A NOVEL USE OF OPTICAL COHERENCE TOMOGRAPHY FOR THE ASSESSMENT OF OCULAR TORSION

by

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ABSTRACT

Abnormal ocular torsion is most frequently the result paresis of the fourth cranial nerve. The presence of torsion can be a barrier to fusion; in which case, surgical intervention is required for a patient to have single vision. Clinically, ocular torsion can be measured either subjectively or objectively, the latter traditionally using the relationship between the fovea and the optic disc. However, previous literature has shown inconsistencies between torsion a patient's perceived subjective torsion, and the amount of anatomical fundus torsion. Therefore, the aim of the current study was to investigate the relationship of subjective and objective ocular torsion in patients with cranial nerve four palsies, and more specifically, a potentially novel objective method using the retinal raphe. The subjective tests used in this study were modified Bagolini Lenses, Double Maddox Rods, the Synoptophore, and the Harms Tangent Screen. The three objective tests used were fundus photographs, optical coherence tomography using Bruch's membrane opening, and the temporal raphe. The first two methods used the traditional relationship between the fovea and optic disc. The current study also assessed the relationship of these measuring methods to the Subjective Horizontal. The results of this study found that the torsional angle measured by subjective tests was not significantly-different than the objective angles of the fovea-optic nerve relationship or the temporal raphe when accounting for the physiological position of the retina. The current study also found that the Subjective Horizontal of participants with cranial nerve four palsies was significantly different than the subjective and objective tests, except for the temporal raphe. Therefore, it was concluded that the previously-reported significant differences between subjective torsion and the fovea-optic nerve angles may not take the physiological retinal position into account. It was also concluded that participants with long-standing cranial nerve four palsies were on a spectrum of adaption and that the Subjective Horizontal adjusts to the orientation of the temporal raphe.

LIST OF ABBREVIATIONS USED

CN IV	Cranial Nerve Four
DMR	Double Maddox Rod
ETDRS	Early Treatment Diabetic Retinopathy Screening Vision Chat
Fovea-ONH	Angle from the center optic disc/Bruch's membrane to the fovea
GMPE	Glaucoma Module Premium Edition
H	Kruskal-Wallis statistical test
HTS	Harms Tangent Screen
ICC	Intraclass Correlation Coefficient
IWK	Izaak Walton Killam
MWW	Mann-Whitney U statistical test description
FL	Nerve Fiber Layer
OCT	Optical Coherence Tomography
ONH	Optic Nerve Head
PI	Principle Investigator
sd	Standard Deviation
SD-OCT	Spectral Optical Coherence Tomography
SPSS	Statistical Package for Social Sciences software program
U	Mann-Whitney U statistical test
VG	Victoria General
W	Wilcoxon Signed-Rank Sum statistical test

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CHAPTER 1: INTRODUCTION

Strabismus, or misalignment of the eyes, is a visual condition arising from a misalignment of the visual axis between the two eyes; it can be horizontal, vertical, or torsional. This disrupts the binocular retinal correspondence resulting in two disparate images seen by each eye. The visual system responds to the abnormal alignment with either diplopia (double vision), confusion (superimposition of images), or suppression of one image. A matured visual system is less able to suppress one image, thereby resulting in diplopia, making everyday tasks such as walking, reaching, driving, nearly impossible, especially for the elderly (Good, 2012).

The importance of quantifying cyclotorsional (torsion) eye movements is to understand and treat particular complaints of patients (Good, 2012). Torsion of images can be a barrier to fusion preventing the two eyes working together to create a single image. The presence of torsion can affect the type of treatment a patient may receive (Good, 2012). Unlike horizontal or vertical diplopia, torsional diplopia cannot be corrected with prismatic correction. In some cases, patients can adapt by being able to fuse the torsional images when existing vertical or horizontal deviations are also corrected by way of "cyclofusion" (rotation around the anteroposterior axis in order to align images). However, if cyclofusion cannot take place, the torsional deviation must be surgically corrected (Good, 2012). Therefore, having accurate measurements of ocular torsion is essential for patient management and treatment.

In a clinical setting, measurement of torsional rotation falls into two categories: subjective and objective. Subjective measurements require patient input; the patient relays what they perceive. However, what the patient perceives is a neurosensorial interpretation, and may not correspond with the anatomical position of the eye (Guyton, 1983). The most common subjective techniques of measuring torsional fusion are the Bagolini Lenses, Double Maddox Rod test (DMR), the amblyoscope (Synoptophore), and the Harms Tangent Screen (HTS) (Johnson, Fox, and Harcourt, 1987; Pfenninger, Landau, and Bergamin, 2006).

Objective measurements, on the other hand, determine the relative anatomical

position around the visual axis of ocular landmarks such as the optic disc, fovea, and the retinal nerve fibers raphe projections; measurements are independent of patient perception (Guyton, 1988). Objective measurements are done using photographs or scans of the ocular fundus (Guyton, 1983). The results yield an estimate of the horizontality of the two more striking fundus landmarks: the optic nerve head and fovea; any deviation is traditionally called the ocular torsional angle (Guyton, 1983).

The most common methods of objective measurements of the ocular torsional angle are fundus imaging by means of direct live observation (ophthalmoscopy) or by photography (Morton, Lucchese, and Kushner, 1983). Optical Coherence Tomography (OCT) has recently been added in the analysis of the anatomical details of the optic nerve (Chauhan and Burgoyne, 2013). Chauhan and Burgoyne (2013) presented a novel use of the OCT that enables visualization of the superior and inferior raphe orientation of the Nerve Fiber Layer (NFL), specifically the point at which these projections meet.

The path of the raphe represents the horizontal anatomical organisation of the upper and lower fields of vision of each eye. However, the exact relationship between the temporal raphe positioning and subjective torsional measurements of the visual fields has yet to be determined clearly in patients with abnormal torsional positioning of their retina. There is a gap in the current literature understanding that the frequently observed differences between these objective and subjective findings in subjects suffering from torsional strabismus. Therefore, the current study aims at establishing a quantitative relationship between subjective and objective torsional measurements obtained with current clinical methods and the novel OCT method.

1.1 Structure of Thesis

The current thesis is organized into four chapters following the two introductory sections of Introduction and Literature Review. Chapter 1 identifies the gap in the current knowledge on ocular torsion. This chapter also outlines the resulting purpose of this study with the questions and hypothesis. Chapter 2 discusses previous work on relevant anatomy of the eye, as well as current clinical testing procedures of ocular

torsion. Chapter 3 describes the research design and testing protocol of the study which is at the basis of this thesis. Chapter 4 presents the analysis of the study results. Chapter 5 discusses the importance of the current findings and their relevance of the results to clinical practice.

1.2 Gap in Current Knowledge

Although differences in subjective and objective torsional measurements are regularly seen clinically, there is essentially no study that compares the relationship. However, the presence of these differences is widely known throughout the clinical literature (Guyton, 1983; von Noorden, 1984). Guyton (1983) described subjective torsion as "a different entity" to that of objective torsion. This could be due to the fact that subjective perception and testing of ocular torsion is commonly done under binocular conditions whereas objective testing is typically done monocularly. Binocular testing can allow sensory adaptions to reduce or even eliminate subjective perception of the torted image (Guyton, 1983). Subjective testing uses information provided by the entire retina whereas objective torsional testing methods primarily assess the angle between the fovea and optic nerve head (Fovea-ONH).

One study did look at the larger fundus area, using the retinal vasculature to assess fundus torsion (Parsa and Kumar, 2013). The authors speculated that looking at more than just the fovea-ONH relationship could provide a greater amount of detail with regards to the fundus torsion, especially if the fovea or optic nerve were obscured. The study also noted that the retinal vasculature follows the path of temporal raphe as they develop together embryologically (Parsa and Kumar, 2013). This study, however, did not compare the results of fundus torsion assessed by retinal vasculature to traditional fovea-ONH angles or subjective results. Piedrahita-Alonso, Valverde-Megias, and Gomez-de-Liano (2014) compared the fovea-ONH angle to the vascular angles determined by viens, arteries, and the mean value between the two. Their results indicated that the fovea-ONH angle was the "gold-standard" measurement for cyclorotation and that the measurements obtained by the vasculature assessment were imprecise and scattered.

Studies that do speculate on these differences between subjective and objective measurements have all centred around cortical adaptations (Guyton and von Noorden, 1978; von Noorden, 1984). The specifics of these studies are discussed later in Section 2.4.

The current study investigates the use of retinal temporal raphe imaging as a more anatomically accurate quantitative assessment of objective ocular torsion compared to methods using conventional fundus photography. The results could also help to better understand torsional strabismus by explaining the frequent dichotomy between objective and subjective torsional measurements in chronic torsional strabismus.

The results of this research could establish the analysis of the retinal NFL raphe using OCT in conjunction with subjective testing, as a new standard of practice for assessment of patients with torsional diplopia.

1.3 Purpose of Study

The overall purpose of this study is to explain the difference between subjective and objective angle of ocular torsion in chronic torsional strabismus through the results of a new objective method of torsional measurements. The four commonly-used subjective measurements used in the study are: Bagolini Lenses, DMR, Synoptophore, and the HTS. The objective methods used were traditional fundus photography, a novel method using OCT scans for a better anatomical definition of the optic nerve location by analysis of Bruchs membrane, and the position of the temporal retinal NFL raphe.

1.3.1 Research Question

1. To which of the objective measurements (fovea-optic nerve angle or temporal raphe) do the subjective measurements correspond more closely? However, due to inconsistencies in the literature regarding the average range of torsion in normal and paretic eyes as well as the novelty of using the temporal raphe orientation in quantifying torsional strabismus, the current study prefaced answering the above

research question in two parts:

a. For participants with CN IV palsies, is there a statistically significant relationship between subjective measuring techniques of?:

   i Bagolini Lenses

   ii Double Maddox Rod

   iii Synoptophore

   iv Harms Tangent Screen

b. Is there a statistically significant difference between the temporal raphe angle in normal participants and those with CN IV palsies?

1.3.2 Hypotheses

With regard to question 1a; based on previous research, it is hypothesized that there would be a statistically significant difference when measuring subjective ocular torsion using Bagolini Lenses compared to the three others methods (DMR, Synoptophore, HTS) in participants with CN IV palsies.

With regard to question 1b; it is hypothesized that the angles of the temporal raphe in participants with CN IV palsies are statistically significantly different than those of participants in the Control group.

Therefore, for the main research question, it was hypothesised that the results of the Bagolini Lens test would be most simlar to the torsional angles obtained by the position of the temporal raphe.

CHAPTER 2: LITERATURE REVIEW

2.1 Anatomy and Physiology

Understanding the anatomy and physiology of torsional ocular movements is the initial stage for a diagnosis and possible treatments of patients with torsional strabismus. Torsional strabismus results from paralysis or restriction of cyclovertical muscles, over- or under-actions of oblique muscles, pattern strabismus, or neurological conditions such as skew deviations (Guyton, 1983). The most common cause of torsional strabismus is a paresis of the fourth cranial nerve (Holmes et al., 1999).

2.1.1 Trochlear Nerve

Anatomically, the fourth nerve is the longest and most tenuous of the cranial nerves and the only one to exit the brainstem dorsally, after which it loops around the brainstem towards its anterior course. The nerve is involved in a series of critical anatomical relationships which make it very susceptible to damage along its path (Keane, 1993). Expectedly, head trauma is the leading cause of CN IV palsies. In a study of 215 patients with a diagnosis of CN IV, Keane (1993) showed that head trauma was the leading etiology. Other causes included surgical injury, inflammation of the meninges, tumours, strokes, vascular insults, congenital malformations, and so-called idiopathic.

Damaged CN IVs can affect both children and adults at any age, but the symptoms are not always obvious at the time of insult. Even when these are present, a diagnosis of CN IV weakness can be difficult to make (Keane, 1993). Initially the diagnosis of CN IV palsies can be made by observing a vertical misalignment; the affected eye being higher than the non-affected eye?that increases in the opposite gaze to the higher-positioned eye. This finding, however, is a feature of other ocular conditions as well, such as a skew deviation.

Bielschowsky (1935) described a diagnostic head tilt-test that allowed for a more definitive diagnosis of a CN IV palsy. Currently, two clinical features for diagnosing a CN IV palsy are considered to be reliable; namely, a vertical misalignment which

increases in the opposite gaze of, and same-side head-tilt to, the affected eye. However, torsional findings, in keeping with the main function of the superior oblique muscle, have proven to be most useful in the diagnosis of uni- and bilateral cases of CN IV nerve weakness.

Three major factors affect the presentation of a CN IV palsy: the number of nerves affected (unilateral or bilateral); age of onset; and chronicity. Three features differentiate a bilateral from a unilateral CN IV palsy: a reversal of hypertropia (a right hypertropia in left gaze and a left hypertropia in right gaze); a significant V-pattern (the eyes are turned in more when looking down than when looking up), generally greater than 10 diopters difference; and a significant amount of excyclotorsion, generally of more than 10–12 degrees; especially worse in down-gaze.

Bilaterality of CN IV weakness can be a masked problem; only an initial surgical repair of the worse side can expose the bilaterality. Recently, however, reports have highlighted the value of assessing the amount of torsional diplopia as a more reliable differentiating indicator between unilateral or bilateral CN IV. For example, Kraft, OReilly, Quigley, Allen, and Eustis (1993) compared the results of common clinical tests (Bagolini lenses (discussed in section 2.2.1) and DMR (discussed in section 2.2.3.)) in cases of unilateral and bilateral CN IV palsies. The study showed that the DMR test was better at differentiating unilateral from bilateral cases.

Understanding the chronicity of CN IV weakness, or length of time patients have had their deviation, has been found to be of use in understanding patient symptoms of torsional deviations. As mentioned previously, adults are less capable than children in adapting to acquired ocular misalignment; thus, diplopia is more common among strabismic adults. If a strabismus is longstanding (the patient has lived with the condition for many years), changes to both subjective and objective measurements of ocular alignment can occur, possibly due to sensory and motor adaptive mechanisms.

Typical signs of longstanding CN IV palsies are: increased vertical fusional amplitudes (ability to maintain ocular alignment despite a tendency for vertical strabismus); spread of comitance (an incomitant deviation becomes similar in all positions of gaze over time); and a frequent absence of subjective torsional diplopia.

Patients with CN IV palsies rarely complain of torsional diplopia, but rather of vertical, horizontal, or oblique diplopia (Woo, Seo, and Hwang, 2005). Some authors have observed that there could be motor torsional amplitudes which could facilitate sensory fusion of torsional diplopic images once the associated horizontal, and more importantly vertical deviations are corrected (Guyton, 1983). From these and other's findings, (Ruttum and von Noorden, 1984), it has been said that it is essential to assess the torsional aspect of any ocular deviation.

Fusional amplitudes control independent movement of the eyes in order to maintain single vision; thus, aiding in overcoming diplopia in the case of extra-ocular muscle dysfunctions (Sharma, Prasad, and Khokhar, 1999; Brodsky, 2002). To ensure that an image remains single in torsional strabismus, the visual system compensates either through sensory fusion (cyclofusion) or motor fusion (cyclovergence). Sensory fusion is a higher-level processing adaptation, whereby the visual system combines two monocular images into one. Motor fusion is the necessary rotation of the eyes to align the two images together.

Guyton (1988) reported that cyclovergence is a component of cyclofusion which enables binocular single vision to be possible with slight torsional movements of approximately five degrees (Brodsky, 2002). One can simulate torsional disparities (Georgievski, Sleep, and Koklanis, 2007); however,it is not felt to be the same as one's ability to tolerate physical cyclorotation of the globe around its visual axis as it occurs in CN IV weakness for example (Sharma et al., 1999). The authors could not explain why patients with CN IV palsies as well as normal subjects can become symptomatic with a small degree of cyclorotation despite being able to tolerate a greater amount of torsion when simulated (Sharma at al., 1999). Therefore, it appeared to these authors that it is when critical amplitudes of fusional torsion are exceeded in an attempt to correct a deviation that diplopia results; becoming symptomatic and measurable.

The amount of torsion that is significant to a patient can be difficult to assess due to the wide variability of physiological (anatomical) torsion. Most studies reporting the range of physiologic torsion assessed anatomical torsion with objective

methods (discussed in section 1.4.2). There are reports of a mean fovea-ONH angle of $7.25^\circ \pm 2.57$ excyclotorsion but the range can be anywhere from 5 to 12 degrees of torsion (Bixenman and von Noorden, 1982). However, the presence of cyclofusion can change these values on a daily basis (Simons, Arnoldi, and Brown, 1994). It is also important to realize that there is not a linear relationship between a measurable torsion (subjectively and/or objectively) and its effect that it has for the patient's visual experience (Bixenmann and von Noorden, 1982).

2.1.2 Ocular Fundus Anatomy

There exist several important normal retinal and other ocular fundus landmarks that pertain to the thesis study. The foveal pit, a darker spot in the centre of the macular area, is the location of the highest concentration of cone photoreceptors. As a result, that area of the retina is responsible for our highest resolution visual ability and is the point of the retina aligned without visual attention (central fixation). On the nasal side of the fovea is the optic nerve head or disk, (ONH) which is noticeably visible on imaging of the ocular fundus. It is where the ganglion nerve cell axons collect from the rest of the retina and exit the eye to travel as the optic nerve to join the optic tract into the brain.

One landmark that is not readily identifiable by fundus photography is Bruch's membrane. This membrane is the outermost layer of the retina, separating the outermost retinal epithelium layer and the choroid. Unlike the neural retinal rim of the ONH that one can see in a photograph, Bruch's membrane is the real anatomical margin of the optic disk within which the nerve axons exit the eye. Delineation of the edges of the optic disc by using the location of Bruch,s membrane limits leads to an accurate assessment of the size and finite location of the ONH in the fundus (Chauhan and Burgonye, 2013).

Torsion of the eye around its anteroposterior axis is traditionally measured by the angle between the fovea and optic nerve head. Typically, the fovea is horizontally in line within the bottom one-third of the ONH surface. In a normal fundus, the NFL creates arcuate bundles superiorly and inferiorly from the optic nerve head that meet

temporally in an almost horizontal line passing through the fovea, as seen in Figure 2.1. This area is often called the horizontal raphe; however, despite its name, is often not horizontal, and varies between individuals (Chauhan, Sharpe, and Hutchison, 2014).

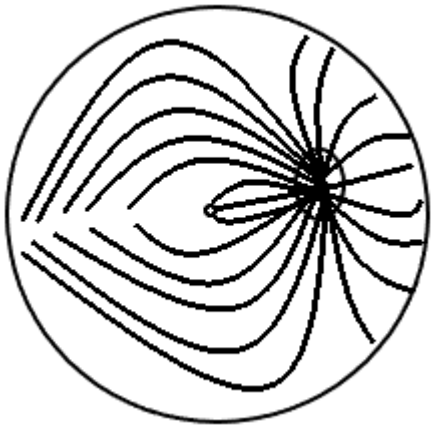


Figure 2.1 Graphic representation of the retinal nerve fiber layer orientation, right eye

The angle of the fovea to the temporal raphe, unlike the angle between the fovea and the ONH is not susceptible to daily variation from imaging challenges, as explained previously in Section 2.1.1. Therefore, the current study hypothesized that the temporal raphe positioning is a more reliable marker for torsional measurements. Along with the variation in orientation of the raphe, the spacing between where the superior and inferior arcs meet in the temporal retinal can vary.

