On Cyclodeviation – Strategies for Investigation, Management and Quality of Life

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“Ut imago est animi voltus sic indices oculi”

“The face is a picture of the mind with the eyes as its interpreter”

— Marcus Tullius Cicero (106–43 B.C)

ABSTRACT

Introduction: Cyclodeviation is a form of strabismus that is not externally visible. It is measured subjectively and in degrees, as incyclotorsion or excyclotorsion. The perception of subjective tilting does not always accompany ocular torsion, and vice versa; and patients rarely complain specifically about cyclodiplopia. Therefore, it is important to have a good understanding of the processes behind cyclodeviation, how the condition affects compensatory mechanisms, binocularity, and the implications in everyday life.

Aims and Methods: To (**1**) evaluate measurement techniques for reliability and repeatability in adult patients with a vertical deviation. Cyclotorsion was measured using three different clinical tests, the single Maddox rod (SMR), KMScreen and the synoptophore; (**2**) to investigate normative subjective cyclotorsion values and cyclofusion ranges in a non-strabismic adult population aged 18–69 years, using the synoptophore and SMR; (**3**) to evaluate surgical outcomes and the management of cyclodeviation by reviewing pre-operative assessments and post-operative surgical results retrospectively from 2012 to 2019; (**4**) to assess the effect of cyclodeviation on health-related quality of life (HRQoL) using the Adult Strabismus-20 (AS-20) questionnaire, in adults with cyclodeviation. Scores were collected pre- and post-operatively and pre-operative scores were compared with scores from a non-strabismic control group.

Results: We found: (**1**) significant differences between clinical tests, especially between the synoptophore and the SMR. All tests showed high correlation and repeatability; (**2**) all age groups showed low values of subjective torsion, demonstrating excyclotorsion with mean values of -1 degree; (**3**) post-operative results of the modified Harada-Ito procedure corresponded well to the aimed-for correction of cyclodeviation, yet the dose-effect assessment showed variable effects**.** (**4**) There was a significant difference in pre-operative scores between patients and controls. Post-operative scores overall improved significantly for patients, specifically the functional subscale score, which differs from other forms of strabismus.

Conclusion: Investigation for the presence of cyclodeviation requires detailed diagnostic testing, as it can greatly influence the management and outcome of patient care. Reference data of what to expect as normal values of cyclotorsion and cyclofusion in clinical situations suggests that already a small increase in cyclotorsion (>-2 degrees) may disrupt the ability to fuse binocular images. Fusion evaluation and individually based pre-operative assessments are key factors in determining individual doses for successful surgical outcomes. Including HRQoL evaluation in strabismus management expands assessments. Patients complaining of double vision or difficulties in maintaining binocularity without other obvious strabismic signs should be assessed for cyclodeviation as this may be the disruptive factor to fusion.

Keywords: cyclodeviation, HRQoL, orthoptics, strabismus, synoptophore

Om cyklodeviation - strategier för utredning, behandling och livskvalitet

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SAMMANFATTNING PÅ SVENSKA

Introduktion: Cyklodeviation är en typ av skelning som inte syns utvändigt, och uppstår vanligtvis i kombination med en skelning i höjdled (vertikal skelning). Cyklodeviation är den totala cyklotorsionen (graden av ögats rotation) uppmätt mellan höger och vänster öga i grader, som excyklotorsion (utåtroterat öga) eller incyklotorsion (inåtroterat öga), och mäts oftast subjektivt. Det är en besvärande åkomma för patienter, eftersom uppfattningen av subjektiv lutning inte alltid åtföljer ögats vridning, och vice versa; samt att det är svårt att upptäcka bildrotationen vid dubbelseende. Därav är cyklodeviation svårvärderad, och missas ibland vid kliniska undersökningar. Följaktligen är det viktigt att ha en god förståelse för mekanismen bakom cyklodeviation, hur tillståndet påverkar patientens kompensationsmekanismer, samsyn och konsekvenserna av cyklodeviation i vardagen.

Syften och Metoder: Hittills finns det litet dokumenterat kring tillförlitligheten av olika mätmetoder, behandlingar och riktlinjer för denna diagnos. Huvudsyftet med avhandlingen är att skapa rutiner för undersökning, diagnostisering och behandling av patienter med cyklodeviation. Avhandlingen innefattar fyra delprojekt: (**1**) utvärdering av kliniska mätmetoder med avseende på tillförlitlighet och repeterbarhet vid mätning av cyklodeviation hos vuxna patienter med vertikal skelning. Cyklodeviation mättes med tre olika kliniska tester, singel Maddox Rod (SMR), KMScreen och synoptophor. (**2**) Ta fram en referensram för cyklodeviation och cyklofusion (sammanhållningen av bilden) inom en icke-skelande, normalpopulation i åldern 18–69 år, genom att mäta detta hos 120 individer med SMR och synoptophor. (**3**) Utvärdering av den bästa undersöknings- och behandlingsmetoden för patientgruppen genom att bedöma cyklotorsionsmätningar före och efter operation i förhållande till operationsteknik och kirurgiska resultat genom att granska slutresultaten från 2012 till 2019. (**4**) Utvärdera effekten av cyklodeviation på patienternas livskvalitet med hjälp av enkätundersökningen Adult Strabismus-20 (AS-20). En kohortstudie utfördes under 2014–2019 på vuxna som genomgått korrigerande kirurgi pga. fusionsstörande cyklodeviation, för att fånga patienternas subjektiva upplevelser. Resultatet av AS-20 enkäten jämfördes före och efter operation, samt pre-operativt med en kontrollgrupp utan skelning.

Resultat: Vi har påvisat att: (**1**) Det är en signifikant skillnad i uppmätt cyklotorsion mellan olika mätmetoder, speciellt mellan synoptophor och SMR. Samtliga metoder uppvisar dock en god repeterbarhet. (**2**) Alla åldersgrupper visade låga värden av cyklotorsion, medelvärdet visade excyklotorsion på -1 grad. (**3**) Post-operativa resultat av den modifierade Harada-Ito-operationen motsvarade väl den avsedda korrigeringen av cyklodeviation. (**4**) Det var en signifikant skillnad i AS-20 resultat före operation mellan patienter och kontroller. Post-operativt förbättrades resultaten signifikant för patienter, särskilt för funktionsfrågorna. Detta särskiljer cyklodeviation från andra former av skelning, där den psykosociala skalan ger ett större utslag.

Slutsatser: Undersökning av cyklodeviation kräver specifik testning och diagnostik, eftersom det kan påverka behandlingen och resultaten inom patientvård. Referensvärderna inom en normalpopulation antyder att redan en liten ökning av cyklotorsion (>2 grader) kan störa förmågan att hålla ihop samsynen. Fusionsutvärdering och individ-baserade pre-operativa bedömningar är nyckelfaktorer för att avgöra doseringen för framgångsrika kirurgiska resultat. Att inkludera livskvalitet i utvärdering och undersökning av skelning förbättrar bedömningarna. Implikationen av resultaten är att patienter som klagar över dubbelseende eller svårigheter med att upprätthålla samsynen utan andra uppenbara störande faktorer bör undersökas för cyklodeviation, eftersom detta kan vara den utlösande faktorn.

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LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. Flodin S, Karlsson P, Andersson Grönlund M. Cyclotorsion Measured in a Patient Population Using Three Different Methods: A Comparative Study. *Strabismus* 2016; 24(1); 28-36.*

II. Flodin S, Pansell T, Rydberg A, Andersson Grönlund M. Clinical Measurements of Normative Subjective Cyclotorsion and Cyclofusion in a Healthy Adult Population. *Acta Ophthalmol.* 2020; 98(2): 177-181.**

III. Flodin S, Karlsson P, Rydberg A, Andersson Grönlund M, Pansell T. A Modified Harada-Ito Procedure Based on Cyclofusion Ability Improves Surgical Outcome in Individuals with Cyclodeviation. *Submitted manuscript 2020*.

IV. Flodin S, Rydberg A, Pansell T, Andersson Grönlund M. Measuring Health-Related Quality of Life in Individuals with Cyclodeviation Using the Adult Strabismus-20 (AS-20) Questionnaire. *Submitted manuscript 2020*.

*This is an Accepted Manuscript of an article published by Taylor & Francis in *Strabismus 2016*, available online: *http://wwww.tandfonline.com/* DOI: 10.3109/09273972.2015.1135967

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CONTENT

ABBREVIATIONS

ANOVA	analysis of variance
AS-20	Adult Strabismus 20-questionnaire
BHTT	Bielschowsky Head Tilt Test
BSV	binocular single vision
BV	binocular vision
CI	confidence interval
CTT	computerised torsion test
DFA	disc-foveal angle
DMR	double Maddox rod
DMRT	double Maddox rod test
EOM	extraocular muscles
HRQoL	health-related quality of life
ICC	intra-class correlation coefficient
IO	inferior oblique
IQR	interquartile range
IR	inferior rectus

L	left
LoA	limits of agreement
LR	lateral rectus
LRGT	Lancaster red-green test
MR	medial rectus
OCR	ocular counter-rolling
OKN	optokinetic nystagmus
OKR	optokinetic reflex
OTR	ocular tilt reaction
PP	primary position
PROM	patient-related outcome measure
QoL	quality of life
R	right
SD	standard deviation
SMR	single Maddox rod
SMRT	single Maddox rod test
SO	superior oblique

SOP	superior oblique palsy
SR	superior rectus
SVV	subjective visual vertical
V1	primary visual cortex area
VA	visual acuity
VOR	vestibulo-ocular reflex

GLOSSARY

Afterimage	image that continues to appear in the visual field after a period of exposure to the original image
Amblyopia	cortical visual deprivation with reduced vision
Asthenopia	a sense of strain and weakness caused by the use of the eyes
Binocular vision	ability to use both eyes simultaneously
Binocular single vision	the ability to see one image with both eyes simultaneously. Levels of BSV; (i) simultaneous perception; (ii) fusion; (iii) stereopsis
Cover Test	An objective dissociation test to elicit the presence, type and amount of a manifest or latent deviation. Used in two ways:(1) the cover/uncover test in which one eye is covered, observes movement of the uncovered eye (2) the alternate cover test in which one eye or the other is covered throughout the test, fully dissociating the eyes to observe movement of the covered eye as the cover is changed.
Cyclodeviation	torsional strabismus characterised by a misalignment or imbalance of cyclotorsion between the two eyes
Cyclodisparity	difference in the rotation angle of the visual percept of an object or scene viewed by the left and right eye, resulting from the eyes' different torsional rotation

Cycloduction	torsional movement of one eye
Cyclofusion	is the sensory and motor torsional fusional reserves whereby cyclodeviations are controlled
Cyclotorsion	amount of ocular torsion (cycle = degree)
Cycloversion	conjugate cycloductions of both eyes in the same direction
Diplopia	the simultaneous appreciation of two images of one object (double vision)
Donders Law	During fixation with the head upright, the eye adopts a unique torsional position for each gaze direction.
Ductions	monocular movements
Fick's axes	coordinate system of three axes thought to pass through the geometrical centre of the eye bulb, that describes the movement of the eye around a theoretical centre of rotation
Fusion	Unification of visual excitations from the corresponding retinal images into a single visual percept. *Sensory fusion* is the ability to perceive two similar images and interpret them as one, while *motor fusion* is the ability to maintain sensory fusion through a range of vergence, which may be horizontal, vertical or cyclovergence.
Hering's law	During any conjugate eye movements, equal and simultaneous innervation flows to yoke muscles.
Heterophoria	both visual axes are directed towards the fixation point but deviate on dissociation,

	controlled by fusional mechanisms (latent deviation)
Heterotropia	one or other visual axis is not directed towards the fixation point (manifest deviation)
Kinematics	mechanism that describe motion
Latent deviation	a deviation that only appears when binocular viewing is broken and the two eyes are no longer looking at the same object, see heterophoria
Listing’s Law	All tertiary positons of gaze are reached by a single rotation of the eye about one axis.
Listing’s plane	axis plane through which rotation of the eyeball occurs
Manifest deviation	a deviation that is apparent when viewing a target binocularly, with no occlusion of either eye, see heterotropia
Muscle pulleys	rings of collagen tissues encircling the EOM
Nystagmus	repetitive oscillatory movement of one or both eyes
Ocular torsion	rotation of the eye around its visual axis
Paralysis	complete loss of function of a muscle
Paresis	partial loss of function of a muscle
Pseudotorsion (false torsion)	tilt of image in tertiary positions of gaze

Retinal correspondence	concerns the area of each eye which have the same visual direction during binocular single vision
Saccades	rapid eye movements that direct the fovea to a target
Sherrington's law	Increased innervation to an agonist extraocular muscle (EOM) is accompanied by reciprocal inhibition of its antagonist.
Simultaneous perception	simultaneously perceiving an object with each eye, the first grade of binocular single vision
Smooth pursuits	slow, smooth following movements of the eyes to keep a moving object within the fovea
Stereopsis	highest level of BSV where images are fused and binocular disparity gives the perception of depth
Strabismus	misalignment of the eyes disrupting single binocular vision
Vergence	binocular, disconjugate eye movements
Versions	binocular, conjugate eye movements

1 INTRODUCTION

1.1 BACKGROUND

The human visual system is complex and highly specialised. Binocular vision (BV) is obtained from two retinal images that are fused through motor and sensory processes, generating a single image – binocular single vision (BSV) and stereoscopic depth perception. Prerequisites for BSV are normal eye movements and aligned visual axes that share a common visual direction. Impaired eye movements affect control and misalignment causes strabismus, which leads to disturbed binocularity, usually diplopia, unless suppression occurs.

Ocular misalignment of the visual axes can be in the horizontal, vertical, and/or torsional direction and disrupts BSV. Cyclodeviation is an imbalance between muscle pairs, which affects intorsion and extorsion of the globe (von Noorden and Campos 2002) and is a form of strabismus that is not externally visible. Ocular torsion has been described as: "one of the most perplexing problems in strabismus diagnosis and management" (Good 2013). Cyclodeviation is measured in degrees (cyclotorsion), and is most commonly tested subjectively using the double Maddox rod test (DMRT), Bagolini striated glasses or the synoptophore (Ansons and Davis 2014; von Noorden and Campos 2002).

Assessment of cyclotorsion can also be made qualitatively or objectively. Observing conjunctival vessels at the limbus of the eye on ophthalmic examination is a gross objective estimation to decide whether intorsion or extorsion is present. A better method is fundus photography examination, to establish whether the level of the optic disc relative to the macula and position of the fovea is displaced higher or lower than the average, of about 0.3 disc diameters (Guyton 1983; Parsa and Kumar 2013). This method has become more advanced, and there is now a web-based software tool (www.cyclocheck.com) for the assessment of objective cyclotorsion, based on measuring the disc-foveal angle (DFA) (Simiera and Loba 2017). However, objective and subjective methods of torsion testing play very different roles, as in some patients the correlation may be good and in others not (Kushner and Hariharan 2009). The perception of visual tilt does not always accompany ocular torsion of the globe and vice versa; patients rarely specifically complain about torsional diplopia (Kushner 1992). Objective methods are considered to be time consuming, and not practical for standard clinical use (Guyton 2008).

