2006). Dividing the mind: The necessary role of the frontal lobes in separating memory from search. Neuropsychologia 44(8):1282-1289.

Van der Geest JN, Frens MA (2002). Recording eye movements with video-oculography and scleral search coils: a direct comparison of two methods. J Neurosci Methods 114(2):185-195.

Van der Geest JN, Lagers-van Haselen GC, van Hagen JM, Govaerts LC, de Coo IF, de Zeeuw CI, Frens MA (2004). Saccade dysmetria in Williams–Beuren syndrome. Neuropsychologia 42(5):569–576.

Van der Geest JN, Lagers-van Haselen GC, van Hagen JM, Brenner E, Govaerts LC, de Coo IF, Frens MA (2005). Visual depth processing in Williams–Beuren syndrome. Exp Brain Res 166(2):200–209.

Van der Geest JN, Lagers-van Haselen GC, Frens MA (2006). Saccade adaptation in Williams-Beuren syndrome. Invest Ophthalmol Vis Sci 47(4):1464-1468.

Van Loon EM, Hooge IT, van den Berg AV (2002). The timing of sequences of saccades in visual search. Proc Biol Sci 269(1500):1571-1579.

Vicari S, Bellucci S, Carlesimo GA (2005). Visual and spatial long-term memory: differential pattern of impairments in Williams and Down syndromes. Dev Med Child Neurol 47(5):305-311.

Viviani P (1990). Eye movements in visual search: cognitive, perceptual and motor control aspects. Rev Oculomot Res 4: 353-393.

Withers S (1996). A new clinical sign in Williams syndrome. Arch Dis Child 75(1):89.

Zingale CM, Kowler E (1987). Planning sequences of saccades. Vision Res 27(8):1327-1341.

C H A P T E R 6

Discussion

GENERAL DISCUSSION

In the past chapters we have investigated eye movement behaviour in individuals with Williams-Beuren (WBS) syndrome, whiplash injury (WAD) patients and healthy controls. We have shown that adaptation of the VOR is an individual characteristic feature. Analyses of eye movement recordings have indicated a lack of adaptation and a lack of synergy of two ocular stabilisation reflexes in WAD patients. Furthermore, we observed a decreased efficiency of visual search in individuals with WBS. Finally, we have learned from the ceasing of our randomized clinical trial in WAD-patients. Below, the results and their implications are evaluated and recommendations for future studies are made.

Lack of synergy between ocular stabilisation reflexes in whiplash injury patients

Our data in chapter 3 confirm the results reported by Kelders et al. (2005). Compared to healthy controls in WAD patients, the COR gain values were significantly increased. Also in elderly and bilateral labyrinthine defective subjects a higher COR gain has been found (Kelders et al., 2003; Bronstein and Hood, 1986; Bronstein et al., 1995; Huygen et al., 1991; Bouyer and Watt, 1999). In the latter groups the elevated COR gain partly compensates for the diminished VOR ((Bronstein and Hood, 1986; Huygen et al., 1991; Heimbrand et al., 1996). After restoration of the vestibular function, the COR gain decreases again (Bronstein et al., 1995). In healthy controls both the VOR (Zee, 1989; Koizuka et al., 2000; Shelhamer et al., 2002; Watanabe et al., 2003) and the COR (Rijkaart et al., 2004) are able to adapt, suggesting a synergy between these two stabilization reflexes. Synergy means that when the VOR gain is relatively low, the COR gain is high and vice versa. In our study, despite the higher COR gain, the values of the VOR seemed to be unaffected in WAD patients.

A decreased mobility of the neck, insufficient head motion or disorganisation of plastic modifications in the reflex pathway might explain the lack of synergy.

Reduced neck mobility increases COR gain

Many whiplash injury patients report neck pain, which might result in reduced neck mobility (Spitzer et al., 1995) and subsequently leads to alteration in proprioception of the neck. This, in turn, may result in an increase in COR gain. In chapter 4, we actively diminished the neck mobility of healthy controls by making them

wear a cervical collar for two hours. Which lead to a significant rise in COR gain. This effect was reversible: the COR gain declined two hours after the cervical collar was removed. Therefore, the higher COR gain observed in WAD patients could be induced by insufficient head motion. On the other hand, it may well be that the VOR needs a certain level of adaptive input, which is lacking in WAD patients due to a diminished neck motion. Both the limited range of motion (Dall'Alba et al., 2001) and the neck pain (Spitzer et al., 1995) makes this plausible. Reduced neck motion may render the vestibular information inadequate to induce alterations in VOR gain. The VOR responds best to high frequency input (Tabak et al., 1997), while the COR performs best at low velocities. However, whether the higher COR gain arises on the basis of neck stiffness itself or too little head movement remains to be elucidated. Whether in daily life whiplash injury patients actually limit their neck motion has not been demonstrated.

In the prospective randomised controlled clinical trial, described in chapter 2, 120 individuals with whiplash injury complaints would have been subjected to a variety of tests. Also the cervical range of motion at the various time intervals was to be determined. We planned to correlate the degree of limitation of the neck mobility to the gain value of the COR. Additionally, we wanted to invite individuals with asymptotic chronic neck pain to participate. It was hypothesized that if these latter persons also would show a higher COR gain, a disorganisation of the plasticity in the COR related neural reflex pathways could still be present in patients with WAD, but it would make the other causes, neck stiffness and/or insufficient head motion, more likely. Therefore, it would still be valuable to fulfil such a clinical trial.

Relationship muscle activity and COR gain

In chapter 4 we investigated whether the higher COR gain in WAD patients might result from an increase in cervical muscle activity. Nederhand et al. (2000) found a decreased relaxation ability of the cervical trapezoid muscles in both whiplash injury patients and persons with non-specific chronic neck pain (Nederhand et al., 2002). Furthermore, he reported that WAD patients grade 2 tend to activate their cervical muscles (Nederhand et al., 2002). Perhaps a higher muscle activity may alter the information from the neck proprioceptors.

In our study we found no correlation between (superficial) cervical muscle activity and COR gain. This lack of correlation however does not eliminate the above-mentioned hypothesis, since not only superficial neck muscles (sternocleidomastoid,

trapezoid), but also deeper located neck muscles (such as for example the splenius capitis muscle and semispinalis capitis muscle) contribute to neck rotation. Both muscle layers could be affected in whiplash injury patients. Furthermore, the influence of active cervical muscle contraction on the tension of the muscle spindles might be small because of the adjusting counterbalancing effect of gamma motor neurons.

Since surface electrodes mainly reflect superficial muscle activity, the effect of contraction of the deep neck muscles on the COR remains unclear. Ideally, EMG of all participating cervical muscles should be determined. Therefore, a needle electrode should be inserted into the muscle tissue to prevent cross-talk between the various muscles. However, recently Stoykov et al. (2005) succeeded in recording intramuscular EMG, using conventional surface electrodes. Despite the lack of precise information on the contractile characteristics of the various neck muscles, findings from the "cervical collar" and "EMG" exeriments together with earlier reported results on the limited range of motion (Dall'Alba et al., 2001) suggest that in patients with WAD the reduced neck mobility induces the rise in COR gain.

Future experiments as described in chapter 4 with the usage of either needle electrodes or the latter new technique in both whiplash injury patients and healthy controls could provide more information about the relaxation ability as well as the activation pattern of the multilayered cervical muscles.

Lack of adaptation of COR and VOR in whiplash injury patients

Both the COR (Rijkaart et al., 2004) and the VOR (Zee, 1989; Koizuka et al., 2000; Shelhamer et al., 2002; Watanabe et al., 2003) can be modified after concurrent stimulation of visual and vestibular information. In contrast to healthy controls in our study neither the COR nor the VOR eye movement responses appeared to adapt in WAD patients. Possibly, in the patient group more time was needed than the used 10 or 45 minutes, respectively. These findings confirm our assumption that the increased COR gain in patients with WAD results from reduced neck mobility. The lack of modification possibly leads to the reduced synergy between the cervico- and vestibulo-ocular reflex.

Disturbances in cerebellar plasticity could be the cause of the lack of eye movement reflex adaptation. However, cerebellar disturbances, such as ataxia are not commonly observed in whiplash injury patients. Oppositely, several patients with WAD reported symptoms such as vertigo, dizziness and visual problems like reading problems (Eck et al., 2001). These symptoms could be explained by the diminshed capacitiy of eye

movent reflex adaptation. A suboptimal synergy between the COR and the VOR would likely reduce visual accuracy during movement. Together with the head and neck pain this may also lead to fatigue.

Since VOR plasticity is most effective at high movement frequencies (Tabak et al., 1997) one could argue that the frequency used in the VOR training paradigm is quite low and might be insufficient to induce VOR gain modification. Also the stimulus used for COR adaptation was small compared to the neck angle changes that typically occur in daily activities. However, since significant adaptation results were obtained in the group of healthy controls these arguments do not seem too valid.

The COR and VOR share a large fraction of their neural substrate (Gdowski et al., 2001). Since in healthy individuals the COR seems to respond to changes in VOR gain, possibly adaptation of the VOR transfers to the COR. The fact that whiplash injury patients cannot adapt both COR and VOR, is in line with the hypothesis of a common pathway for both eye movement reflexes. If the VOR is not plastic, then neither is the COR. This adaptation transfer can be tested in healthy subjects by examining the COR gain values before and after performing the VOR adaptation paradigm. Likewise, also the reverse process could be hypothesized. However, despite the fact that the COR can adapt within ten minutes (Rijkaart et al., 2004), it has to be taken into account that a longer time frame (about one hour) is needed for the VOR to adjust.

Since whiplash injury presumably affect the cervical extensor and flexor muscles, it would seem justified to assess the vertical VOR and COR. In our lab this has never been performed due to incapability of our experimental set-up for such recordings. To record the vertical COR an apparatus is needed to rotate the human body in a controlled manner against gravity, while the head is held still. For determination of the vertical VOR a similar complex apparatus should be build, but unlike above in which the head would be rotated vertically instead of the body. Likewise, for the same technical reason, never was the combined VOR and COR gain assessed to see whether this joined gain in whiplash injury patients was higher than required.

Since in daily life, all three ocular stabilisation reflexes collaborate to maintain a stable image on the retina, one could wonder about the OKR. After all, just like the

VOR also the optokinetic reflex declines with older age, which also seems to be induced by sensory loss (Paige, 1994; Kelders et al., 2003). Furthermore, an increase in OKR gain can be induced by a VOR adaptation paradigm, irrespective whether the adaptation was intended to rise or lower the gain of the vestibulo-ocular reflex (Collewijn and Grootendorst, 1979; Nagao, 1983). The other way around, adaptation of the OKR also induces a rise of the VOR gain (Collewijn en Grootendorst, 1979; Schairer and Bennett, 1986; Marsh and Baker, 1997). Mutual transfer between both eye movement reflexes has been suggested, since both the OKR and VOR pathway converge in the vestibular nuclei and the cerebellar flocculus (Collewijn and Grootendorst, 1979; Schairer and Bennett, 1986; Marsh and Baker, 1997). Finally, adaptation of both OKR and VOR is frequency specific (Collewijn and Grootendorst, 1978; Schairner and Bennett, 1986; Nagao, 1989; Iwashita, 2000).