A study by Huang, Gast, and Burns (2014) looked at the differences between the raphe in two age groups of participantsmean ages of 25 (standard deviation (s.d.) = 6.7) and 66.3 (s.d. = 6.8) years old. They found that the retinal fibers overlapped significantly more in the younger group whereas less overlapping occurred in the older group. The authors speculated that the change in the spacing between superior and inferior arcuate nerve bundles is age-related and possibly a consequence of decreased visibility of the bundles or a physical loss of ganglion cells with increasing age (Huang et al., 2014). The effect of increased space between the bundle ends makes determining an accurate angle between them more difficult as there is a larger margin of angle variation.

2.2 Subjective Testing Methods

The four most commonly used clinical methods of subjective quantification of ocular torsion are the Double Maddox Rod (DMR) test, (modified) Bagolini Lenses, the Synoptophore (also known as the major amblyoscope), and the Harms Tangent Screen (HTS).

2.2.1 Double Maddox Rod

The DMR test is dissociative, whereby, even under binocular testing conditions, one eye cannot see what the other one sees until the two images are fused in the visual cortex (von Noorden and Campos, 2002). The test was designed by E.E. Maddox in the 1890s and is one of the most widely used tests for measuring the subjective visual perception of ocular torsion (Kushner and Hariharan, 2001). It is conducted by placing one of two differently coloured striated lenses in front of each eye. Due to the optical effect of the parallel striations in the lenses, a point of light seen through them appears as a line. With both eyes open, both lines (one from each eye) are perceived simultaneously. The lenses can be rotated independently from each other in the frontal plane. If torsion exists, the two lines will be oriented differently in the frontal plane.

The patient can subjectively quantify the presence of torsional diplopia by rotating the lenses to achieve a parallelism or overlapping between the two images. While it is standard clinical practice in North America to place the red lens over the paretic eye there is some evidence that this could produce an artefact of increased torsional measurement (Simons et al., 1994). It has been found that regardless of fixation preference or laterality of paresis, the eye with the red lens will show more torsion. This finding suggested that two red lenses should be used for the DMR test to avoid confounding the results (Simons et al., 1994). However, this option is not commonly used in clinical practice as it can cause some confusion to patients when reporting their visual experience.

A study by Almog, Nemet, and Ton (2014) compared the inter-test reliability between DMR and single Maddox rod (using one red lens only). Forty-eight

participants were tested with the red lens of each test over the paretic and non-paretic eye. Congruent with Simons et al. (1994), Almog et al. (2014) found there to be no significant differences between testing methods when the red lens was over the paretic eye ($0.10^\circ \pm 1.34$) but there were significant differences when measuring over the non-paretic eye ($0.69^\circ \pm 1.46$). This finding suggests that the density of lens colour may have an effect on the presence and amount of torsion perceived. Almog et al, (2014) also found no significant difference when the reliability (i.e. variability) of each test.

Despite being a common clinical test, the DMR has several limitations. Along with the colour artifact described above, a major limitation is the inaccuracy of the trial frames used to hold the lenses on the patient, and the lenses themselves. The trial frames are marked at five-degree intervals, each approximately three millimetres apart on the dial. Moreover, the lenses are often poorly marked making it difficult to align the dial's reference points with the orientation of the striations on the lenses. These can be difficult to accurately report a patient's torsion within a few degrees (Marsh, Durking, Hack, Markowitz, and Cheeseman, 2014). For example, it can be difficult for a clinician to differentiate between three and five degrees of torsion. However, consistently across a number of studies, the DMR test has been found to be most accurate for measurements in primary position only (the patient looking straight ahead), and under 20 degrees of torsion (Johnson et al., 1987). Other limitations of the DMR test include the intra-subject variability in aligning the lines to each other and in reporting the true horizontal; proper fit of the trial frames; and the patient's head posture.

2.2.2 Modified Bagolini Lens Test

A second subjective method occasionally used for clinical assessment of torsion is a modification of the Bagolini lenses. Traditional use of the Bagolini lenses is to assess simultaneous perception (a level of binocularity). This method is used to detect the presence of normal central field binocular fusion, suppression, diplopia, and abnormal retinal correspondence, all of which can apply to the evaluation of any strabismus

including cyclotorsion. Bagolini lenses can have the advantage of testing binocular visual experience in a less-dissociative environment for the measure of torsional diplopia. This allows the tested subject to preserve binocular vision of most of the visual environment, therefore more in keeping with an unaltered visual experience.

A modified use of these lenses is to assess if the correction of a torsional deviation is really needed for a diplopic patient to see single vision. In this instant, the patient uses the availability of the non-dissociated environment to facilitate cyclofusion (Ruttum and von Noorden, 1984).

Ruttum and von Noorden (1984) compared DMR and Bagolini lenses in patients with acquired CN IV palsies. The modified procedure of Bagolini lenses in their study was similar to that of the DMR. The Bagolini lenses were placed in trial frames at 90° markings. Their striations created the visual perception of two lines originating from a single point source of light. With the room lights on, and the details of a panorama projected on a wall ahead of them, subjects were asked to adjust the lines seen, not only parallel to each other but also with reference to the horizontal visual reference of the "real world" projected in front of them.

These authors showed that both tests yielded similar results under dissociative conditions. Since the Bagolini lenses are less dissociative (finer striations allowing a better binocular view of the projected image), they let adaptive mechanisms overcome the disparity allowing for the assessment of both dynamic and static subjective torsion. A comparison of DMR to Bagolini lenses showed that adaptive mechanisms are dependent on intact sensory mechanisms to fuse retinal disparities. Both the DMR and Bagolini lenses can be used for assessing torsional diplopia in primary position (with the patient looking straight ahead) and in down-gaze, two important positions in the case of torsional diplopia caused by CN IV.

2.2.3 Synoptophore

The major amblyoscope, or Synoptophore, unlike the Bagolini lenses or DMR, can measure objective and subjective strabismus deviations in all diagnostic positions of gaze. The Synoptophore can also assess the fusional and stereoacuity potential of a

patient. It is also one of the few instruments that is able to assess all directions of motor fusional amplitudes (torsional, horizontal, and vertical). Georievski et al. (2007) conducted a study with normal participants, looking at the effect of increasing torsional disparity on binocular single vision. Their results showed that the amount of fusion a patient can maintain decreases as torsion increased. This work however, did not examine the effect of increased fusional amplitudes in patients with longstanding deviations. The study also did not compare the results of Synoptophore to other subjective tests.

Sen, Singh, and Mathur (1980) presented normal participants with Synoptophore, visual targets used to measure torsional fusional vergence. Their results showed that in primary gaze position, the mean amplitude of torsional fusional vergence was the lowest compared with other positions. Torsional fusional vergence was also greater when fusing vertical lines than horizontal ones. The authors suggested that their results showed that it is more advantageous to assess torsion using horizontal lines because the cyclo-fusional reflex is less apparent than when using vertical lines (Sen et al., 1980). However, the authors did not propose an explanation for these results.

2.2.4 Harms Tangent Screen

Another multi-purpose test is the Harms Tangent Screen (HTS), first described by Heinrich Harms in 1941. The HTS is an accurate and unique method for the strabismic diagnostic positions of gaze because of its better control and assessment of the eye positions during measurements (Aust, Bedwell, and Obstfeld, 1970). The HTS is regularly used in Europe to quantify strabismus and torsion in all diagnostic positions of gaze (von Noorden and Campos, 1974). However, there is little in the literature that compares the HTS to the other subjective methods like the DMR, Bagolini Lenses, and Synoptophore.

2.2.5 Comparison of Subjective Testing Methods

There are few studies comparing the four methods of subjective torsional measurements. Previous research has assessed the compatibility between different subjective tests which provides the intra-reliability of the tests themselves. However, much of the research has also shown that the different tests do not have high inter-testing reliability.

There have been a few studies that compared inter-test reliability among a number of subjective tests for measurement of ocular torsion; however, no objective measure was used for comparison. A study by Klainguti, Stickler, and Chamero (1992) used 50 ocularly-normal subjects whereas Capdepon, Klainguti, Stickler, and van Melle (1994) assessed 30 participants with CN IV palsies. Both studies used the Synoptophore and HTS along with three other subjective methods that are less common in current clinical practice. For example, a single Maddox rod test used was performed with one red Maddox lens instead of the routinely used two; in the one lens method, the patient rotates the lens such that the perceived horizontal line is parallel to the environmental surroundings (Almog et al., 2014).

A large-diameter double Maddox rod test was preformed in the same way as conventional DMR testing except that the lenses are seven centimeters diameter instead of three centimetres (Capdepon et al., 1994). The Synoptometer used is a modification of the Synoptophore and allows deviations in the periphery to be measured using mirrors (Nema and Nema, 2014). The simple Maddox rod, large-diameter Maddox lenses and synoptometer were not be used in the current study because they are not commonly used in North American practices or the clinical site of this study.

Results of both studies above were similar; the authors stating that based on median values, the methods tested were reliable within one test, but there were differences between the tests (Klainguit et al., 1992). Both studies found that the DMR was more reliable for primary position measurements, and the HTS was more reliable for measuring torsion in all positions of gaze (Klainguit et al., 1992;

Capdepon et al., 1994). It was also concluded that the same test should be used before and after surgery to quantify the surgical effect (Klainguti et al., 1992).

A study by Flodin, Karlsson, and Andersson-Grnlund (2016) assessed the repeatability and compatibility of three different tests to measure torsion: the single Maddox rod (using one red Maddox lens instead of two lenses); Synoptophore; and a KMScreena novel test for cyclotorsion developed in Sweden and designed as a digital Hess Screen that is currently used only in some Swedish clinics (Flodin et al., 2016). Each test was repeated three times on two separate visits. Results between the two visits showed the torsional measurements for each test were not significantly different, suggesting repeatability. Comparison of the tests together, however, showed significant differences between the single Maddox Rod and the Synoptophore, and between the single Maddox Rod and the KMScreen. Therefore, the results suggest that while the tests themselves are reliable, they do not all measure torsion in the same way. As is common with studies on this topic, only subjective torsional tests were assessed without a comparison to objective measurements.

2.3 Objective Testing Methods

Currently there is no precise "gold standard" for the assessment of objective ocular torsion. Fundus inspection by direct or indirect ophthalmoscopy and photography are the most widely-used methods. Within these methods, the subject measured is fully dissociated since both eyes cannot look at the same target simultaneously. Illumination conditions, flashes, and so-called apparatus accommodation are all examples of fusional obstacles. Despite objective tests typically being under monocular conditions, the combination (summation) of torsional angles between the two eyes is necessary for making a diagnosis of abnormal cyclotorsion (Parsa and Kumar, 2013).

For the current study, fundus photography and OCT scans were used to provide static images. These imaging methods estimate the amount of globe rotation by comparing the orientation of the foveal pit to the centre of the optic disc.

2.3.1 Normal Variation of Ocular Torsion

Studies reported in the literature on objective torsional measurements show a relatively large variation of fovea-ONH angles. A study by Bixenmann and von Noorden (1982) used fundus photographs on 42 non-strabismic participants. They measured the angle between the horizontal line from the optic nerve head and line passing through the fovea. The authors reported that the average torsion was $7.25^\circ \pm 2.57^\circ$ of excyclotorsion from the horizontal line passing through the centre of the optic nerve head. The range however was from near the horizontal (value not given) and 12.5° excyclotorsion.

Other studies have shown a similar variation of fundus torsional appearance: Williams and Wilkinson (1992) reported ocular torsion by fundus photography in normal participants to be 6.11 3.32; Jethani, Seethapathy, Purohit, and Shah in 2010 reported $10.6^\circ \pm 2.6^\circ$ excyclotorsion for normal children; and Herzau and Joos-Kratsch (1984) reported $6.8^\circ \pm 2.5^\circ$ in normal eyes with variations of up to four degrees within the same subjects. This variability of torsion in normal participants makes identifying abnormal torsion challenging by conventional fundus photography. It is therefore predictable that studies on pathological torsional measurements will be difficult to interpret.

Many have postulated the reasons for a large range of normal torsion. As mentioned previously, the appearance of the optic disc in photographs can be misleading due to the variable position of the nerve axons within the apparent choroidal opening of the nerve. Another source of variability is the refractive error of the eye. Highly myopic eyes are more likely to have a greater fovea-optic disc distance, possibly due to a larger globe size (Parsa and Kumar, 2013); however, no effect of astigmatism has been found in the literature (Jonas et al., 2015).

A study by Jonas et al. (2015) compared the ocular torsional angle of 3468 normal individuals and examined a variety of possible associations with systemic and ocular factors. Significant associations to torsional angles were found for high cylindrical refractive errors and shorter disc-fovea distance (contrary to other

studies). Non-significant associations were found between torsional angles and other variables: spherical refractive error (range not specified), axis of the astigmatic refractive error, contrary to other studies high refractive myopia (greater than 8 diopters), high axial myopia (greater than 26.5 mm), intraocular pressure, and glaucoma (both open-angle and angle-closure).

2.3.2 Fundus Photography

When measuring torsion on a fundus photograph, traditionally the torsional angle is calculated using the locations of the fovelar pit and the centre of the optic disc. The centre of the optic disc is the intersection between the vertical and horizontal maximal widths of the visible optic disc margins (Figure 2.2).

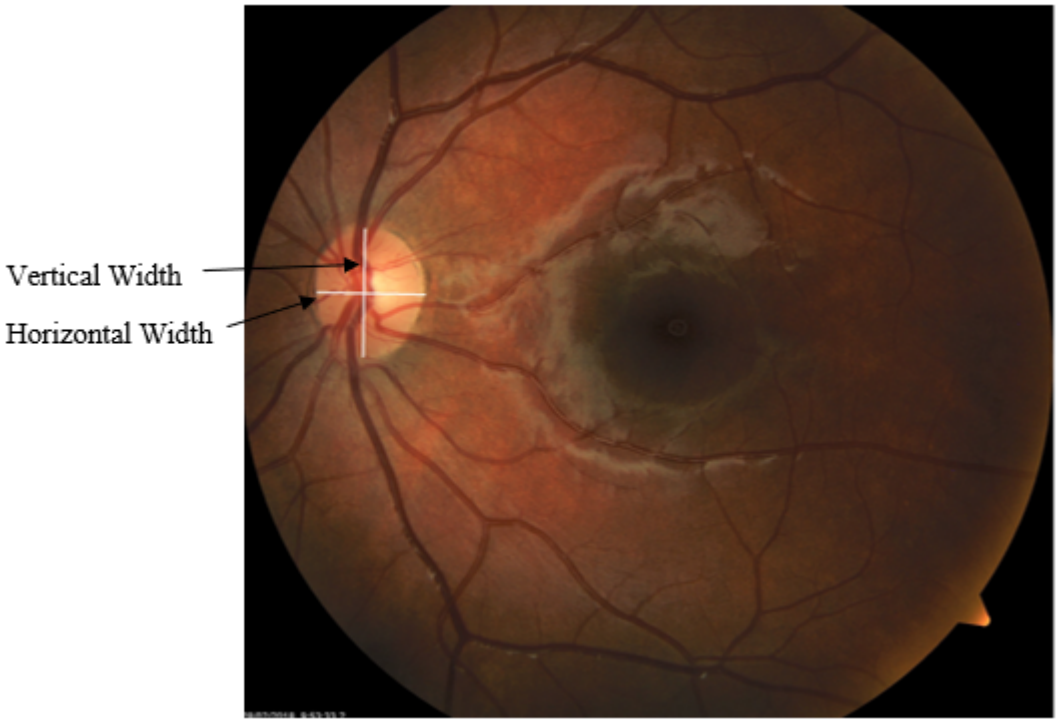


Figure 2.2 Depiction of the visible margins of the optic nerve head on a fundus photograph

As mentioned previously (Section 2.1.2), these visable margins are not necessarily the actual limits of the ON itself; rather, they are the visible surface features present on a 2-D plane of the photograph. These margins vary between

individuals and their appearance is affected by refractive error and a variety of systemic and ocular conditions (glaucoma, diabetes, high intercranial pressure). Therefore, the apparent size of the optic disc can create a difference of torsional angles measurements of nearly five degrees (Chauhan and Burgoyne, 2013; Parsa and Kumar, 2013).

Chauhan and Burgoyne (2013) argued for another method of marking the centre of the optic disc that is based, not on the visible margins, but rather on Bruch's membrane opening. The end limit of Bruchs membrane around the optic disc is typically masked by the nerve axons, but in fact it marks the real anatomical limits of the ON. Another argument for why the utilisation of Bruch's membrane as a landmark to delineate the centre of the optic disc is because it is not influenced by changes in the eye such as intra-ocular pressure or refractive error. Bruch's membrane is not visible in photographs, and requires high quality OCT scans to be located and to determine the real centre of the disk. However, this imaging methods is thought to provide a more accurate assessment of the disc centre as comapred to using the visible surface margins on a photograph (Chauhan and Burgoyne, 2013; Park, Lee, Lee, Shin, and Park, 2015).

2.3.3 Optical Coherence Tomography

Optical Coherence Tomography was first described by Huang et al. (1991) for detection and monitoring of a variety of eye conditions; its applications have increased within the last few years. This technique uses cross-sectional images measured with time-delay and intensity from back-scattered light incident on the retina (Huang et al., 2014). Two popular commercial OCTs are the Zeiss Cirrus© and the Heidelberg Spectralis©; both of which have been suggested in the measurement of ocular torsion (Choi, Kim, Park, Park, and Park, 2014).

The current study used the Heidelberg Spectralis© spectral domain OCT (SD-OCT) for its capabilities of imaging the temporal raphe. The SD-OCT produces *en face* (frontal) visualization of the anatomical orientation of the nerve fiber layer.

The Spectralis© SD-OCT is capable of visualizing the anatomical path of the

retina NFL bundles. These have been shown to take an arched course above and below the papilomacular bundle (Chauhan et al., 2014), exiting the eye through the ONH. The SD-OCT allows visualization of the raphe path in order to measure ocular torsion. Unlike fundus photography, these SD-OCT-assisted measurements are proposed as more accurate for ocular torsion. With this new information, we seek to understand better, the relationship between subjective and anatomical torsion in normal subjects and patients with CN IV weaknesses.