The diagnostic process is the basis of any health care management (Grimes and Schulz 2005). The investigation for the presence of cyclodeviation requires detailed diagnostic testing. Orthoptists play an important role in investigating, detecting, diagnosing and treating various defects of BV and abnormalities of eye movement. In strabismus management, it is crucial to have reached a correct diagnosis – especially when treatment involves surgery. Through a unique set of skills, it is the orthoptists responsibility to carry out precise and accurate diagnostic testing (Vukicevic, Koklanis and Giribaldi 2013). The orthoptist provides the patient with prognostic information and treatment options. In cooperation with the strabismus surgeon, the measurements obtained from diagnostic testing are converted into appropriate surgical technique.

Cyclodeviation is a troublesome condition both for patients and for clinicians, and is often overlooked during clinical examinations. This may result in patients receiving incorrect prism glasses, having non-optimal surgical interventions, or, at worst, remaining undiagnosed, resulting in reduced health related quality of life (HRQoL). For these reasons, it is important to have a good understanding of the components of cyclodeviation. To gain knowledge of how cyclodeviation affects compensatory mechanisms and binocularity, and its implications in everyday life. To date there is little documentation regarding reliable techniques or directives to measure and manage cyclodeviation in clinical practice.

This thesis aims to create awareness about cyclodeviation, both from a clinical and from a patient perspective. Studying methods of investigation and management, and quality of life (QoL) implications will aid in providing a better understanding, and enhance treatment of cyclodeviation.

1.2 ANATOMY AND PHYSIOLOGY

The eyes move in the cardinal directions with the aid of the extraocular muscles (EOM) that attach the eyeball to the socket, and rotate. The axis through which rotation of the eyeball occurs is confined to a common plane known as *Listing's plane*. Six EOM control and rotate the eyeball. Four of these are rectus muscles; they originate from the back of the orbit, attach directly to the front half of the eye, and are recognised as "straight muscles". They are named after their paths, *medial, lateral, superior and inferior*. The other two muscles are the oblique muscles, superior and inferior. The superior oblique (SO) muscle is the longest of the eye muscles. It originates at the back of the orbit, and loops through a pulley called the trochlea, on the upper nasal wall of the orbit, before travelling back posteriorly over the top of the eye, passing the equator of the bulb. The inferior oblique (IO) originates at the lower front of the nasal orbital wall, and runs underneath the lateral rectus (LR) on its way to the posterior. The EOM are innervated by the cranial nerves III, IV and VI. See Table 1 for each of the EOMs' innervation and actions, and Figure 1 for illustration.

Table 1. *Innervation and actions of the six extraocular muscles (EOM).*

Muscle	Cranial nerve	Muscle actions		
		Primary	Secondary	Tertiary
Medial rectus (MR)	Oculomotor nerve (inferior branch)	Adduction		
Lateral rectus (LR)	Abducens nerve	Abduction		
Superior rectus (SR)	Oculomotor nerve (superior branch)	Elevation	Incyclotorsion	Adduction
Inferior rectus (IR)	Oculomotor nerve (inferior branch)	Depression	Excyclotorsion	Adduction
Superior oblique (SO)	Trochlear nerve	Incyclotorsion	Depression	Abduction
Inferior oblique (IO)	Oculomotor nerve	Excyclotorsion	Elevation	Abduction

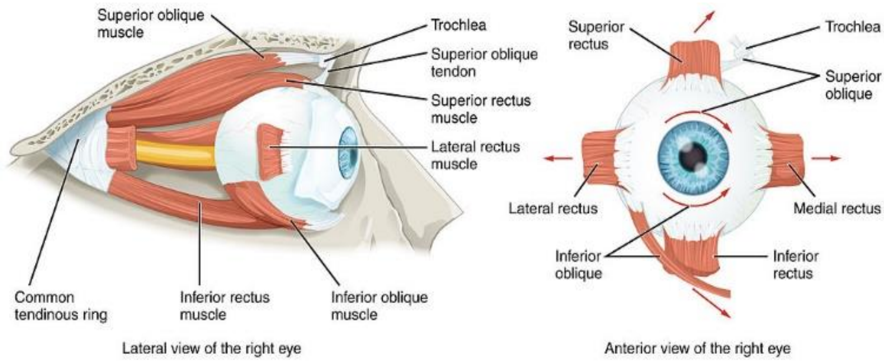


Figure 1. *Illustration of the eyeball and its muscles, lateral and anterior view. Illustration from: Anatomy & Physiology, Connexions Web site,* ***https://commons.wikimedia.org/wiki/File:1412_Extraocular_Muscles.jpg***

At the origin of the EOM, connective tissue forms sleeves around the muscles creating *muscle pulleys* (Demer, Miller, Poukens et al. 1995). Muscle pulleys are rings of collagen tissues encircling the EOM, and their purpose is to redirect the muscle, and prevent displacements during movement. The pulley is at an angle to the orbital axis, and influences the muscle path during eye movements.

1.3 BINOCULAR FUNCTIONS AND RETINAL CORRESPONDENCE

As we have two frontally placed eyes, we receive input and stimuli from both. Signals are sent into the primary visual cortex or V1, where parts of the visual processing is believed to take place. The visual cortex receives two similar images. Under normal conditions, the brain will receive these images simultaneously, and fuse them into one single binocular image. The images from the left (L) and the right (R) eye need to fall on corresponding parts of the retina, and be approximately equal in size, shape, contrast and colour, to avoid binocular disturbance. If visual development is normal, this leads to *normal retinal correspondence*. When the two eyes are misaligned, due to strabismus, ocular deviation occurs, resulting in double vision. In young children with good neural plasticity, this will lead to a re-organization of the visual cortex and an *abnormal retinal correspondence*.

The fact that the two eyes operate as one unit rather than independently was first reflected upon by Aristotle; 384–322 BCE (Wade 2010). As the images are incorporated as one, they also need to remain as one through movement of both the eyes and the head. We usually tend to think of these movements as horizontal and vertical; however, they are also torsional. Torsional alignment, as well as horizontal and vertical ocular alignment with certain tolerances, contribute to the control of the binocular function system, i.e. vergence eye movements, enabling BSV, fusion and stereopsis.

1.4 EYE MOVEMENTS

Movements of the eyes are intricate, and there is a long history of eye movement studies. Scientists have speculated, investigated and applied theories of kinematics, the ways in which the eyes move, since the late 18th century. It was during this period that it was determined that the bulb moves through a combination of rotations enabled by muscle balance, innervation and fixation.

In 1845, a German ophthalmologist by the name of Ruete developed a mechanical model of the eyes called the ophthalmotrope (Keeler, Singh and Dua 2009). The model demonstrated the movements of the eyes and its muscles (Figure 2).

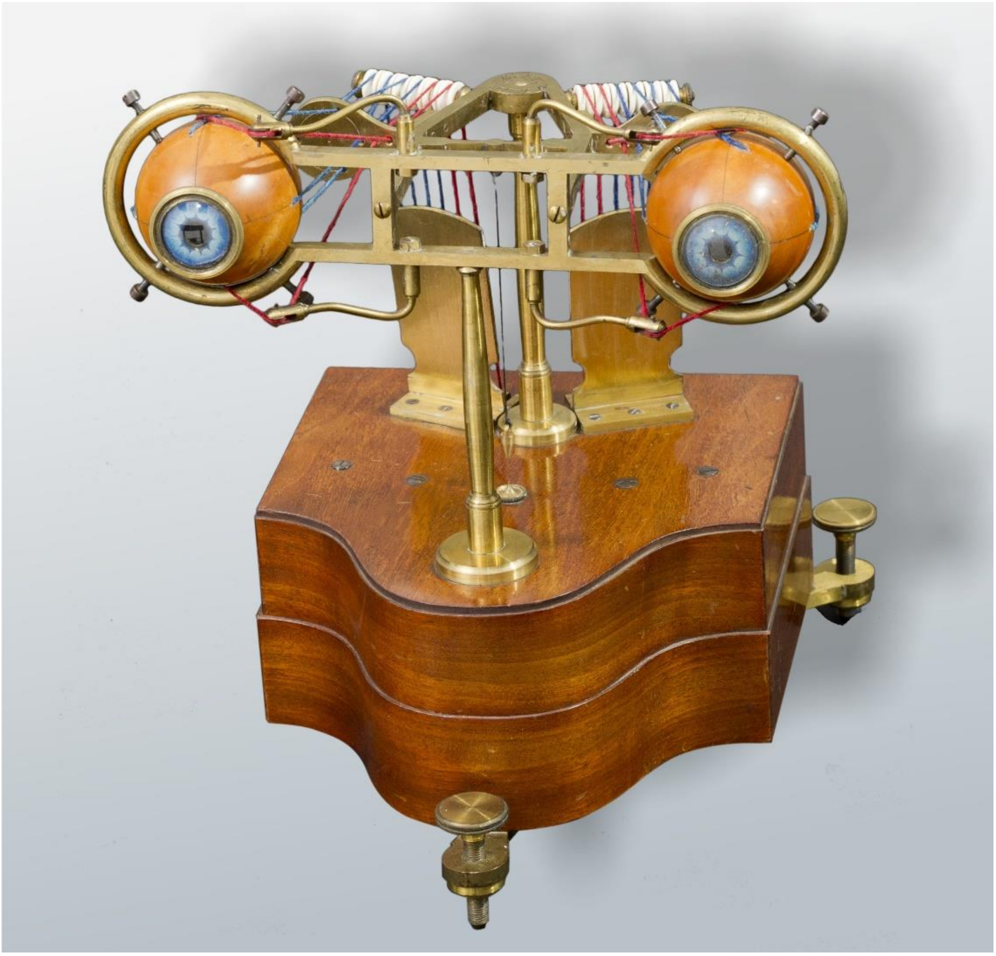


Figure 2. *An ophthalmotrope, a mechanical model constructed by Reute to demonstrate the movements of the eyes and the action of the different muscles that produce them.*
With permission from Richard Keeler, Courtesy of The Royal College of Ophthalmologists.

Ruete also studied the phenomenon of the rotation of the eyes by using an afterimage cross (Simonsz and Tonkelaar 1990). An illustration of an afterimage cross is given in Figure 3. The Dutch ophthalmologist Franz Donders (1818-1889) further advanced these experiments, and found that the afterimage cross tilted upon looking in tertiary positions of gaze. This led him to conclude that the rotation of the eye around the line of sight is involuntary, and that the amount of torsion is dependent upon the amount of elevation or depression or side gaze. This was formulated into Donders' law, which states that during fixation with the head upright, "the eye adopts a unique torsional position for each gaze direction" (Thurtell, Joshi and Walker 2012).

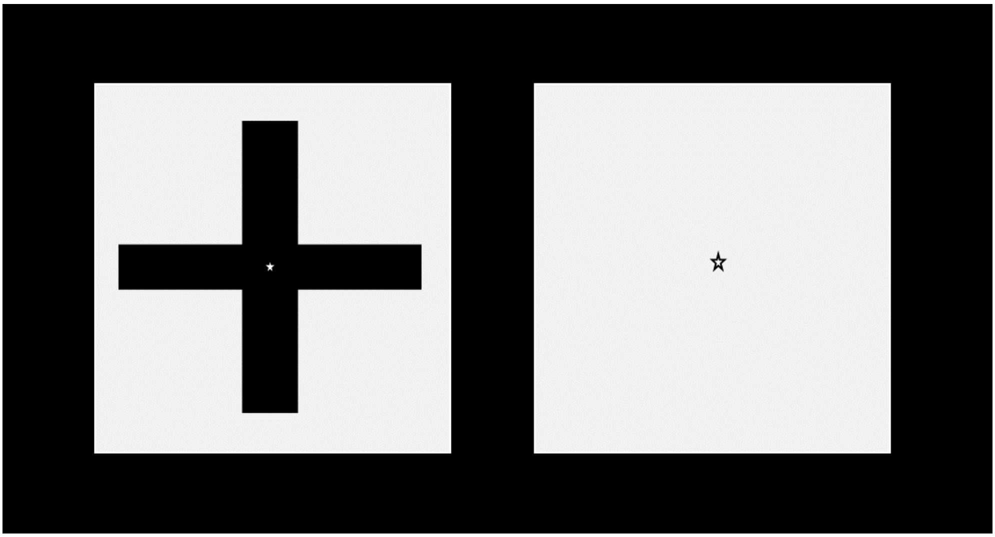


Figure 3 . *Illustration of an afterimage (S. Flodin). Look intensely at the star positioned in the middle of the black cross for at least 30 seconds. Then look over at the star in the white box on the right. You will see an afterimage of the cross.*

The theory was expanded by Johann Listing in 1856, and by von Helmholtz in 1866. Von Helmholtz experimented yet again by using the afterimage technique. By staring at mounted grids on the wall displaying vertical and horizontal lines, he discovered that upon shifting gaze from primary position (pp) to a tertiary position, the arms of the after image cross appeared to have undergone separate and opposed rotations. He concluded that the eye "only assumes positions that can be reached from a reference position by single rotations about position axes that lie within a two-dimensional plane in a three-dimensional space". The reference position is known as *primary position* (pp), and the horizontal plane that can be considered as passing through the centres of rotation of the eye balls was named *Listing's plane* (Thurtell, Joshi and Walker 2012).

To fully describe the position of the eyes in the head, three coordinates are necessary. The reference position, or starting position, is known as the *pp* of the eye. Two of these coordinates specify the vertical and horizontal rotation for elevation and depression, and for R and L gaze. The third coordinate is the "angle of torsion" and specifies the torsional rotation (cyclorotation) defined as "*rollung*" by Helmholtz in 1863 (Cahan 1993). Hence, what Donders had described earlier was in fact "pseudotorsion". Pseudotorsion occurs because when looking in the tertiary positions of gaze, the vertical and horizontal retina meridian do not coincide with a vertical or horizontal line in space, causing a tilt of image in tertiary positions (Simonsz and Tonkelaar 1990). A true rotation about the optic axis is ocular counter-rolling (OCR), where both eyes rotate when the head is tilted towards either shoulder. It is achieved by actions of the vertical recti and oblique eye muscles.

A more reliable system for describing eye rotations is the polar coordinate system. The position of the eyes is determined by two angles: the first angle defines the **direction** of the eye movement from the pp, and the second angle defines the **angle** of eye movement out of the pp. In this system, which was originally invented by Listing, all tertiary positons of gaze are reached by a simple rotation about a single axis. The system is based on what is known as *"Listings Law*" (Thurtell, Joshi and Walker 2012).

On clinical investigation of ocular movements, an examiner commonly uses the term *pp of the eyes*. This is the straight-ahead, upright position of gaze, and is used as a starting point from which all ocular movements to be examined are initiated. There are nine positions of gaze, one primary, four secondary and four tertiary.

Eye movements can be described by a set of defined rotations around axes known as *axes of Fick*. This is a coordinate system, and was first described in 1854 by a German physician, Adolf Eugen Fick. There are three axes, thought to pass through the centre of the eye, that help to describe the movement of the eye around a theoretical centre of rotation (Figure 4).