Learning points and recommendations on performing clincical trials in patients with WAD

Inclusion problems of whiplash injury patients forced us to cease our randomized controlled clinical trial one year after the start. The overall aim of the clinical trial was to determine the effectiveness of proprioceptive training (performed by physiotherapists) compared to usual care (given by general practitioners) on the development of chronic complaints of WAD and to find out to what extent psychosocial indicators can influence the complaints of whiplash injury patients. The proprioceptive training specifically aimed at restoring cervical muscle stabilization.

It proved to be too difficult to recruit enough WAD patients, despite the preceding investigation of social relevance and feasibility. Additional recruitment efforts did not increase patient inflow. Eventually, terminating the trial prematurely became inevitable. Although various studies reported successful patient recruitment (Borchrevink et al.,1998; Rosenfeld et al., 2000), several problematic enrollments of WAD patients have also been published (Scholten-Peeters et al., 2006; Van der Windt et al., 2000).) However, these successful studies and patient recruitment occurred a decade ago. Possibly Lasagna's Law (Gorringe, 1970; Huibers et al., 2004), an abrupt draw back in the number of potential patients just after the beginning of the trial, emerged, even though our preliminary calculations were based on conservative estimations of whiplash incidence.

The incidence of whiplash injury varies greatly between different parts of the world with rates between 70 in Quebec (Spitzer et al., 1995), 106 in Australia (Mills

and Horne, 1986) and 94-188 per 100.000 inhabitants in the Netherlands (Wismans and Huijkens, 1994). More recent figures found that in the Netherlands annually 8 percent of the 600.000 insurance claims concern car crashes (CEA Insurers of Europe, 2002). 40 percent of these car crash insurance claims concerned patients with WAD. The estimated annual incidence of people suffering from WAD can therefore be estimated at 19.200 in the Netherlands. In the Netherlands, 40 percent of the total amount of 800 million euro insurance claims (320 million) paid concern WAD related claims (PIV-infosite, 2006).
A further cause of poor recruitment could be that whiplash injury is a decreasing syndrome these days. Whereas insurance companies disburse many claims because of neck complaints after car collisions, general practitioners report seeing on average one or two whiplash patients per year only (personal communication). Furthermore, it should be mentioned that recruiting eligible incident cases is more difficult than including prevalent cases (Van der Wouden et al., 2007).

More manpower (i.e. recruiting more general practitioners and/or collaborating emergency departments) could be put forward as a partial solution to the low attendance. Factors, such as a clear and simple protocol, demanding minimum effort of participating clinicians, carefully planning and monitoring the recruitment process and extra support to the eligible patients, who still have to decide whether to participate or not, might further improve recruitment (Ross et al., 1999). Furthermore, too stringent entry criteria could also hamper patient enrolment (Haidich and Ioannidis, 2001). In our clinical trial, relatively many patients willing to cooperate did not meet our inclusion criteria. Major reasons for exclusion were: collision appeared more than 3 months ago, subjects already had received a form of physiotherapy and no rear-end collision but frontally or sideways. Attractiveness of the protocol affects patient enrolment too (Haidich and Ioannidis, 2001). We hardly met eligible whiplash injury patients who refused participating in the clinical trial on forehand. However, we did have participants withdrawing from the trial after the start.

Also a doctor reminder (or clinical trial alert) system could be helpful. It reminds the doctor that the patient in his office might be suitable for the trial the physician is participating in. However, since general practitioners in the Netherlands make use of several different software programs, the implementation of such alert system might be difficult and forgetfulness or lack of time plays an important part in patient recruitment.

Finally, financing for participating the clinical trial would perhaps increase the recruitment number. In our study, when necessary (i.e. when not covered by their (health) insurance), travelling expenses and physiotherapy costs were reimbursed. However, extra allowance besides these expenses costs a lot of money. Funding agencies are not always willing to meet these financial needs.

The recently created international trial register for the registration of future prospective clinical trials should prevent from double studies and positive publication bias. (Controlled trials, 2006). However, at the moment registration of trials is voluntarily. Therefore, unless registration becomes obligatory some researchers will still be tempted to withhold negative experimental outcomes.

In spite of all research on whiplash injuries there is still no clear explanation for the various complaints. Often diagnostic techniques fail to identify any lesion or pain origin. Consequently the signs and symptoms are frequently indicated as of psychological origin or even as affectation. Sceptics could even mention mass illness or a trend. In a systematic review no clear influence of having an insurance claim on the prognosis of whiplash complaints could be found, although many people still assume such a relationship (Scholten-Peeters et al., 2003).

Since to date there is no objective treatment for whiplash injuries complaints, it would be useful to fulfil an analogous clinical trial. Also because in our design multiple factors would be taken into account, such as several signs and symptoms of whiplash injuries, cervical range of motion and eye movement reflex values could be correlated. Furthermore, the course of WAD could be monitored and linked to various aspects, such as reported complaints. Recently, a comparable trial has started with whiplash injury patients entering the Department of Rehabilitation.

Less effective visual search in individuals with WBS

The results described in chapter 5 indicate that visual search behavior of WBS subjects is less systematic compared to healthy controls. The qualitative less-structured scan-patterns already suggest that individuals with WBS search less efficient. Compared with healthy controls, WBS subjects made more fixations in general, consisting of more fixations at a stimulus element they already looked at (refixations) and more fixations that were not aimed at a stimulus element at all (misfixations).

Inaccurate oculomotor control, impaired visual spatial processing and deficits in visual spatial working memory could all or partly be responsible for this inefficient search pattern.

It could well be that mild saccadic dysmetria (Van der Geest et al., 2004; Van der Geest et al., 2006) increases the total number of fixations. However it cannot account for the higher number of misfixations, refixations and the more chaotic search behavior in general. These might result from the often reported visual spatial processing and/or visual spatial working memory deficits in WBS (Bellugi et al., 2000; Bihrle et al., 1989; Georgopoulos et al., 2004; Vicari et al., 2005; Hocking et al., 2008). Individuals with WBS might have problems in processing and remembering the spatial properties of the search display, suggested by the differences in the timing of the first saccade.

The increase in number of refixations could result from an impaired visual spatial working memory (Baddeley and Hitch, 1974). Both the frontal cortex, which is involved in separating relevant from irrelevant object information (Soto et al., 2006) and the parietal lobe, which is involved in encoding relative position information of objects (Mishkin et al., 1983; Milner and Goodale, 1995), are thought to be crucial for intact functioning of working memory (Owen et al., 1999; Berryhill and Olson, 2008). The visual search deficits observed in WBS may stem from dysfunctioning of either system. Parietal lobe abnormalities, such as smaller superior parietal lobe gray matter volumes (Eckert et al., 2005) and hypoactivation during fMRI of the parietal portion of the dorsal stream (Meyer-Lindenberg et al., 2004; Mobbs et al., 2007) have been reported in subjects with WBS. These findings corroborates with the alleged deficits within the dorsal stream involving planning and control of movement (Atkinson et al., 2003). Furthermore, parietal damage negatively affects the remembrance of searched locations (Husain et al., 2001). Patients with damage of the right intraparietal sulcus or right inferior frontal lobe much more often misjudge a refixated target as a new one (Mannan et al., 2005). In a sequentially presented short-term memory task WBS subjects performed worse than age matched healthy controls on the spatial condition as opposed to the visual part of the working memory task (Vicari et al., 2003). Indeed, the increase in number of refixations in the WBS group in our study might suggest poor spatial working memory. However, when the information was presented in parallel, an impaired memory for either spatial or visual information could not be found (Jarrold

et al., 2007). The lack of increase in number of refixations correlated with a rise in total number of stimulus elements indicate that the results found can not solely be ascribed to a selectively impaired working memory for spatial information. Whether the deviant visual search behavior reflects dorsal stream abnormalities or whether this is due to developmental anomalies of the visual system (Galaburda et al., 2002; Eckert et al., 2006) has to be established. Also abnormal neural connectivity has been proposed to be involved in the visuomotor deficits (Hocking et al., 2008). Furthermore, since projections from the cerbellar cortex to parietal brain regions have been reported (Allen et al., 2005; Clower et al., 2001), possibly dysfunction of the cerebellum or cerebellar-parietal connectivity problems might play a role in the visual search deficits. In the future fMRI studies could further elucidate this theory.

The occurrence of misfixations are rather suggestive of deficits on a more perceptual or visuo-motor level. The search performance of WBS subjects was worse than search behavior without a memory. Including the misfixations, this performance was even worse than random.

Since the search patterns in the low-IQ controls qualitively looked quite similar to normal controls and quantitative analyses of this low-IQ group did not reveil an impaired search performance, the differences in search behavior between healthy controls and the WBS-group can not be ascribed to differences in mental age or IQ. One could argue that deficits in sustained attention explain the impaired search process in the WBS group. However, no impaired search process was seen as function of trial number. This would be expected if shortness of concentration span would be the cause of bad search performance. With the expanding number of trials the search time in the WBS group did not increase compared to healthy controls.

The pattern of deficits of WBS might reflect a general slowing of information processing instead of specific deficits in visual search. Should a test assessing simple reaction time be included in the assessment? Recently, Van der Geest et al. (2006) reported about saccadic adaptation experiments in WBS subjects. These experiments were performed in a population which partly participated in our visual search experiments as well. In the baseline trials subjects were instructed to look from one dot to another at the moment the second dot appeared. Extra analyses on this data (unpublished) showed that the WBS-subjects were slower in reaction time

compared to healthy controls ($p = 0.033$). Although this might reflect a general slowing of information processing, this would explain the longer duration of fixations but not the less structured search behavior. A test for auditory reaction time would be a good way for determination of the simple reaction time in WBS subjects, as this does not involve visual spatial behavior.

In our study there is no information about the individual differences. Analogous to our randomized controlled clinical trial successful patient recruitment depends on several factors. We were in the unique situation of having more WBS subjects than trials. To consider different parameters per subject would be a more classical approach and therfore provide information on the individual differences. However if we would analyze the data in this more classical way we would come across low statistical power problems. Because of the low concentration spam in WBS subjects we have limited our number of experiments. Therefore, although we did not follow the classical approach, we analyzed the data in a way to be as precise as possible statistically.

Although the size of the deletion on the long arm of chromosome 7, band 7q11.23 is known to a large extent, much is unknown about the consequences of the missing expression of the lacking genes. I.e. LIMK1 and GTF21 have been linked to visual spatial functioning (Hirota et al., 2003). Furthermore, GTF21 and CYLN2 should be involved in motor coordination and memory formation (Van Hagen et al., 2007). As suggested by Hocking et al. (2008), knock-out mouse models and post mortem studies might characterize further details about the visuo-motor abnormalities in WBS subjects.

Further investigation of eye movement behavior in WBS subjects, by investigating the interaction between the eye stabilisation reflexes and saccadic behavior with subjects' free head movement could shed more light on the neuroanatomical components of the WBS syndrome.