2.3.4 Temporal Raphe

Assessing the entire retina rather than just the fovea-ONH angle, in most cases, provides a more obvious image of fundus torsion (Parsa and Kumar, 2013). The orientation of the temporal retina has been proposed as better predictor of anatomical torsion rather than the fovea-ONH angle (Chauhan et al., 2014). There have been a number of imaging studies that show that the linear region of the fundus image where the superior and inferior temporal retinal ganglion fibers meet, although straight, is often not horizontal (Chauhan et al., 2014; Parsa and Kumar, 2013). There is, however, an average angle of six degrees of apparent excyclotorsion from the horizontal line passing through the fovea (Parsa and Kumar, 2013). The raphe is generally undetectable in standard fundus photographs as the nerve fiber bundles become thinner as they approach each other (Huang et al., 2014). Imaging by SD-OCT allows a better mapping of the area between the superior and inferior arcades to show the angle the temporal raphe makes with the fovea.

Using the temporal raphe angle as the basis for ocular torsion, two suggestions have been proposed with the relationships depicted in Figure 2.3.

First, that it is the torsional measurements of the temporal raphe between the two eyes combined which gives the actual angle of cyclorotation, rather than the torsional angle of either eye individually (Parsa and Kumar, 2013). Second is that the angle created at the imaginary intersection of the temporal raphe in each eye is the actual torsional angle for both eyes (Parsa and Kumar, 2013). Of note, is that the fovea-ONH angle is proposed not to have an effect on overall fundus and

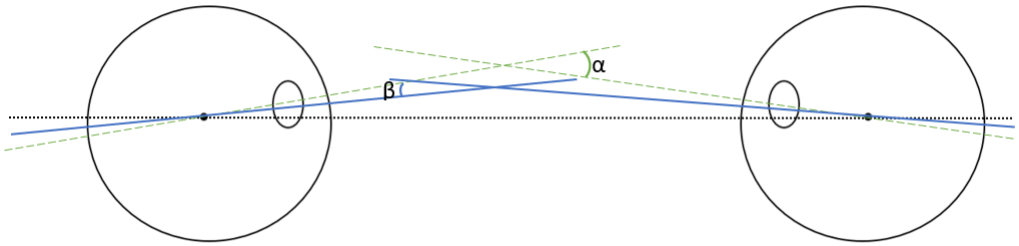


Figure 2.3 Extrapolation of bilateral fovea-ONH (α) and temporal raphe angles (β)

subjective torsion.

In their study, Parsa and Kumar (2013) looked at the orientation of retinal vascular arcades as another way to quantify objective ocular torsion. The authors acknowledged that the vessels follow the path of the temporal raphe. In fact, there is a strong link between the development of axons and the corresponding development of vasculature therefore the orientation of both should follow similar paths (Parsa and Kumar, 2013). However, quantifying ocular torsion by retinal vasculature is a complex process, requiring measurements at many points within the fundus. Since the retinal vessels follow the same path as the nerve axons, imaging the temporal raphe and assessing an angle from the fovea is a more straightforward method using SD-OCT imaging.

2.4 Comparison of Subjective and Objective Torsional Angles

A major challenge for clinicians has been the frequent discordance between subjective and objective torsional measurements. Authors have highlighted the difficulty of explaining the differences between the two (Kushner and Hariharan, 2009; Schworm, Eithoff, Schaumberger, and Boergen, 1997). For example, a patient might have 15 degrees of torsion on a fundus photography but does not perceive a tilted image with DMR.

One study has compared subjective tests to objective fundus photographs. Roh and Hwang (2011) compared the DMR and Lancaster Red-Green tests (similar to the HTS) to fundus photographs. They found that there was a significant difference

between the subjective and objective torsional results, further agreeing with previous work by others on the disparity between the two. These authors compared the length of time the subject had their CN IV palsy to the amount of torsion recorded and found no significant relationship. They proposed that while subjects may have adaptive mechanisms, the ability to use them may differ between people.

The adaptive mechanisms mentioned by Roh and Hwang (2011) have been long speculated as a reason for the difference between recorded subjective and objective torsion. Herzau and Joos-Kratsch (1984) proposed three reasons for these phenomena.

The first being explained by proprioception and a physical adaption of a new globe position after, for example, an acquired CN IV palsy. It is suggested that the patient ceases to feel the physical sensation of the abnormal rotation of the globe despite its presence on objective testing. However, there is no evidence in the literature of the role of this type of ocular proprioceptive abilities in humans, yet.

Their second theory is also based on motor adaption. The eye requires micro-motor vergence movements to position itself so that images fall on corresponding retinal points and help maintain a stable binocular single vision. In the case of torsional disparities, the vergence movements also attempt to maintain an upright image. The authors found that the paretic eye, especially under monocular conditions would become properly oriented by cyclovergence leading to excyclotorsion of the fellow normal eye. They proposed that the shifting of torsion between eyes was the reason for the disappearance of head-tilts during testing. It could also explain why the subjective torsional measurements, especially under binocular conditions, do not correspond to the objective or monocular torsions in the same patient.

The third mechanism proposed by Herzau and Joos-Kratsch (1984) focuses on cortical adaption. In conjunction with the anatomical positioning of the retina, early visual experiences are critical for the correspondence between retinal meridians. In cases of newly-acquired torsion, the brain receives images that are different from each retina. Typically, there is a range of non-corresponding retinal points where the brain is still able to maintain binocular single vision. This is called Panum's fusion space. Panum's fusion space for torsion is hypothesised to be the same as the variability of

the temporal raphe angle (approximately six degrees) as discussed above (Parsa and Kumar, 2013). It occurs when globe torsion is greater than Panum's fusional space that the perception of cyclorotation occurs and diplopia is generally perceived. However, in the cases where anomalous retinal correspondence occurs before visual maturity, patients have shown no presence of subjective torsion despite objective torsion being outside Panum's fusional space. This suggests that perceived torsion can be related to one's visual experience rather than globe rotation alone (Herzau and Joos-Kratsch, 1984).

Guyton (1983) also suggested that visually-immature subjects are capable of sensory adaptation by perceptual reorientation of the retinal horizontal meridians at a cortical level. Visually-mature individuals on the other hand could possibly be able to adapt to long-standing torsional deviations by learning to interpret their visual environment on a perceptual level rather than by cortical reorientation (Guyton, 1983).

In his discussion, Guyton (1983) categorized symptoms related to these adaptation mechanisms. He postulated dependence of these symptoms on one of three time frames of onset:

1. Patients who showed objective but no subjective torsion, were thought to have congenital or childhood onset torsional deviation, with a cortical reorientation adaptation mechanisms;
2. Those showing subjective torsion of a lesser amount than their measured objective torsion were thought to have a longstanding acquired deviation with a learned ability to interpret their torsion as the new normal;
3. Patients whose subjective and objective torsional deviations were comparable were said to have had a recent onset, most likely at an adult age, and without any adaptation.

A study by von Noorden (1984) supported Guyton's work (1983) as did Herzau and Joos-Kratsch (1984) with regards to cortical adaption as an explanation for the difference between subjective and objective torsion. von Noorden (1984) compared subjective torsion to an awareness of image tilting. Patients who were aware of image tilt and showed both subjective and objective torsion were more likely to have had a

recent onset of a CN IV palsy. Patients who were unaware of image-tilt but showed both subjective and objective torsion on testing were more likely to be using an adaptive mechanism such as cyclofusion, suppression, anomalous retinal correspondence, or anomalous head posture under natural viewing conditions.

A third group of patients showed only objective torsion with no subjective measurements or awareness of tilting images. von Noorden (1984) suggested that these patients were more likely to have congenital deviations. It is this unawareness of perceived torsion in the presence of objective ocular torsion that is thought to be caused by a sensory reorientation of spatial values of the paretic eyes retinal meridians. This spatial reorientation prevents awareness of torsion under both monocular and binocular conditions.

Some patients had an additional adaptive mechanism which prevented image tilting and its related phenomenon of so-called "Subjective Horizontal." This refers to using familiar objects in ones environment as a basis for perception (von Noorden, 1984). Using objects that are known to be horizontal, such as door frames, windows, stairs, and the natural horizon, provides a reference point for the rest of the visual environment, allowing the patient to perceive their world as level.

The Subjective Horizontal is tested monocularly by measuring torsion under both light and fully dark conditions. An accurate localization of the horizontal in both light and dark in the presence of anatomical torsion suggests that complete sensory adaptation with reorientation of retinal spatial values has occurred; whereas accurate localization in light but not in dark conditions suggests that the patient uses spatial clues for their environment.

A final group described by von Noorden (1984) consisted of patients with CN IV palsies who fixated with the paretic eye, thereby localizing ("migrating") their torsion to the non-paretic eye. von Noorden speculated that the change in fixation is a sesnory adaptation when the paretic eye provides a clearer image; for example, ffrom better vision in that eye (Olivier and von Noorden, 1982).

A study by Dieterich and Brandt (1993) attempted to explain the differences of torsional measurements and adaptive mechanisms by combining objective torsion,

subjective torsion, and the "Subjective Vertical." The Subjective Vertical, in theory, is similar to the Subjective Horizontal as Panums fusional space for torsion is said to be zero at the fovea and increase radially in proportion of eccentricity (Crone and Everhard-Halm, 1975).

Dieterich and Brandt (1993) found that the Subjective Vertical was more common in subjects with ocular torsion; however, pathological ocular torsion was characterised as greater than their reported normal torsion range of 0–11 ° excyclotorsion. The Subjective Vertical was noted in the paretic eye for acute cases (3 days to 2 months) but shifted to the non-paretic eye for more chronic deviations (3 months to 4 years). The authors reasoned that the Subjective Vertical did not occur simultaneously with ocular torsion because localization of an image was a combination of the position of the image on the retina and an awareness of the position of eye. The motor perception of the eye's position is more accurate than the sensory information provided from the retina especially during pursuits and saccades (Dieterich and Brandt, 1993). Therefore, motor compensation by excess innervation corrects for the ocular torsion but not the Subjective Vertical.

Dieterich and Brandt (1993) also compared the findings of the Subjective Vertical to the DMR, reporting that when subjects localize subjective torsion to the non-paretic eye, it is a result of re-ordering spatial responses of the retina along new vertical and horizontal meridians (Dieterich and Brandt, 1993; Roh and Hwang, 2011). This was most often seen in patients who fixated with their paretic eye; their paretic eye would normalize their ocular torsion and transpose it to the non-paretic, non-fixating eye.

Therefore, one can conclude from these studies on adaption of ocular torsion that patients with longstanding CN IV palsies undergo a shift in their perception of horizontal in order to cope with an acquired tilted visual environment. The literature also proposes that the current clinical methods of measuring a subject's torsion do not correlate with the anatomical position of the fundus. Therefore, the current study was designed to provide qualitative relationships between subjective and objective torsion, as well as the cortical perception of torsion.

CHAPTER 3 METHODS

3.1 Research Design

The section current study is a prospective, non-interventional, cross-sectional design intended to compare subjective and objective ocular torsional measurement techniques.

3.1.1 Rational for Chosen Methods

A cross-sectional design was chosen because the parameters of the current study are not time dependent. By nature, cross-section designs can only measure differences between groups rather than a process of change. In a clinical setting, the tests used in this study are "snapshots" of a subject, not typically dependent on assessing changes over time. As well, the current study is comparing these tests between two independent groups.

3.2 Study Population

Potential participants in the study included current patients of the Izaak Walton Killam (IWK) Health Centre Eye Clinic in Halifax, Canada. Participants for the Control Group were recruited from the general population. A master list of all known patients with CN IV palsies was screened by the Principle Investigator (PI). Patients identified as potential participants were contacted by the PI first by mail and then by telephone. Information provided through the mail-out and telephone call included purpose of the study, and how appointments for the testing for the study would proceed. Upon verbal consent, potential participants were informed that the PI would meet them at their scheduled appointment to review all relevant information again prior to the enrollment in the study.

On the day of the potential participant's regular clinical appointment, written consent was obtained by the orthoptist scheduled to see the potential participant (patient) for that appointment. Once written consent was obtained, the study protocol proceeded as described. If consent was not granted, the regularly scheduled

orthoptic appointment continued as planned in the management schedule of the patient.

3.2.1 Inclusion Criteria

Participants in the CN IV palsies group were required to have a confirmed diagnosis of a CN IV palsy (unilateral or bilateral) stable for at least one year; an onset of the condition prior to at least five years; and cyclo-rotation of the eyes determined by subjective perception, DMR, and/or objective fundus rotation. Inclusion of participants for the Control Group required subjects to be normali.e. without any pf the exclusion criteria outlined below.

3.2.2 Exclusion Criteria

Exclusion criteria for both the CN IV and normal participant groups included:

1. combinations of other cranial nerve palsies or ocular motility abnormalities;
2. history of ocular muscle disorder, orbital disorder, retinal disease, glaucoma with field defect;
3. history of ocular trauma or surgery (extra-ocular muscle, decompression, retinal, glaucoma);
4. present retinal disease or media opacity; 5. latent or manifest nystagmus;
5. visual acuity of less than 6/12 in either eye on the Early Treatment Diabetic Retinopathy Study (ETDRS) chart;
6. neurologic disorder or developmental delay;
7. lack of self-consent ability;
8. extreme fatigue or inattentive behaviour, or lack of cooperation for, or comprehension of the tests.

3.2.3 Sample Size

The calculation of sample size for this study was guided by previous research studies conducted in this field. A sample size calculation was completed with a significant power of 50 participants; however, the majority of previous research work investigating the comparability of subjective torsional testing had a sample size of

2030 participants. Therefore, a sample size of 25 participants for the CN IV Group was chosen for the current research. The sample size for the Control Group was 25 as well, as this group will be age-matched to the CN IV palsy group.

3.2.4 Participants

Potential participants for the CN IV Group were found using a clinic master list of all current patients with the diagnosis of CN IV palsy. From this list, the PI determined any applicable exclusion criteria. Bias was limited by contacting all potential participants with a booked appointment if they met the inclusion and exclusion criteria. An introductory letter (Appendix A) and consent document (Appendix B) were mailed to each potential participant as well as a child assent-document if applicable (Appendix C). Potential participants were kept on a Master List until they gave or declined consent for participation.

Potential participants were contacted until 25 subjects were enrolled in the study. This resulted in thirty-eight participants initially being contacted, of which five declined participation prior to enrollment. Of the enrolled 31 participants, three were removed: two had large strabismus angles without the ability to perceive images simultaneously, as required for some of the tests, and one recruited subject was removed due to a possible diagnosis of *myasthenia gravis* upon subsequent testing.

All 28 remaining enrolled participants were included in subjective testing; however, three participants were not included in the objective tests analysis due to lack of proper imaging of their ocular fundus. Three more participants did not have the temporal raphe imaging data collected prior to their planned extra-ocular muscles surgery. Two participants could not be contacted to finish their testing after their initial appointment. In the end, a total of 22 participants completed all testing. Participants for the Control Group were recruited from the community using a poster (Appendix D). They were age-matched (5 years) to participants in the CN IV palsy group. Twenty-six participants were recruited, one was excluded due to the inability to complete imaging.

3.3 Data Collection

The data collection form used is attached in Appendix E. Along with results of each study tests, information collected for each participant included: lensometry, lateralization of palsy, fixing eye, visual acuity, and approximate time of onset of condition. All data were kept in a locked cabinet located in the orthoptic office, or on secure research cameras at the IWK Health Centre and Victoria General (VG) Hospital Eye Clinics.

3.4 Experimental Procedures

The following sections describe the overall testing protocol as well as the protocol for each specific test used during the study. Participants in both groups (CN IV paresis and Control) underwent the same procedures.

3.4.1 Clinical Testing Protocol

All equipment was readily available at the IWK Eye Clinic with the exception of the SD-OCT which was located at the Victoria General (VG) Hospital Ophthalmic Clinical Investigative Unit of the Eye Centre, within 10 minutes walk. All testing was completed per the clinical standard with regards to optical correction: best optic correction worn for Bagolini Lenses and Synoptophore tests, all other tests were completed without correction. Tests were completed without any compensatory head posture the participants might have routinely used. Prior to testing, participants were instructed on how to preform each test.

The specific protocol for each test is described below. To avoid uncontrolled changes to participant's fusional ability, the testing order is non-randomized ensuring a smooth progression from least to most dissociating tests. For example, the Bagolini Lenses test is conducted first, immediately after the consent is obtained, followed by the DMR. After both these tests are completed, the participant finishes their regularly-scheduled appointment with the orthoptist. Following the latter, testing continues with the Synoptophore, the "Subjective Horizontal," HTS with torsional measurements, and fundus photographs. The SD-OCT scans were completed at the

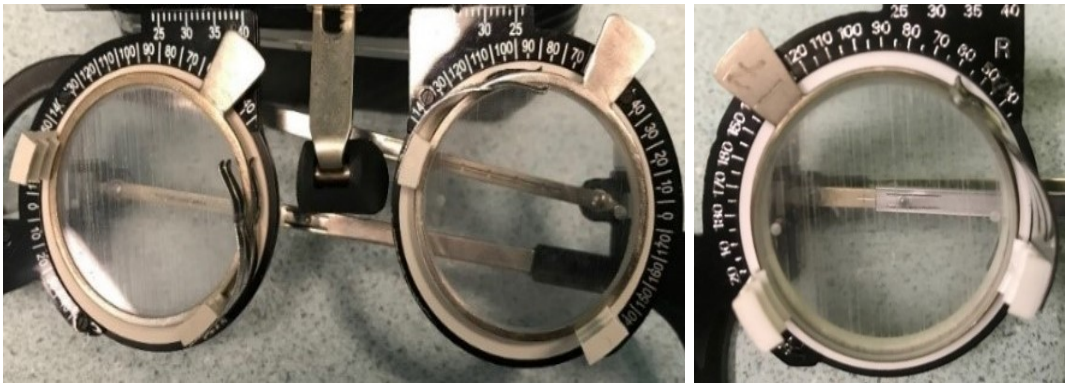
VG Eye Clinic at a different appointment if necessary.

3.4.1.1 Bagolini Lens

Participants wore standard trial frames (Good-lite, Elgin, IL, USA) with the Bagolini Lens (Good-lit, Elgin, IL, USA) striations set at 90° (Figure3.1A). This created horizontal lines that were comparable to DMR. Participants wore their optical correction, as is standard protocol for fusion assessment, in order to provide the most similar conditions to everyday life. To avoid cyclofusion, which can result in lower readings of torsional measurements, the perceived lines were separated using a six-diopter prism placed in front of the non-fixing so as not to correct the vertical deviation, paretic eye (Ruttum and von Noorden, 1984). Room lights were dimmed, but still allowed the participant to see their environment. Participants were instructed to rotate the lenses so that the perceived lines were parallel with each other (Figure 3.1B). Torsional measurements were read off the trial frames prior to removing them. When tested, vision was not affected by the Bagolini Lens striations thereby allowing this test to be a good representation of the participants' normal viewing conditions.

Two measurements were taken with a fixation light held at eye level at two and six meters. The order of the distances was randomized to avoid a potential confounding variable of learning effects. The two distances allowed the measurements to be compared with the HTS (set at two meters) and with the Synoptophore, which is considered to be a distance test (≤ 6). If no statistical differences were found between two- and six-meter measurements, the values were averaged and used as a singular value for statistical analysis. If there were differences found, the two were be used as separate values for analysis.