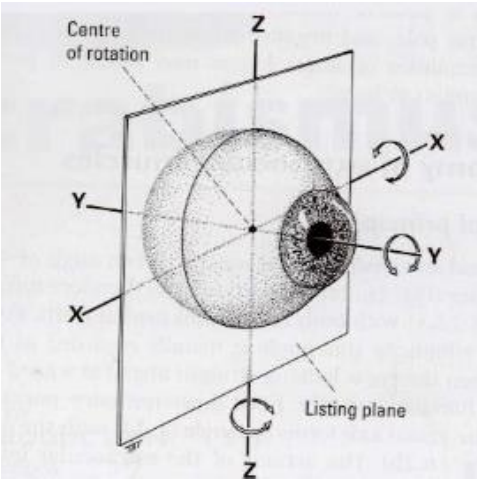


Figure 4. *Listing's plane and the axes of Fick. Illustration from:* [*https://images.app.goo.gl/4ivscCXbuWx8jMQR7*](https://images.app.goo.gl/4ivscCXbuWx8jMQR7)

Imagine a plane passing through the centre of rotation of the eye, containing an x, y and z-axis.

x-axis: Horizontal axis, for vertical rotations (elevation and depression)

y-axis: Antero-posterior axis, for torsion (extorsion and intorsion)

z-axis: Vertical axis, serves for horizontal rotations (adduction and abduction)

The eye muscles with their innervation achieve ocular movements. There are three types of basic ocular movements:

1) Ductions – monocular movements around axes of Fick
2) Versions – binocular, simultaneous, conjugate movements
3) Vergences – binocular, simultaneous, disconjugate movements (convergence, divergence)

In addition, involuntary and voluntary movements controlled by the brain serve to obtain, fixate and track visual stimuli. Eye movements serve to direct the fovea to an object of interest. Slow, smooth following movements of eye are known as *smooth pursuit*, and rapid eye movements that direct the fovea to a target are known as *saccades*. The vergence eye movements maintain binocular fixation when targets move in depth.

In order to maintain BSV during normal viewing, the two eyes need to move in unison. Muscles in the same eye that move the eye in the same direction, for example the R superior rectus (RSR) and the RIO, are called *synergists*. *Antagonists*, by contrast, are a pair of muscles in the same eye that move the eyes in opposite directions, such as the RLR and R medial rectus (RMR). *Yoke muscles* are a pair of muscles in each eye, that produce conjugate ocular movement, moving the eyes in the same direction, such as the RLR and the LMR on looking to the right (dextroversion).

There are also some laws regarding movements that govern ocular motility. In 1864, Karl Ewald Konstantin Hering established a theory of depth perception, called *Hering's law of equal innervation* (Cahan 1993). This law states that, during any conjugate eye movements, equal and simultaneous innervation flows to the yoke muscles, thus providing unity. Finally, *Sherrington's law of reciprocal innervation* states that "increased innervation to an EOM is accompanied by reciprocal inhibition of its antagonist"; thus, a muscle will relax when its opposite partner muscle, the antagonist, is activated (Lord and Wright 1950).

During normal viewing, retinal images need to be stable. If affected by head movement, there will be a motion blur, degrading visual acuity (VA). Compensatory eye movements moderated by two reflexes counteract this: the vestibulo-ocular reflex (VOR), which stabilises the retinal image and maintains fixation during brief head movements, and the optokinetic reflex (OKR), which stabilises retinal image motion during prolonged head movements. The two reflexes ensure that the retinal images are stabilised by counter-rotating the eyes relative to the head. An example is the optokinetic response called *optokinetic nystagmus* (OKN) that occurs in response to a moving visual stimulus on the retina. It allows the eye to observe the entire field of view, as the head remains stable. For example, if looking out of a window of a moving train, objects will rapidly move out of the field of vision, and the eyes will continually move back to their original position through a combination of slow- and fast-phase eye movements.

1.5 TORSION

The vestibulo-ocular system is highly complex. Although many great pioneers have given us the knowledge and understanding we have today, the phenomena related to ocular torsion still remain complex and are not yet fully understood (Wade 2010). Torsion of the eyes in near vision was studied by Meissner (1858), Volkmann, Helmholtz, and others, and torsional eye movements were studied in detail in 1869 by Le Conte (Maddox 1921). In 1943 Hermans concluded that torsion is a "normal phenomenon of vision"(Hermans 1943).

The entire history of the study of torsional eye movements up until 1985 has been summarized by Simonsz (Simonsz 1985).

Ocular torsion is a rotational eye movement around the ocular anterior-posterior visual axis. It is primarily thought of as an involuntary movement, but has been demonstrated as partly voluntary after training (Balliet and Nakayama 1978). The torsional physiological position of rest is referred to as *excyclotorsion* (Graf, Maxwell and Schor 2002).

Cyclorotation of both eyes in opposite directions is known as *cyclovergence*, and aids in obtaining or maintaining BSV. It affects the orientation of both eyes, and a change will affect the correspondence of retinal images. Conjugate cyclorotations of the eyes in the same direction are called *cycloversion*; these are naturally elicited via vestibular stimulation and keep images stable during head tilt.

Cycloversion and cyclovergence have been investigated under a number of experimental conditions. Spontaneous variability is reported as much lower in cyclovergence than in cycloversion. Cyclovergence stability is enhanced by a visual stimulus that provides clues for torsional eye position. It has been suggested that cyclovergence is therefore stabilised through visual feedback and that tolerance for errors in image correspondence is smaller than for image stability (Van Rijn, Van Der Steen and Collewijn 1994). Pansell et al. found enhanced torsional vergence stability during binocular compared with monocular viewing and proposed that this was probably an effect of the visual feedback during binocular viewing, presumably linked to correcting for vergence errors induced by head tilt (Pansell, Schworm and Ygge 2003). As with horizontal and vertical alignment of the eyes, torsional alignment is dependent on neural feedback. A faulty feedback from the binocular fusion process, will misguide the vergence process and lead to a sensory deviation (Guyton 2008). Fusion-based neuromuscular control mechanisms also maintain torsional position (Deng, Irsch, Gutmark et al. 2013).

Objective eye trackers allowed insights into eye movements, and much of the modern knowledge is derived from complex recording devices with the assistance of computers. Technological advancements identify mechanisms involved during voluntary and involuntary eye movements, as do digital images of eye position. However, these are all objective recordings and neither they nor laboratory tests can assess subjective deviations in depth. There is a gap between vision science and clinicians' work with patients, since both sensory aspects and ocular motility and ocular motor systems need to be considered. Also, it is not realistic to use these eye tracking methods in daily practice. Clinical experience and observations are important (Sackett, Rosenberg, Gray et al. 1996). Objective torsion only demonstrates how far the eye is rotated anatomically away from the normal position (Bixenman and von Noorden 1982; Guyton 1983). Subjective torsion testing, by contrast, records the patient's perceived torsional orientation of an object (Fray and Phillips 2003) (Figure 5a and 5b). As clinicians, we focus on the subjective torsion, especially as there are significant differences between subjective and objective torsion (Kushner and Hariharan 2009).

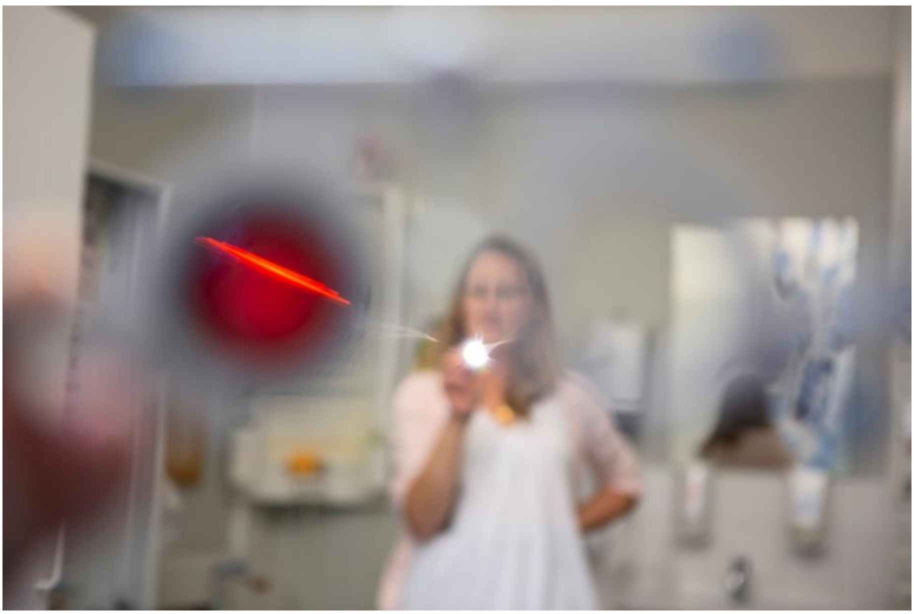


Figure 5a *The patient's view, illustrating a subjective tilt of the image when the patient is fixating a light source through a red Maddox lens. The patient will see an intorted image from the right (R) eye, as the eye is excyclorotated. We record the patient's subjective position of the eye, i.e. 10 degrees of excyclotorsion.*

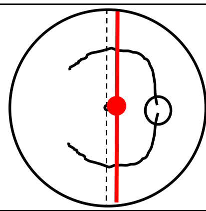
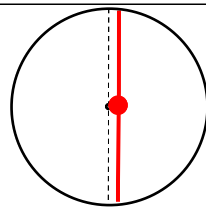
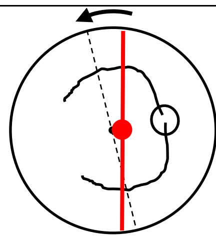
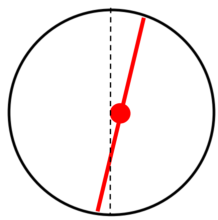
Illustration of the effect of a cyclo-deviated eye on the perception of visual direction		
	Normal eye position	Normal perception of visual direction
The normal eye position with the retinal vertical meridian (dashed line) in line with true verticality. The red line will be perceived as elongated in "earth vertical".		
	Excyclo-deviated eye	Tilted percept of the vertical line
The excyclo-deviated eye will project the red line in incyclo-direction relative the retinal meridian (dashed line). This will give a visual tilt of the line in opposite direction to the eye position.		

Figure 5b. *Illustration of the effect of a cyclo-deviated eye on the perception of visual direction (T. Pansell).*

As well as distinguishing between subjective and objective torsion, there is also a need to distinguish between symptomatic and asymptomatic torsion. The latter is sometimes combined with skew deviation and a head tilt and then forms part of the ocular tilt reaction (OTR), which consists of: skew deviation (vertical vergence), head tilt, and ocular torsion (cycloversion) elicited by the OTR components in the brainstem. If a head tilt is applied, OCR occurs. Although discovered 2 centuries ago, OCR has remained a controversial issue, as the rolling movements of the eyes about the line of sight are not easily detected or measured (Simonsz and Wade 2018). The extent of the rotation of the eyes is a fraction of the head tilt. Ocular counter-rolling has a gain of 0.1 when the head tilts laterally by 30 degrees, and the eyes rotate opposite by 3 degrees (Wade 2010).

In OCR measurements, it is important to discern between objective and subjective methods. A subjective method, such as the use of afterimages, utilises subjective localisation, i.e. the subjective perception of place in vision.

This localisation is dependent upon cerebral circuitry; and sensory adaptations to cyclodeviations are possible (Guyton 1988).

Subjective visual vertical (SVV) is the perceptual correlate of OTR. It is the ability to perceive verticality, and is tested to detect an abnormal subjective estimation of verticality. A person with vestibular disease may not perceive a vertical line as vertical because of an incorrect estimation of gravitational direction. In a study of 79 patients with acute unilateral brainstem lesions due to stroke, 53% had pathological SVV tilts, while ocular torsion was found in only 18%. Based on statistical lesion-behaviour mapping analysis, ocular torsion and tilt of SVV seem to share similar regions in the brainstem. These are: the vestibular nucleus, the medial longitudinal fasciculus, the inferior and superior cerebellar peduncles and the oculomotor nucleus (Lemos and Eggenberger 2013). Asymptomatic torsion has a reported prevalence of 94% in patients with acute lesions of the brainstem (Brandt and Dieterich 1992). However, in 2012 Frisén revealed a strong correlation between ocular torsions and subjective deviations in patients with lesions likely to affect the central vestibulo-ocular system (Frisén 2012).

1.6 STRABISMUS

For optimal visual function, the retinal image needs to be centred and stable, and projected on corresponding retinal points of the two eyes to allow binocularity. If the eyes do not align on corresponding areas when viewing an object, binocularity will be disrupted, leading to diplopia. If the motor vergence system is incapable of correcting for the misalignment, there will be a deviation, defined as strabismus. Strabismus may be caused by abnormal neuromuscular control of ocular motility, or abnormalities in BV. The prevalence of strabismus is approximately 1–5%, with some geographic variation (Bommireddy, Taylor and Clarke 2020; Hashemi, Pakzad, Heydarian et al. 2019; Hultman, Beth Høeg, Munch et al. 2019). The nomenclature and classification of *strabismus* is dependent upon the presence, amount and direction of the deviation. The deviation can be latent (a *phoria*) or constant (a *tropia*), and may be intermittent depending on binocular stability. Depending on age of onset, a strabismus can cause various symptoms. In childhood, because of the ongoing development, the brain will supress the image from the deviated (weaker) eye, and if constant, this results in abnormal visual development with loss of VA (amblyopia). This can be treated by vision therapy if detected in time. In adults, who already have a fully developed visual system, the most common symptom will be diplopia or asthenopia. In both children and adults, strabismus will degrade BV, and may cause appearance-related psychosocial distress.

1.7 CYCLODEVIATION

Cyclodeviation is the misalignment of cyclotorsion between the two eyes, which may or may not be fused depending on cyclovergence and any other disturbing factors on binocularity. A cyclodeviated eye does not correct itself when the other eye is torted (von Noorden and Campos 2002), hence it is not a tropia. Cyclodeviation needs to be judged on the basis of the relative position of the two eyes. Torsion leading to cyclodeviation is difficult to detect, unlike other misalignment of the eyes that is visible on appearance and in response to a clinical cover test.

Alison Bradburne described the condition in the literature as early as 1910, as follows:

> It can, when untreated, lead to a state of matters which becomes really serious for the patients and most unsatisfactory for those whose duty it is to treat them. The cause must be of a trifling but persistent nature. Persistent because of its effects, and trifling because of its escaped detection (Bradburne 1910).

Evaluation of cyclotorsion is clearly indicated if a patient complains of torsional diplopia, perceiving a tilted image with both eyes open. This assessment is often neglected in patients who are unable to fuse, yet lacking to describe this specific complaint (Rosenbaum and Santiago 1999), or who are without a measurable strabismus (Miller 2015). These symptoms are infrequently reported in isolation (Lemos and Eggenberger 2013). However, cyclodeviation may become an obstacle for patients to obtain or maintain binocular fusion, either in combination with other deviations or alone depending on the amount. Clinically relevant disturbances of cyclodeviation are primarily encountered in superior oblique palsies (SOP). Patients with cyclodeviation in infancy/early childhood are often able to make a sensory adaptation to compensate for the condition. (Guyton 1988).