Finally, not only visual search performance of WBS subjects should be compared to the performance of individuals with other syndromes that affect the brain regions mentioned above, but several techniques, such as fMRI, voxel based morphometry, detailed gene research should be combined to various tests, such as body and eye movement tests in order to increase the neuroanatomical under-

standing of the Williams-Beuren syndrome as a whole. Ideally this research should be performed prospectively from early childhood and extending into adulthood at several moments in time.

Eye movement behaviour has been studied widely for decades. An expansion of understanding oculo-motor behaviour in both physiologic and pathophysiologic processes has been accomplished. Although much progress has been made in elucidating the neural mechanisms underlying sensory-motor pathologies, such as seen in whiplash injury patients and individuals with Williams-Beuren syndrome, much research still has to be done. Looking at eye movements contributes te our understanding of human brain deficiencies. Eye movements provide a window on sensory and motor deficits.

REFERENCES

Allen G, McColl R, Barnard H, Ringe WK, Fleckenstein J, Cullum CM (2005). Magnetic resonance imaging of cerebellar-prefrontal and cerebellar-parietal functional connectivity. Neuroimage 28(1):39-48.

Atkinson J, Braddick O, Anker S, Curran W, Andrew R, Wattam-Bell J, Braddick F (2003). Neurobiological models of visuospatial cognition in children with Williams syndrome: measures of dorsal-stream and frontal function. Dev Neuropsychol 23(1-2):139-172.

Baddeley AD, Hitch, G (1974). Working memory. In G.A. Bower (ed.), The Psychology of Learning and Motivation, Vol. 8, pp. 47-90. New York: Academic Press.

Bellugi U, Lichtenberger L, Jones W, Lai Z, St George MI (2000). The neurocognitive profile of Williams Syndrome: a complex pattern of strengths and weaknesses. J Cogn Neurosci 12 Suppl 1:7-29.

Berryhill ME, Olson IR (2008). The right parietal lobe is critical for visual working memory. Neuropsychologia 46(7):1767-1774.

Bihrle AM, Bellugi U, Delis D, Marks S (1989). Seeing either the forest or the trees: dissociation in visuospatial processing. Brain and Cognition 11(1):37-49.

Borchgrevink GE, Kaasa A, McDonagh D, Stiles TC, Haraldseth O, Lereim I (1998). Acute treatment of whiplash neck sprain injuries. A randomized trial of treatment during the first 14 days after a car accident. Spine 23(1):25-31.

Bouyer LJ, Watt DG (1999). "Torso Rotation" experiments. 4: the role of vision and the cervico-ocular reflex in compensation for a deficient VOR. J Vestib Res 9(2):89-101.

Bronstein AM, Hood JD (1986). The cervico-ocular reflex in normal subjects and patients with absent vestibular function. Brain Res 373(1-2):399-408.

Bronstein AM, Morland AB, Ruddock KH, Gresty MA (1995). Recovery from bilateral vestibular failure: implications for visual and cervico-ocular function. Acta Otolaryngol Suppl 520 Pt 2:405-407.

CEA Insurers of Europe [homepage on the Internet]. Comité Européen des Assurances; [updated 2006 Aug 15; cited 2002]. Available from http://www.cea.assur.org

Clower DM, West RA, Lynch JC, Strick PL (2001). The inferior parietal lobule is the target of output from the superior colliculus, hippocampus, and cerebellum. J Neurosci 21(16):6283-6291.

Collewijn H, Grootendorst AF (1978). Adaptation of the rabbit's vestibulo-ocular reflex to modified visual input: importance of stimulus conditions. Arch Ital Biol 116(3-4):273-280.

Collewijn H, Grootendorst AF (1979). Adaptation of optokinetic and vestibulo-ocular reflexes to modified visual input in the rabbit. Prog Brain Res 50:771-781.

Controlled-trials [homepage on the Internet]. London: Current Controlled Trials, Ltd.; [updated 2006 Aug 15]. Available from http://www.controlled-trials.com

Dall'Alba PT, Sterling MM, Treleaven JM, Edwards SL, Jull GA (2001). Cervical range of motion discriminates between asymptomatic persons and those with whiplash. Spine 26(19): 2090-2094.

Eck JC, Hodges SD, Humphreys SC (2001). Whiplash: a review of a commonly misunderstood injury. Am J Med 110(8):651-656.

Eckert MA, Hu D, Eliez S, Bellugi U, Galaburda A, Korenberg J, Mills D, Reiss AL (2005). Evidence for superior parietal impairment in Williams syndrome. Neurology, 64(1):152-153.

Eckert MA, Tenforde A, Galaburda AM, Bellugi U, Korenberg JR, Mills D, Reiss AL (2006). To modulate or not to modulate: differing results in uniquely shaped Williams syndrome brains. Neuroimage 32(3):1001-1007.

Galaburda AM, Holinger DP, Bellugi U, Sherman GF (2002). Neuronal size and neuronal-packing density in primary visual cortex. Arch Neurol 59(9):1461-1467.

Gdowski GT, Belton T, McCrea RA (2001). Neurophysiological substrate for the cervical-ocular reflex in the squirrel monkey. Exp Brain Res 140(3):253-264.

Georgopoulos MA, Georgopoulos AP, Kurz N, Landau B (2004). Figure copying in Williams syndrome and normal subjects. Exp Brain Res 157(2):137-146.

Gorringe JAL (1970). Initial preparation for clinical trials. In: Harris EL, Fitzgerald JD, editors. The principles and practice of clinical trials. Edinburgh/London: Livingstone.

Haidich AB, Ioannidis JP (2001). Patterns of patient enrollment in randomized controlled trials. J Clin Epidemiol 54(9):877-883.

Heimbrand S, Bronstein AM, Gresty MA, Faldon ME (1996). Optically induced plasticity of the cervico-ocular reflex in patients with bilateral absence of vestibular function. Exp Brain Res 112(3):372-380.

Hirota H, Matsuoka R, Chen XN, Salandanan LS, Lincoln A, Rose FE, Sunahara M, OsawaM, Bellugi U, Korenberg JR (2003). Williams syndrome deficits in visual spatial processing linked to GTF2IRD1 and GTF2I on chromosome 7q11.23. Genet Med 5(4):311-321.

Hocking DR, Bradshaw JL, Rinehart NJ (2008). Fronto-parietal and cerebellar contributions to motor dysfunction in Williams syndrome: a review and future directions. Neurosci Biobehav Rev 32(3):497-507.

Huibers MJ, Bleijenberg G, Beurskens AJ, Kant IJ, Knottnerus JA, van der Windt DA, Bazelmans E, van Schayck CP (2004). An alternative trial design to overcome validity and recruitment problems in primary care research. Fam Pract 21(2): 213-218.

Husain M, Mannan S, Hodgson T, Wojciulik E, Driver J, Kennard C (2001). Impaired spatial working memory across saccades contributes to abnormal search in parietal neglect. Brain 124(Pt 5):941-52.

Huygen PL, Verhagen WI, Nicolasen MG (1991). Cervico-ocular reflex enhancement in labyrinthine-defective and normal subjects. Exp Brain Res 87(2):457-464.

Iwashita M, Kanai R, Funabiki K, Matsuda K, Hirano T (2000). Dynamic properties, interactions and adaptive modifications of vestibulo-ocular reflex and optokinetic response in mice. Neurosci Res 39(3):299-311.

Jarrold C, Phillips C, Baddeley AD (2007). Binding of visual and spatial short-term memory in Williams syndrome and in moderate learning disability. Dev Med Child Neurol 2007 Apr;49(4):270-3.

Kelders WP, Kleinrensink GJ, van der Geest JN, Feenstra L, de Zeeuw CI, Frens MA (2003). Compensatory increase of the cervico-ocular reflex with age in healthy humans. J Physiol 553(Pt 1):311-317.

Kelders WP, Kleinrensink GJ, van der Geest JN, Schipper IB, Feenstra L, de Zeeuw CI, Frens MA (2005). The cervico-ocular reflex is increased in whiplash injury patients. J Neurotrauma 22(1):133-137.

Koizuka I, Katsumi N, Hattori K, Okada T, Kato I (2000). Effect of adaptive plasticity of linear vestibulo-ocular reflex upon angular vestibulo-ocular reflex. Auris Nasus Larynx 27(2):89-93.

Mannan SK, Mort DJ, Hodgson TL, Driver J, Kennard C, Husain M (2005). Revisiting Previously Searched Locations in Visual Neglect: Role of Right Parietal and Frontal Lesions in Misjudging Old Locations as New. J Cogn Neurosci 17(2):340-354.

Marsh E, Baker R (1997). Normal and adapted visuooculomotor reflexes in goldfish. J. Neurophysiol 77:1099-1118.

Meyer-Lindenberg A, Kohn P, Mervis CB, Kippenhan JS, Olsen RK, Morris CA, Berman KF (2004). Neural basis of genetically determined visuospatial construction deficit in Williams syndrome. Neuron 43(5):623-631.

Mills H, Horne G (1986). Whiplash—manmade disease?. N Z Med J 99:373–374.

Milner AD, Goodale MA (1995). The visual Brain in Action, Oxford University Press.

Mishkin M, Ungerleider L, Macko KA (1983). Object vision and spatial vision: two cortical pathways. Trends Neurosci 6: 414-417.

Mobbs D, Eckert MA, Menon V, Mills D, Korenberg J, Galaburda AM, Rose FE, Bellugi U, Reiss AL (2007). Reduced parietal and visual cortical activation during global processing in Williams syndrome. Dev Med Child Neurol 49(6):433-8.

Nagao S (1983). Effects of vestibulocerebellar lesions upon dynamic characteristics and adaptation of vestibulo-ocular and optokinetic responses in pigmented rabbits. Exp Brain Res 53(1):36-46.

Nagao S (1989). Role of cerebellar flocculus in adaptive interaction between optokinetic eye movement response and vestibule-ocular reflex in pigmented rabbits. Exp Brain Res 77:541-551.

Nederhand MJ, IJzerman MJ, Hermens HJ, Baten CTM, Zilvold G (2000). Cervical muscle dysfunction in the chronic whiplash associated disorder grade II (WAD-II). Spine 25(15):1938-1943.

Nederhand MJ, Hermens HJ, IJzerman MJ, Turk DC, Zilvold G (2002). Cervical muscle dysfunction in chronic whiplash associated disorder grade II: the relevance of the trauma. Spine 27(10):1056-1061.

Owen AM, Herrod NJ, Menon DK, Clark JC, Downey SP, Carpenter TA, Minhas PS, Turkheimer FE, Williams EJ, Robbins TW, Sahakian BJ, Petrides M, Pickard JD (1999). Redefining the functional organization of working memory processes within human lateral prefrontal cortex. Eur J Neurosci 11(2):567-574.

Paige GD (1994). Senescence of human visual-vestibular interactions: smooth pursuit, optokinetic, and vestibular control of eye movements with aging. Exp Brain Res 98(2):355-372.