A



B

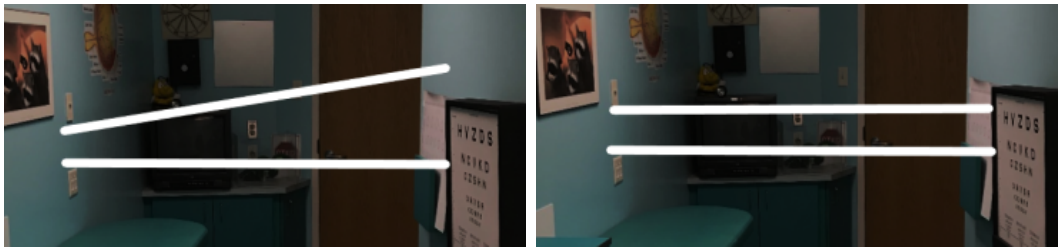


Figure 3.1 The Modified Bagolini Lens Tests

(A) The Modified Bagolini Lens test, striations at 90-degree markings

(B) Representation of patient perception before (left) and after (right) torsional correction.

3.4.1.2 Double Maddox Rod

The DMR test was completed using a similar procedure as the Bagolini Lens test. Using the same trial frames—this time without participants optical correction—a red lens was placed in front of the paretic eye and a white lens in front of the other eye (Figure 3.2 A). For participants in the control group, the red lens was placed in front of the right eye as is standard clinical procedure for patients without a fixating preference. Room lights were turned off for maximal dissociating conditions. As with the Bagolini lenses, a six-diopter prism was placed over the non-fixing eye in order to prevent any cyclofusion occurring. Participants were asked to make the two lines parallel to each other (Figure 3.2B). Measurements were taken at two and six meters, the order of which were randomized.

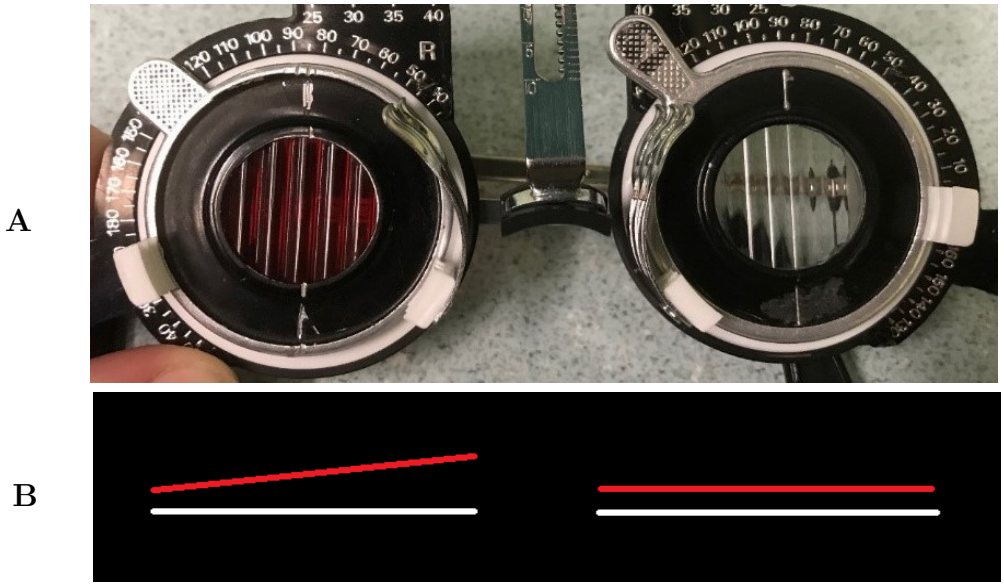


Figure 3.2 The Double Maddox Rod Test
(A) Double Maddox Rod lens striations at 90-degrees.
(B) Representation of subject perception before (left) and after (right) torsional correction.

As with the Bagolini Lenses, if measurements were the same for both distances, the values were averaged and used as one value for the analysis. If differences were found, both would be used separately in all subsequent statistical analysis.

3.4.1.3 Synoptophore

The Synoptophore (Clement Clarke, Harlow, UK) testing was completed in dim room lighting with the participants' best distance correction. The apparatus was placed in front of the participants, and the inter-pupillary distance was corrected. Simultaneous-perception slides (Clement Clarke, Harlow, UK) were used to correct the horizontal and vertical deviations. The objective measurements were done by a cover test and subjectively refined by the participant to ensure that the presented halo optic images overlapped.

To assess the torsional aspect of the deviation, torsion slides (Clement Clarke, Harlow, UK) (Figure 3.3) were presented with the solid image (cross) shown to the fixating eye. Participants were asked if the dotted cross was in the centre of the solid

image. The investigator rotated the dotted cross until the participant observed that the arms were not touching the solid image. The torsional measurement was then read.

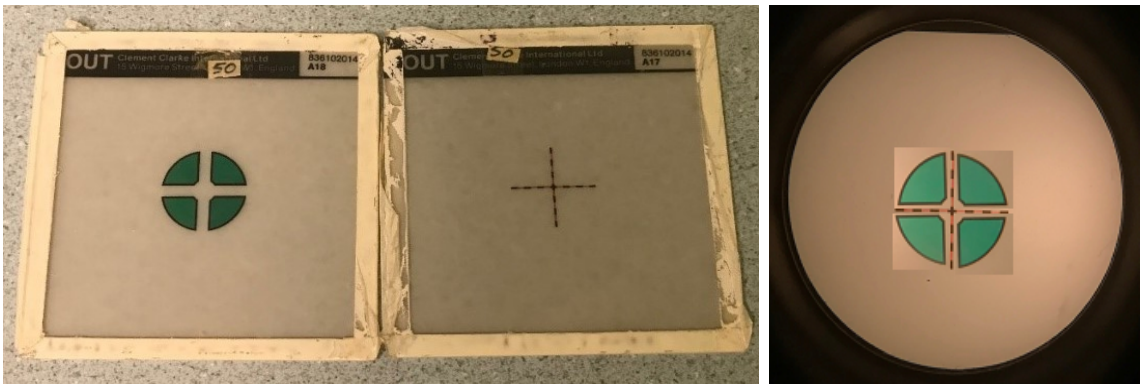


Figure 3.3 Synoptophore torsional perception slides (left).
Representation of corrected slides (right)

3.4.1.1 Harms Tangent Screen

The HTS was used for two purposes in the current study, assessment of the Subjective Horizontal and diagnostic measurements of ocular misalignment. To assess the Subjective Horizontal, the screen was covered with white sheets to prevent the participant seeing the grid; thereby reducing visualization of horizontal and vertical reference points (Figure 3.4). The test was performed with best correction worn. Both eyes were assessed separately under light and dark conditions using the centre slit-light. Participants were asked to rotate the slit-light until it was perceived to be horizontal.

Figure 3.4 Harms Tangent Screen covered for assessment of Subjective Horizontal

With the sheets removed, diagnostic measurements with head tilts were taken following the standard procedure described in previous research (Kaufmann, Steffen, and Esser, 2012). Without optical correction, participants were seated two meters in front of the tangent screen. The screen was specially manufactured on specifications to accommodate a distance of two meters to fit the exam room as opposed to the standard 2.5 meters (Tyedmers and Roper-Hall, 2006). Participants wore a helmet with a fixation light that ensured head position was consistent. A central fixation light seen by participants through a red filter was held over the fixating eye. A green torch light held by the subject is positioned over their perceived red light, giving the tester measurements of ocular deviations on the grid of the screen (Aust, et al., 1970) (Figure 3.5).

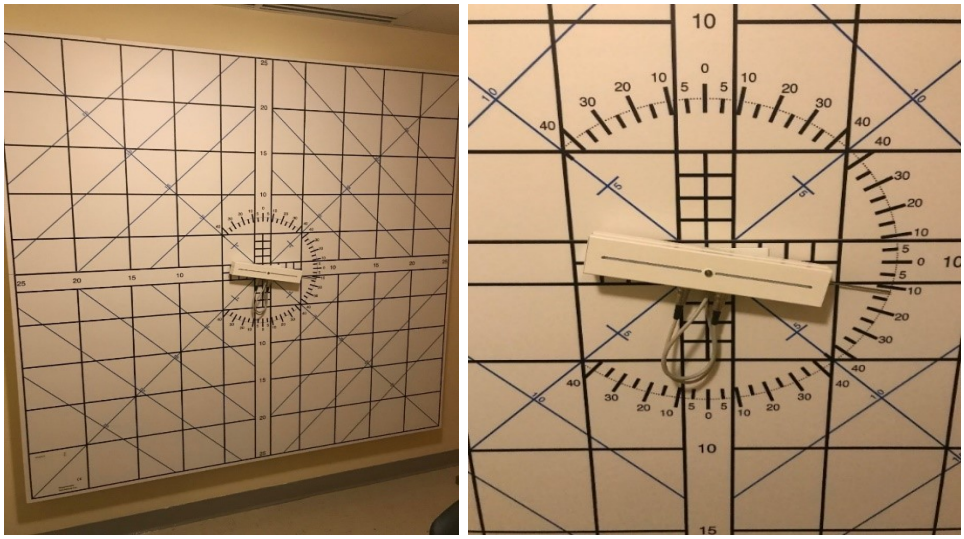


Figure 3.5 Uncovered Tangent Screen with close-up of the torsional markings

Torsional measurements, using the slit-light, were completed in all positions of gaze as is the current clinical practise with the HTS; however, only the primary position measurements were used for statistical comparison in this study in order to be comparable with the DMR and Bagolini Lenses.

3.4.1.1 Fundus Photography

Photographs were taken of both posterior poles of each participant while using a Zeiss Visucam Pro NM (North York, ON, Canada) the cameras internal fixation target seen by the subject. Previous research showed that there is no difference between using internal or external fixation targets for the same eye being photographed (Kushner and Hariharan, 2009). Photographs were converted to a jpeg format and processed through a program called MB Ruler (Triagonal screen ruler 5.3©) was used (Bader, 2016). This program presents a transparent protractor on a computer screen. The investigator placed the centre of the protractor on the fovea to measure from the horizontal. The torsional angle was then measured from the fovea to the centre of the optic nerve head by placing the ruler over the fovea and reading the alpha angle (Figure 3.6).

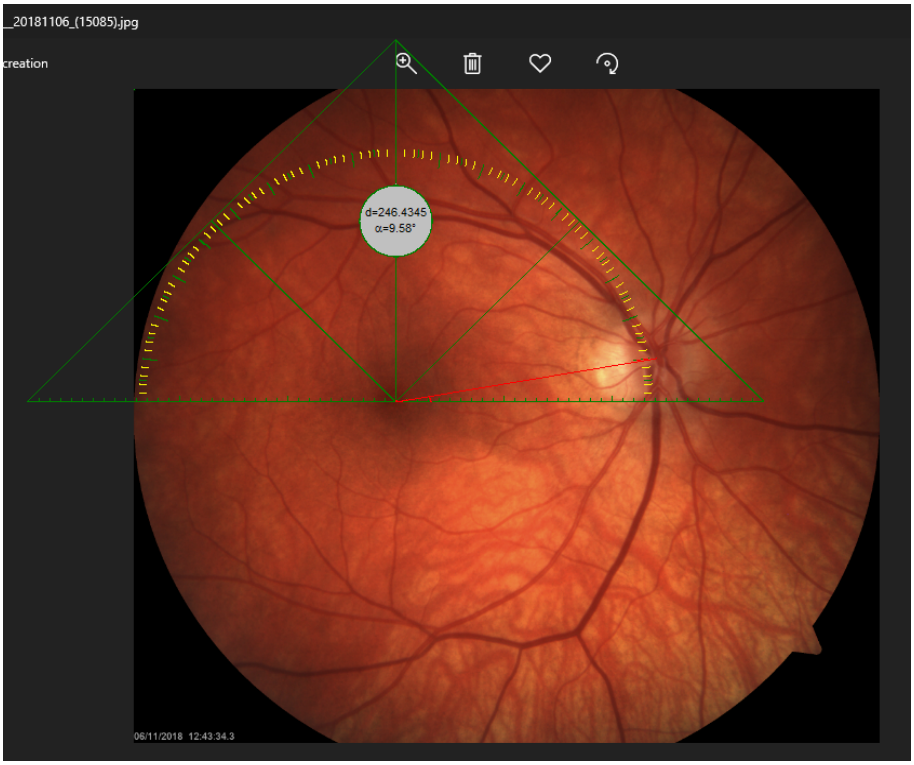


Figure 3.6 Representation of fundus torsion measurements

A novel technique for measuring ocular torsion by fundus photography that has yet to be verified is called CycloCheck. It uses a computer-uploaded image of the fundus and subsequently calculates the torsional angle (Simiera and Loba, 2017). While the process of measuring is the same as traditional methods, this program is quite new and has yet to be implemented in research or clinical settings. Without available validity assessment of this new technology, the more traditional method was used for the present study.

In order to prevent measurement bias, photographs of both CN IV and normal participants were randomly given to four clinicians from the eye clinic with similar experience to the PI. Each one completed the measurements as outlined above. The measures obtained by the clinicians were then compared to the ones done by the PI to ensure consistent and reliable measurements.

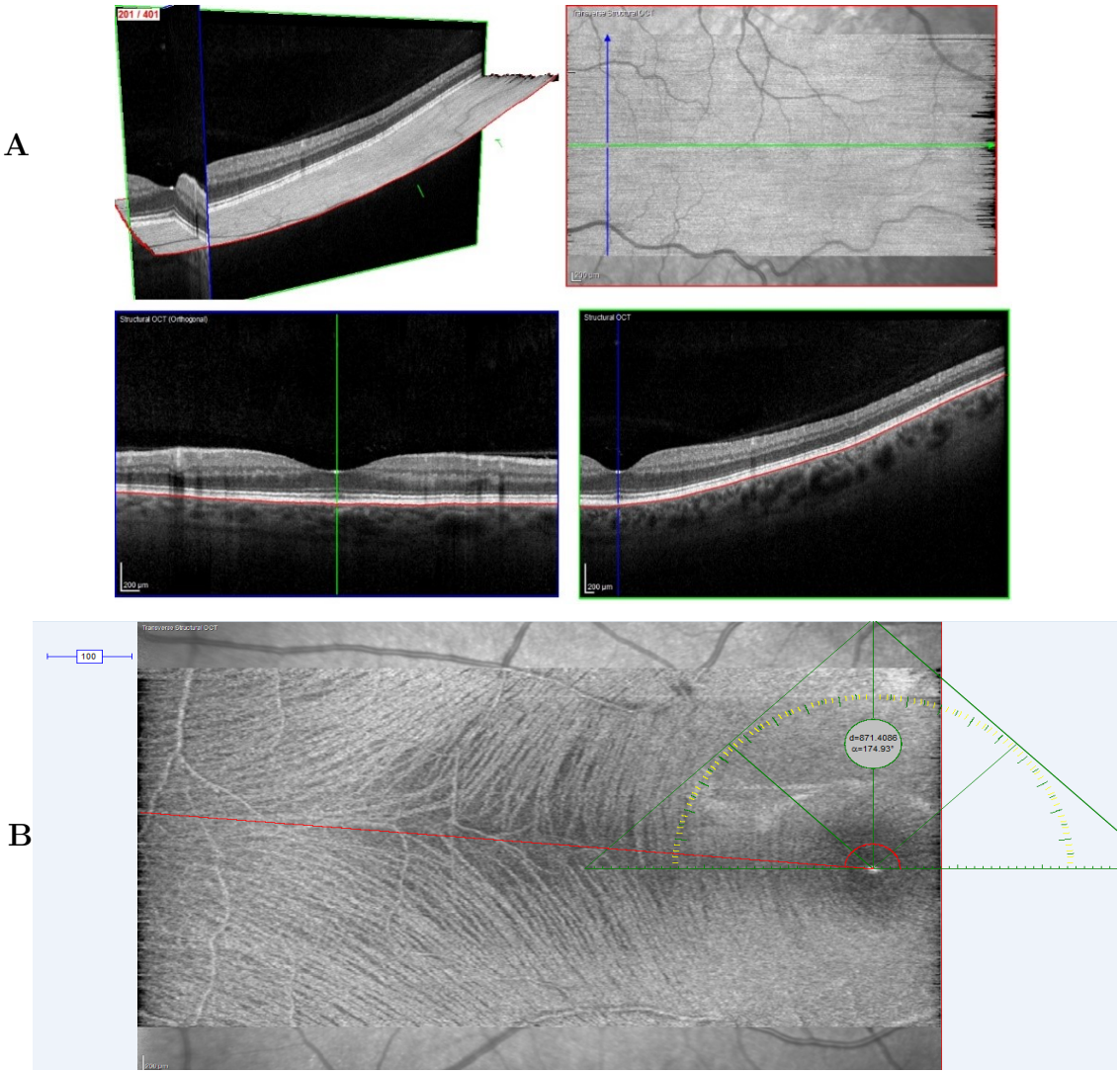
3.4.1.1 Optical Coherence Tomography

The Spectralis OCT 2 (North York, ON, Canada) with a Glaucoma Module Premium Edition (GMPE module) was used to complete both the torsional angle measurements and the temporal raphe scans. Throughout OCT testing, eye tracking was enabled to ensure a more accurate measurement of both Bruchs membrane and the temporal raphe.

The scans were completed in two continual steps. The first step was to measure the torsional angle using a similar procedure to fundus photography. B-scans were used to mark the fovea as well as make 24 radial and three circular scans to assess the edge of Bruchs membrane surrounding the optic nerve. The centre of Bruchs membrane"opening/circle" was then derived from these scans. The torsional angle was calculated by comparing the foveal location to the centre of Bruchs membrane circle to the horizontal (Chauhan and Burgoyne, 2013).

The second step was to image the temporal raphe. The process of imaging the temporal raphe has been described by Chauhan et al., 2014. Again, using B-scans at 11 microns apart, approximately 4000 were done for each eye in groups of ten, resulting in 400 scans reported in the final image. The nerve fiber layer was set as a reference plane for the analysis software (Transverse Section Analysis v. 6.0.06, Heidelberg Engineering) to use *en face* visualization of the reflectance images taken.

To measure the angle of the temporal raphe, two images were created. The first jpeg had reference lines marking the centre of the fovea (Figure 3.7), the second without the reference lines. Using the program MB Ruler, the protractor was centred on the fovea using the reference lines. Finally, the second jpeg image was used to draw the angle line where the location of the space between the nerve fibers was marked and the angle was given from the ruler.



(A) Horizontal and vertical dissection at foveolar reflex.
(B) Representation of temporal raphe angle measurement.

Figure 3.7 Foveal Marking for Torsional Measurements

3.5 Risk Analysis

No potential risks were identified to the participant of this study other than potential breach of confidentiality. All of the tests used in this study have been well-established as safe for clinical use. To protect participant confidentiality, non-identifiable study codes were given to each participant. These codes were used for all study documents

pertaining to that participant. A master list connecting the participant to their code was kept in a secured location.