Adults with cyclodeviaton and cyclodiplopia require surgical intervention to reposition the eyes into normal correspondence to restore normal binocularity and fusion.

1.8 SUPERIOR OBLIQUE PALSY

Fourth nerve palsy, or SOP, is the most common isolated EOM palsy (Khawam, Scott and Jampolsky 1967; Sheeley and Arnoldi 2014). It may be acquired or congenital; the congenital version can develop problems over time if decompensation occurs. Time of onset and diagnosis is of relevance, as sensory and motor adaptations can take place. The more severe the cause of the innervation interruption, the more symptoms there will be from the resulting strabismus. The classic presenting external signs are hypertropia of the affected eye, and a head tilt to the non-affected hypotropic eye. The non-visible symptom is a large excyclotorsion, as the SO torsional actions fail to function normally.

The diagnostic procedure for a vertical muscle pareses or paralysis or a head tilt, is aided by the three-step test also known as the *Parks three-step test* or the *Bielschowsky Head Tilt Test* (*BHTT*). Step one determines which eye is hypertropic in pp; step two, in which direction of gaze the vertical angle increases; and step three, on which side of the head tilt the hypertropia increases. For example, a patient presents with a R hypertropia. There are four muscles that can be at fault: RSO, RIR, LIO, LSR. Does the hypertropia increase in right or left gaze? If the angle is larger in left gaze, this reduces the possible muscles to two: the LSR or the RSO. On tilting to which side does the size of the deviation increase? If the increase is larger on R tilt, the isolated muscle at fault is the RSO. Tilting the head towards the L causes intorsion of the L eye, and extorsion of the R eye. In a SOP, if the SO muscle is not functioning normally, the eyes will compensate the defect through its synergist – the opposing SR. The test tends to be most useful and demonstrative in acute onset, due to compensatory mechanisms associated with muscle sequeale. Torsion must also be measured.

1.9 THE ROLE OF THE ORTHOPTIST

The world's first orthoptist was Mary Maddox (1897–1972), the daughter of Dr Ernest Maddox (1863–1933), a British surgeon and ophthalmologist. He was a specialist in abnormal vision and heterophoria (Maddox 1921) and invented several devices for investigating orthoptic conditions, such as the Maddox rod, Maddox cross and Maddox wing. In diagnosing and treating abnormalities of the ocular muscles and BV, he saw the need for a new medical auxiliary profession and taught his daughter the principles of orthoptics. Orthoptists are recognised as allied health professionals, and the orthoptists role in eye health care has expanded significantly since the 1930s. One of the important areas of treatment for strabismus is known as *orthoptic treatment*, and was started by Mary Maddox in London in 1919 (Rankin 1939). It has been said that "orthoptics is the most important part in the treatment of strabismus" (Macneil 1942).

1.10 CLINICAL IMPLICATIONS

The topic of torsion continues to intrigue and baffle us, as the ocular system is: "phenomenally complex yet elegantly functional" (Kushner 2004). Torsion is a normal phenomenon, occurring in normal vision, most commonly as excyclotorsion. Cyclodeviation is frequent in SOP; however, the measurement of torsion should always be part of a complete orthoptic assessment in patients with a vertical deviation. Correct diagnosis is essential, and can only be achieved by a thorough clinical investigation. To carry out a full clinical assessment it is important to choose appropriate clinical tests and know how to interpret the results in order to plan suitable management. It is also important to be aware of limitations and normal variability. To ensure a high level of care, it is imperative to evaluate outcomes and individual needs.

2 AIMS

2.1 OVERALL AIM

The overall aim of this thesis was to explore the past, investigate the present and gain knowledge for future management of cyclodeviation. To validate methods for diagnosis and treatment and reflect on healthcare management for patients with cyclodeviation.

2.2 SPECIFIC AIMS

2.2.1 PAPER I

To evaluate different techniques and clinical tests that measure cyclotorsion, and therefore cyclodeviation, and to determine their reliability and repeatability and clinical relevance.

2.2.2 PAPER II

To investigate cyclotorsion, cyclodeviation and cyclofusion in a group of healthy subjects to establish standard reference ranges.

2.2.3 PAPER III

To review cyclodeviation measurements in clinical practice pre- and post-operatively, to assess and verify management guidelines.

To evaluate the surgical outcome, dose-effect relationship and long-term results of a graded approach to the modified Harada-Ito procedure in patients with symptomatic cyclodeviation.

2.2.4 PAPER IV

To evaluate and reflect upon the impact and influence of cyclodeviation on HRQoL in patients before and after surgery.

To assess HRQoL in patients diagnosed with cyclodeviation, and evaluate subjective change following surgical treatment using the Adult Strabismus-20 (AS-20) questionnaire, consisting of a functional and a psychosocial subscale.

3 METHODS

3.1 BACKGROUND TO THE PAPERS/A SURVEY OF THE FIELD

3.1.1 PAPER I

Study I (*Paper I*) has several purposes:

1) to investigate whether subjective cyclotorsion measurements, in degrees, differ when using different methods of testing.
2) for each test, to investigate whether subjective cyclotorsion measurements are repeatable over time.
3) to investigate and decide on an appropriate test to use in the clinic.

Due to variations of methods for measuring cyclotorsion, the main aim of this study was to investigate whether cyclotorsion measurements, in degrees, differ between different measuring methods; in other words, does it matter which method we choose, and are the measurements comparable and repeatable? Reviewing leading textbooks for orthoptic degree courses shows variations in recommended methods for measuring cyclotorsion. The study focuses on subjective methods. Appropriate and detailed diagnostic testing form the basis of suitable treatment plans in orthoptic patient care.

A number of tests have been described as useful in measuring the amount of subjective cyclotorsion and cyclodeviation. These include:

- The *Awaya cyclo test*, developed by Awaya in 1982 for quick quantitative measurements of cyclodeviation (Awaya, Sato, Kora et al. 1997). A series of pairs of half-moons, one red and one green, are viewed through a pair of red-green glasses. The half-moons are tilted by various degrees, and measurement of cyclodeviation is thus obtained.
- The *afterimage test* on the synoptophore using special synoptophore slides (Sood and Sen 1970) and further modified special synoptophore slides without after-image method (Sen, Singh and Shroff 1977).

- The *Maddox wing* with a torsion lever (Charters 1936), the *Maddox double prism*, and *Maddox rod tests* (Almog, Nemet and Ton 2014; Howard and Evans 1963; Roper-Hall 2009).
- *Bagolini striated glasses* (Ruttum and von Noorden 1984).
- The *Lancaster red green test* (LRGT) (Awadein 2013; Christoff and Guyton 2006; Roper-Hall 2013).
- The s*ynoptophore* (Harden and Dulley 1974; Pratt-Johnson and Tillson 1987; Veronneau-Troutman 1972).
- The *Lee screen* using an adapter (Ansons and Davis 2014).
- The *torsionometer* (Georgievski and Kowal 1996).
- The *Harms tangent screen* (Schworm, Boergen and Eithoff 1995; Schworm, Eithoff, Schaumberger et al. 1997).
- *The computerised torsion test* (CTT) (Kim, Yang and Hwang 2017).

Some of these test methods are rare, experimental and barely heard of, and moreover, they are not available in clinical practice. Methods of preference and availability vary across orthoptic practices in Europe, and some apparatus may not be available everywhere (Tyedmers and Roper-Hall 2006). The most common tests in the clinic are the synoptophore and the DMRT (Guyton 1983).

The *synoptophore* is used with "traditional" Maddox synoptophore slides, or phoria slides (Figure 6a and b). An advantage of using the synoptophore is the static position of the subject, and the ability to perform measurements in different positions of gaze (Sharma, Thanikachalam, Kedar et al. 2008).

Figure 6a. *The Haag-Streit Clement Clarke Synoptophore "model 2003".*

Figure 6b. *Slides A17/18, top, and A17a/18a, bottom, used when assessing cyclotorsion.*

The *DMRT* can be performed with either two red Maddox lenses (Ansons and Davis 2014) or one white and one red lens (Pratt-Johnson and Tillson 1987; von Noorden and Campos 2002). Wright and colleagues describe using the Maddox Rod test with any variant using either a single lens, *the single Maddox rod test (SMRT)*, or a lens on each eye, the DMRT, which can be either red and white or only red (Wright, Spiegel and Thompson 2006). This is in direct contrast to the finding by Simons and colleagues, that using both a red and a clear lens induces artificial cyclodeviations to one eye in patients with SOP, and hence the recommendation to use two red lenses (Simons, Arnoldi and Brown 1994). The DMRT has been described as one of the methods most commonly used in clinics, although it may cause artefacts in the results and there are discrepancies in the technique.

The *SMRT* is the preferred method used in our clinic (Figure 7). It is a dissociative test, as one eye is used for fixation and the other eye has the red glass in front for adjustment of torsion.

The original Maddox rod was a hand-held paddle, and consequently only one Maddox was used. Almog et al. compared measurements between the DMRT (two red lenses) and the SMRT on patients with SOP, and found no statistically significant difference between measurements (Almog, Nemet and Ton 2014).

Figure 7. *Single Maddox rod test (SMRT)*

In Sweden, a new device for measuring cyclotorsion, the *KMScreen*, had been introduced by the time the present study was planned. This is a digital Hess screen which also records torsion (Figure 8). The use of computerised testing, such as by this method, is becoming increasingly popular in clinical practice across the country. There have been no published studies evaluating this method so far. However, Harden & Dulley stated already in 1974 that, "with a technique of measuring torsion that is reproducible, more insight into some ocular motility problems will come" (Harden and Dulley 1974). It is hoped that the KMScreen method will contribute to such insight.

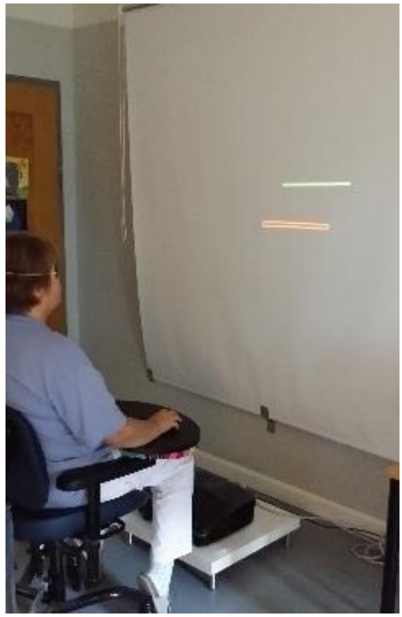


Figure 8. *The KMScreen test.*

3.1.2 PAPER II

The aim of this study was to investigate how much cyclotorsion is present in a healthy subject, and what is "normal" to fuse? The purpose of this investigation was to establish clinical parameters of cyclotorsion and cyclofusion in a healthy adult population. To investigate how much cyclodeviation is present and tolerated before it is perceived to interfere with binocular viewing. A general reference range will aid in clinical management of patients suffering binocular disruptions.

A reference range is a basis for comparison for health professionals to interpret a set of test results for a particular patient. So far there have been no studies or literature describing what to expect as "normal" clinical values of cyclotorsion in a patient population, and therefore there are at present no reference ranges for cyclodeviation. Having established the differences between measurement techniques, we need to know where the norm lies within the methods with the highest and lowest measurement ranges. Unless a normal reference range is known, the limits of cyclotorsion and cyclofusion cannot be established, nor can it be determined when and why cyclotorsion can become a fusional problem for the patient. What should clinicians be observant for?

Cyclofusion is the sensory and motor torsional fusional reserves whereby cyclodeviations are controlled. It is known that BSV is affected by torsion, but it is currently unknown at what degree torsion becomes significant, or what healthy cyclofusion ranges are (Georgievski, Sleep and Koklanis 2007). Previous investigations on how much deviation can be controlled without needing treatment were mainly observations on objective status through fundus photography, or through simulated deviations using experimental haploscopic devices (Guyton 1988; Herzau and Joos-Kratsch 1984; Sen, Singh and Mathur 1980; Sharma, Prasad and Khokhar 1999). Therefore, none of these studies used ordinary clinical tests.

3.1.3 PAPER III

The next step was to evaluate our clinical approach to management of cylodeviation. The purpose of this study was to evaluate and validate the measurements of cyclodeviation and cyclofusion in the clinic using the graded approach we adopted for the modified Harada-Ito surgical technique.

Modified Harada-Ito surgery is a well-established surgical procedure to correct cyclodeviation (Fells 1974; Mitchell and Parks 1982). In order to review our measurement technique and success rate of correcting the cyclodeviation, we evaluated the dose-effect scale of modified Harada-Ito surgery based on our measurements of cyclodeviation pre- and post-operatively.

3.1.4 PAPER IV

In the fourth study (*Paper IV*), we looked at the impact of cyclodeviation on HRQoL. Specifically, we asked, How do patients experience their symptoms of cyclodeviation? Evaluating subjective measurements and reference ranges gives us values of cyclodeviation and angles that need to be treated. The purpose of this paper was to evaluate the main symptoms and problems relating to the condition of cyclotorsion are as experienced by the individual. Is there a specific common denominator? Can a questionnaire be helpful in finding, diagnosing and improving management of cyclodeviation?

Cyclodeviation disrupts the ability to fuse images, yet clinical experience and literature review shows that it is very rarely a specific patient complaint. When images are perceived as double, it is not always recognised that they may also be tilted. How do patients with cyclodeviation experience their symptoms, and after alleviation, are they aware of what they suffered from?

What do clinicians and examiners need to be vigilant upon? What are the primary factors to be aware of, apart from purely measuring strabismus and torsion? What are the key areas in a patient's condition that disconnect the fusional abilities and create symptoms of cyclodeviation? What can these patients tell us that can improve patient care, and can these experiences aid in the decision for, and choice of, surgical interventions, such as type of surgical procedure and timing?

Patient-related outcome measures (PROMs) are tools used to assess outcomes for the patient, such as quality of care, and health gains. They allow measurements of efficacy of the clinical intervention from the patient's perspective, and give the clinician a report directly from the patient. They completely represent the patient's viewpoint on a disease or treatment, which may not otherwise be captured but may be as important as a clinical measure.

3.2 DESIGN, METHODS AND PARTICIPANTS

3.2.1 PAPER I

Design and methods:

The first study (*Paper I*) had a quantitative prospective design, and is an experimental, longitudinal, repeated-measures study. The amount of cyclotorsion present, in degrees (dependent variable) was measured using the following measuring methods (independent variables):

1) Synoptophore (Haag Streit UK, Harlow, UK)
2) Single Maddox rod (SMR)
3) KMScreen

Measurements were compared, and individual methods checked for repeatability.

Participants:

Participants were all new referrals from the orthoptic waiting list at the Department of Ophthalmology, Sahlgrenska University Hospital, Mölndal, with a vertical deviation stated as the primary reason for referral. The reason for the criterion of a vertical deviation was to increase the chances of cyclodeviation being present. The subjects were recruited by criterion and convenience, a non-probability and non-random sampling procedure. Participants were selected based on their availability for the study, and by meeting the criterion.