PIV-infosite [homepage on the Internet]. Stichting Personenschade Instituut van Verzekeraars; [updated 2006 Aug 15]. Available from http://www.stichtingpiv.nl

Rijkaart DC, van der Geest JN, Kelders WP, de Zeeuw CI, Frens MA (2004). Short-term adaptation of the cervico-ocular reflex. Exp Brain Res 156(1):124-128.

Rosenfeld M, Gunnarson R, Borenstein P (2000). Early intervention in whiplash associated disorders. A comparison of two treatment protocols. Spine 25(14):1782-1787.

Ross S, Grant A, Counsell C, Gillespie W, Russell I, Prescott R (1999). Barriers to participation in randomised controlled trials: a systematic review. J Clin Epidemiol 52(12):1143-1156.

Schairer JO, Bennett MV (1986). Changes in gain of the vestibulo-ocular reflex induced by combined visual and vestibular stimulation in goldfish. Brain Res 373(1-2):164-176.

Scholten-Peeters GG, Verhagen AP, Bekkering GE, van der Windt DA, Barnsley L, Oostendorp RA, Hendriks EJ (2003). Prognostic factors of whiplash associated disorders: a systematic review of prospective cohort studies. Pain 104(1-2):303-322.

Scholten-Peeters GG, Neeleman-van der Steen CW, van der Windt DA, Hendriks EJ, Verhagen AP, Oostendorp RA (2006). Education by general practitioners or education and exercises by physiotherapists for patients with whiplash associated disorders? A randomized clinical trial. Spine 31(7):723-731.

Shelhamer M, Peng GC, Ramat S, Patel V (2002). Context-specific adaptation of the gain of the oculomotor response to lateral translation using roll and pitch head tilts as contexts. Exp Brain Res 146(3):388-393.

Soto D, Humphreys GW, Heinke D (2006). Dividing the mind: The necessary role of the frontal lobes in separating memory from search. Neuropsychologia 44(8):1282-1289.

Spitzer WO, Skovron ML, Salmi LR, Cassidy JD, Duranceau J, Suissa S, Zeiss E (1995). Scientific monograph of the Quebec Task Force on whiplash associated disorders: redefining "whiplash" and its management. Spine 20(8 Suppl):1S-73S.

Stoykov NS, Lowery MM, Heckman CJ, Taflove A, Kuiken TA (2005). Recording intramuscular EMG signals using surface electrodes. ICORR 2005. 9th International Conference on Rehabilitation Robotics, Chicago, June 291–294.

Tabak S, Collewijn H, Boumans LJ, van der Steen J (1997). Gain and delay of human vestibulo-ocular reflexes to oscillation and steps of the head by a reactive torque helmet. I. Normal subjects. Acta Otolaryngol 117(6):785-795.

Van der Geest JN, Lagers-van Haselen GC, van Hagen JM, Govaerts LC, De Coo IF, de Zeeuw CI, Frens MA (2004). Saccade dysmetria in Williams–Beuren syndrome. Neuropsychologia 42(5):569–576.

Van der Geest JN, Lagers-van Haselen GC, Frens MA (2006). Saccade adaptation in Williams-Beuren syndrome. Invest Ophthalmol Vis Sci 47(4):1464-1468.

Van der Windt DA, Koes BW, Van Aarts M, Heemskerk MA, Bouter LM (2000). Practical aspects of conducting a pragmatic randomised trial in primary care: patient recruitment and outcome assessment. Br J Gen Pract 50(454):371-374.

Van der Wouden JC, Blankenstein AH, Huibers MJ, van der Windt DA, Stalman WA. Verhagen AP (2007). Survey among 78 studies showed that Lasagna's law holds in Dutch primary care research. J Clin Epidemiol 60(8):819-24.

Van Hagen JM, van der Geest JN, van der Giessen RS, Lagers-van Haselen GC, Eussen HJ, Gille JJ, Govaerts LC, Wouters CH, de Coo IF, Hoogenraad CC, Koekkoek SK, Frens MA, van Camp N, van der Linden A, Jansweijer MC, Thorgeirsson SS, De Zeeuw CI (2007). Contribution of CYLN2 and GTF2IRD1 to neurological and cognitive symptoms in Williams Syndrome. Neurobiol Dis 26(1):112-124.

Vicari S, Bellucci S, Carlesimo GA (2003). Visual and spatial working memory dissociation: evidence from Williams syndrome. Dev Med Child Neurol 45(4):269-273.

Vicari S, Bellucci S, Carlesimo GA (2005). Visual and spatial long-term memory: differential pattern of impairments in Williams and Down syndromes. Dev Med Child Neurol 47(5):305-311.

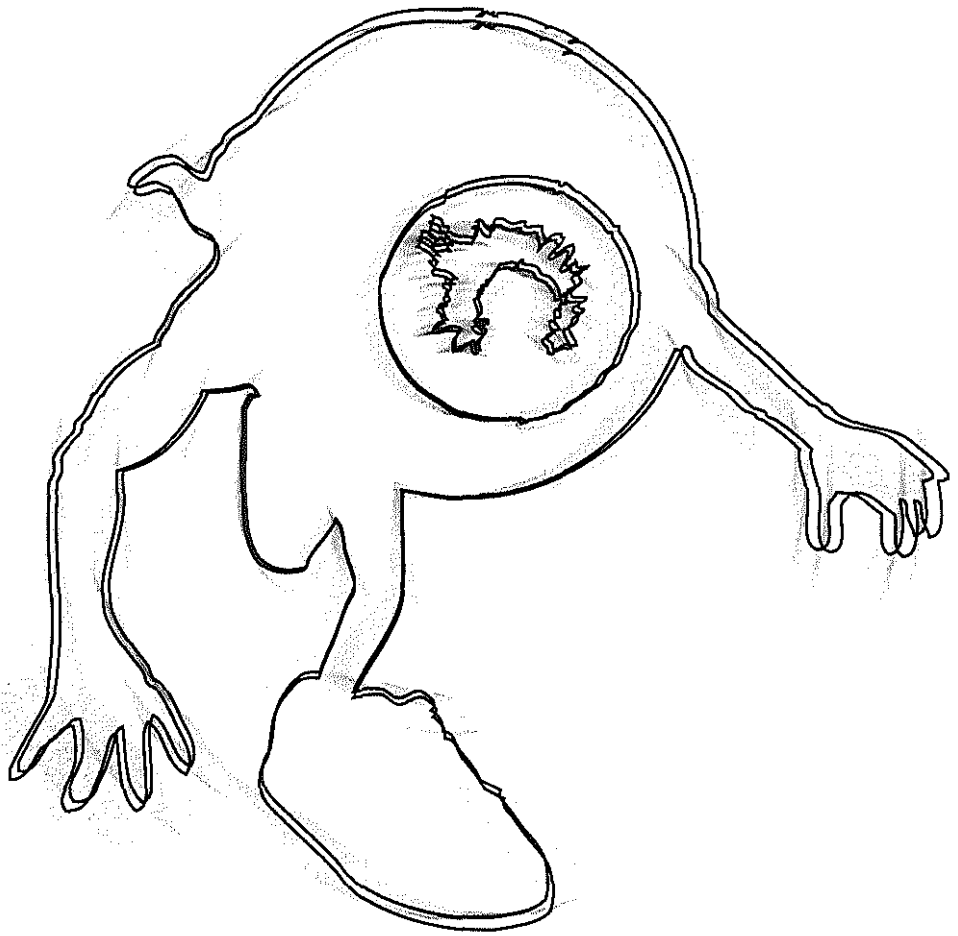
Watanabe S, Hattori K, Koizuka I (2003). Flexibility of vestibulo-ocular reflex adaptation to modified visual input in human. Auris Nasus Larynx 30 Suppl:S29-34.

Wismans KSHM, Huijkens CG. Incidentie en prevalentie van het 'whiplash'-trauma. TNO report 94. R.B.V.041.1/JW, TNO Road-Vehicle Research Institute. Delft; 1994.

Zee DS (1989). Adaptation and the ocular motor system. Bull Soc Belge Ophtalmol 237:191-207.

C H A P T E R 7

Summary / Samenvatting



SUMMARY

Studying eye movement behavior helps to further unravel some of the underlying neural processes of both sensory and motor deficits. It's accessibility, the encompassing of the conversion of sensory input to the generation of movement, its ability to learn and remember and the exhibition of both voluntary and reflexive behavior combined with the generation of data suitable for quantative analysis makes the ocluomotor system an attractive model for investigating sensory-motor pathologies.

Eye movements play a leading role in our interaction with the world and are generally used to inspect the environment. They can be divided into two categories: voluntary eye movements (such as saccadic eye movements, in which the fovea is aimed onto the object of interest) and eye stabilization reflexes (compensatory eye movements to prevent visual slip across the retina during head motion, i.e. the optokinetic reflex (OKR), vestibulo-ocular reflex (VOR) and cervico-ocular reflex (COR)). In daily life, these reflexes work in conjunction to maintain a stable image on the retina. The OKR moves the eyes on the basis of visual information, the VOR on the basis of vestibular information and the COR on the basis of cervical information. By inducing a mismatch between the vestibular and visual information the VOR can be adapted. Likewise, the COR can be modified by concurrent visual and cervical stimulation.

Chapter 2 reports on problematic patient recruitment in clinical trials. Despite promising incidence figures, enthusiastic participating general practitioners, emergency department collaborators and physiotherapists and in spite of all the extra effort, such as newsletters, advertisement and a live interview on local radio, to increase the number of eligible patients, we were unable to recruit the number of enrolling patients planned. Consequently, due to marginal inclusion of patients we were forced to cease our randomized clinical trial on the effectiveness of proprioceptive training on the development of chronic whiplash complaints a year after the start. Possibly Lasagna's Law has struck us to a major extend. Also other studies experienced patient recruitment difficulties. Several motives, such as more manpower or a doctor reminder real-time clinical trial alert system, can be proposed that would have prevented this obliged halting from happening. Although, we failed to reach our planned sample size, the findings of the trial are of clinical interest and may serve as a learning point for future researchers planning on doing analogous randomized controlled trials.