3.6 Benefit Analysis

No direct benefits were expected to occur for participant during this study. This study did not include intervention or treatment; rather all testing except the Subjective Horizontal and OCT testing (both the fovea-Bruchs membrane angle and temporal raphe scans) are standard of care for patients with CN IV. Therefore, the information gathered during this study would have been completed and sent to the ophthalmologist regardless of participating in this study or not.

3.7 Ethical Considerations

Ethical approval was obtained by the IWK Health Centre Research Ethics Board prior to initiating the study. Testing took place in individual examining rooms of the IWK Eye Clinic and at the VG Ophthalmic Clinical Investigative Unit of the Nova Scotia Health Authority Eye Centre. Raw data and results contained only a non-identifiable code; the master list connecting the code to the participant which was held separately in a secured location. Data documents were stored in a locked filing cabinet located in a restricted-access office. All participants were given sufficient amount of time to read and ask questions regarding the consent forms and study (Appendix B). Participants were informed that they may discontinue the study at any point throughout without penalization or changes to the care provided.

3.7.1 Funding and Compensation

Funding was obtained through a Category A Research Grant from the IWK Health Centre Research Department. Upon completion of testing at the IWK Eye Clinic participants were given a $5 gift card to Tim Hortons. Another $5 gift card was given upon completion of the OCT testing.

CHAPTER 4: RESULTS

The following chapter presents the statistical analysis of the data for the current study. The descriptive statistics for both CN IV and control groups are included, followed by the analysis of the results on subjective and objective testing. All data collection was analyzed using version 25 of SPSS Statistics (IBM, 2017).

4.1 Subject Analysis (Descriptive Statistics)

The descriptive statistics for this study that were obtained are the age range of participants, gender, lateralization of palsy, fixing eye, and age at onset.

Thirty-eight potential participants were contacted for the CN IV Palsy Group of which, five declined participation; the remaining 31 were enrolled in the study. Three participants were removed after enrollment: two due to large strabismus angles and subsequent inability to simultaneously perceive images and necessary for the study; one due to potential *myasthenia gravis* diagnosis following further testing.

All 28 remaining enrolled participants were included in subjective testing; however, four participants suppressed on at least one distance of testing with the Bagolini Lenses, and one participant was unable to perceive images on the HTS simultaneously for unknown reasons. Six participants were could not be included in all objective analysis due to lack of imaging: two participants did not have the temporal raphe imaging completed; three participants were unable to return to their appointments for unknown reasons; the temporal raphe images from one participant were corrupted during data transfer and the participant had surgery before a scan could be repeated. Therefore, a total of 22 participants completed all testing.

After recruitment of the CN IV Palsy Group participants, subjects for the Control Group were enrolled. These subjects were age-matched of (5 years) to the participants in the CN IV Palsy Group.

Table 4.1 outlines the age ranges and refractive error of the two groups as well as the lateralization and onset of palsy in the CN IV Palsy Group. Gender was included; however, it was not felt to be a confounding variable and therefore was not

controlled in either group. The range of refractive error was calculated using an average of spherical equivalencies between the right and left eyes. An intraclass correlation was used to determine if the refractive error between the CN IV Palsy and Control Group were comparable.

Table 4.1: Descriptive Statistics for CN IV and Control Groups

ITEM	**CN IV GROUP**	**CONTROL GROUP**
Age	$\overline{x} = 44.3$ (s.d. $= 18.0$)	$\overline{x} = 43.3$ (s.d. $= 14.8$)
Gender	18 Males; 10 Females	6 Males; 16 Females
Refractive Error:	$\overline{x} = -1.48$ D (s.d. 2.9 D)	$\overline{x} = -2.18$ D (s.d. 3.1 D)
Mean spherical equivalent and range	-9.00 D to $+5.75$ D	-9.00 D to $+1.50$ D
Type of CN IV Palsy	1 Bilateral, 2 Unilateral	N/A
Lateralization of Palsy	11 right nerve 16 left nerve	N/A
Fixating Eye	23 non-affected eye fixation 4 affected eye fixation 1 non-affected eye with alternation	N/A
Onset	$28 > 5$ year, $18 > 10$ year	N/A

4.2 Subjective Testing Analysis

In this section, analysis of the results for the subjective testing methods in both the CN IV Palsy and Control Groups are presented. All analyses used a significance value of $\alpha = 0.05$. The Bagolini Lenses and DMR were analysed first, for possible differences of testing between distances (2- and 6-meters). The HTS was also analysed for possible differences between fixing either eye. The Synoptophore did not require an extra analysis as it is primarily designed to assess torsion under binocular conditions in the distance. Finally, all four of the subjective tests (Bagolini Lenses, DMR, HTS, and Synoptophore) were analysed for any differences between each method.

4.2.1 Effect of Testing Distances for Bagolini Lens Test

Data for the Bagolini Lenses testing in the CN IV Palsy Group showed both normal and non-normal distribution; therefore, a paranormal test was required. As the data obtained for one participant are related, a 2-tailed Wilcoxon Signed-Ranked Sum (W) Test was preformed as it is the paranormal alternative to a standard t-test. Exact significance was used because of the small sample size of the data.

For participants in the CN IV Palsy Group, the results from the W Test indicated no significant difference when measuring torsion using the Bagolini Lenses at 2- or 6-meters ($Z = 1.80$, $p = 0.125$). The data were averaged over two distances and the resulting one set was used for the remainder of analysis. Results for the Control Group also indicated a non-significant difference between the two testing distances for Bagolini Lenses ($Z = -1.34$, $p = 0.500$). Again, the data from the two distances was averaged and used as one set for the remainder of analysis.

4.2.2 Effect of Testing Distances for Double Maddox Rod Test

Data for the DMR test showed a non-normal distribution for related data samples for both the CN IV Palsy and Control Group; therefore a W Test was used. The results for this test in the CN IV Palsy Group indicated a non-significant relationship between torsional angles at 2- and 6-meters ($Z = -0.34$, $p = 0.859$).

Results from the Control Group also indicated a non-significant relationship between measuring torsion at 2- and 6-meters ($Z = -1.00$, $p = 1.00$). As with the Bagolini Lenses, the data for each group were averaged between the two distances and used as one set per group.

4.2.3 Effect of Fixating Eyes on the Harms Tangent Screen

Comparison of data from the CN IV Palsy Group was done for the paretic and no-paretic eyes. These data were paired but not normally distributed therefore testing for differences between the means of each eye required a W Test. Interestingly, the results indicated that there was no significant difference between the mean torsion measured by the paretic and non-paretic eye ($Z = 0.49$, $p = 0.641$). The data for the HTS eyes were summed together, and the one set was used for the remainder of analysis. Summation was also used to compare to the results of the Bagolini Lenses and DMR which are both a summation of the measurements of the two eyes under binocular conditions.

Analyses of the results obtained for the Control Group on the HTS was carried out for each eye. The results of a W Test for this group also indicated a non-significant difference whether either eye was fixating ($Z = -1.34$, $p = 0.500$). Results for the Control Group were therefore also summed over the two eyes and used for the remainder of analysis.

4.2.4 Comparison of Subjective Tests

The descriptive statistics of the four subjective assessments for both groups are presented in Table 4.2 for the Bagolini Lens test averaged over the 2- and 6-meters testing distances; DMR averaged 2- and 6-meters; HTS summed over the two eyes; and the Synoptophore which did not require additional analysis.

Table 4.2: Descriptive Statistics of Torsion Angles* for Subjective Tests

	CN IV GROUP			CONTROL GROUP		
TEST	N	Range	$\overline{X}$ (s.d.)	N	Range	$\overline{X}$ (s.d.)
Bagnolini Lens (2- and 6-m Avg.)	28	$-3.5°$ to $+14°$	$+4.73°$ ($\pm 3.72°$)	22	$0°$ to $+5°$	$0.34°$ ($\pm 1.13°$)
DMR (2- and 6-m Avg.)	24	$-5°$ to $+15°$	$+4.69°$ ($\pm 4.18°$)	22	$0°$ to $+4°$	$0.71°$ ($\pm 1.24°$)
Synoptophore	27	$0°$ to $+13°$	$+4.65°$ ($\pm 3.46°$)	22	$-1°$ $+3°$	$+0.36°$ ($\pm 0.90°$)
HTS Both Eyes Summed	27	$-2°$ to $+23°$	$+7.89°$ ($\pm 7.72°$)	22	$0°$ to $+4°$	$0.36°$ ($\pm 1.10°$)

* Positive degree values indicate excyclotorsion; negative degree values indicate incyclotorsion

A Friedman test with exact significance was used to analysis for possible differences between the four subjective testing means. As the data were not normally distrusted, the Friedman test was used as a non-parametric alternative to the one-way ANOVA with repeated measures. Exact significance is used typically when the sample size of data is less than 100 data points.

The results of the Friedman test for the CN IV Palsy Group indicated a significant relationship between the means ($\chi^2(3) = 8.19$, p = 0.040). A post-hoc 2-tailed W test was preformed for the four tests paired with each other to determine specific differences. The results of the post-hoc using exact significance (Table 4.3) showed that there were significant differences only between the torsional angles measured by the HTS and DMR, and the HTS and Synoptophore.

Table 4.3: Post-hoc Results for Subjective Testing Methods in CN IV Palsy Group

TESTING PAIRS	**p-VALUE**
HTS and DMR	0.002*
HTS and Synoptophore	0.001*
HTS and Bagolini Lenses	0.063
Bagolini Lenses and DMR	0.760
Bagolini Lenses and Synoptophore	0.848
DMR and Synoptophore	0.748

Data from all subjective testing methods for the Control Group were also analyzed using the Friedman test; results indicated a non-significant relationship between the four means ($\chi^2(3) = 1.813$, $p = 0.63$). As there were no differences seen within this group, no post-hoc analysis was required.

Comparison between the two groups of subjects using a Mann-Whitney U (MWW) Test, presented in Table 4.4, indicated significant differences for each testing method.

Table 4.4: Comparison of Subjective Testing Methods Between Groups

TESTS	**STATISTICAL VALUES**	
Bagolini Lenses	$Z = -4.353$	$p = 0.000^*$
Double Maddox Rod	$Z = -4.389$	$p = 0.000^*$
Synoptophore	$Z = -4.577$	$p = 0.000^*$
Harms Tangent Screen	$Z = -4.696$	$p = 0.000^*$

4.3 Objective Testing Analysis

The following section presents the analysis of objective torsional measurements (fundus photographs, OCT fovea-Bruchs membrane, and temporal raphe scans) for both CN IV and Control group. Comparison of the PI's measurements to other clinicians' is also included for the determination of the torsional angles from fundus photographs and temporal raphe. All analyses used a significance value of 0.05.

4.3.1 Effect of Individual Eyes on Fundus Photography

Fundus photographs of each eye were taken for both groups. They were analyzed for differences of torsional measurements within each group. Both the CN IV Palsy and Control Group data were not normally distributed; therefore, a 2-tailed W Test was used with exact significance. The following results and descriptive statistics are shown in Table 4.5.

Twenty-two participants from the CN IV Palsy Group were analyzed and the results indicated a non-significant difference between the torsion measured from the paretic and non-paretic eyes ($Z = -0.41$, $p = 0.702$). The Control Group also showed a non-significant difference between the right and left eyes ($Z = -0.34$, $p = 0.750$). Similar to the HTS, the degree angles from each eye were summed together in order to represent a patient's binocular viewing conditions.

However, the value measured directly from a fundus photograph does not take into account the amount of ocular torsion already found in the normal population. The true amount of abnormal torsion is not calculated from zero, but rather it is the difference between the measured torsion and the mean normal torsion; i.e. the natural position of the ON relative to the fovea that is extorted by approximately 7° per eye in the current study. Therefore, to determine the presence and quantify the true amount of abnormal torsion, the difference between the mean of the Control Group and individual participants was calculated. For example, the mean torsional angle summed between the two eyes of the Control Group is $+15.04^\circ$; if a participant has $+17^\circ$ of excyclotorsion summed between the two eyes, their true torsional angle would be $+1.96^\circ$.

Table 4.5: Descriptive Statistics of Torsional Angles by Fundus Photography

MEASURE	ITEM	CN IV PALSY (n = 22)	CONTROL (n = 22)
Total Torsion Individual Eyes	Mean	Paretic: $+10.42^\circ \pm 4.85^\circ$	Right: $+7.64^\circ \pm 3.70^\circ$
		Non-paretic: $+10.40^\circ \pm 5.64^\circ$	Left: $+7.40^\circ \pm 3.21^\circ$
	Range	Paretic: $+5.05^\circ$ to $+24.46^\circ$	Right: $+0.94^\circ$ to $+14.95^\circ$
		non-Paretic: -3.50° to 21.64°	Left: $+0.57^\circ$ to $+13.75^\circ$
Total Torsion Summed Eyes	Mean	$\bar{x} = +20.85^\circ \pm 6.59^\circ$	$\bar{x} = +15.04^\circ \pm 6.59^\circ$
	Range	$+8.39^\circ$ to $+36.52^\circ$	$+4.66^\circ$ to $+26.84^\circ$
Abnormal Torsion Angles	Mean	$\bar{x} = +5.81^\circ \pm 6.59^\circ$	$\bar{x} = 0 \pm 5.60^\circ$
	Range	-6.65° to $+21.48^\circ$	-10.38° to $+11.80^\circ$

The torsional angles of all fundus photographs from both the CN IV Palsy and Control Groups were measured twice by the PI to assess reliability, and also by four clinicians, blind to the groups, to assess the inter-rater variability of this measuring technique.

In order to assess how closely the torsional angles from each clinician and the PI resemble each other, an intra-class correlation (ICC) was preformed for each eye in both groups. A 2-way mixed model was used because error could arise from either the images or the raters (clinicians and PI). An absolute agreement type was chosen to assess if the torsional angles measured by the different clinicians were consistent with each other. Table 4.6 reports the average measures for the test-retest results of the ICC. The results show a high consistency between the four clinicians and the two measurements completed by the PI for each eye in both groups.

Table 4.6: Clinician Comparison of Fundus Photography Angles

TORSIONAL ANGLE MEASUREMENTS		AVERAGES
CN IV Palsy Group	Paretic Eye	0.979
	Non-paretic Eye	0.990
Control Group	Right Eye	0.976
	Left Eye	0.963

4.3.2 Effect of Individual Eyes on Optical Coherence Tomography

Data for the fovea-ONH angle was assessed by OCT marking the fovea and Bruch's membrane rim. The data was analysed using a 2-tailed W Test with exact significance for possible differences between the paretic and non-paretic eyes of the CN IV Palsy Group, and for the right and left eyes of the Control Group. The results, presented in Table 4.7, indicated a non-significant difference of torsion measured between eyes within either the CN IV Palsy ($Z = -0.89$), $p = 0.388$) or Control Group ($Z = -1.03$), $p = 0.320$).

However, similar to the fundus photograph angles, the torsional angles are a combination of the normal excyclo-rotary position of the fovea-ONH to any abnormal torsion that may be present. Therefore, the true abnormal torsion variability of both groups was calculated by subtracting the mean angle of the summed eyes of the Control Group from each individual summed value of torsion, the mean and range of which is presented in Table 4.7.

The fovea-Bruch's membrane angle is calculated directly from the SD-OCT data base and does not require an examiner's subjective assessment or interpretation of the angle; therefore, no measurement comparison between different examiners was done for the test-retest reliability (Chen and Kardon, 2016).

Table 4.7: Descriptive Statistics of Torsional Angles by OCT

MEASURE	ITEM	CN IV PALSY (n = 22)	CONTROL (n = 22)
Total Torsion Individual Eyes	Mean	Paretic: $+9.78^\circ \pm 4.01^\circ$	Right: $+7.04^\circ \pm 3.56^\circ$
		Non-paretic: $+11.13^\circ \pm 4.73^\circ$	Left: $+6.90^\circ \pm 3.20^\circ$
	Range	Paretic: $+1.30^\circ$ to $+15.00^\circ$	Right: -1.20° to $+14.80^\circ$
		non-Paretic: $+3.00^\circ$ to 21.10°	Left: -0.60° to $+12.30^\circ$
Total Torsion Summed Eyes	Mean	$\bar{x} = +20.44^\circ \pm 6.48^\circ$	$\bar{x} = +13.95^\circ \pm 5.03^\circ$
	Range	$+6.30^\circ$ to $+32.50^\circ$	$+3.70^\circ$ to $+25.20^\circ$
Abnormal Torsion Angles	Mean	$\bar{x} = +6.48^\circ \pm 6.48^\circ$	$\bar{x} = -0.56^\circ \pm 5.60^\circ$
	Range	-7.65° to $+18.55^\circ$	-10.25° to $+11.25^\circ$

4.3.3 Effect of Individual Eyes on Temporal Raphe Scans

The temporal raphe angles were first analysed for potential difference between eyes within both groups. The results of a 2-tailed W Test with exact significance for the comparison of the paretic and non-paretic eyes of the CN IV Palsy Group and the right and left eyes of the Control Group indicated a non-statistical difference between the angles measured in either the CN IV Palsy ($Z = 1.03$, $p = 0.320$) or Control Group ($Z = 0.63$, $p = 0.545$).

However, as seen with both the fundus photograph and OCT angles, the angle obtained from a temporal raphe scans includes a physiological range of torsion; therefore, the summed mean torsional angle from the Control Group, as seen in Table 4.8, was subtracted from each summed torsional values in both groups.

Table 4.8: Descriptive Statistics of Torsional Angles by Temporal Raphe Scans

MEASURE	ITEM	CN IV PALSY (n = 22)	CONTROL (n = 22)
Total Torsion Individual Eyes	Mean	Paretic: $-0.57^\circ \pm 4.85^\circ$	Right: $-3.15^\circ \pm 3.07^\circ$
		Non-paretic: $+0.90^\circ \pm 4.87^\circ$	Left: $+2.49^\circ \pm 3.66^\circ$
	Range	Paretic: -5.88° to $+6.58^\circ$	Right: -8.29° to $+3.73^\circ$
		non-Paretic-9.54° to $+9.63^\circ$	Left: $+9.64^\circ$ to $+6.45^\circ$
Total Torsion Summed Eyes	Mean	$\bar{x} = -0.73^\circ \pm 6.41^\circ$	$\bar{x} = +2.79^\circ \pm 7.63^\circ$
	Range	-12.30° to $+15.29^\circ$	-13.77° to $+14.76^\circ$
Abnormal Torsion Angles	Mean	$\bar{x} = +6.48^\circ \pm 6.48^\circ$	$\bar{x} = +0.30^\circ$ to $\pm 8.22^\circ$
	Range	-7.65° to $+18.55^\circ$	-10.98° to $+18.56^\circ$

The torsional angles of all temporal raphe scans from both the CN IV Palsy and Control Groups were measured twice by the PI and four other clinician examiners, masked to the groups to assess the inter-examiner variability of this measuring technique.