The sample size was 20 patients. This size was the average number achieved from a power calculation using standard deviation (SD) and difference in means from previous comparative studies (Georgievski and Kowal 1996; Sharma et al. 2008).

All individuals were examined by the same orthoptist (S.F.). Each patient was measured for cyclotorsion on two occasions using the three different methods. The aim was to repeat the measurements for each subject after 4–6 weeks, under the same conditions; notes were not looked at between visits.

3.2.2 PAPER II

Design and methods:

Paper II reports a cross-sectional, prospective cohort study. The amount of cyclotorsion, in degrees, and cyclofusion was measured using two measurement methods:

1) Synoptophore
2) SMR

These two methods measured the highest and lowest values of cyclotorsion in the sample reported in *Paper I*.

Participants:

The measurements were performed on a random sample group of 120 healthy, non-strabismic adults (60 women, 60 men) in the age range of 18–69 years, representing a "normal population". Patients were recruited if they met the inclusion criterion (healthy, no previous eye disorders) and by convenience, i.e. their availability for the study, a non-probability and a non-random sampling procedure. The number of participants were derived from power calculations based upon references from previous research and *Paper I*. According to guidelines from Statistiska centralbyrån (SCB), reference ranges should be established locally and with at least 120 patient samples to establish a statistically significant reference interval (Sweden 2016).

The sample were divided into three age brackets during statistical analysis: group 1 = 18–34 years, group 2 = 35–51 years, and group 3 = 52–69 years old. Cyclofusion was investigated with the synoptophore in 60 subjects, 20 from each age bracket and including an equal number of men and women. All individuals were examined by the same orthoptist (S.F.).

3.2.3 PAPER III

Design and methods:

Paper III reports on a cross-sectional retrospective cohort study of results after surgery for cyclodeviation. The medical records of patients diagnosed with cyclodeviation, and having undergone the modified Harada-Ito procedure at the Sahlgrenska University hospital using a graded approach, were reviewed retrospectively from 2012, when the technique was introduced, to 2019, a 7-

year period. The efficacy of the procedure was evaluated by comparing pre-operative with post-operative torsion and reviewing how much effect was aimed to be achieved vs how much effect was actually achieved.

Participants:

The study included 27 patients aged 22–80 years who had undergone Harada-Ito surgery by the same surgeon (P.K.). Cyclodeviation was measured using the SMR method and the synoptophore; all measurements were performed by the same orthoptist (S.F.). All patients had undergone a full orthoptic and ophthalmological assessment and were found to have SOPs of different aetiologies. Data reviewed included aetiology, ocular motility assessment, pre- and post-operative measurements, pre-operative fusion, factors affecting surgical choice, post-operative outcomes, and time elapsed from surgery to the last post-operative assessment.

3.2.4 PAPER IV

Design and methods:

Paper IV reports on a prospective cohort study using PROMs. Health-related QoL was measured in patients diagnosed with cyclodeviation, and change following surgical treatment was subjectively evaluated. The AS-20 questionnaire, consisting of a functional and a psychosocial subscale, was used as assessment tool.

Participants:

The study was performed between 2014 and 2019. Adult patients diagnosed with cyclodeviation, and due to undergo corrective strabismus surgery at Sahlgrenska University Hospital during that period, were included. All patients were examined and treated by the same orthoptist (S.F.) and surgeon (P.K.). Pre-operative and post-operative QoL scores were collected from 26 patients, who self-completed the AS-20 questionnaire (score 0–100).

4 STATISTICAL ANALYSIS

All the study data for all studies (*Papers I-IV*) were recorded into Excel (Microsoft Corporation, Seattle, WA, USA), stored, and analysed in SPSS (IBM Corporation, Somers, NY, USA) by S.F. A positive value was assigned to incyclotorsion, and a negative value to excyclotorsion.

Percentages, means, medians, SD, ranges and 95% confidence intervals (95% CIs) were calculated for descriptive purposes. Statistical analyses were performed using Microsoft Excel for *Papers II–IV*, SPSS Statistics, version 24 (IBM Corporation) for *Papers I–IV*, Graph Pad Prism 7 XLM, version 7.02 (GraphPad Software, San Diego, SA, USA), for *Paper II*,and SAS/STAT® software (SAS Institute Inc., Cary, NC, USA) for *Paper IV*. The level of significance was set at $p<0.05$. Statistical analysis was performed by S.F. and T.P. for *Papers II–IV*, and S.F. for *Papers I–IV*, with help from Statistik gruppen, Gothenburg, Sweden, for *Papers I* and *IV* and Anna Rehammar from Akademistatistik for *Paper III*.

For *Paper I*, once the data were collected, they were found not to be normally distributed. The normality of the data was assessed using histograms and plots, and calculated for skewness and kurtosis. The Friedman test is the non-parametric alternative to one-way analysis of variance (ANOVA) with repeated measures, and was used for analysis once the data showed deviations from normality. This was followed by the Wilcoxon signed-ranks test, and a post-hoc analysis to identify where the differences lay. Bonferroni adjustment was used to minimise the risk of a type I error. To evaluate the repeatability of each test, the distribution of the change from test to retest, Bland-Altman's limits of agreement (LoA) method, intra-individual SD and intra-class correlation coefficient (ICC) were used. Systematic changes between test and retest were analysed with an exact permutation test.

For *Paper II*, the mean and median degree of cyclotorsion and cyclodeviation (summed fixing R eye and fixing L eye for the SMRT) in a straight-ahead gaze position was used for each subject. Cyclotorsion and cyclofusion data were found to be normally distributed and were then analysed using parametric methods. The ANOVA test was conducted with SPSS and multiple comparisons were done after applying Bonferroni correction to the p-values. Correlation analysis was done with Pearson's correlation coefficient. Variations were checked for gender or age specificity.

In *Paper III*, subjective cyclodeviation pre- and post-operatively in straight-ahead gaze was assessed for surgical outcomes. The change in alignment from pre-op to final post-op was evaluated using the Wilcoxon signed-rank test (SPSS). Bivariate regression analysis was performed for each independent variable (predictor) that may influence the dependent variable of the final amount of cyclodeviation post-operatively. For this purpose, aetiology was graded on a severity scale.

In *Paper IV*, to enable comparisons between groups, Fisher's non-parametric permutation test was used for continuous variables. For comparison within groups, Fisher's non-parametric permutation test for matched pairs was used. To evaluate potential baseline characteristic differences, the chi-square test for non-ordered categorical variables and the Mann-Whitney U-test and Kruskal-Wallis test for continuous variables were used. Spearman's correlation was used for correlations analysis of age and response.

5 RESULTS AND DISCUSSION OF SPECIFIC PAPERS

5.1 PAPER I

The majority of subjects demonstrated excyclotorsion. Counterbalancing determined the test order. Cyclotorsion was measured first with the SMR in eight study subjects, with the synoptophore in six subjects and with the KMScreen in six subjects during the first round of measurements. In the second round, cyclodeviation was measured first with the synoptophore in eight study subjects, with the SMR in six subjects and the KMScreen in six subjects. This also meant that all the subjects had a different test order in measuring rounds one and two.

There were significant differences in torsional values between the synoptophore and the SMR (p=0.025), and between the SMR and the KMScreen test (p=0.025), but not between the synoptophore and the KMScreen test (p=0.90).

We also looked at total cyclodeviation measurements between the three tests. This showed a statistically significant difference between all three methods, X^2 (2) = 15.65, p<0.001. At the p<0.05 significance level there were significant differences between the synoptophore and the SMR (p=0.001), the SMR and the KMScreen (p=0.046), and the KMScreen and the synoptophore (p=0.012) (Figure 9).

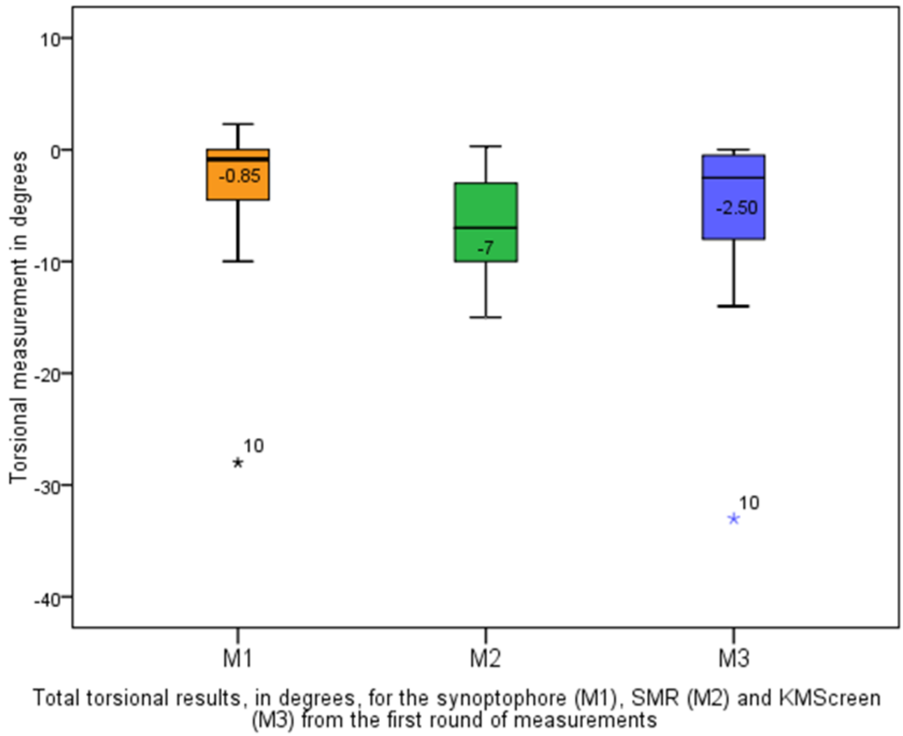


Figure 9. *Box and whisker plots showing the group median values for excyclotorsion and incyclotorsion, measured using three different methods (M1–M3), the synoptophore, single Maddox rod (SMR) and KMScreen, and analysed using the Friedman test and Wilcoxon analysis. The band in the box displays the median value, the whiskers the interquartile range (IQR); and the asterisks represent outliers not included in the whiskers.*

Post-hoc analysis with Wilcoxon signed-rank tests was conducted with a Bonferroni correction applied, resulting in a significance level set at p<0.017. Median (IQR) perceived torsional measurements for the synoptophore, SMR and KMScreen tests were -0.85 (-5.10 to 0.00), -7.00 (-10 to -2.50) and -2.50 (-8 to -0.25), respectively. At the p<0.017 significance level, there were no significant differences between the KMScreen and SMR tests (*Z*= -2.35, p=0.19) despite an overall difference perceived in torsional measurements. However, there was a statistically significant difference in torsional measurements between the synoptophore and the SMR (*Z*= -2.64, p=0.008) and between the KMScreen and the synoptophore (Z= -2.46, p=0.014) (Table 2).

***Table 2**. Results of the post-hoc analysis with the Wilcoxon signed-rank test to compare three methods of measurement, using the synoptophore, single Maddox rod (SMR) and KMScreen, for measurement of torsion. [b] =Based on positive ranks; M = method, Z = score of how many standard deviations (SDs) the value is from the mean; Asympt. sig. (two-tailed) p = asymptotic significance p-value.*

	Synoptophore (M1) vs SMR (M2)	**KMScreen (M3) vs SMR (M2)**	**KMScreen (M3) vs synoptophore (M1)**
Z	-2.64[b]	-2.35[b]	-2.46[b]
Asympt. sig. (two-tailed) p	0.008	0.19	0.14

For repeatability, graphs of differences against means were plotted for the different methods (Bland and Altman 2010, 2012). The Wilcoxon paired measurements test was performed on the repeatability measures of each test. No statistically significant differences were found between the two sets of data for each subject on each test. A Wilcoxon signed-rank test showed that measuring with the same test on two different occasions did not elicit a statistically significant change in torsional measurements in individuals with vertical deviations. Values for the synoptophore were Z = -0.66, p= 0.51; for SMR, Z= -1.07, p=0.29, and for KMScreen, Z= -1.32, p=0.19. The synoptophore yielded the best, and the KMScreen the worst repeatability. Median (IQR) perceived torsional measurements for the synoptophore, SMR and KMScreen tests are presented in Table 3.

Table 3. *Results of the repeatability analysis using the Wilcoxon signed-rank test: torsion measured by three methods, using the synoptophore, single Maddox rod (SMR) and KMScreen, at two rounds of measurements. [b] =Based on positive ranks; Z = score of how many standard deviations (SDs) the value is from the mean; Asympt. sig. (two-tailed) p = asymptotic significance p-value.*

	Synoptophore		**SMR**		**KM Screen**	
Visit	1st	2nd	1st	2nd	1st	2nd
Median (IQR)	-0.85 (-5.1; 0.0)	-1.65 (-4.8; 0.0)	-7 (-10.0;-2.5)	-7.15 (-10.0; -1.4)	-2.5 (-8.0;-0.25)	-1.5 (-6.0; -0.0)
Z	-0.66[b]		-1.07[b]		-1.32[b]	
Asympt. sig. (two-tailed) p	0.51		0.29		0.19	

In *Paper I*, we showed that:

1) The measurements of cyclotorsion varied considerably between the methods, which differ in how they measure cyclotorsion. The results showed significant differences in the same population, measured under the same conditions by the same examiner. The SMR method measured a larger amount of excyclotorsion compared with the other two methods, while the synoptophore method gave the smallest amount. The smallest difference between methods were between the SMR and the KMScreen, while the largest difference was found between the SMR and the synoptophore, which was significant (p=0.008).
2) All three methods were repeatable; they can all be relied upon to measure torsion in the same subjects. The synoptophore showed the most repeatable values, while the values obtained with the SMR and the KM Screen were similar between the measuring occasions.

5.1.1 CLINICAL RELEVANCE

Both of these findings are clinically relevant. The validity of a test, and knowing that "what we set out to measure; is what we get", is crucial when it comes to treatment plans. The best way to achieve validity is to evaluate the tests we use in our everyday clinical work and see if tests are comparable and, hence valid to use. Gaining various different measurements in the same patient by using different tests or methods may affect management options and choice of surgical procedure. Some tests may prove better suited for screening/investigation purposes and others better for management. We need to ensure that follow-up is always done using the same test, and we further need to consider the testing quality when measuring torsion pre-operatively. Hence, when investigating and evaluating cyclotorsion in patients with vertical deviations, we should be aware of the differences between test methods.

5.1.2 TECHNIQUE, FIXATION DISTANCES AND IMAGE DISSOCIATION

The results indicate that the SMR "overestimates" the degree of torsion compared with the other two methods. This may be due to the "free space" and dissociative character of the SMR test. Possibly the "overestimation" also has to do with the illumination. When performing the SMR, the subject is dissociated and in a darkened room fixating on a light diode. The normal references or clues used in everyday fixation disappear; and under these circumstances, patients may become more aware of their cyclotorsion. This circumstance completely dissociate the patient from any other fusional reserves which otherwise aid in compensating for the cyclodeviation. As otherwise the patients could be expected to describe more complaints and symptoms, we believe that this is quite feasible.