In **chapter 3**, we investigated whether the reported elevation of the cervico-ocular reflex (COR) in whiplash injury patients was accompanied by changes in VOR and/ or OKR. Therefore, we analyzed eye movement behavior of both whiplash injury

patients and healthy controls. In accordance with earlier results, in whiplash injury patients a significant increase in COR gain was found. Meanwhile the VOR gain and OKR gain remained the same. No synergy was found between the COR and VOR in the WAD patient group. This is in contrast with earlier observations in elderly and labyrinthine-defective subjects, who showed an increase in COR gain accompanied by a decrease in VOR gain. Three hypotheses can provide an explanation for this lack of synergy in patients with whiplash injury: First, maybe a decreased mobility of the neck leads to alteration in proprioception of the neck, which in turn results in an augmented gain of the COR without any problems in the VOR pathway. Second, possibly adaptation of the VOR requires sufficient head motion, and, because of impaired neck motion, the patient has too little adaptive input for the VOR to induce a negative adaptation in VOR gain. It is known that the VOR responds best at high velocities, whereas the COR is most responsive at low frequencies. This could explain the lack of decrease in VOR gain. Third, it may be that there is a disorganization in the process of VOR plasticity because of micro-trauma in the VOR pathway, such as in the flocculonodular area of the cerebellum. In **chapter 4** we investigated the underlying mechanisms of the increased gains of the cervico-ocular reflex and the lack of synergy between the COR and the vestibulo-ocular reflex in patients with whiplash associated disorders (WAD). Eye movements during COR or VOR stimulation were recorded in four different experiments. 16 healthy controls wore a rigid cervical collar for 2 hours. Before, immediately after wearing the collar and two hours later eye movements were recorded in response to COR stimulation. In 8 healthy subjects eye movements in response to COR stimulation were recorded simultaneously with the superficial electromyography (EMG) activity of cervical muscles in a relax and tense condition. Finally, the adaptive ability of the COR and of the VOR was tested in WAD patients and healthy controls. Restricted neck motion resulted in an increase in COR gain. No correlation between COR gain and muscle activity was observed. This might be explained by the possibility that the deep neck muscles are the major proprioceptive input for the COR, rather than the superficial cervical muscles we recorded from. Adaptation of both the COR and VOR was observed in healthy controls, but not in WAD patients. The lack of adaptation of the two stabilization reflexes may result in a lack of synergy between them. It may very well be that in WAD patients adaptation of the COR and the VOR take more time than 10 and 45 minutes, respectively. The absence of VOR adaptation may be a result from the limited neck motion. The VOR responds best at high head-movement velocities.

The limited neck motion of whiplash injury patients may not provide the optimal input for the VOR adaptation process. These abnormalities may underlie several of the symptoms observed in WAD. From these findings we conclude that the increased COR gain of WAD patients may be related to the reduced neck mobility of these patients, rather than an upregulation of the superficial neck muscle proprioceptors.

In **chapter 5**, visual search behavior of subjects with Williams-Beuren syndrome (WBS) was investigated. Williams-Beuren syndrome is a rare genetic condition characterized by several physical and mental traits, such as a poor visuo-spatial processing and a relative strength in language. Both WBS subjects and healthy controls were instructed to find a target out of several stimulus elements displayed on a computer screen. Eye movement patterns were analyzed for fixation characteristics and systematicy of search. The scan-patterns of WBS subjects both qualitively and quantitatively were different compared to those of healthy controls. Fixations generally lasted longer in WBS subjects than in control subjects. WBS subjects made more fixations at a stimulus element they had already looked at (refixations) and more fixations that were not aimed at a stimulus element at all (misfixations), decreasing the efficiency of search. Three causes could explain the inefficient visual search behavior of individuals with WBS. Inaccurate oculomotor control and/or impaired visual spatial processing and/or deficits in visual spatial working memory. WBS subjects do show mild inaccuracies in oculomotor control yielding some degree of saccadic dysmetria and a higher number of correction saccades before reaching a saccadic target. However, the saccadic inaccuracies are too mild to explain adequately the misfixations and they cannot explain the less structured search behavior nor the increase in number of refixations. To assess the contribution of impaired visual spatial processing on visual search behavior we looked at the durations of fixations. As in healthy controls, in WBS subjects the duration of the first fixation was longer than the mean duration of the subsequent fixations. However, although it failed to reach significance, the difference in duration between the first and other fixations seemed to be smaller in the patient group. Deficits in visual spatial working memory might explain the increase in number of refixations in subjects with Williams-Beuren syndrome. Spatial working memory temporarily stores and processes small amounts of position information which can be used later on for the execution of a saccade. Working memory is thought to involve the frontal cortex and the parietal lobe. Parietal lobe abnormalities have been reported in WBS.

Finally, **chapter 6** summarizes and discusses the main results as well as limitations of our studies. In addition recommendations for future research are made.

SAMENVATTING

Het bestuderen van oogbewegingen verschaft ons inzicht in enkele neurale processen die ten grondslag liggen aan sensorische en motorische aandoeningen. Oogbewegingen zijn eenvoudig te meten. Ook de stimuli die deze oogbewegingen veroorzaken zijn makkelijk te genereren of te controleren. Hierdoor valt het hele traject van sensorische input tot en met het uitvoeren van een beweging duidelijk in kaart te brengen. Daarnaast zijn oogbewegingen te trainen en goed kwantificeerbaar. Dit alles maakt het oculomotor systeem tot een aantrekkelijk instrument om sensorisch-motorische afwijkingen te onderzoeken.

In het dagelijks leven bewegen we voortdurend onze ogen om dingen om ons heen in ons op te nemen. Oogbewegingen zijn in te delen in twee categorieën: vrijwillige oogbewegingen (o.a. saccades, snelle verspringende oogbewegingen waarbij de fovea (gebied in het oog waarmee het scherpst gezien kan worden) op het voorwerp gericht wordt dat onze interesse heeft) en oogstabilisatie reflexen (compensatoire reflexmatige oogbewegingen die ervoor zorgen dat we een stilstaand beeld zien terwijl we ons hoofd bewegen). Er zijn 3 oogstabilisatie reflexen: de optokinetische reflex (OKR), de vestibulo-oculaire reflex (VOR) en de cervico-oculaire reflex (COR). Normaliter werken deze 3 reflexen samen om te voorkomen dat wat wij zien voor onze ogen danst ongeacht wat wij op dat moment aan het doen zijn. De OKR beweegt de ogen ten gevolge van visuele informatie, de VOR doet dit op basis van informatie uit de evenwichtsorganen en de COR maakt gebruik van informatie afkomstig van de nekspieren. Als de vestibulaire en visuele informatie niet met elkaar overeenkomen past de VOR zich aan. Evenzo adapteert de COR als er een discrepantie bestaat tussen de visuele en cervicale informatie.

In **hoofdstuk 2** wordt nader ingegaan op de moeizame werving van proefpersonen voor wetenschappelijk onderzoek. Ondanks dat de berekeningen veelbelovende resultaten opleverden en de huisartsen, spoedeisende hulpmedewerkers en fysiotherapeuten zeer enthousiast hun medewerking verleenden, is het ons niet gelukt om voldoende proefpersonen met whiplashklachten deel te laten nemen aan ons onderzoek. Middels nieuwsbrieven, advertenties in kranten en een live interview voor een lokaal radiostation hebben we nog getracht de toestroom van proefpersonen te verhogen, maar het mocht niet baten. Het gevolg was dat we een jaar na de start van het onderzoek naar de effectiviteit van proprioceptieve training op het ontwikkelen van chronische whiplashklachten, dit onderzoek moesten staken. Mogelijk hebben we extreem veel hinder ondervonden van de wet van Lasagna.

Volgens deze wet daalt op het moment dat een onderzoek van start gaat het aantal geschikte proefpersonen met 90% en stijgt dit aantal weer vlak nadat de werving gestopt is. We zijn niet de enige die moeite hebben om voldoende proefpersonen te werven. Meerdere wetenschappers melden hier problemen mee te hebben. Diverse maatregelen, zoals meer mankracht, een electronisch waarschuwingssysteem die de huisarts eraan herinnert dat de whiplashpatiënt voor hem in de spreekkamer mogelijk deel zou kunnen nemen aan ons onderzoek, hadden wellicht het aantal proefpersonen kunnen doen toenemen. Ondanks de magere toestroom van deelnemende mensen met whiplashklachten, heeft ons onderzoek toch zin gehad. Mogelijk dat andere wetenschappers die een vergelijkbaar onderzoek willen starten in de toekomst lering kunnen trekken uit onze resultaten.

In **hoofdstuk 3** onderzoeken we of er naast de eerder gerapporteerde verhoogde waarde van de cervico-oculaire reflex bij whiplashpatiënten ook sprake is van veranderingen in de waarden van de VOR en/of de OKR. Om dit te onderzoeken hebben we oogbewegingen van whiplashpatiënten en personen zonder klachten geanalyseerd. Ook wij vonden een hogere COR gain bij de mensen met whiplashklachten. De waarden van de VOR en de OKR bleven echter onveranderd. We vonden geen samenwerking tussen de COR en de VOR bij whiplashpatiënten, in tegenstelling tot eerdere bevindingen bij ouderen (> 60 jaar) en mensen waarbij de evenwichtsorganen slecht functioneren. Daar nam de VOR af wanneer de COR toenam. Drie hypotheses kunnen dit gebrek aan samenwerking tussen deze oogstabilisatiereflexen bij whiplashpatiënten verklaren. Ten eerste leidt een verminderde beweeglijkheid van de nek mogelijk tot een verandering in de proprioceptie (waarneming van de locatie en stand) van de nek wat leidt tot een toename van de COR zonder dat er veranderingen in het VOR circuit optreden. Ten tweede heeft de VOR mogelijk een bepaalde hoeveelheid hoofdbeweging nodig om zich aan te kunnen passen. Wellicht is er bij mensen met whiplashklachten vanwege een stijve of pijnlijke nek een verminderde beweging van de nek en ontstaat daardoor te weinig beweging van het hoofd om de VOR te kunnen laten adapteren. Immers de VOR adapteert voornamelijk bij hoofdbewegingen met een hoge snelheid, terwijl de COR juist adapteert bij lage snelheden. Als laatste kan er ook sprake zijn van een verstoring in de plasticiteit (overdracht van informatie in de hersenen via biochemische processen) van de VOR, bijvoorbeeld doordat er een minuscule beschadiging is opgetreden in het neuronale netwerk in de hersenen. Deze beschadiging kan zich bijvoorbeeld bevinden in de flocculonodular lobe in het cerebellum.