An ICC test was used in the same way analysis of inter-personal variably was assessed for fundus photographs. The results of a 2-way mixed model with absolute agreement. Table 4.9 indicates a high consistency between the four examiners and the two measurements by the PI for each eye in both groups.

Table 4.9: Clinician Comparison of Temporal Raphe Angles

TORSIONAL ANGLE MEASUREMENTS		AVERAGES
CN IV Palsy Group	Paretic Eye	0.981
	Non-paretic Eye	0.986
Control Group	Right Eye	0.977
	Left Eye	0.982

4.3.4 Comparison of Objective Tests

The data summed across the paretic and non-paretic eyes for participants in the CN IV Palsy Group, and the summation of torsional angles from the right and left eyes for participants in the Control Group were used to analyze for differences between testing methods. As the data were paired, a Friedman statistical test was used to determine if at least one of these tests differed from the others. A pair-wise comparison (t-test) post-hoc test was done to identify specific differences between means.

For the CN IV Palsy Group using the non-adjusted torsional values, the test indicated a significant result suggesting that at least one of the objective testing methods differed from the others ($\chi^2(2) = 33.36, \mathrm{p} < 0.05$). In order to determine which, if not all tests, differed from each other, a 2-tailed pairwise W post-hoc test was preformed for each pair. Results indicated significant differences between the temporal raphe scans and both the fundus photographs ($\mathrm{Z} = -4.11$, $\mathrm{p} = 0.000$) and OCT torsional angles ($\mathrm{Z} = -4.11$, $\mathrm{p} = 0.000$). There was no significant difference between the angles measured by fundus photography and OCT ($\mathrm{Z} = -0.44$, $\mathrm{p} = 0.679$).

The objective data was then assessed using the angles adjusted for physiological positions of landmarks; i.e. the angle that is the difference between the Control Group mean and the CN IV Palsy Group subjects. The results of a Friedman Test indicate that there was no significant difference between the three testing methods ($\chi^2(2) = 4.36, \mathrm{p} = 0.113$)

The Control Group was also analysed using the non-adjusted data summed over the two eyes for each of the three testing methods. Results of a Friedman test for the Control Group using the non-adjusted torsional values indicated a statistically significant result ($\chi^2(2) = 29.55, \mathrm{p} < 0.05$). A 2-tailed W post-hoc test was used to determine which of the objective testing methods showed differences. The results of this test indicated that each pairing was significantly different from each other: temporal raphe and fundus photographs ($\mathrm{Z} = -4.04$, $\mathrm{p} = 0.000$); temporal raphe and OCT ($\mathrm{Z} = -4.01$, $\mathrm{p} = 0.000$); fundus photographs and OCT

($Z = -2.19$, $p = 0.013$). Analysis by Friedman testing using the adjusted torsional values however, indicated a non-significant value between any of the objective testing methods ($\chi^2(2) = 1.18, p = 0.554$).

The individual tests were also compared to each other for both the adjusted and non-adjusted torsional angles; the results for each test are presented in Table 4.10. For fundus photographs, the non-adjusted summed torsional angles for the CN IV Palsy Group were compared to the Control Group using an MWW test with exact significance. The results showed a significant difference between torsion angles measured in the CN IV Palsy and Control Group participants. Using the adjusted torsional values, results of an MWW test indicated a significant difference between the two groups as well.

Table 4.10: Non-Adjusted and Adjusted Objective Torsional Angles

TESTS	**STATISTICAL VALUES**	
	NON-ADJUSTED TORSIONAL ANGLES	**ADJUSTED TORSIONAL ANGLES**
Fundus Photographs	$U = 131.00$ $p = 0.002^*$	$U = 131.00$ $p = 0.002^*$
OCT	$U = 100.50$ $p = 0.000^*$	$U = 95.50$ $p = 0.000^*$
Temporal Raphe	$U = 189.00$ $p = 0.220$	$U = 174.00$ $p = 0.114$

For OCT, the MWW test results with exact significance for both the non-adjusted and adjusted torsional values indicated a significant difference between the CN IV Palsy and Control Groups.

When analysing the temporal raphe, results of an MWW test with exact significance indicated non-significant differences between the CN IV Palsy and Control Group for both non-adjusted and adjusted torsional values.

4.4 Subjective Horizontal

The Subjective Horizontal was assessed for differences between lighting conditions, followed by the assessment of possible differences between eyes in both groups.

4.4.1 Effect of Lighting Conditions on the Subjective Horizontal

The analysis of Subjective Horizontal angles measured in both light and dark conditions was done for the paretic and non-paretic eyes of the CN IV Palsy Group. Results of a 2-tailed W test with exact significance indicated there to be a non-significant relationship between angles measured under light or dark conditions for either the paretic eye ($Z = -0.28$, $p = 0.859$) or non-paretic eye ($Z = -0.71$, p 0.555). The Subjective Horizontal angles were averaged across lighting conditions for the paretic and non-paretic eyes in the CN IV Palsy Group and used as a singular data set for the remainder of analysis.

Data for the Control Group were analysed the same way, except that a difference between right and left eyes was used as there was no paretic eye. A non-significant result was also found for the Control Group when measuring the Subjective Horizontal under light and dark conditions for the right eye ($Z = -1.00$, $p = 1.000$) and left eye ($Z = 0.00$, $p = 1.000$). The Subjective Horizontal angles were averaged across lighting conditions and used as a singular data set.

4.4.2 Effect of Individual Eyes on the Subjective Horizontal

The two eyes in the CN IV Palsy Group were analysed for possible differences between the Subjective Horizontal angles. A 2-tailed W test with exact significance was preformed and indicated a non-significant difference between the paretic and non-paretic eyes ($Z = -0.45$, $p = 0.681$).

Similar to the objective tests where the difference between the CN IV Palsy and Control was calculated, the difference between the paretic and non-paretic eyes was created using the non-paretic eye value as a reference point. In other words, the amount of degree difference between the paretic eye Subjective Horizontal value in reference to the non-paretic eye Subjective Horizontal was calculated. The descriptive statistics of the singular data set of the difference between the paretic eye to the

non-paretic eye showed a range of -2.5° incyclotorsion to $+4.0^\circ$ excyclotorsion ($\overline{x} = +0.13^\circ \pm 1.24^\circ$).

Comparison of the right and left eyes of the Control Group using a 2-tailed W test with exact significance was completed to determine if there was a difference between eyes. The results indicated a non-significant difference between the two eyes of this group ($Z = -1.34$, $p = 0.500$). The difference between the Subjective Horizontal of the right and left eyes was calculated; it showed a range of 0° to 1.0° excyclotorsion ($\overline{x} = +0.70^\circ \pm 0.23^\circ$).

The data set of the averaged torsion from the paretic and non-paretic eyes in the CN IV Palsy Group was compared to the averaged data of right and left eyes of the Control Group for possible differences of cortical adaption. A 2-tailed MWW analysis with exact significance was preformed and indicated a non-significant difference between the Control Group and the non-paretic eye of the CN IV Palsy Group ($U = 261.00$, $p = 0.256$). The MWW analysis also indicated a non-significant result between the Control Group and the paretic eye of the CN IV Palsy Group ($U = 251.50$, $p = 0.173$).

4.5 Comparison of All Testing Methods

Data presented in this section are in response to the main research question: to which of the objective measurements (fundus photography, OCT, or temporal raphe) do the subjective measurements (Bagolini Lenses, DMR, Synoptophore, HTS) show a significant relationship. Comparison with the Subjective Horizontal is also included in this analysis to address possible cortical adaption cited in previous literature.

A Friedman non-parametric comparison of means analysis was preformed to compare the individual means of each subjective and objective tests to the Subjective Horizontal. The data sets that were used in this calculation were: Bagolini Lenses and DMR each averaged over 2- and 6-meters; HTS summed over the paretic and non-paretic eyes; Synoptophore; fundus photographs, OCT, and temporal raphe each summed over the paretic and non-paretic eyes; and the difference between the paretic and non-paretic eye Subjective Horizontal.

Results of the Friedman test for the CN IV Palsy Group indicated a significant difference between at least one group mean ($\chi^2(7) = 85.39$, $p < 0.05$). A 2-tailed W test post-hoc with exact significance was conducted to determine which of the group means were significantly different. Results of the post-hoc analysis, presented in Table 4.11, indicated significant relationships ($p < 0.05$) between each pair analysed except the Subjective Horizontal and temporal raphe ($p > 0.05$).

Table 4.11: Post-hoc Analysis of All Test Methods for CN IV Palsy Group

TEST		**p-VALUE**
Bagolini Lenses	Fundus Photographs	0.000*
	OCT	0.000*
	Temporal Raphe	0.004*
	Subjective Horizontal	0.000*
Double Maddox Rod	Fundus Photographs	0.000*
	OCT	0.000*
	Temporal Raphe	0.001*
	Subjective Horizontal	0.000*
Synoptophore	Fundus Photographs	0.000*
	OCT	0.000*
	Temporal Raphe	0.002*
	Subjective Horizontal	0.000*
Harms Tangent Screen	Fundus Photographs	0.000*
	OCT	0.000*
	Temporal Raphe	0.000*
	Subjective Horizontal	0.000*
Subjective Horizontal	Fundus Photographs	0.000*
	OCT	0.000*
	Temporal Raphe	0.424

The spread of the data points for each of the eight tests is shown in Figure 4.1 as a box and whisker plot.

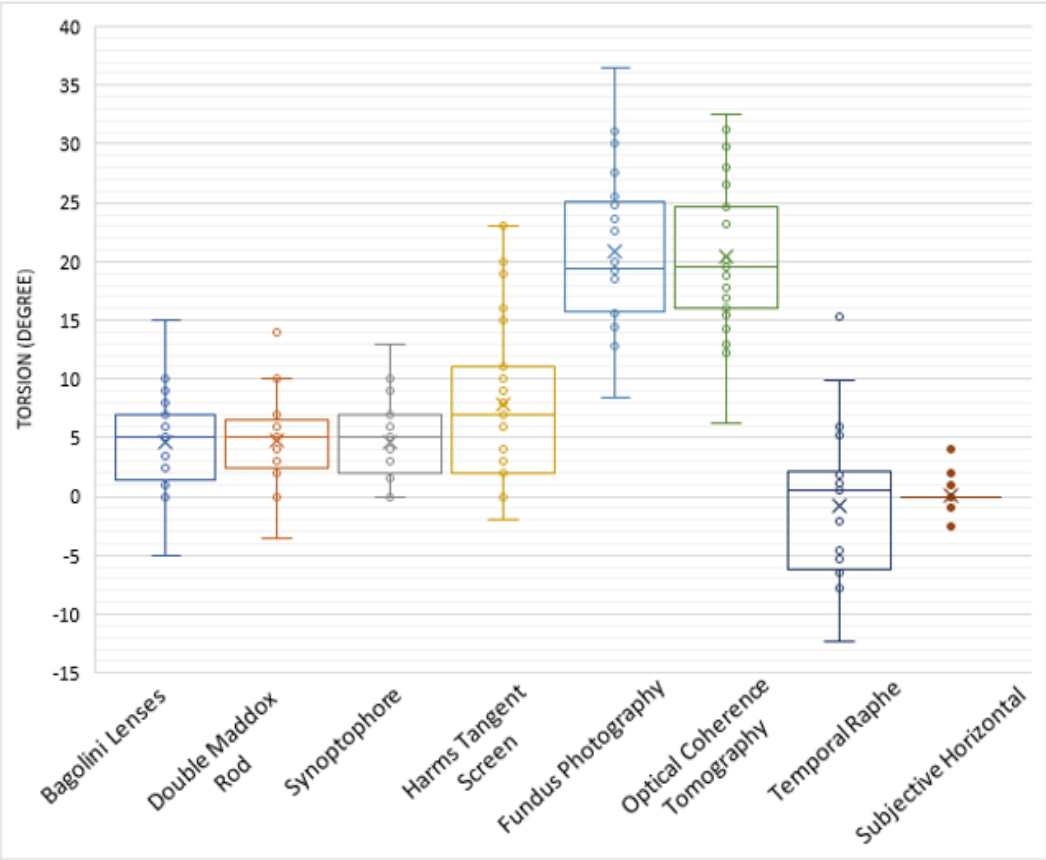


Figure 4.1 Spread of non-adjusted torsional angles measured by each testing methods for the CN IV Palsy Group

On the figure, the box encompasses 50% of the data surrounding the median; the X represents the mean of the data. The upper and lower whiskers represents scores outside 50% range, with the outiers beyond the outer 50% shown beyond the whisker range.

A Friedman Test was again used to compare the eight tests together using the calculated "true" amount of torsion in both the CN IV Palsy and Control Groups. The data sets that were used in this calculation were: Bagolini Lenses and DMR each averaged over 2- and 6-meters; HTS summed over the paretic and non-paretic eyes; Synoptophore; fundus photographs, OCT, and temporal raphe each summed over the paretic and non-paretic eyes minus the mean torsion of the Control Group; and the difference between the paretic and non-paretic eye Subjective Horizontal.

Results of the Friedman test for the CN IV Palsy Group indicated a significant difference between at least one group mean ($\chi^2(7) = 24.54$, $p < 0.05$). A 2-tailed W test post-hoc with exact significance was conducted to determine which of the group means were significantly different. Results of the post-hoc analysis, presented in Table 4.12, indicated significant differences ($p < 0.05$) between the Subjective Horizontal and all other tests except for the Synoptophore. All other pairings were not significantly difference ($p > 0.05$). The spread of the data points for each of the eight tests is shown in Figure 4.2 as a box and whisker plot.

The results indicated that fundus photographs and OCT were significantly different than Bagolini Lenses, DMR, Synoptophore, HTS, and the Subjective Horizontal. Significant differences were found between the temporal raphe and DMR, temporal raphe and the Synoptophore, as well as DMR and the Subjective Horizontal.

Table 4.12: Post-hoc Analysis of All Testing Methods for Control Group

TEST		**p-VALUE**
Bagolini Lenses	Fundus Photographs	1.000
	OCT	1.000
	Temporal Raphe	0.529
	Subjective Horizontal	0.0150*
Double Maddox Rod	Fundus Photographs	1.000
	OCT	1.000
	Temporal Raphe	1.000
	Subjective Horizontal	0.038*
Synoptophore	Fundus Photographs	1.000
	OCT	1.000
	Temporal Raphe	1.000
	Subjective Horizontal	0.351
Harms Tangent Screen	Fundus Photographs	1.000
	OCT	1.000
	Temporal Raphe	0.102
	Subjective Horizontal	0.002*
Subjective Horizontal	Fundus Photographs	0.049*
	OCT	0.022*
	Temporal Raphe	1.000

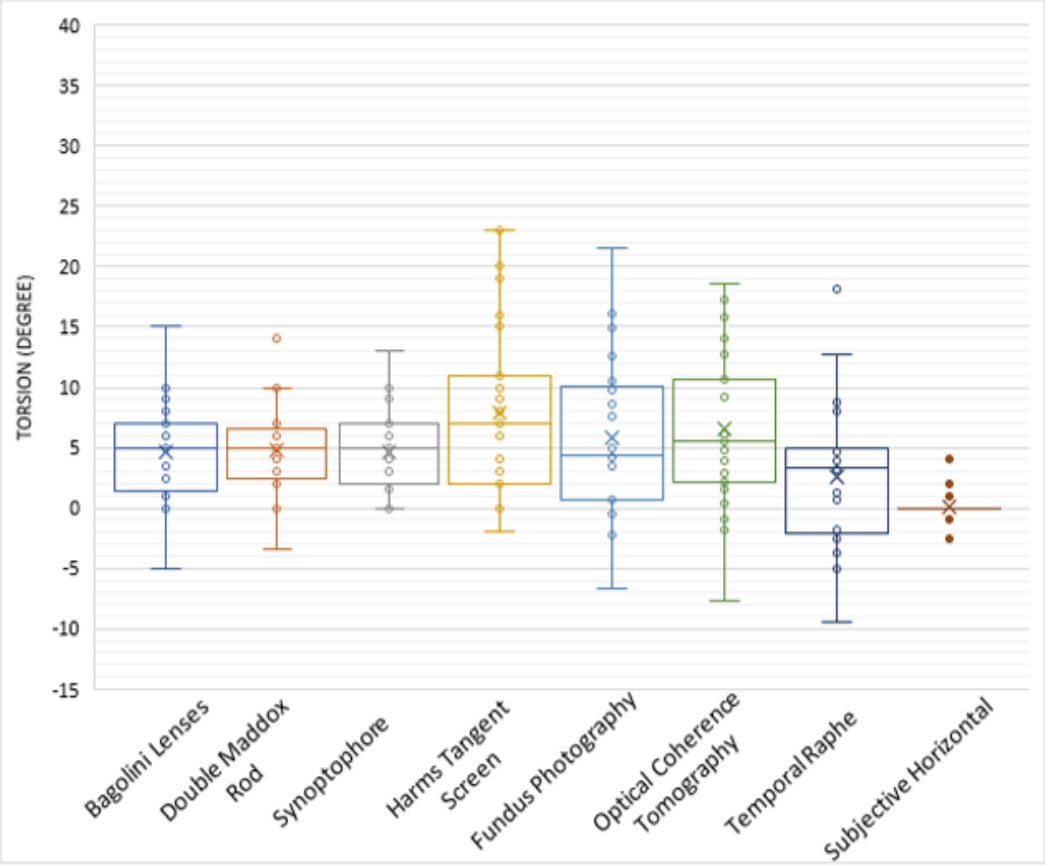


Figure 4.2 Spread of adjusted torsional angles measured by each testing methods for the CN IV Palsy Group

In the Control Group, the results of a Friedman non-parametric analysis indicated a significant difference between the Subjective Horizontal, subjective, and objective torsional tests ($\chi^2(7) = 107.48$, $p < 0.05$). A pairwise comparison post-hoc analysis was conducted to determine specifically which means were different (Table 4.13). Figure 4.3 shows the spread of data for each of the eight tests as a box and whisker plot.