The synoptophore gave a lower measure of torsion in the same patients. This difference may be due to the controlled nature of the test, which allows adjustment for any horizontal and vertical component of the deviation, and measures only the torsional component of the deviation. When planning management, it is important to establish whether cyclotorsion makes a difference to the patient's fusional abilities. It is necessary to get as accurate results as possible, especially when surgery is the choice of management. Although the SMR method has proved sufficient to establish the presence or absence of torsion in a patient and to monitor change, if a patient has consistent diplopia and requires surgical management, the synoptophore is more suitable. Overestimating torsion would greatly affect the surgical procedure, and patients would suffer if left with overcorrections.

The subjects in this study who required surgery for their deviations did not experience any trouble with torsional images. None of them had a “new” deviation; they were all congenital or decompensated. Only one patient had a “fresh” SOP (caused by head trauma), which resolved without treatment by the time the study was completed. Results may have been different if torsion had been measured in subjects with newly developed SOP only. There is probably a difference between the cyclotorsion of a congenital or decompensated condition of strabismus, and an acquired one. Cyclodeviation is compensated for by cyclofusion through cyclovergence. To find out the “average” amount of torsion, one would need to establish how much torsion is present and controlled in a normal subject.

The SMR is performed at 3 m, the KMScreen at 1m, and the synoptophore simulates an infinite fixation distance. The fixation distance may influence the torsion results, due to oblique muscle action. The oblique muscles have a greater influence on vertical power for near (Ansons and Davis 2014); this would increase torsional action and favour the KMScreen which gives larger torsional values in subjects with oblique dysfunction. The SMR should neutralise this influence, by using an in-between distance. However, there were no trends in the results to indicate effect of fixation distance on amount of torsion. Again, torsional values are probably more dependent on the cause and duration of the strabismus.

Both the synoptophore and the KMScreen measure deviation via testing for parallelism of images; retinal rivalry may influence movement. With the SMR, by contrast, the subject needs to see only one horizontal line and place it straight; there is no reference for comparison or adjustment. Free space performance vs the static positioning in the synoptophore must also influence the ability to fuse images, as eyes are more relaxed in free space under dissociative conditions. The higher yield of torsion measured using the SMR and the KMScreen reflects the dissociative factors and probably ocular dominance. It is not known how much the digital technique in the KMScreen contributes to possible distortion of the projected image, and in turn affects perceived torsional tilt. The scale reading of the KMScreen is computed; and the scale on the synoptophore is more precise than the reading on the trial frames of the SMR.

It was assumed not necessary for subjects to wear refractive correction during testing, due to possible prismatic displacements of images being induced. Also not deemed fundamental for performance. In this study, all subjects had good VA for distance; near vision was not examined. However, in patients who suffer from large refractive errors (especially large degrees of astigmatism) this could influence performance and results, especially in perceiving images in the digital KM Screen test (Tjon-Fo-Sang, de Faber, Kingma et al. 2002).

5.2 PAPER II

Healthy, non-strabismic adults in all age groups showed low values of cyclotorsion, mainly excyclotorsion. Mean and median values for the whole sample were -1 degree for both methods. Standard reference ranges of cyclotorsion for men and women were between -0.7 and -1.5 degrees for the SMR method and between -0.6 and -1.4 degrees for the synoptophore method. Cyclofusion ranges in adults showed a total mean amplitude of 16 (SD 3.96) degrees. The mean cyclofusion range for the whole sample group was +7 (SD 1.97) degrees incyclofusion to -9 (SD 2.59) degrees excyclofusion. The excyclofusion range (min; max values -2; -16 degrees) was significantly larger than the incyclofusion range (min; max values 3; 12 degrees), p=<0.001.

This is the first study providing subjective cyclofusion measures in a normal adult population. The results suggest that cyclotorsion >7 degrees of excyclotorsion or >9 degrees of incyclotorsion interferes with vergences, BSV and cyclofusion. The individual values for each subject are presented in Figure 10.

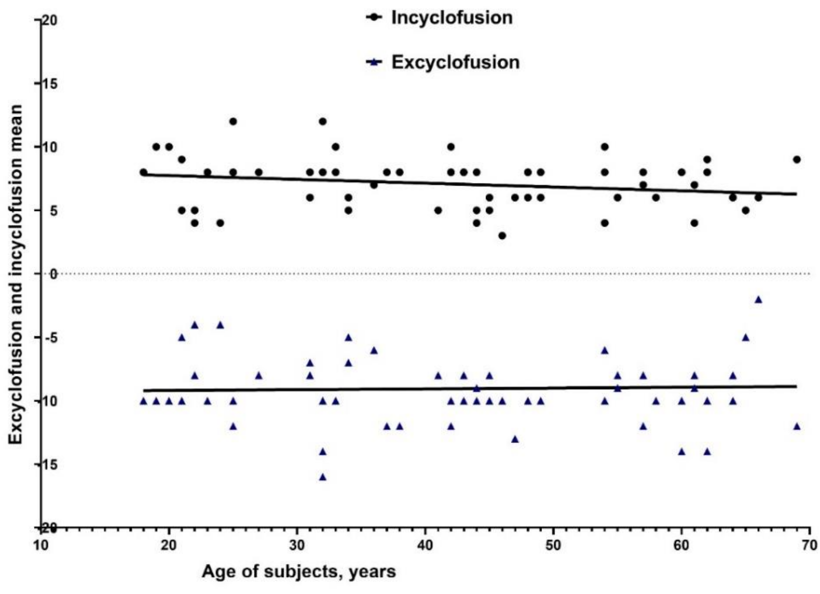


Figure 10. *Scatter plot of individual cyclofusion values by age (18-69) showing incyclofusion (positive) and excyclofusion (negative).*

There was no significant age or gender-related effect on incyclofusion, excyclofusion or the total cyclofusion range, p=0.59. Nor was there a significant gender effect on excyclofusion However, a slight increase in excyclotorsion with age was observed, which was statistically significant, p=0.026.

In *Paper II*, we report normative values of cylotorsion, which provides clinicians with a reference range considered as useful in clinical investigation and management of cyclodeviation. The results suggest that a small increase in cyclotorsion (>-2°), may be sufficient to disrupt the ability to fuse binocular images, and that cyclotorsion >10 degrees disrupts vergence, causing dissociating of BSV.

5.2.1 CLINICAL RELEVANCE

These results are valuable in aiding the clinical investigation and management of patients who are experiencing fusional problems. Patients who complain of problems with double vision or with maintaining binocularity, with no other obvious strabismic or neurological cause, should be assessed for cyclotorsion and cyclofusion during clinical examination. If values of cyclotorsion are found to be outside of these ranges, further investigations of fusion capacity with horizontal vergence control and cyclofusion amplitudes may be necessary. Cyclotorsion may be a possible disruptive factor to binocularity and fusion.

5.2.2 TECHNIQUE, IMAGE STABILITY, DYNAMICS AND FIELD SIZE

How stable is the retinal image in, and correspondence between, the R and L eye? How much torsion disparity can be mastered, without horizontal or vertical disruptions to fusion before decompensation of binocularity, in a head-straight position? To investigate this adequately we need to consider binocular, not monocular torsion. Together with the horizontal and/or vertical movements, torsion works by achieving an optimal retinal correspondence and eye position control.

The torsion measures are specific to the tests used. The synoptophore has a maximum field view of 21–24 degrees in diameter. Peripheral fusion contributes to the response of torsional disparity, but when tested in the synoptophore, the lack of peripheral input may reduce the measured angle of disparity that can be fused. Increasing stimulus complexity results in increased cyclofusional amplitude, and torsional “fusional” vergence is practically all sensory with large field sizes. In experimental apparatus using telescopic eyepieces to produces 50-degree fields, torsional motor fusion can occur (Kertesz 1972; Kertesz and Jones 1970). Before these findings, others were claiming that all torsional fusion was sensory, and did not have a true motor component.

5.3 PAPER III

This is a retrospective review and evaluation of our surgical results on cyclodeviation, using a modified version of the Harada-Ito procedure. Cyclodeviation was measured using the SMR and the synoptophore; all measurements were performed by the same orthoptist (S.F.). Correction was based on the amount of cyclodeviation, and how much that could be fused. The cyclofusion assessments were made using the synoptophore, measuring the total range for fusion and at which angle the patient perceived best comfort. The surgical dose was based on the degree of cyclodeviation required to regain comfortable fusion, and once this measure was obtained, the dose was decided from this. Surgical dose was estimated according to a 5-graded scale, involving the anterior fibres of the SO tendon being advanced towards the inferior edge of the LR muscle (Figure 11) by: 1) one-third, 2) half, 3) two-thirds, 4) the full, or 5) an enhanced length (Figure 12). Measurements were individually modified to give the desired effect.

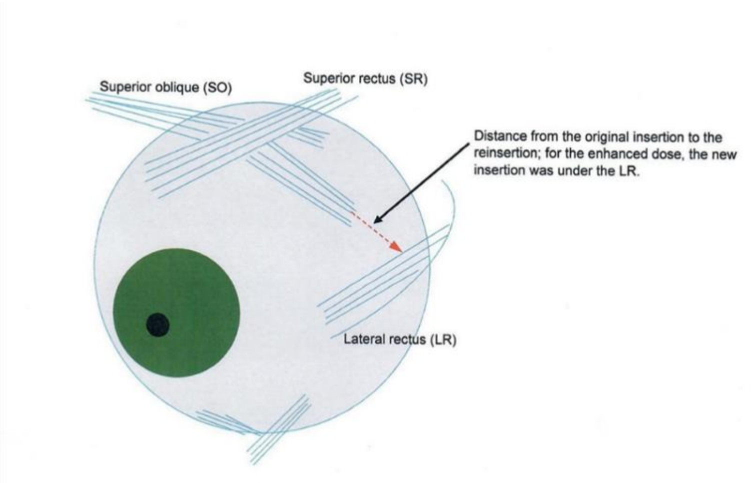


Figure 11. *Modified Harada-Ito procedure in a left eye when transposing and reinserting the anterior segment of the superior oblique (SO) tendon according to a dosage scale (S. Flodin).*

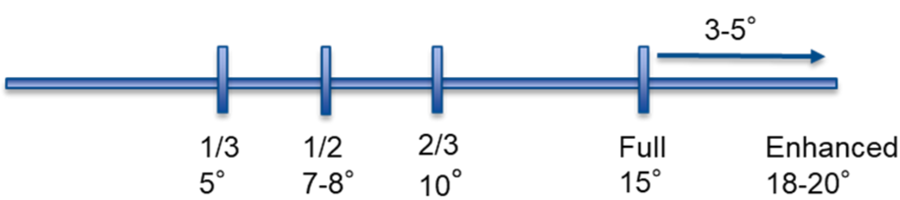


Figure 12. *The scale for advancement position and estimated effect, in degrees, on cyclodeviation.*

Another aspect that influenced the choice of surgical dose from the pre-operative assessments was the ocular motility. Both fusion capacity and ocular motility were dependent on aetiology, and therefore aetiology was graded according to a severity scale of 1-5 to investigate its influence on surgical results. The aetiologies that had most effect on fusion ability, such as a subarachnoid bleed and serious head trauma were graded as most severe (5) and mechanical causes such as a post-operative status after a retinal detachment was graded as least severe (1).

A successful result from the surgery was deemed as having regained fusion, being free from cyclodiplopia at the post-operative assessment.

There were 27 patients in the study, 21 had undergone unilateral surgery, and six patients had undergone bilateral surgery. The evaluation of surgical outcome showed that the post-operative results corresponded well with the pre-operative assessments of cyclodeviation and the individual surgical doses of the modified Harada-Ito procedure. Pre-operative cyclodeviations ranged from 60 to 7 degrees excyclotorsion within the group of patients. Cyclodeviation reduction achieved was between 8.4 and 19.5 degrees. The dose-scale assessment of the pre- to post-operative reduction of cyclodeviation showed that the dosage scales produced a widespread effect (Figure 13a and b).

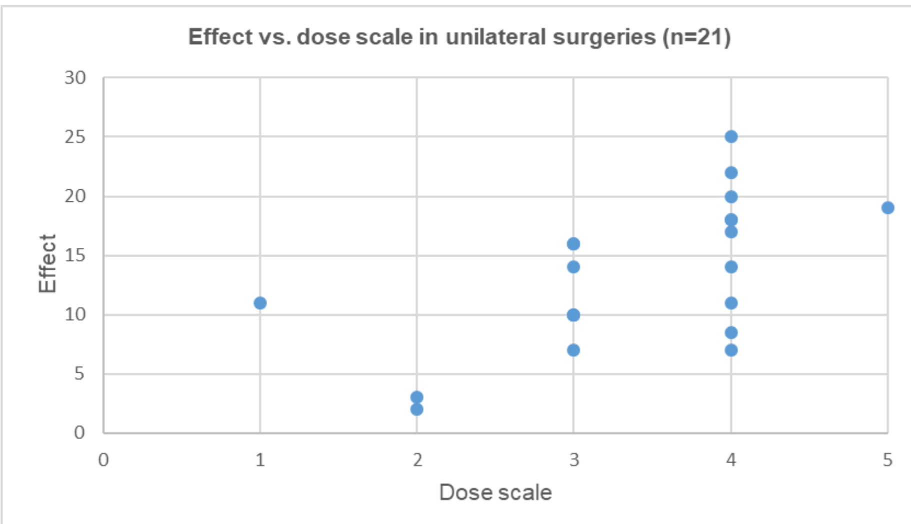


Figure 13 a. *Scatter plot of the achieved (given) effect post-operatively vs. the estimated (wanted) effect, pre-operatively by dose scale, of the unilateral surgical procedure, in degrees.*

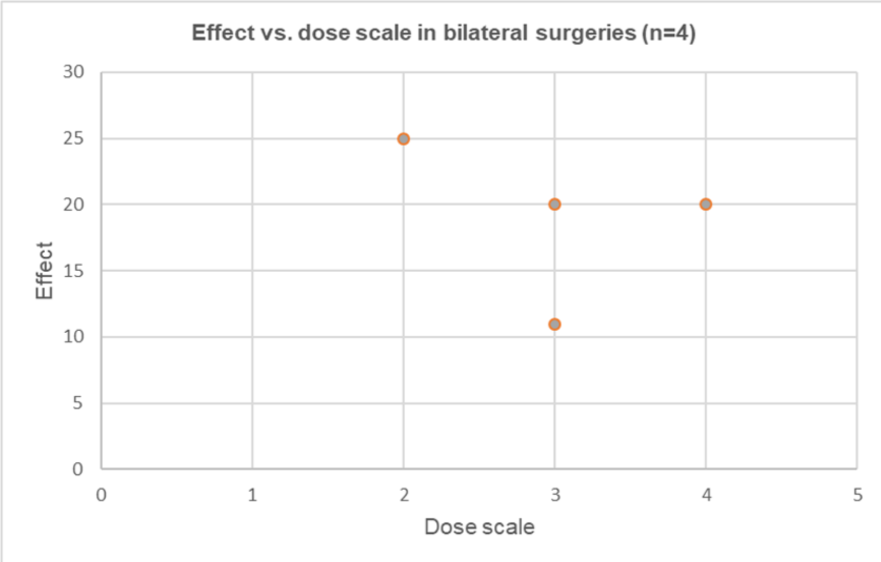


Figure 13b. *Scatter plot of the achieved (given) effect post-operatively vs. the estimated (wanted) effect, pre-operatively by dose scale, of the bilateral surgical procedure, in degrees.*

A multiple regression analysis was run to predict surgical outcome from gender, age, lateral surgery and grade of aetiology. It was found that severity grade of aetiology had a beta value of -0.4, and significantly predicted surgical outcome (p=0.02). Thus, severity grade of aetiology was an explanatory variable indicating a change on the response variable, which was the surgical outcome, measured as the post-operative cyclodeviation. The more severe the aetiology, the effect of surgery would reduce by 0.4 degrees per step on the 5-graded scale.