In **hoofdstuk 4** hebben we getracht meer duidelijkheid te krijgen over het onderliggende mechanisme van de verhoogde waarden van de cervico-oculaire reflex en het gebrek aan samenwerking tussen de COR en de VOR bij whiplashpatiënten. Hiertoe hebben we verschillende experimenten gedaan. We hebben 16 mensen zonder whiplashklachten bereid gevonden gedurende 2 uur een nekkraag te dragen. Voor het aanbrengen van de nekkraag, net na het verwijderen daarvan en 2 uur later hebben we de oogbewegingen als reactie op COR stimulatie gemeten. Daarnaast hebben we bij 8 mensen zonder whiplashklachten naast de oogbewegingen tevens de spierspanning (via EMG) van de nekspieren gemeten in ontspannen en aangespannen toestand als reactie op COR stimulatie. Tot slot hebben we de adaptieve eigenschappen van de COR en van de VOR onderzocht in zowel whiplashpatiënten als mensen zonder whiplashklachten.
De beperkte bewegingsvrijheid van de nek resulteerde in een stijging van de COR gain. We konden geen relatie vinden tussen de waarde van de COR en de spanning van de nekspieren. Wellicht komt dit doordat de proprioceptieve informatie voor de COR met name verzorgd wordt door de dieper gelegen nekspieren. Voor ons was het slechts mogelijk om de spanning van de meer oppervlakkig gelegen spieren te meten. Bij mensen zonder whiplashklachten adapteerden zowel de COR als de VOR, maar dit gebeurde niet bij whiplashpatiënten. Het kan heel goed zijn dat het gebrek aan aanpassingsvermogen de oorzaak is van de afwezige samenwerking tussen de beide oogstabilisatiereflexen. Maar het kan ook dat bij whiplashpatiënten de COR en de VOR meer tijd nodig hebben om zich aan te passen dan de geboden respectievelijke 10 en 45 minuten die voldoende waren voor mensen zonder whiplashklachten. Daarnaast kan de beperkte nekbeweging te weinig input opleveren voor de VOR om te adapteren. Bovenstaande afwijkingen kunnen ten grondslag liggen aan een aantal klachten die whiplashpatiënten ervaren. Uit de bevindingen kunnen we concluderen dat de verhoogde COR gain bij mensen met whiplashklachten waarschijnlijk het resultaat is van een verminderde beweeglijkheid van de nek en niet komt doordat de proprioceptoren van de nekspieren gevoeliger zijn geworden.
In **hoofdstuk 5** bestudeerden we het visueel zoekgedrag van mensen met het Williams-Beuren syndroom (WBS). Het Williams-Beuren syndroom is een zeldzame genetische aandoening met diverse fysieke en mentale kenmerken, waaronder beperkt visueel-ruimtelijk vermogen, schijnbaar hoog verbaal functioneren, cardiovasculaire afwijkingen, een karakteristiek gelaat en een opvallend vriendelijk karakter. Zowel mensen met dit syndroom als gezonde controlepersonen hebben we zoektaken

gegeven waarbij de opdracht was een afwijkend doel te vinden tussen diverse, op een computerscherm, weergegeven elementen. De oogbewegingen werden geanalyseerd, waarbij specifiek gelet werd op de fixaties en de systematiek van het zoeken. Fixaties bevinden zich tussen de saccades. Tijdens fixaties staan de ogen vrijwel stil, wordt de informatie van het object, waarnaar gekeken wordt, verwerkt en vindt de voorbereiding voor de volgende saccade plaats. Zowel op het eerste oog als kwantitatief bleek het kijkgedrag van personen met WBS verschillend ten opzichte van dat van de controlepersonen. Bij mensen met WBS duurden fixaties langer, werden er meer fixaties gericht op al eerder bekeken objecten (refixaties) en op plaatsen waar helemaal geen object stond (misfixaties), hetgeen de efficiëntie van het zoeken omlaag haalde. Drie mogelijke oorzaken zouden dit inefficiënte zoekgedrag kunnen verklaren: onnauwkeurige aansturing van de ogen en/of verminderde verwerking van visueel ruimtelijke informatie en/of manco's in het visueel ruimtelijk werkgeheugen. Het is bekend dat mensen met WBS milde afwijkingen hebben in het aansturen van de ogen. Zo vertonen ze enige afwijking in de coördinatie van de saccades en maken ze meer correctiesaccades voordat ze met hun ogen het visuele doel bereikt hebben. Deze afwijkingen zijn echter te mild om de toename in mis- en refixaties te verklaren. Ook kan hierdoor het meer chaotische zoekgedrag niet veroorzaakt worden. Om te achterhalen in hoeverre een verminderde werking van visueel ruimtelijke informatie ten grondslag ligt aan het afwijkende zoekgedrag hebben we de duur van de fixaties geanalyseerd. Zowel bij mensen met WBS als bij de controlepersonen duurde de eerste fixatie langer dan het gemiddelde van de daarna volgende fixaties. Alhoewel de uitkomst net niet significant bleek te zijn, leek het verschil tussen de eerste en de opvolgende fixaties in de WBS groep kleiner dan in de controle groep. Manco's in het visueel ruimtelijk werkgeheugen zouden een verklaring kunnen zijn voor het hogere aantal refixaties bij mensen met WBS. Informatie over de positie van voorwerpen wordt in dit werkgeheugen tijdelijk opgeslagen en verwerkt. Later worden deze gegevens weer gebruikt om een saccade te maken. Met name de frontale cortex en de pariëtale lob zijn betrokken bij het werkgeheugen. Bij mensen met WBS zijn afwijkingen aangetoond in deze pariëtale lob.

Tot slot worden in **hoofdstuk 6** de belangrijkste resultaten samengevat en besproken, waarbij tevens enkele kanttekeningen van ons onderzoek worden belicht. Daarnaast worden enkele aanbevelingen voor toekomstig onderzoek gedaan.

List of abbreviations / publications

LIST OF ABBREVIATIONS

BAP-135	Bruton's tyrosine kinase-associated protein-135
CLIP-115	Cytoplasmic linker protein of 115 kDa
COR	Cervico-ocular reflex
CROM	Cervical range of motion
CS	Control subjects
CYLN2	Cytoplasmic linker-2 gene
ΔG	Change in gain
ED	Emergency Department
ELN	Elastin
EMG	Electromyography
FD	Fixation duration
FISH	Fluorescence in situ hybridization
GP	General Practitioner
GTF2I	General transcription factor II, i (gene)
GTF2IRD1	GTF2I repeat domain containing 1
IQ	Intelligent Quotient
KS	Kolmogorov-Smirnov
LIMK1	LIM domain kinase 1
OKN	Optokinetic nystagmus
OKR	Optokinetic reflex
PT	Physiotherapist
QL	Extra control subjects with a lower IQ
QTF	Quebec Task Force
SD	Standard Deviation
SEM	Standard error of the mean
TFII-I	Transcription factor II, i (protein)
VOR	Vestibulo-ocular reflex
WAD	Whiplash associated disorders
WBS	Williams-Beuren syndrome

LIST OF PUBLICATIONS

Montfoort I, Kelders WP, van der Geest JN, Schipper IB, Feenstra L, de Zeeuw CI, Frens MA (2006). Interaction between ocular stabilization reflexes in patients with whiplash injury. Invest Ophthalmol Vis Sci 47(7):2881-2884.

Montfoort I, Frens MA, Hooge IT, Haselen GC, van der Geest JN (2007). Visual search deficits in Williams-Beuren syndrome. Neuropsychologia 14;45(5):931-938.

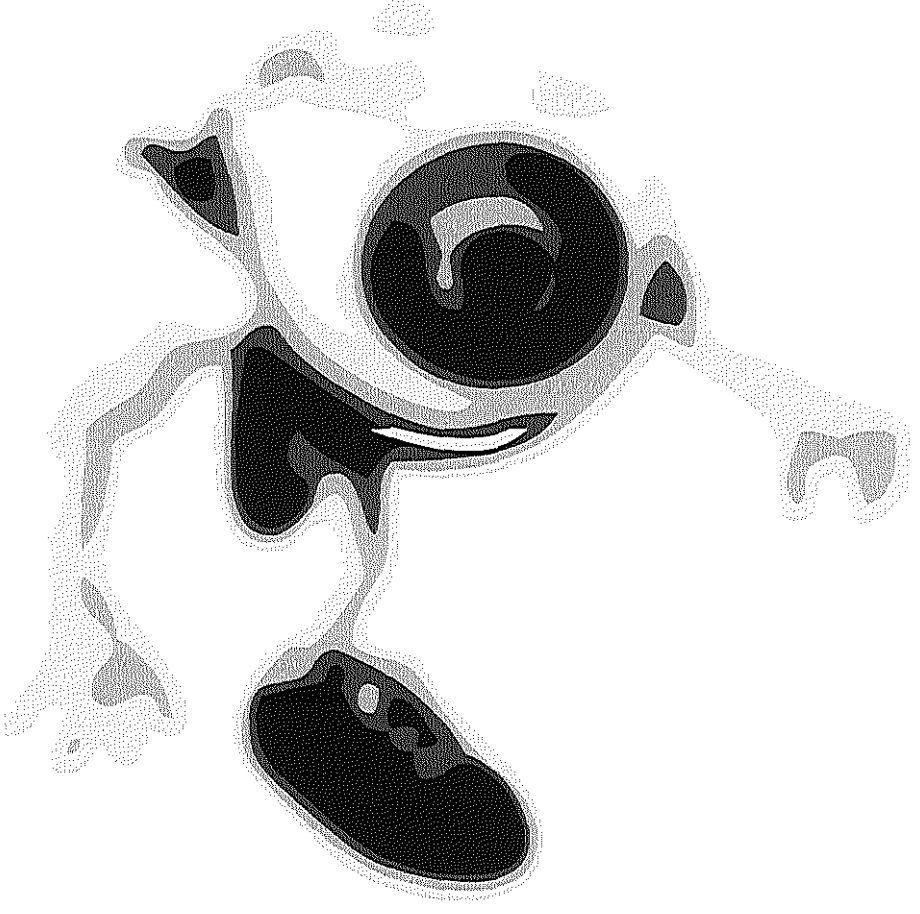
Montfoort I, Frens MA, Koes BW, Lagers-van Haselen GC, de Zeeuw CI, Verhagen AP (2008). Tragedy of conducting a clinical trial; Generic alert system needed. J Clin Epidemiol 61(5):415-418.

Montfoort I, Van Der Geest JN, Slijper HP, De Zeeuw CI, Frens MA (2008). Adaptation of the cervico- and vestibulo-ocular reflex in whiplash injury patients. J Neurotrauma. 25(6):687-93.

Montfoort I, Frens MA, De Jeu MTG, Van der Geest JN, De Zeeuw CI, Andreescu CE. Human vestibulo-ocular reflex. (in preparation)

Turina MC, Andreescu CE, Montfoort I, Valkenburg O, Lie Fong S, de Jong FH, Laven JS, De Zeeuw CI, Frens MA. The influence of estradiol on motor learning in humans. (in preparation)

Dankwoord



Het is zover! Ik ben aangeland bij de laatste pagina's. Hiermee nadert ook het einde van mijn promotietijd. Het voelt bijna onwerkelijk dat alles klaar is en dat ik echt ga promoveren. De tijd is omgevlogen. En nu wil ik graag iedereen hartelijk bedanken voor alle steun en hulp die ik gekregen heb tijdens mijn werk. Mede daardoor heb ik het ontzettend naar mijn zin gehad.

Om te beginnen wil ik mijn beide promotoren Prof.Dr. M.A. Frens en Prof.Dr. C.I. de Zeeuw van harte bedanken. Beste Maarten, goede leermeesters zijn schaars. Ik heb het geluk gehad er in jou één te vinden. Ik zou wel een hele pagina aan je willen wijden om je te bedanken voor alle steun, gezelligheid en vriendschap. We leerden elkaar kennen tijdens mijn eerste jaar in de medische collegebanken. Ik was snel gegrepen door de gedrevenheid en passie waarmee jij jouw vak presenteerde. Jouw enthousiasme heeft me uiteindelijk naar de wetenschap en de neurowetenschappen getrokken. De afgelopen jaren waren een boeiende, leerzame en leuke tijd. Naast de wetenschap was er ook altijd ruimte voor gesprekken over hele andere onderwerpen en ben je op meerdere terreinen een steunende factor geweest. Het voelt als een eer om de eerste promovendus in jouw functie als 1e promotor te mogen zijn in de beginfase van jouw hoogleraarschap. Ik hoop dat we in de toekomst nog veel samen zullen werken.
Beste Chris, als hoogleraar Neurowetenschappen sta je aan het hoofd van een bijzondere afdeling, waar ik met veel plezier onderzoek heb gedaan. Ik herinner me onze eerste ontmoeting nog heel goed. Het gesprek was zeer kort en krachtig. Ik zocht per acuut een onderzoeksplek en wat jou betrof kon ik dezelfde dag nog beginnen. Ik wil je bedanken voor de mogelijkheid die je mij hebt gegeven om binnen jouw groep een promotieonderzoek te doen. Tevens ben ik je dankbaar voor het mogen volgen van de Master of Science opleiding in Neurowetenschappen. Ik bewonder jouw enorme hoeveelheid kennis, aanstekelijk enthousiasme en de manier waarop je, zo op het oog moeiteloos, belangrijke beurzen weet binnen te halen.