Table 4.13: Post-hoc Analysis of Torsional Angles Measured by Subjective Tests, Objective Tests, and Subjective Horizontal for the Control Group

TEST		**p-VALUE**
Bagolini Lenses	Fundus Photographs	0.000*
	OCT	0.000*
	Temporal Raphe	0.068
	Subjective Horizontal	0.500
Double Maddox Rod	Fundus Photographs	0.000*
	OCT	0.000*
	Temporal Raphe	0.042*
	Subjective Horizontal	$0.031^{(*)}$
Synoptophore	Fundus Photographs	0.000*
	OCT	0.000*
	Temporal Raphe	0.042*
	Subjective Horizontal	0.219
Harms Tangent Screen	Fundus Photographs	0.000*
	OCT	0.000*
	Temporal Raphe	0.059
	Subjective Horizontal	0.313
Subjective Horizontal	Fundus Photographs	0.000*
	OCT	0.000*
	Temporal Raphe	.074

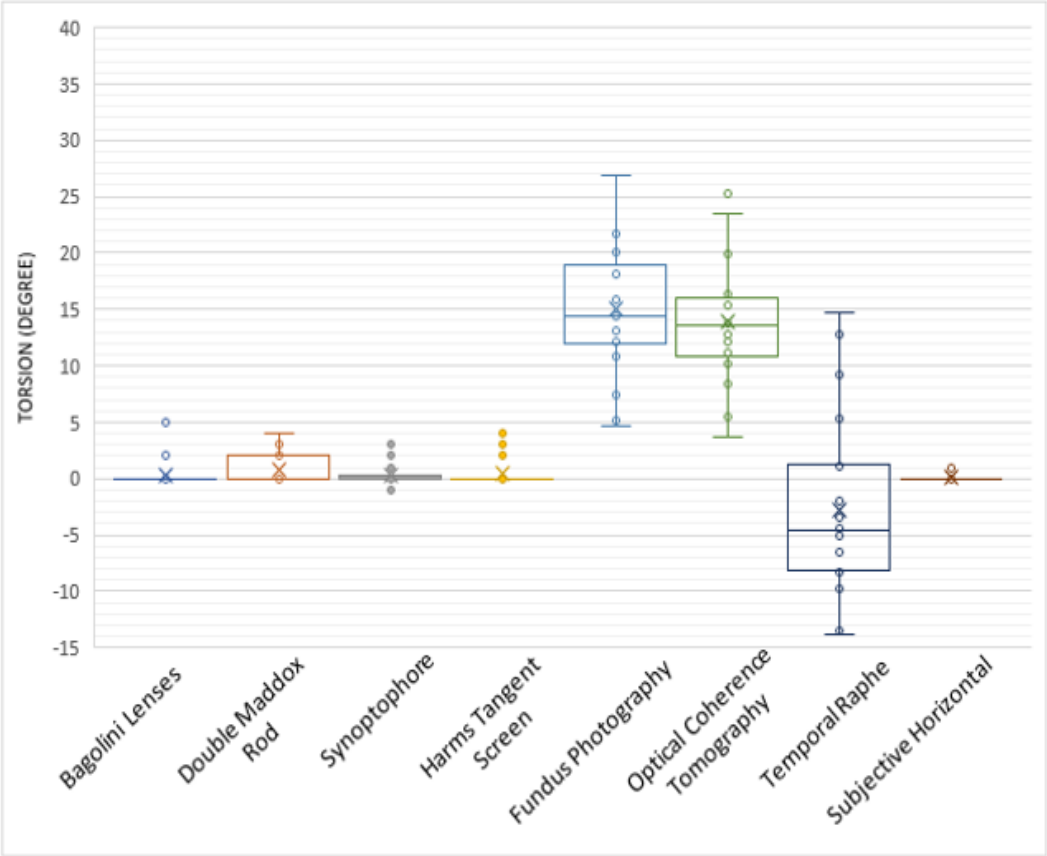


Figure 4.3 Spread of non-adjusted torsional angles measured by each testing methods for the Control Group

Comparison of the eight tests in the Control Group using the adjusted values of the objective tests that account for the average fovea-ONH value, were analysed using a Friedman Test. The results of this test indicated no significant difference between any of the eight testing methods ($\chi^2(7)) = 7.73$, p = 0.357). The spread of the data is represented by a box and whisker plot in Figure 4.4.

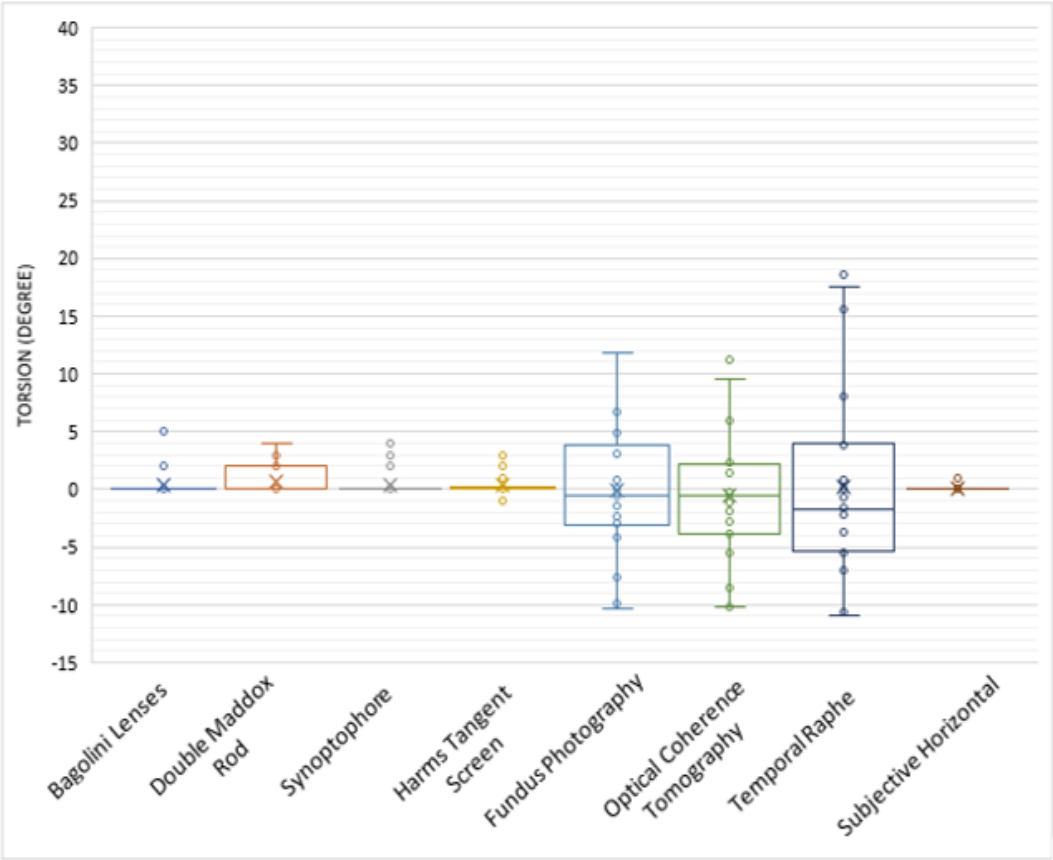


Figure 4.4 Spread of adjusted torsional angles measured by each testing methods for the Control Group

CHAPTER 5: DISCUSSION

Patients with CN IV palsies commonly suffer from binocular diplopia. However, patients with long-standing deviations often have subjective perception of torsion that is inconsistent with the anatomical orientation of their fundus (torsion). Previous research has focused primarily on the reliability of subjective testing methods as well as the theory of cortical adaptation of ocular torsion; however, no data are available on the comparison between subjective and objective torsional angles or their relationship to a patient's Subjective Horizontal.

To fill that gap, the current study analyzed the relationship of four commonly used subjective testing methods to objective torsion tests. As well, in order to better explain the theories of linking ocular torsion with cortical adaptation, a novel technique of imaging the temporal raphe was used to explore a new dimension of anatomical landmark assessment. One of the goals of the current study was therefore to investigate the utility of using temporal raphe scans as a measure of ocular torsion.

The comparison of different subjective torsional tests needed to be included in this study due to the lack of consistency in the results available in previous research and the need to use reliable subjective torsional measurements to test our novel objective measurement method (temporal raphe orientation). The current study also looked at the comparison of subjective and objective torsional testing methods to the Subjective Horizontal to look for a possible link to the study's new raphe orientation data and further explore of the different hypothesis of cortical adaption to ocular torsion.

5.1 Summary of Findings

The results will be discussed in four sections:

1. Subjective testing;
2. Objective testing (fovea-ON angles and temporal raphe angles);
3. Subjective Horizontal analysis;
4. Comparison of subjective and objective tests to the Subjective Horizontal.

Here is a summary of their significance:

1. The subjective tests (Bagolini Lenses, DMR, Synoptophore; HTS) were analysed for differences in their measurements of perceived torsional angles. The results indicate significant differences between the mean torsional angle measured by the HTS and both the DMR and Synoptophore but not the Bagolini Lenses in the CN IV Palsy Group. No difference was found between any of the subjective testing methods in the Control Group.

2. Results of the objective tests indicated there was no difference between the amount of measured torsion in either eye from either group. Analysis for each group was completed for both the raw torsional angles obtained directly of the photograph or scan, and the adjusted torsional angles that accounted for the physiological position of the fundus landmarks. Both groups of subjects showed significant differences for fundus photography and OCT; however, the temporal raphe scans were not significantly different between the two groups.

   When the three objective testing methods were compared to each other within each group, the non-adjusted torsional angles showed significant differences between the temporal raphe and the fovea-ONH tests in the CN IV Palsy Group. The Control Group showed significant differences between all objective tests. However, when comparing the three objective testing methods using adjusted torsional angles, no differences were found in either group.

3. Analysis of the Subjective Horizontal first looked at potential differences between the angles measured under light and dark conditions. Results indicated there was no statistical difference between the lighting conditions for either the CN IV Palsy or Control Group. As well, no statistical difference was seen between either eye for the CN IV Palsy or Control Groups. For participants in the CN IV Palsy Group, the Subjective Horizontal angle measured in the non-paretic eye was used as a "reference point" and the difference between the non-paretic and paretic eye was calculated. This difference in the CN IV Palsy Group was

not statistically different than the difference found between the right and left eyes of the Control Group.

4. Each of the individual tests from the subjective testing methods, objective testing methods, and the Subjective Horizontal were compared together; once, using the non-adjusted torsional angles, and then again using the adjusted angles.

   The non-adjusted torsional angle analysis indicated there were significant differences between each in the CN IV Palsy Group except for the Subjective Horizontal and the temporal raphe angle. In the Control Group, the fovea-ONH angle measured by fundus photography and OCT were different than all other testing methods. Significant differences were also seen in this group for the DMR compared to each other testing methods, as well as for the Synoptophore and the temporal raphe.

   When using the adjusted torsional values, the CN IV Palsy Group showed differences; however, the Subjective Horizontal was significantly different than each of the other tests except for the Synoptophore. the results of the Control Group showed no differences between any of the eight methods.

5.2 Discussion of Subjective Testing Methods

The first part of the study assessed the comparability of four subjective testing methods for measuring ocular torsion. For the Control Groups, the results indicated that there were no significant differences between each if the testing means. However, there were differences found in the CN IV Palsy Group, specifically for the HTS. Figure 4.14 showed a trend for the HTS to measure a larger amount of torsion supports the significant difference found between the HTS to the DMR and Synoptophore. The alternative hypothesis proposed in Section 1.3.2; that at least one, specifically the Bagolini Lenses, would be different than the other three and is to be accepted, in part. Indeed, a difference between the means was found; however, the HTS—not the Bagolini Lenses—was more significantly different than the other three testing methods.

Previous literature has shown inconsistencies when comparing different subjective testing methods. Ruttum and von Noorden (1984) found similarities of torsional angles measured by modified Bagolini Lenses and the DMR; the results of the current study support this finding. Other studies have found the DMR to be more accurate for torsional measurements in primary position (Johnson et al., 1987; Klainguiti et al., 1992; Capdepon et al., 1994).

It is difficult to determine what an accurate measurement of torsion is for these studies as they did not have an objective standard to which to compare. A study by Roh and Hwang (2011) did compare two subjective testing methods (DMR and Lancaster Red-Green) to objective fundus photos and found there to be significant difference between them. The current study also compared subjective and objective torsional outcomes; these are discussed in further detail in Section 5.5 along with the Subjective Horizontal.

A challenge in comparing different subjective testing methods is that the previous literature is not consistent with the methods of testing. There are a number of different testing methods, and each clinic has its own protocol for what is considered standard practice. For example, studies by Klainguti et al. (1992) and Capdepon et al. (1994) assessed the differences between the Synoptophore, synoptometer, HTS, single Maddox Rods, and large-diameter Maddox Rods; Flodin et al. (2016) looked at the Synoptophore, single Maddox Rod, and the KMScreen; Roh and Huang (2011) used the DMR and Lancaster Red-Green Screen.

Therefore, the significant finding between the subjective tests in the current study is not unexpected. One explanation for why a difference was found with the HTS compared with the DMR and Synptophore is the higher degree of dissociation induced by the HTS. However, the DMR also uses dissociated striated lenses, one of them a red opaque white filter. As well, neither test allows any significant binocular view of the surrounding environment. Furthermore, the Synoptophore presents two separate distinct images to each eye with very little view of the peripheral field of view of each eye. However, the degree of dissociation of the HTS does not explain why no difference was found in the torsion measured between the HTS and Bagolini

Lens itself a non-dissociative test.

One can nevertheless offer that the smaller cluster of values of lesser torsion found with the DMR could be related to measuring inaccuracies of that test. As mentioned in Section 2.2.1, the torsion measurements of the DMR test are limited by the inaccuracy of the equipment which indicates clearly only increments of 5°. Therefore, the torsional values of the DMR test have a tendency to cluster together whereas the degree markings of the HTS allow a more precise diversity of measurements. Both the DMR and the HTS have very similar dissociative characteristics; however, the trial frame itself used to hold the DMR lenses offers similar visual reference clues to both eyes not present in the conditions of the HTS test. Similarly, the spread of data seen with the Bagolini Lenses is most likely due to the non-dissociative nature of the lenses thereby allowing participants to see quite clearly the environment with both eyes at once. In these conditions, the measurements are more likely to vary between subjects based on individual sensory adaptation (see below).

A neuro-physiological explanation for the non-significant difference between the HTS and Bagolini Lenses could be based on the effect of chronicity of the torsional deviations of the participants of the CN IV group. Indeed, the cortical adaptation proposed by Guyton (1983) and von Noorden (1984) would suggest that subjects with CN IV palsies in this study have adapted to the tilted image under both light and dark conditions (i.e. with and without environmental clues) and therefore, regardless of dissociation, there is no difference in the perceived amount of torsion. This theory, in part, is supported by other results in this study looking at the Subjective Horizontal under light and dark conditions.

Finally, insufficient data from a small sample size might be a confounding factor on the results of differences between testing methods. Thirty-one participants in the CN IV Group and 22 participants in the Control Group were included in the subjective testing analysis; whereas a power calculation determined that a minimum of 50 subjects were needed to achieve statistical power. Therefore, it is possible that the amount of data is simply insufficient.

5.3 Discussion of Objective Testing Methods

The second aspect of this study assessed objective torsional angles by fundus photography, OCT, and temporal raphe scans. The literature and common clinical practise currently indicate that the most common method in assessing the fovea-ONH torsional relationship is fundus photographs. This technique provides the same static image seen when performing ophthalmoscopy to assess torsion.

The relationship of the fovea and the centre of the perimeter of the optic nerve head delineated by visualization of Bruch's membrane on OCT has been proposed to be a more accurate measurement of the relationship leading to the determination of a possible torsion of the fundus (Chauhan and Burgoyne, 2013). With similar OCT methods, the easily-seen temporal raphe and its orientation according to the horizontal and the centre of the optic disc as through to potentially represent a more reliable method of assessing the real fundus and retinal torsion in relations to the perceived (subjective)experience of patients with chronic CN IV palsies. Therefore, the results serve to evaluate the potential role of this—a novel approach of assessing real ocular torsion. The current study examines the relationships between the new method of torsional measurement with other currently-used objective methods, as well as with the subjective finding in both controls and CN IV palsy subjects.

5.3.1 Fovea-Optic Nerve Angle

Previous studies have shown variable ranges of fovea-ONH objective ocular torsion by fundus photographs in the normal population. Bixenmann and von Noorden (1982) measured a mean angle of $7.25^\circ \pm 2.57^\circ$ of excyclotorsion, ranging from near the horizontal to 12.5° of excyclotorsion; Williams and Wilkinson (1992) reported $6.11^\circ \pm 3.32^\circ$; Jethrani et al. (2010) reported $10.6^\circ \pm 2.6^\circ$; and Herzau and Joos-Kratsch (1984) reported $6.8^\circ \pm 2.5^\circ$, all of excylotorsion. These normative values were supported by the current study's data that found a mean value of $7.25^\circ \pm 6.59^\circ$ of excyclotorsion per eye in the Control Group by fundus photography.

Inaccuracies of visualizing anatomical landmarks on a conventional fundus photograph can lead to a variation of up to five degrees in torsional measurements

(Herzau and Joos-Kratsch, 1984). As well, it has been hypothesized that a sensory cyclofusion within a vertical Panum's fusional space could lead to as much as nine degrees of variability of the fovea-ONH angle in normal eyes; with larger variation in cases of long-term adaption (Parsa and Kumar, 2013). This would explain unexpectedly large variations of torsional measurements in cases of long-term adaption, typically in chronic cranial IV palsy.

The current study that found fundus photography led to a higher than the normal torsional range of fovea-ONH angle in both groups when compared to literature data. The amount of torsion deemed significant currently estimates the position of the fovea in relation to the optic nerve head on fundus examination or imaging; within the bottom one third of the optic nerve head is considered normal. That physiological range, as mentioned previously, is approximately 7 ° excyclotorsion in the normal population. Abnormal torsion is then typically indicated when there is an obvious shift in this relationship.

The values of torsion in abnormal subjects found in this study showed approximately 5–6 ° more excyclotorsion than the Control Group for fundus photography and OCT. This greater amount of excyclotorsion found in the CN IV Palsy Group is, in fact, consistent with the clinical findings of CN IV palsies. This is further supported by the significant difference found when comparing the torsional angles between the CN IV Palsy and Control Group for both fundus photography and OCT.

There was, however, a large variability of torsion for both fundus photographs and OCT scans. This large range could be related to the small sample size; a smaller sample size can appear to have a greater number of outliers rather than presenting a true population variability. Another factor of variability could be the number of myopic participants enrolled in the current study. Some literature reports that neither high refractive errors (Jonas et al., 2015), nor the axial length of the globe (Amini et al., 2014; Tanabe, Matsumoto, McKendrick, Okuyama, Hashimono, Shimomura, 2018) have an effect on the fovea-ONH angle. However, other studies have found a significant effect of high refractive error (greater than 5) on the overall

thickness and thickness profile of the retinal NFL. The effect of retinal NFL thickness on fundus torsion is further explained in Section 5.3.2.

One unexpected finding in this study was that no significant difference was found between the torsion of the paretic and non-paretic eyes in the CN IV Palsy Group measured by both fundus photographs and OCT. Since the participants all had unilateral palsies (this study did not look at post-surgical results, so a masked bilateral case could not be confirmed); it was expected for there to be a difference, specifically a greater amount of torsion in the paretic eye. One reason for the non-significant results could be due to the long-standing nature of the CN IV palsy cases included thereby creating a spread of comitance between the eyes which is known in chronic cases.

A second reason could be the localization of torsion to the non-fixing eye. Fundus photography is a dissociative, monocular test where the participant fixates with one eye at a time regardless of using the internal or external fixation target. Therefore, an inherent issue with imaging the fundus, is that the patient is unable to be binocular and has the opportunity to naturally upright the image they are looking at, while simultaneously developing a torsion of the non-fixing eye von Nooeden, 1984). This can reduce the amount of torsion captured on a fundus photograph in the paretic eye.