In *Paper III*, we found that an individually graded approach to the modified Harada-Ito procedure had a high success rate. Evaluation of the surgical outcome based on custom-made pre-operative assessments, showed that 93% of the patients regained cyclofusion. Torsional diplopia was resolved and visual symptoms relieved in all but two patients, one of whom is still under management in the clinic. The severity grade of aetiology and individual fusion abilities had an effect on cyclodeviation, and therefore influenced surgical outcome. Measurement of cyclofusional ability is critical for the successful outcome in the modified Harada-Ito procedure.

5.3.1 CLINICAL RELEVANCE

It is important to establish whether the post-operative results correspond to the pre-operative measurements and assessments of cyclodeviation, and the given dose of the Harada-Ito surgery. The results of this retrospective study stress the importance of individual assessments, specifically a reliable pre-operative assessment mapping the patient's cyclofusional abilities using a synoptophore. Surgery based on cyclofusional ability improves the outcome in individuals with cyclodeviation. Optimal patient care involves teamwork between the health care professionals and patients. In strabismus management, the ophthalmologists and orthoptists work closely together to create this.

5.3.2 TECHNIQUE AND GENERAL OBSERVATIONS

These surgical results are the results of a single surgeon's technique, which enables *unique* consistency. Half the SO tendon width was always transposed and 6.0-polyglactin absorbable suture was always used.

As cyclotorsion was reduced in the operated eye, the cyclotorsion in the non-operated eye was also reduced. Consequently, the total cyclodeviation was reduced. Evaluating surgical outcome showed a significant difference in pre- to post-operative cyclodeviation measurements, which were positively correlated ($r=0.84$, $p=<0.001$). The individually given effects of the unilateral and bilateral surgeries per dose were widespread compared to the estimated effect of the dose scales (Figure 13a and 13b.). The aetiology played an important part in cyclofusional abilities, as did paresis/paralysis, and anatomical variations found during surgery. The patients who got less effect from the surgery than the predicted effect of the dose scale, were those who were most severe in terms of aetiological severity grade. Thus, those who had most cyclodeviation to start with and weakest fusional abilities did not gain as much effect per dose as those with smaller angles to fuse and better motility.

5.3.3 REFLECTION

Dosage scaling was challenging when it came to statistical analysis of the data. Analysing the data gave rise to several issues. For the unilateral cases, we could analyse a dose-response, as they only received one surgical dose. The bilateral cases were more difficult to analyse. There were few patients in this group. Some cases were severe, and some patients received more than one surgery on different occasions, and sometimes different doses for the R and L eye. We wanted to review the finished results, to establish whether the patient had been "cured". However, when evaluating the dose effect alone, each dose should be calculated from the first pre-operative measure to the initial post-operative measure. Patients who received different doses on each eye or the same doses but at different surgeries, were not included in the dose effect, as their results was an overall effect of surgery and not a dose effect (Table 4).

Table 4. *The dose-scale used for the modified Harada-Ito procedure, showing the predicted effect and the given effect for all unilateral surgeries, and the bilateral surgeries where the same dose was performed on both eyes at the same surgery.*

Dose-scale	Predicted effect in degrees	Given median (min;max) effect in degrees		
		Unilateral (n=21)	**Bilateral (n=4)**	**Uni and bilateral cases (n=23)**
1	5	11 (n=1)		
2	7-8	2.5 (2;3) (n=2)	25 (n=1)	3 (2;25) (n=3)
3	10	12 (7;18) (n=7)	15.5 (11;20) (n=2)	11 (7;20) (n=9)
4	15	17.5 (7;25) (n=10)	20 (n=1)	18 (7;25) (n=11)
5	18-20	19 (n=1)		

A patient may have received several doses, and in order to see the final result of the surgery, all the individual doses need to be summed together. Although the effect of each dose varied, the surgical result and overall outcome was successful. Calculating pure dose response per individual eye may not be clinically relevant. Our methodology is based on measuring angles at which fusion occurs, giving intact binocular vision, and this becomes our “angle of surgery” or surgical dose (i.e., 17 degrees of image rotation on the synoptophore reflects binocular fusion => the surgeon operates 17 degrees which gives success). This angle itself will then be dosed according to 1/3, 1/2, etc. of the modified Harada-Ito procedure. Hence, how we arrive at the required angle from the beginning appears to be the key to a successful outcome, and not the dose. This comes from the individual pre-operative assessments and primarily the fusion measurements. The aim was to evaluate whether our assessments and management were successful in leaving the patients asymptomatic and free from cyclodiplopia. We “hit the target” of regaining fusion in 25 out of 27 patients with cyclodeviation, at their last post-operative assessment. In our experience, it is always better to “tread carefully” in order to reach the goal, rather than to “shoot over the goalpost”; as an overcorrected patient is not a happy patient. Thus in conclusion the *predicted* effect of our dosage-scale varied between individuals, but the *wanted* effect from our pre-operative assessment was achieved.

5.4 PAPER IV

Paper IV gives the patients’ perspective on surgical outcomes, through PROMs. The instrument used was the AS-20 questionnaire. This questionnaire was developed specifically for adult strabismus patients, and contains statements about how strabismus may affect you in your everyday life. The AS-20 questionnaire consists of ten psychosocial and ten functional statements. The overall scores and subscale scores are calculated as a mean of 20 (or 1–10, 11–20) scores. If an item is not answered, the overall score is calculated as the mean of all answered items. The maximum score is 100 and the minimum score is 0. The questionnaire is presented in Appendix I.

Thirty-one adults diagnosed with cyclodeviation 2014-2019 were given the AS-20 questionnaire to self-complete before and after surgery, to find out whether there were any common traits between patients and also to evaluate improvement. Patients were classed as symptomatic if suffering from cyclodiplopia, and unable to regain fusion unless cyclotorsion was corrected. The same orthoptist and surgeon examined all subjects. The questionnaire was also issued to a control group for comparison of healthy vs the strabismic cyclodeviation subjects. Total scores and the two subscales (psychosocial and functional) were analysed. Any relationships between gender, age, aetiology and bilateral/unilateral surgery was investigated.

The questionnaire was successfully completed before and after surgery by 26 patients; ten women and 16 men in the age range of 23–82 years, mean age 56 years, whereby 20 of these patients were classed as symptomatic and had undergone the modified Harada-Ito procedure.

Scores were significantly higher for the control group than for the cyclodeviation group (p=0.0001). Post-operative scores for all 20 questionnaire questions were significantly improved for all patients compared with pre-operative scores (p=0.002). There was a significant improvement in the functional subscale score (p=0.001), but not in the psychosocial subscale score (p=0.23). There was no effect of age or gender on the scores. The individual mean scores of each patient pre-operatively are displayed in Figure 14, and the post-operative scores in Figure 15.

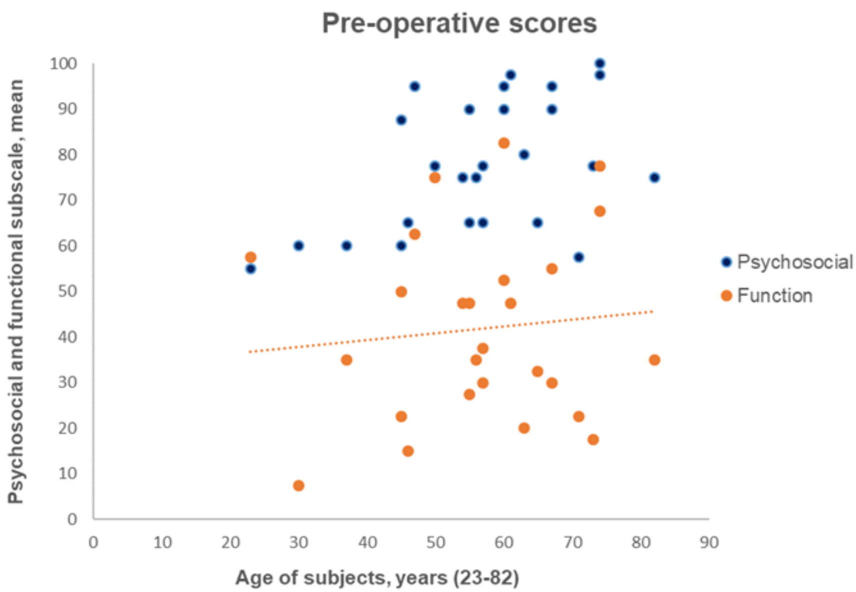


Figure 14. *Scatter plot of age vs mean individual scores on the psychosocial and function subscale at pre-operative assessment in 26 patients.*

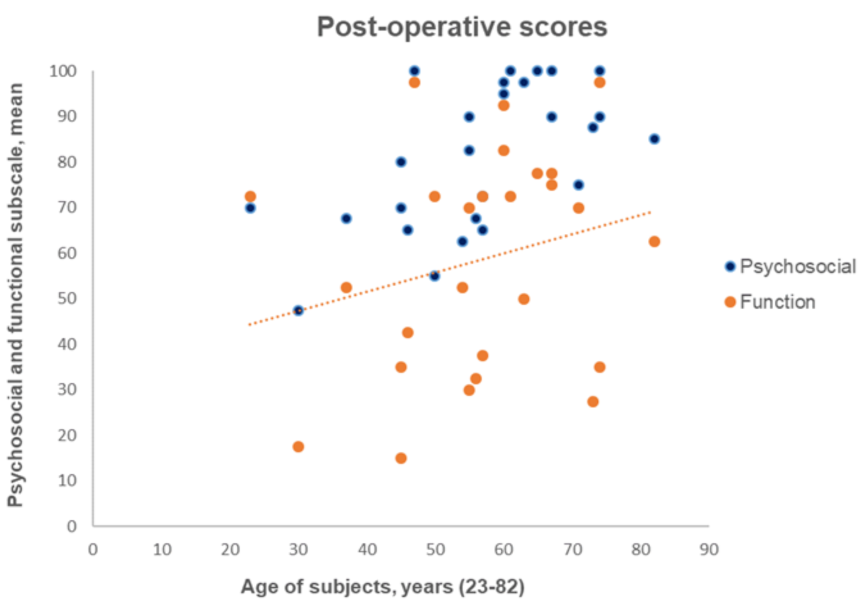


Figure 15. *Scatter plot of age vs mean individual scores on the psychosocial and function subscale at post-operative assessment in 26 patients.*

Cyclodeviation patients had significantly lower scores than controls. The functional scores were significantly lower than the psychosocial scores, in contrast to other forms of strabismus. Strabismus surgery has a significant positive impact on QoL scores in this group of patients, specifically in the functional sub score.

5.4.1 CLINICAL RELEVANCE

Including PROMs provides a more complete understanding of the impact of a condition, and of a clinical intervention, on patients. Therefore, using the AS-20 questionnaire to evaluate strabismus management can aid in improving assessment as well as outcomes among patients with cyclodeviation, as it gives a better intuitive understanding of patients' individual needs.

Patients in this study scored lower on the functional subscale, indicating that the scores in our patients were inferior to those of a normal population and were reversed for the subscales compared with other forms of strabismus (Glasman, Cheeseman, Wong et al. 2013; Power, Murphy and Stokes 2018).

5.4.2 REFLECTION

Patients with cyclodeviation perceive more problems with function than with psychosocial aspects. The AS-20 questionnaire may be too broad for this patient group.

6 ETHICAL REVIEW AND CONSIDERATIONS

Confidentiality and ethical considerations are important in any studies involving testing in humans. Confidentiality was ensured by upholding the clinical standards of Sahlgrenska University Hospital. Research protocols were adhered to for the data collection, and the tenets of the Helsinki Declaration followed. The data was processed anonymously and will not be used for any purpose other than that stated in the study aims. In addition, the data were coded to avoid identification, and archived separately. Study subjects were recruited by volunteering only, and were given written information about the study and asked to sign consent forms.

Ethical consideration was applied for through an “application for ethical vetting of research involving humans”. The research was approved by the Regional Ethical Committee at the Medical Faculty, Sahlgrenska Academy at Gothenburg University, Gothenburg, Sweden (Dnr 765-13, 2013-11-22 and Dnr 308-16, 2016-05-04). From an ethical point of view there is no harm or risk involved in the testing procedures; rather, the examination is beneficial as any disturbing strabismus that is discovered is treated. Results from the study will benefit society in terms of better practice for management of cyclodeviation worldwide.

7 GENERAL DISCUSSION AND REFLECTION ON, AND CONCLUSIONS OF THE PAPERS AND FINDINGS

Defining cyclotorsion – using correct classification and interpreting our clinical results

7.1 NOMENCLATURE

"The beginning of wisdom is to call things by their proper name."

Confucius, 551–479 BC

Cyclotropia, cyclophoria, cyclodeviation, cycloduction, cyclotorsion and *ocular torsion* are common terms used in the current literature about the phenomena of rotational or torsional strabismus. But do they all refer to the same condition, are they all of the same definition, or are they different things? We need to clarify our terminology and use the correct nomenclature, and therefore need to define the true meanings and definitions of these terms. The most vital advantage of nomenclature is communicative ability. Using the correct terminology is necessary when interpreting our clinical results, and when discussing these among peers.

Awaya et al.'s definitions on introducing their cyclo test (Awaya et al. 1997) were fairly neat. They defined ocular torsion as monocular cycloduction, and cyclodeviation implies addition of cyclotorsion from both eyes, or a difference in cycloduction between the two eyes when one eye shows incycloduction (or intorsion) and the other eye excycloduction (extorsion). Thus, we should clearly distinguish the words *torsion* and *cyclodeviation*.

This corresponds to the observations of Wright and colleagues, who note that the Maddox rod tests and most subjective torsion tests do not localise the eye with the torsional deviation. They only measure the relative difference in torsion between the two eyes. A monocular torsion is found with the subjective Maddox rod test because which eye the patient perceives as having torsional misalignment depends on which eye is fixing (ocular dominance). To find the total torsion with the double Maddox rod (DMR), the torsion of the two eyes is added together (Wright, Spiegel and Thompson 2006).