Mijn copromotor Dr. J.N. van der Geest. Beste Jos, ook voor jou een speciaal woord van dank. We begonnen als kamergenoten op de 15e. Inmiddels ben ik afgezakt naar de 14e en jij naar de hogere regionen van de 12e. Naast het feit dat je een kei in Matlab bent (en ik veel van jouw programmatuur heb mogen profiteren), is het vooral jouw belangstelling (ook voor zaken buiten de wetenschap), jouw persoonlijke benadering en positieve houding, doorspekt met humor, die ik zeer waardeer. Voeg daarbij dat ik, ondanks je razend drukke leven, nooit langer

THANX! BEDANKT! THANX! BEDANKT! THANX! BEDANKT! THANX!

dan een aantal dagen heb hoeven wachten op je altijd opbouwende commentaren op soms wel tig pagina's tellende manuscripten en het zal een ieder duidelijk zijn waarom je een fijne begeleider bent. Zonder jouw inspanningen, creatieve en scherpzinnige inbreng had dit proefschrift er niet alleen anders uitgezien, maar zou ik zeker ook een hoop lol misgelopen zijn! Ik heb veel van je geleerd en kijk met veel plezier terug op onze samenwerking. Bedankt voor alle hulp en begeleiding die je hebt gegeven.

De overige leden van de kleine commissie, Prof. Dr. J. Passchier, Prof. Dr. H.J. Stam en Dr. G.J. Kleinrensink wil ik bedanken voor hun snelle beoordeling en goedkeuring van het manuscript (het kritisch doorkijken van een eindeloos pak papier is toch altijd weer een hele klus) en de bereidheid deel te nemen aan deze promotie. Professor Passchier, bedankt voor de hulp bij de Amsterdamse Biografische Vragenlijsten, jammer dat ze bij de whiplashpatiënten niet meer resultaat opleverden.

Ook Prof. Dr. B.W. Koes verdient een speciale vermelding. Beste Bart, in het begin van de Whamm...-trial hebben we regelmatig in een zeer plezierige sfeer overlegd. Helaas moesten we deze studie voortijdig beëindigen. Ik ben je zeer erkentelijk voor het vertrouwen dat je in mij gesteld hebt om dit onderzoek te doen. Jammer dat je niet bij de verdediging kan zijn.

Speciale dank verdient mijn begeleidster Dr. A.P. Verhagen. Beste Arianne, jouw advies, steun, vertrouwen, positieve feedback, tijd en hulp hebben ertoe geleid dat de Whamm...-trial vrij soepel van start is gegaan en hebben, ook toen het allemaal wat anders liep dan we gepland hadden, een belangrijke bijdrage geleverd aan de uiteindelijke publicatie. Ik kijk dan ook met veel plezier terug op onze samenwerking en hoop dat deze in de toekomst een vervolg krijgt.

I would like to thank Prof. Dr. S.A. Kushner for his willingness to read the manuscript and to accept the invitation to be member of the PhD-committee.

Ook voor Dr. I.Th.C. Hooge een extra woord van dank. Beste Ignace, als je over was uit Utrecht maakte je vaak even een gaatje vrij om met me mee te denken over lastige wetenschappelijke kwesties of moeilijke vragen van referenten. Hartelijk dank hiervoor. Fijn dat je deel uitmaakt van de commissie.

Prof.Dr. I.B. Schipper. Beste Inger, hartelijk dank voor het meedenken, het aansturen van de artsen op de Spoedeisende Hulp en natuurlijk het uitlenen van de nekkraag.

Dr. H.P. Slijper. Beste Harm, bedankt voor jouw hulp met de uitvoering en de analyse van de EMG-metingen, voor de gezelligheid, het veelvuldig in de meetopstelling plaatsnemen (je hebt aan vrijwel elk experiment deelgenomen) en voor het begrip als ik weer eens opgesloten zat en er een paar voeten op jouw bureau verschenen omdat ik onverwachts met een knal door het luik jouw kamer kwam binnenkruipen.

Dr. G.Ch. Lagers-van Haselen. Beste Dieke, mijn kamergenoot halverwege het promotietraject, dank je wel voor het volhardend invoeren van vragenlijsten in SPSS, het nabellen van huisartsen, jouw humor en natuurlijk niet te vergeten, de gezellige kopjes thee. Zonder jouw witte 'vogeltjestheepot' was het leven tijdens experimenten in de naburige kamer een stuk minder aangenaam geweest. Onze samenwerking duurde veel te kort.

Na de pensionering van Dieke werden haar invoerwerkzaamheden overgenomen door Suzan Markesteijn. Suzan, bedankt dat je dit er bij hebt willen nemen en bedankt voor het verrichten van enkele opzoekwerkzaamheden.

Alle proefpersonen, personen met whiplashklachten, mensen met het Williams-Beuren syndroom, de groep controlepersonen van het Maasstad Orthopedagogisch Centrum in Rotterdam, ouders, collega's en vrienden die belangeloos medewerking verleenden aan diverse onderzoeken en alle contactpersonen die hebben geholpen bij het vinden van proefpersonen. Allemaal heel hartelijk bedankt. Zonder jullie zou dit proefschrift er niet zijn.

De huisartsen en medewerkers van de Spoedeisende Hulp afdelingen bedank ik voor hun bereidwilligheid whiplashpatiënten te interesseren voor ons wetenschappelijk onderzoek en voor het doorfaxen van de benodigde gegevens.

De fysiotherapeuten in Rotterdam en omgeving die enthousiast meededen aan de Whamm...-trial wil ik bedanken voor de prettige samenwerking en de bereidheid whiplashpatiënten op speciale wijze therapeutisch te begeleiden. In het bijzonder

noem ik Ingrid Jaape. Ingrid, bedankt voor de korte opleiding in proprioceptieve training.

Persvoorlichter F.P. Balvert MSc, wil ik bedanken voor de media-aandacht die hij verzorgd heeft in een poging meer whiplashpatiënten deel te laten nemen aan ons onderzoek. In het kader hiervan ook hartelijke dank aan het Whiplash Informatiecentrum Europa voor de oproep op internet.

Dr. C.E. Andreescu. Dear Corina, thank you for your collaboration in the human study.

Dr. W.P.A. Kelders wil ik hier ook zeker noemen. Beste Willem, als promovendus "voor" mij heb je het stokje aan mij overgedragen. Met veel enthousiasme heb je me geleerd hoe ik oogreflexen moest meten. Bedankt voor het wegwijs maken in het gebruik van de opstelling.

Hartelijk dank Dr. J.M. van Hagen, Dr. I.F.M. de Coo, en Dr. L.C.P. Govaerts voor het klinisch en genetisch screenen van mensen met het Williams-Beuren syndroom.

Een aparte vermelding voor de technische man achter "de stoel", J. van der Burg, lijkt me zeer terecht. Beste Hans, hartelijk dank voor het oplossen van technische problemen met de meetopstelling en voor het meedenken met verbeteringen.

"Buren" en collega-promovendi, Drs. A.E. Smit en Drs. J.M. Richter verdienen ook een plaatsje in deze opsomming. Janneke, bij deze nogmaals bedankt voor het bellen van een tiental huisartsen, toen de Whamm...trial maar niet van de grond kwam. Ik weet zeker dat ook jij je 's' snel kwijt bent. Albertine, ik hoop dat je een geweldige wereldreis hebt en als je weer terug bent, wil ik er alles van horen. Beiden bedankt voor alle tips, medeleven, steun, de gezelligheid, de kopjes thee en het lekkers! Het was een stuk gezelliger met jullie in de buurt. Veel succes met jullie verdere wetenschappelijke carrière.

"Mijn"studenten, Drs. M.C. Turina MSc en Drs. Y. Benard, mogen ook zeker niet in dit dankwoord ontbreken. Ik heb met veel plezier met jullie samengewerkt en vond het een leuke ervaring om jullie te mogen begeleiden. Maureen, dank je wel voor het meten van whiplashpatiënten in de verlengde Whamm...-variant.

Jouw coschappen verlopen vast net zo succesvol als de Masteropleiding. Yolanda, bedankt voor het meten van "gezonden". Helaas leverde dit niet het resultaat op dat we hoopten. Heel veel succes Down Under, met jouw talent en enthousiasme wordt het vast een groot succes.

Mijn oorspronkelijke kamergenoten, Dr. M.M.J. Houben, Drs. J. Goumans, Drs. M.P. Vermaak en Drs. P.C.A. van Broekhoven. Beste Mark, Janine, Michiel en Flip, bedankt voor de gezellige en broodnodige pauzemomenten, waarin we soms heerlijk onze frustraties over het onderzoek konden spuien.

De uitstekende sfeer in de "groep Frens" ga ik ongetwijfeld erg missen. (Ex-)leden, bedankt voor het meedenken met problemen op wetenschappelijk, technisch, onderwijskundig of welk vlak dan ook (en op welk tijdstip dan ook). Ik heb erg veel geleerd van de wetenschappelijke discussies, de praktische tips en de waardevolle adviezen tijdens de wekelijkse bijeenkomsten en vond het een voorrecht deel uit te mogen maken van zo'n bijzondere groep.

Mijn woord van dank wil ik ook richten tot de collega's van de afdeling Huisartsgeneeskunde, in het bijzonder Drs. F. Vonk, M.W.C.T. Luiten en Dr. P.A.J. Luijsterburg en tot Dr. L.M. Lamers van het iMTA. Beste Frieke, Marlies, Pim en Leida, bedankt voor de gastvrijheid, de hulp bij logistieke zaken van de Whamm...-trial en het verzamelen van vragenlijsten. Hoewel we elkaar slechts in de beginfase van het onderzoek hebben gesproken, waren jullie altijd bereid me met tips op weg te helpen.

Dankzij de dames van het secretariaat, Edith Klink en Loes M.R. Nijs-de Langen, was er op druilerige dagen altijd wel iets opbeurend lekkers te snaaien uit de grote glazen pot. Bedankt voor de thee, de koekjes, de hulp bij enkele administratieve formaliteiten en de gezelligheid.

Ook alle andere medewerkers van de afdeling Neurowetenschappen, te veel om hier allemaal op te noemen, wil ik bedanken voor de gezellige babbels, de koffieuurtjes en lunchpauzes, maar met name voor de fijne, motiverende en vooral relaxte sfeer de afgelopen jaren.

De afgelopen jaren hebben niet alleen in het teken van dit proefschrift gestaan. Een juiste balans vinden in het vervullen van twee uiteenlopende functies bij twee

verschillende werkgevers viel niet altijd mee. Het parttime werken in een psychiatrische kliniek. Alle psychiaters, arts-assistenten, SPV'-ers, verpleegkundigen, managers, overige medewerkers en patiënten die steeds met veel belangstelling vroegen naar mijn vorderingen op "mijn andere werkplek". Dank voor jullie steun, opbeurende, stimulerende en relativerende woorden. Ik ben blij dat ik zulke leuke collega's heb.

André Verzijlbergh, veel dank voor de illustraties in dit boekje en voor het ontwerpen van het prachtige logo van de Whamm...-trial.

Mijn goede vrienden en paranimfen, J.P. Helmonds-Bruinenberg AA en T. Fijnekam. De keuze voor jullie als paranimfen was snel gemaakt. Ik ben blij dat jullie mijn paranimfen willen zijn. Jolanda, je bent een lieve vriendin van me geworden. Ondanks dat je wat verder weg bent gaan wonen, hoop ik dat we in de toekomst nog vaak bij elkaar over de vloer zullen komen. Toon, wanneer zullen we gaan wokken? Bedankt dat jullie me bij willen staan tijdens de laatste loodjes.

Mijn lieve ouders, papa en mama, bedankt voor jullie onmisbare steun en vertrouwen en voor de mogelijkheden die jullie me altijd hebben geboden. Nooit is iets te gek geweest qua opleiding. Lieve papa, ik had graag met jou mijn onderzoek bediscussieerd. Ik weet zeker dat je trots op me bent, daar waar je nu ook bent.

Mijn aanstaande schoonfamilie wil ik graag bedanken voor alle support. Jullie volgden altijd vol interesse mijn vorderingen en probeerden menigmaal te begrijpen waar ik precies mee bezig was.

Lieve vrienden, bedankt voor jullie nooit aflatende belangstelling en steun, ook al was het niet altijd even duidelijk wat ik nu eigenlijk precies deed.

Nu alles af is, wil ik nog enkele persoonlijke woorden richten tot 'thuis'.

Maiko, mijn trouwe viervoeter. Jij was steevast degene die, als ik weer eens vergat pauze te houden, me met jouw natte neus en tennisbal kwispelend duidelijk maakte dat het tijd werd voor een ommetje. Jongen, de tijd van langere wandelingen is weer aangebroken.

THANX! BEDANKT! THANX! BEDANKT! THANX! BEDANKT! THANX!

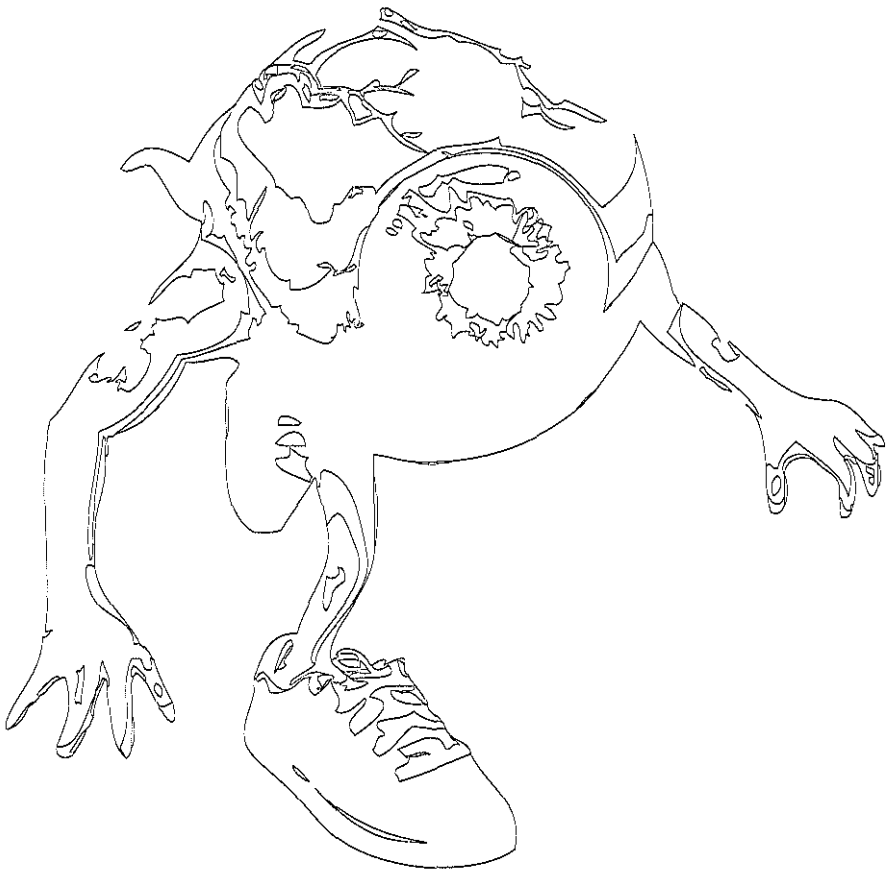
Jasper, lieve Jasper, toen ik als AIO begon had ik niet kunnen dromen dat ik als jouw verloofde zou promoveren, onze band is voor mijn gevoel uniek. Je hebt als geen ander met me meegeleefd de afgelopen jaren. Bedankt voor je steun, liefde en warmte. De computer is nu echt van jou, de kamer wordt voor.....Ik hoop dat we samen oud worden. En Marit, lieve kleine vrolijke eigenwijze meid, wat ben ik blij dat jij er bent. Laten we wat leuks gaan doen!

Tot slot is het haast onmogelijk om iedereen hier persoonlijk te noemen en te bedanken. Ik ben heel veel mensen bijzonder dankbaar. Bedenk, dat jij waarschijnlijk ook één van die personen bent. Bedankt dus!

Inger

THANX! BEDANKT! THANX! BEDANKT! THANX! BEDANKT! THANX! BEDANKT!

Curriculum Vitae



ABOUT THE AUTHOR

Inger Montfoort werd op 31 juli 1972 geboren in Rotterdam. Ze groeide op in Dordrecht en ging in deze stad na de lagere school in 1984 naar het Johan de Witt-gymnasium en in 1989 naar het Titus Brandsma College. Vervolgens begon het studie-avontuur. Allereerst doorliep ze van 1990 tot 1992 in Den Haag aan de MTS - Haagland Techniek versneld de MTS met als richting elektronica. Dit kreeg een vervolg in 1992 in de HTS-studie elektrotechniek aan de Hogeschool Rotterdam en Omstreken te Rotterdam. In het eerste studiejaar werkte ze in haar vrije tijd als geluidstechnicus bij een lokaal radiostation en als beeldtechnicus bij een regionaal televisiestation. Tijdens dit propedeusejaar begon het te kriebelen en besloot ze zich in te schrijven voor de studie geneeskunde. Echter, het lot bepaalde dat ze nog geen medicijnen mocht gaan studeren. In het derde studiejaar startte ze op de avondschool als tweede studie de tweedegraads docentenopleiding wiskunde aan de Hogeschool Holland te Dordrecht. Een bedrijfsstage in datzelfde jaar bij de medische instrumentele dienst van het Merwede Ziekenhuis te Dordrecht, waar ze onderhoud en reparatiewerkzaamheden verrichtte aan medische apparatuur, bevestigde haar enthousiasme voor de medische richting. In 1996 studeerde ze cum laude af aan de HTS in de informatietechniek (een verzamelnaam voor de vakgebieden: elektronica (analoog/digitaal), meet- en regeltechniek en tele- en datacommunicatie), waarbij ze zich voor haar afstudeerproject verdiepte in het principe van Magnetic Resonance Imaging (MRI) en onderzoek deed naar zowel de technische kanten als de economische aspecten van de phased-array spoel. Dit gebeurde in opdracht van de afdeling Klinische Fysica van het Merwede Ziekenhuis te Dordrecht. Tevens heeft ze in 1996 met positief resultaat een extra cursus spreekvaardigheid commercieel-technisch Duits gevolgd aan de HTS. In datzelfde jaar ontwikkelde ze voor deze hogeschool ook een lesprogramma voor zelfstudie in de digitale techniek, volgde ze in de avonduren een versnelde cursus scheikunde en behaalde ze haar VWO certificaat (wat nog ontbrak om toegelaten te kunnen worden tot de geneeskundestudie). Echter ook nu weer leidde een ongunstige loting niet tot het gewenste resultaat. Een baan als commercieel/technisch ingenieur volgde in 1996 in de scheepselektrotechniek. Na driekwart jaar stopte ze met deze functie en heeft ze de docentenopleiding wiskunde in 1997 versneld afgerond. Helaas lootte ze weer uit voor de studie geneeskunde en startte ze, ook in 1997, met de eerstegraads docentenopleiding wiskunde. Ditmaal aan de Fontys Hogeschool in Tilburg. Tussendoor heeft ze datzelfde jaar een zomercursus wiskunde verzorgd voor aankomend HTS-studenten

met een deficiëntie in het betreffende vakgebied. Toen het lot haar een jaar later gunstig gezind was, startte ze in 1998 met de studie geneeskunde aan de Erasmus Universiteit te Rotterdam. Na een jaar de aandacht tussen de beide opleidingen in Rotterdam en Tilburg verdeeld te hebben, behaalde ze haar propedeuse geneeskunde cum laude in 1999 en verwierf ze tevens haar onderwijsbevoegdheid eerstegraads wiskunde. In dat zelfde jaar werkte ze ook als trainer studievaardigheden ten behoeve van eerstejaars geneeskundestudenten. In 2002 werd haar de mogelijkheid geboden een Master Of Science opleiding in de klinische epidemiologie te gaan volgen aan het NIHES (Netherlands Institute For Health Sciences, Erasmus MC) wat resulteerde in onderzoek op de afdeling Fysiologie van de Erasmus Universiteit. In 2002 behaalde ze zowel haar doctoraal geneeskunde als haar masterstitel in de klinische epidemiologie. In datzelfde jaar startte ze zowel met de coschappen als met een Master Of Science opleiding in Neurowetenschappen. In 2004 behaalde ze haar artsexamen cum laude en startte ze tevens met het promotie-onderzoek dat geleid heeft tot dit proefschrift, waarna ze een jaar later haar tweede masterstitel behaalde. Dit onderzoek werd in 2006 gecombineerd met een parttimebaam als arts-assistent psychiatrie bij De Grote Rivieren te Dordrecht. Verder heeft ze gedurende vrijwel haar hele geneeskundestudie in de avonduren en in de weekenden op oproepbasis gewerkt als verpleeghulp op diverse afdelingen van het Albert Schweitzerziekenhuis te Dordrecht. Ze is aangenomen voor de opleiding tot psychiater bij De Grote Rivieren in Dordrecht. In haar vrije tijd is ze voorzitter van de medische commissie van de Dordtse Reddingsbrigade, geeft ze af en toe EHBO-lessen en volgt ze zanglessen.