My definition is that *ocular torsion* is the rotation of the eye around its visual axis, and that the measure of this rotation is cyclotorsion (cycles = degrees), which is monocular. *Cyclodeviation* is a torsional strabismus characterised by a misalignment or imbalance of cyclotorsion between the two eyes. It can be detected when fusion is disrupted; and may or may not be fused depending on cyclovergence ability and the extent of cyclofusion (cyclofusion range). The correct clinical terminology would be *troublesome cyclodeviation*, depending on how much cyclotorsion is measured. As for *cyclotropia* and *cyclophoria*, I personally would avoid using these terms when discussing cyclodeviation. They were probably introduced to differentiate between a manifest and a latent condition, and thus to define whether a fusional disturbance was constant. The definition of a *tropia* is a constant misalignment that is apparent. The characteristics of a tropia are identified when conducting a cover-uncover test, and any changes in the amount and type of movement can be further observed by performing the more dissociative alternate cover test. A *phoria* is a misalignment of the eyes that only appears when binocular viewing is broken, and is diagnosed by the alternate cover test that ensures full dissociation. However, a cyclodeviation can never be seen on a cover test, as it is not an externally visible strabismus. A cyclodeviated eye does not correct itself when the other eye is covered (von Noorden and Campos 2002). Cyclodeviation should not be judged on the basis of the position of one eye only, but on the basis of the relative position of the two eyes in absence and presence of (cyclo) fusional stimuli (Van Rijn, Van Der Steen and Collewijn 1994).

7.2 DIAGNOSTIC TESTING

"One lesson learned was the extreme importance of careful diagnosis."

Bernard Chavasse, 1890–1941

Once terminology is set, and correct definitions are established, it is important to be clear about the following questions:

1) What are we measuring?

2) How are we measuring it?

3) How do we validate it?

4) How is it relevant?

The object of measurement is the cyclodeviation. In order to investigate how to measure this most accurately, different tests for subjective torsion measurements in the clinic were evaluated in *Paper I*. These showed statistically significant differences in reproducibility and repeatability.

One of the issues raised during the clinical test evaluation, was that of using the SMRT. The most commonly used method across clinics internationally is the DMRT, and SMRT use is nearly unheard of. Initially it was just an unwritten routine procedure that was used at our clinic as far back as my early years of clinical employment, a good 20 years. However, once the test methods were evaluated, it was confirmed that this method was reliable against itself. It is a simple and quick screening method for measuring cyclodeviation. In terms of technique, it can be compared to the very much more complicated Harms test, as it uses the same principle of assessing subjective cyclodeviation. Although the Harms test examines the subject binocularly, with one eye covered with a red filter, and the other fixing (Schworm, Boergen and Eithoff 1995). Using net torsion, rather than torsion of individual eyes, has the advantage that there is less contamination by spontaneous variation (Van Rijn, Van Der Steen and Collewijn 1994). However, we believe that the SMR test is sufficient for screening purposes, investigation and diagnosis, and for monitoring torsion in SOP. Moreover, it has been shown that there are no differences in results between the SMR and the DMR method (Liebermann, Leske, Hatt et al. 2018).

7.3 EVALUATION OF MEASUREMENTS AND CLINICAL OBSERVATIONS

Another issue to raise is how we evaluated the data. We used our measurements of the total torsional deviation. To explain, we need to go back to our definitions. Although monocular eye torsion was measured in the studies using the SMR test, the results were calculated on the net torsion or the absolute amount of cyclodeviation. We need to interpret and take into account the meaning of *binocular cycloversion* and *cyclovergence*. It is of importance to regain and/or maintain binocularity and this is our aim as clinicians.

Cycloversion is defined as conjugate cyclorotations of both eyes in the same direction. It is the component of torsion that is directed similarly in both eyes, and is calculated as the “mean of the torsion of the L and R eyes”. The formula is (R eye + L eye) / 2 (Van Rijn, Van Der Steen, and Collewijn 1994). These cyclorotations occur primarily because of head movements, OCR, which under normal circumstances constrain the cyclorotation dependent on the vertical and horizontal movements of the eye. During eye movements, natural torsion occurs (Donders law) and the amount of this torsion is described in Listing's law. However, Listing's law does not account for all cyclorotations. When there is cyclodisparity, two retinal images are presented that need to be rotated in relation to one another. In order to allow visual fusion to take place, cyclovergence occurs.

Cyclovergence is the simultaneous cyclorotation of the eyes in opposite directions to maintain BSV. Cyclovergence is calculated as the "difference of the torsion of the L and R eyes", and the formula is L eye - R eye (Van Rijn, Van Der Steen, and Collewijn 1994). It has been stated that cycloversion is related to image stability; while cyclovergence is related to image correspondence. The explanation is that the compensation for head movement by counter-rolling of the eyes needs to be equally large in the L and R eyes. Hence, this compensation requires a cycloversion movement of the eyes, while cyclovergence affects the relative orientation of both eyes. A change in relative orientation will affect correspondence of the retinal images. This implies that cyclovergence is controlled much better than cycloversion (Balliet and Nakayama 1978), and that visual feedback enhances the stability of cyclovergence (Pansell, Ygge, and Schworm 2003) but does not affect cycloversion stability (Van Rijn, Van Der Steen, and Collewijn 1994). Experiments have established that torsional eye movements, at least with respect to cyclovergence, are adaptable (Maxwell, Graf, and Schor 2001).

Some reflections on measurements using the SMR are that some subjects will perceive "straightness" from pp initially, at 0 (zero) degrees. Then once the dial has been adjusted slightly, they will perceive excyclotorsion as straight! Also, when measuring the first eye- the second eye will respond. If, for example, a person has 0 degrees of cycodeviation, this can be found as the R eye measuring 4 degrees of excyclotorsion, and the L eye having 4 degrees of incyclotorsion on using the SMR, while the DMR would measure 0 when viewing with both eyes at the same time. Hence, binocular viewing corrects the cyclodeviation as compared with dissociating the eyes. Subjects with a high degree of astigmatism tend to have more difficulty with *cyclofusion*, but other refractive errors do not appear to have an effect.

Evaluating testing methods and finding differences between tests in the same population triggered the question, What are we really measuring?, and also, What do we need to focus on from a clinical perspective? If we only look at monocular torsion, we will only address monocular torsional deviation, not binocular cyclodeviation, which is what needs to be evaluated. How do we know whether subjective measures are to be considered normal or abnormal? Some subjects are unaware of any fusional problems arising from cyclodeviations or else unable to describe them. Specific complaints or perception of visual tilting due to torsional misalignment are unusual (Good 2013; Kushner 1992), further obfuscating the diagnosis. Patients with substantial amounts of peripheral torsion may be asymptomatic, while others with little torsion may have symptoms. The clinician needs guidelines on normal ranges, before making treatment decisions.

"They speak of 'cydodeclination condition,' 'cyclotorsional trouble,' 'abnormal cyclotorsional condition,' and 'suffering from cyclodiplopia' as if torsion were an abnormality of vision, yet they make no reference to what normal persons or non-clinical cases might show in the way of torsion."

T. G Hermans, 1943

What direction of torsion might be expected in normal BV, and what is the average amount of torsion? How stable is the retinal image and the correspondence between the R and L eye? How does torsion function in a normal subject with no horizontal or vertical disturbances? Together with the horizontal and/or vertical vergence systems, in cycloversion and cyclovergence, the ocular system works to find a balance between achieving, and not achieving optimal retinal correspondence, allowing binocular fusion and eye position control. Some patients only need straightening in the horizontal or the vertical meridian for their torsional symptoms to disappear. For others, these corrective measures make no difference to their (dis)ability to fuse the cyclodisparity, and hence they need a surgical intervention to align the torsional deviation. Why is this so? Investigating a normal reference range in the population and comparing it with asymptomatic subjects with cyclodeviation aids us in understanding the fusional abilities and the importance.

The second paper investigates variability in values of cyclodeviation and cyclofusion in a healthy adult population. Previous studies have given us valuable insights into subjective vs objective ocular torsion Guyton (2008). Therefore, the established guidelines have clinical implications for the interpretation, diagnosis and management of cyclodeviation.

"It is about integrating individual clinical expertise and the best external evidence."

D.L. Sackett, 1996

How can we validate our measurements of cyclotorsion from a patient population and a normal population for clinical and managerial use? In *Paper III* we retrospectively evaluated our clinical measurements and interpretation of subjective torsion. A review of surgical success rate determines whether our methods of measuring and managing cyclodeviations are accurate. The measurements of cyclodeviation and cyclofusion need to tally with corrections to enable symptomatic patients to regain fusion and become asymptomatic.

Adaption in cyclovergence is both a sensory and a motor process, and sometimes the paretic eye is the fixing eye. The part of the cyclodeviation that can be controlled with ease by normal torsional fusional reserve needs no treatment. Once fusion breaks, however, there is a problem. To truly investigate a cyclodeviation, both the net torsion and monocular torsion need to be evaluated. Only then can we see the effect of cyclofusion on the torsional deviation. To my knowledge, the only equipment in the clinic that can tell us this is the synoptophore. By using the synoptophore, we can measure subjective torsion in either eye, and cyclodeviation using both eyes, and, most importantly, we can investigate the fusional abilities. We can measure exactly what is causing the disturbance to BSV, and whether the disturbance is horizontal, vertical or torsional, and we can map out to what extent the patient can fuse and how much they may need extra to maintain a comfortable motor fusion. These measurements can in turn be converted into surgical measures. However, what we found was that success was determined by careful individually based assessments of cyclodeviation, contrasted to cyclofusional reserves. Moreover, it is impossible to create a standardized protocol for surgery based only on the amount of cyclodeviation. The aetiology plays an important part, and subjects who suffer severe disruption to cortical function have severe motor problems and, therefore reduced fusional abilities. Good surgical planning needs a complete orthoptic assessment evaluating both the deviation per se and the ability to regain fusion.

"The study of eye movements is therefore of clinical interest, and may have even deeper implications related to the coordination of mind and body."

M.P Lord, 1950

Finally, we should always aim for progress and improving our skills. The only way to continually learn and develop is through experience and sometimes through our mistakes. An appraisal of surgical success rate should not only be about clinical results, but should also include patient satisfaction. Measurements and results tell us facts, but we have to ask whether this result has really made a difference to someone's daily life? Have we improved their abilities? The only way to evaluate this is through PROMs. Assessing QoL in cyclodeviation patients is covered in *Paper IV*, completing the thesis. The major finding from P*aper IV* was that cyclodeviation patients scored significantly lower in functional areas, such as performing various tasks, because of their eyes, compared with other forms of strabismus.

7.4 RELEVANCE OF THE RESEARCH PROJECTS OF THE THESIS

"*It is up to us to integrate the best available evidence with our expertise as clinicians in order to establish realistic expectations for our patients and predict a successful functional outcome."*

K. Fray, 2010

I would say that there are three areas of knowledge concerned with cyclodeviation:

1) Neurological complexity of the visual system, and binocularity
2) Objective measurements of eye movements using highly scientific electronic monitoring, such as search coils in laboratories for eye tracking, and fundus images for ocular deviations
3) Subjective measurements, estimation of disparity (SMR) and visual estimation of gravitational vertical (posture/balance)

There are several scientific studies on the topic of torsion, exploring the complexity of vestibular actions and objective measuring, visually evoked potentials and search coil data (Brandt and Dieterich 1992; Ehrt and Boergen 2001; Goonetilleke, Mezey, Burgess et al. 2008; Maxwell and Schor 2006; Pansell, Schworm and Ygge 2003; Pansell, Ygge and Schworm 2003; Thurtell, Joshi and Walker 2012). However, the aim of this thesis was to further develop the knowledge related to clinical issues. The relevance of the studies in this thesis are that they add a practical component. Previous research was primarily experimental, conducted in the laboratory. To add depth and scientific evidence to my research I have delved into the history of torsion, reviewing past interpretations and definitions. Subjective torsion is the patient's response to document their perceived torsional orientation of an object and is most reliable when dealing with complaints of diplopia. Sensory adaptive mechanisms play an important part in controlling subjective torsion, and therefore objective torsion measures alone are inadequate, since they do not correspond to subjective complaints.

Optimal patient care is always relevant; it is our responsibility as professionals to constantly appraise and update our knowledge and ensure that we use the most precise examination methods to optimise treatment. Our work is about improving the quality of someone's life. Patients with cyclodeviation often suffer from a troublesome and difficult condition. Symptoms are not always indicative in traditional investigative technique. Strategies for cyclotorsion measurements and evaluation have been scantily studied and described sparsely in the literature, and previously many essential questions remained unanswered. Therefore, this topic required further exploration and attention in orthoptic patient care. Parallel to my clinical work, the four studies making up this thesis work have formed the core of my investigations on the complexity of cyclodeviation, and have led me to fulfil my research questions on how to investigate, diagnose and manage cyclodeviation at a practical level with supporting scientific evidence.

8 FUTURE PERSPECTIVES

Cyclodeviation is not common; during our review of surgery (*Paper III*) we encountered 27 patients over a 7-year period. This calls for collaboration and multicentre approaches for future studies to boost numbers.

In *Paper III* we reviewed the surgical outcome, and in *Paper IV* we looked at QoL of patients pre- and post-operatively. A planned project is to combine the individual surgical outcomes with the QoL assessments for these individuals post-operatively: *"Evaluating surgical outcomes of strabismus surgery for cyclodeviation incorporating health-related QoL using the AS-20".*

Another focus for the future is how we can "catch" cyclodeviation patients at an earlier stage? Several researchers have commented on the fact that cyclodeviation is an area in strabismus management that is difficult to diagnose, and that patients are not always aware of their symptoms. Can a questionnaire be helpful in finding and diagnosing the condition? In *Paper IV*, we found that cyclodeviation patients scored low in the functional subscore of the AS-20 questionnaire. How can we specifically evaluate what the main symptoms/problems of cyclodeviation are? An idea is to expand upon *Paper IV*, by interviewing patients about their precise interpretations, descriptions and difficulties. A lot of information is gained during history taking, but several of the patients in the study did not realise they had cyclodiplopia until it was found and highlighted during investigation, or until it was alleviated at the post-operative control! Adding a qualitative method would improve the present research by giving a wider perspective to answering my research questions. Performing in-depth interviews with patients may show a pattern response in this patient group. Transcription of the interviews could in turn be converted into new specific questions, which could be used for developing a specific "cyclo-questionnaire".

Finally, all of the research projects in this study were undertaken in an adult population. It would be useful to also evaluate cyclodeviation in children.

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Figure 16. *Iza. Photography by Lotta Sultan, https://lottasultan.myportfolio.com/*

“Man kan forska och hålla på, men kan man inte förklara på ett begripligt sätt så hjälper ju inte det.”

Agnes Wold, 2020

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APPENDIX

APPENDIX 1

The Adult Strabismus AS-20 Questionnaire - a quality of life questionnaire for adult strabismus, used in *Paper IV*.

Available free at: https://public.jaeb.org/pedig/view/Forms_AS20