5.3.2 Temporal Raphe Angle

The ability to image the temporal raphe is relatively new. Studies that have investigated the effect of variability of the temporal raphe and retinal NFL focus primarily on glaucoma patients. Glaucoma, unlike high myopia, does not alter the thickness profile of the NFL by pushing the fibers more temporally (Leung et al., 2012), previously mentioned in Section 5.3.1.

Chen and Kardon (2016) discussed the effects of high myopia, stating that myopia is associated with decreased thickness of the peripheral retinal NFL. Huang et al. (2014) reported a larger gap between the superior and inferior arcs of the temporal raphe in glaucomatous eyes than non-glaucomatous eyes. While the current

study did not include subjects with glaucoma, a highly myopic eye can mimic the effects of glaucoma in some patients (Leung et al., 2012). Both Huang et al. (2014) and Leung et al. (2012) noted that the larger spacing between the temporal raphe arcs, either by glaucoma or high myopia, could lead to higher variability when identifying the location of the temporal raphe. However, Tanabe et al. (2018) found no correlation between the axial length of an eye and the fovea-raphe angle.

Quantifying ocular torsion for strabismus using the temporal raphe is relatively novel. Prior to more common ability to visualize the raphe, more obvious fundus landmarks were used. A study by Parsa and Kumar (2013) measured fundus torsion by assessing retinal vasculature orientations; a measure that is similar to the orientation of the nerve fiber layer and location of the temporal raphe due to an interdependent embryological growth (Parsa and Kumar, 2013). The authors reported that there could be a variation of six degrees of excyclotorsion from the horizontal line passing through the fovea (Parsa and Kumar, 2013).

The results of the Control Group in the current study supported the reported variation with a mean angle of -2.79° ($\pm 7.63^\circ$)incyclotorsion. However, the range of raphe angles found was from -13.77° incyclotorsion to $+15.76^\circ$ excyclotorsion and is considerably larger than just six degree of pure excyclotorsion previously reported. Even when adjusting the temporal raphe angles to take the normal average into account, the range was relatively large in the Control Group (-10.98° to $+18.56^\circ$). The results of the CN IV Palsy group showed a similarly large range of temporal raphe angle measurements.

The incyclotorsion trajectory of the temporal raphe is consistent with previous imaging studies although the range found in the current study is much larger than previous literature reports. Chauhan et al. (2014) reported temporal raphe angles ranging from 4° excyclotorsion to 12-degrees incyclotorsion; Huang et al. (2014) reported 6° excyclotorsion to 9° incyclotorsion; and Tanabe et al. (2018) found 6.4° of excyclotorsion to 9.9° incyclotorsion.

The unexpected result was the non-significant difference between the CN IV Palsy and Control Groups, even when adjusting for the physiological range. It would

have been expected that the CN IV Palsy Group would have a greater amount of temporal raphe torsion than the control group, in keeping with the other objective torsional measurements by fundus imaging. A greater amount of correlation of temporal raphe to subjective torsional measurements could also be expected due to closer anatomical correlation with the retino- cortical pathway. This would be a reasonable assumption considering that the retinal NFL proportionally rotates with the globe during torsional movements.

Chen and Kardon (2014) presented a case report of measuring torsion using the retinal NFL thickness map in a patient with skew deviation. They concluded that patients with ocular torsion will not have the same retinal thickness profiles as the normative data due to the shift in the NFL orientation and that the relative difference in thickness from the normative data can provide similar objective torsional measurements to those of fundus photography (Chen and Kardon, 2014).

However, a study by Chauhan et al. (2014) found that the temporal raphe does not follow the orientation of the nerve fibers from the fovea to the center of Bruch?s membrane opening (papillomacular bundle). They suggested that the retinal nerve fiber layer creating the temporal raphe is developed and fixed during ocular development whereas the path of ganglion cells underneath the nerve fiber layer axons, follow a path of least resistance as they are unable to cross axons at the temporal raphe space.

Therefore, the temporal raphe orientation, if indeed established during ocular development, is less susceptible to acquired changes of the eye such as refractive error (Kim, Kim, and Weinred, 2012) or anomalous torsion. The possible insusceptible nature of the temporal raphe to acquired changes could suggest a reason for the results obtained in the current study as there is non-significant differences of temporal raphe angles between the paretic and no-paretic eyes in the CN IV Palsy Group. This would also further support the non-significant results found between the right and left eyes of the Control Group and the non-significant result between both groups. However, another explanation for the results could be the lack of data—too few participants, and limited previous literature—and the large variability when

measuring the temporal raphe angle, both factors negatively influencing correlation to other tests.

When the temporal raphe angle was compared to the angles obtained by fundus photography and OCT, it was found that there was a significant difference between them for both the CN IV Palsy and Control Groups. This suggests that the angle created by the temporal raphe relative to the horizontal is indeed not the temporal projection of the fovea-ONH angle, measured either by the visible margins or OCT-defined Bruch's membrane ON opening. In keeping with this observation, Bedggood, Nguyen, Lakkis, Turpin, McKendrick (2017) as well as Amini et al. (2014) found that a temporal projection of the fovea-ONH angle was not an accurate predictor for the orientation of the temporal raphe; rather, the orientation of the temporal raphe was more closely associated with the horizontal. However, their subjects were not identified as to their oculo-motor status.

Previously reported angles of the temporal raphe were: $-1.67^\circ \pm 4.8^\circ$ (Huang et al., 2014); $-2.23^\circ \pm 2.40^\circ$ (Chauhan et al., 2014); and $-0.80^\circ \pm 0.80^\circ$ (Amini et al, 2014). Tanabe et al. (2018) noted that the angle of ONH-fovea-temporal raphe is less than 180°, which was similar to the current study. The negative values listed above also indicating that the temporal raphe project upwards from the horizontal (incyclotorsion values). This result also supports the theory proposed by Chauhan et al. (2014), as mentioned above, that the orientation of the temporal raphe does not follow the papillomacular bundle.

However, when taking into account the physiological position of the fovea-ONH angle, no difference was found between any of the three testing methods for either the CN IV Palsy or Control Group participants. This suggests that the abnormal amount of fovea-ONH and temporal raphe torsion is measured the same by each of the three objective testing methods.

5.4 Discussion of the Subjective Horizontal

The concept of Subjective Horizontal has been previously offered as a possible explanation for the differences seen between subjective and objective torsion leading

to the theory of cortical adaptation to abnormal torsional images. Currently, no study has yet to combine the assessment of the Subjective Horizontal to subjective and objective testing and no study has looked at the relationship between the Subjective Horizontal and the temporal raphe orientation.

In the current study, the Subjective Horizontal was assessed under light and dark conditions with limited cues of horizontal and vertical orientation. The purpose of limiting perceivable horizontal and vertical stimuli was to test if participants in the CN IV Group had cortically adapted to the torted image as theorized by Guyton (1983) and von Noorden (1984).

Previous discussed in Section 2.4, a group of subjects with long-standing deviations were most likely to use adaptive mechanisms such as orienting themselves to known horizontal and vertical objects therefore, when these references are removed, the subjects would report a non-horizontal image. Subjects with congenital deviations however, were thought to not appreciate subjective tilt or subjective torsion on testing but present with objective torsion. This group of subjects are thought to have cortically adapted to a tilted fundus and therefore report horizontal images under light and dark conditions, with and without orientation reference points.

The results of the current study agree with the proposed above. No difference was seen between light or dark measurements in either the CN IV Palsy or Control Group suggesting that the participants with a CN IV palsy have adapted to a tilted horizontal without the need for horizontal references.

The current study also showed that there was no significant difference found between the right and left eyes of the Control Group, consistent with previous findings (Jethani et al., 2010; Good, 2012). This was expected, as neither eye in this group required adaptation to a new orientation. For the CN IV Palsy Group, no difference was found between the paretic and non-paretic eyes. This again fits with the previous theories that patients with long-standing torsional deviations reorient their horizontal of the paretic eye (Guyton, 1983).

It is noteworthy that these groups are describing the subject at the time of assessment as the chronicity of a patient's nerve palsy is on a continuum from acute

to long-standing. Ruttum and von Noorden (1983) described a "spectrum of effectiveness" where subjects with incomplete adaptions, experiencing constant diplopia, had acutely-acquired deviations; whereas subjects who showed complete adaptions but were easily dissociated had longer acquired deviations. Subjects who had complete adaptations and maintained these under monocular and binocular conditions were said to have very early acquired or congenital deviations (Ruttum and von Noorden, 1983).

Some authors, however, report that there could be inherent differences between true congenital CN IV palsies (i.e. a developmental abnormality *in utero*) and those acquired at a very early age (Sheeley and Arnoldi, 2014). Therefore, the definition of the term "long-standing' can be variable to the true chronicity of acquired CN IV palsies.

Acute cases of a CN IV palsy typically present with a recent and obvious causal event such as a head trauma; whereas long-standing cases may have had a precipitating event several years previous to their diagnosis, or not at all. The current study used the cut-off of five years onset of symptoms, or obvious precipitating event, as the criteria for what constituted as long-standing. Indeed, several studies do not account for the number of years a subject has had their condition, but rather qualify long-standing by the associated signs of facial asymmetry, chronic head-tilt, and large vertical fusional amplitudes (Straumann et al., 2003; Sheeley and Arnoldi, 2014). However, Dieterich and Brandt (1993) classified a chronic deviation lasting anywhere from 3 months to 3 years.

One could conclude that the results from both the CN IV Palsy and Control Groups agree with the above proposed theories. The results of the current study found no difference between any light or dark measurements, suggesting that subjects with chronic CN IV palsies had adapted to a tilted horizontal even without the need for horizontal references.

The current study also found no significant difference between the right and left eyes in the Control Group which was used as a reference for the normal range variability between the two eyes of the Subjective Horizontal. This was compared to

the non-paretic eye of the CN IV Palsy Group. As expected, the results indicated a non-significant relationship of the non-paretic eye to the normal range of measured Subjective Horizontal since the non-paretic eye had a theoretically normal orientation and did not require adaptation. However, a non-significant relationship was also found between the Control Group Subjective Horizontal and the paretic eye of the CN IV Palsy Group. This adds support to the adaption theory, the results for the CN IV Palsy Group indicate that they have possibly adapted to a horizontal close to the values seen in the Control Group.

There were four participants in the CN IV Palsy Group however, who fixated with their paretic eye. This is not unusual, and can be due to a mechanical restriction, a decreased innervation to the contralateral superior rectus expected with the increase comitancy of the paretic eye, or simply better vision in the paretic eye (Dickey, Scott, and Cline, 1988). The four cases were assessed separately in order to determine if the Subjective Horizontal of their fixating eye (paretic eye) were significantly different from the Subjective Horizontal. Three participants matched the normal values for the Subjective Horizontal in either eye, and one had a half-degree difference between the two eyes. Therefore, there would be no significant effect in the current study of participants fixating with their paretic eye.

5.5 Comparison of all Testing Methods

Many studies have recognized the difference between subjective and objective testing methods of ocular torsion; however, few studies have quantified this relationship. The current study is in agreement with the current literature in that the subjective testing methods were significantly different than traditional fovea-ONH angle measured by fundus photography and OCT when looking at the fovea-ONH angles taken directly from the fundus photograph or scan.

The reason for this difference and quantitative answers as to what these tests measure in terms of patient perception initially appears complex. The current study attempts to provide an answer by assessing the relationship of subjective and traditional objective ocular torsion to the retinal orientations—both the

well-described sensory adaptation of retinal meridians through measuring the Subjective Horizontal, and a novel assessment of anatomical orientation of the retinal nerve fiber layer through imaging of the temporal raphe.

In the current study, objective torsional angles first appear to be significantly different than subjective testing methods in patients with CN IV palsies; a result well supported in the literature and the general clinical experience. Looking at the non-adjusted torsional values in Figures 4.11 (CN IV Palsy Group) and 4.13 (Control Group), there is a significant trend for the fundus photographs and OCT to measure a greater amount of excyclotorsion. However, the temporal raphe angles show a significant amount of incyclotorsion. Numerous studies have shown that not only does the temporal raphe not follow the fovea-ONH continuation, but projects upwards above the horizontal (Chauhan et al., 2014; Amini et al, 2014; Huang et al., 2014; Tanabe et al., 2018) in normal.

It is important to look at the Control Group to try to understand the relationship between the temporal raphe and fovea-ONH angles. In the Control Group?s fovea-ONH angle measurements, there was a significant difference from their subjective torsional angles supporting the idea that fovea-ONH angle taken directly from a fundus photograph or OCT does not correlate with the subjective perception of torsion. In the case of normal participants, their subjective torsion is approximately zero; however, their fovea-ONH angle is approximately 14 ° between the two eyes. This provides support for the need to adjust the objective torsional angles measured by subtracting the physiological fovea-ONH angle as this does not contribute to subjective torsion.

Therefore, when the true abnormal torsion (i.e. the change in position from the average physiological fovea-ON orientation) is considered, the difference between the objective and subjective testing methods is no longer a factor, as seen in Figures 4.12 (CN IV Palsy Group) and 4.14 (Control Group). This finding is contrary to previous research. As mentioned above, the results of this study propose that the traditional objective methods and the temporal raphe angle do, in fact, correlate with the angles obtained by subjective testing; it is the analysis of the objective angles that is

incorrect because the normal fovea-ON position is not considered.

This can be seen in Figures 4.1 and 4.3 where the torsion of the both subjective and objective tests in the CN IV Palsy Group are all shifted by approximately 5° in the excylo-direction. There appears to be a consensus in the literature to consider an excess of 5° of perceived torsion to be considered abnormal, corresponding to the 5° limit of compensatory torsional motor movements (Schworm et al., 1997).

For example, if a patient with a long-standing CN IV palsy presents 5° excyclotorsion on subjective testing methods, it should be assumed that the fundus torsion has also deviated from the normal position by 5°. However, due to the physiological retinal position, the non-adjusted objective fovea-ONH angle is typically significantly greater than 5°.

The shift of 5° seen in Figures 4.1 and 4.3 for the CN IV Palsy Group was supported by the significant result comparing the fovea-ONH angles between the two groups. This finding also fits with the expected clinical feature of CN IV palsies is a greater amount of excyclotorsion.

The results of this study further support Ruttum and von Noorden?s theory of "spectrum of effectiveness" proposed in 1983, whereby subjects who had congenital or early acquired deviations showed complete adaptation under monocular or binocular viewing. This was the case for at least 10 participants in the current study. However, the sample size for the study was too small to allow separate groups to be analysed; the results of this would be merely anecdotal.

This study also assesses the relationship between both the subjective and objective testing methods to the Subjective Horizontal. This was done to analyse possible cortical adaption as an explanation for the differences between testing methods.

Initially, when looking at the non-adjusted torsional values across all eight tests (four subjective, three objective, and Subjective Horizontal), the results from both groups found significant differences between each test except between the Subjective Horizontal and the temporal raphe. This result suggests that a participant?s Subjective Horizontal still relates to the orientation of the temporal raphe regardless

of the presence of a strabismic deviation.

However, the unexpected result was the non-significant difference of temporal raphe angle between the two groups, regardless of adjusting for the physiological angle. One would logically assume that when an eye becomes extorted due to a muscle paresis, all aspects of the eye rotate the same amount as was seen in the current study?s result for the fovea-ONH angle.

The lack of difference between the temporal raphe angles from both groups suggests that the position of the temporal raphe is either unaffected by the rest of globe's positioning or that the raphe have the ability to adjust to a new orientation based on visual input. Studies that have investigated the latter have focused primarily on the effect of amblyopia on retinal thickness; however, results are conflicting and non-conclusive, with some studies finding that amblyopia changes the NFL thickness, and other studies reported no changes (Taskiran Ç¨mez, Ulu, and Ekim, 2017).

Despite the non-significance between the two groups, there is a trend for the CN IV Palsy Group to show an excyclotorsion shift in the temporal raphe angles. The most likely reason for this trend to be seen but to remain statistically non-significant could come from the large variability of the data (both the normal variability and investigator measuring technique) as well as from the small sample size of the study.

There is increasing evidence for the link between the temporal raphe and cortical perception of the horizontal. Studies have looked at the orientation of the temporal raphe in relation to the orientation of the horizonal on visual field testing. Their results have shown that accounting for the temporal raphe position can reveal subtle changes related to glaucoma damage not generally apparent when using the horizontal (Tanabe et al., 2018).

When the adjusted torsional values were analysed between all testing methods, the Control Group showed no significant differences, an expected result for subjects who have not required adaption to a paresis. Therefore, combining all the results for the Control Group indicates that, when adjusting for the physiological position of the retina the perceived subjective torsion correlates to both the fovea-ONH angle and temporal raphe, which, in turn, correlates to the Subjective Horizontal. In a subject

who has not experienced an ocular muscle palsy, there would be no need for cortical adaption, therefore, no difference between subjective and objective torsion.

Using the Control Group findings as a reference, trends in the CN IV Palsy Group can be seen. The most obvious was that the amount of torsion measured by subjective and objective tests showed on average, five degrees more excyclotorsion compared to the Control Group. Comparison of all eight tests in the CN IV Palsy Group also showed a significant difference between the Subjective Horizontal and both the subjective and fovea-ONH tests. The Subjective Horizontal and temporal raphe angle, however, were not significantly different, as was seen in the Control Group. This suggests that the perceived subjective torsion in CN IV palsy participants has not yet have fully adapted the temporal raphe angle.

These results again support the "spectrum of effectiveness" of adaption proposed in 1983 by Ruttum and von Noorden, as well as for Guyton (1983), von Noorden (1984), and Herzau and Joos-Kratsch (1984), all of whom discussed the change in subjective perception with long-standing torsional deviations.

The difference between the spread of data for the Subjective Horizontal also suggests that participants in the CN IV Palsy Group may be somewhere along the "spectrum of effectiveness." As seen with the Control Group, the values of the Subjective Horizontal are concentrated around zero, ranging from 0 to $+1^\circ$ of excyclotorsion, whereas the values for the CN IV Palsy Group range from -2.5° incyclotorsion to $+4^\circ$ of excyclotorsion. Therefore, some may not have fully adapted to a horizontal.

An interesting analysis of the current study's data would be to look at the amount of anatomical torsion relative to the amount a subject perceives. However, due to the small sample size of the study, any trend seen would be anecdotal at best. A scatter-plot has been included in Appendix F for the CN IV Palsy Group that outlines the individual torsional amounts for each test across all participants. No trend can be seen from these data, indicating that a participant who has greater anatomical torsion does not necessarily perceive more torsion by either subjective testing or their Subjective Horizontal.

Overall, the results of this study support the previous theories of adaption to torsional strabismus and the spectrum of change that occurs during the course of a chronic torsional deviation. The answer to finding which objective test corresponds most closely with which subjective test as a "gold-standard" for detecting ocular torsion was not determined from the results of this research. Rather, the testing methods assessed in the current study showed that the subjective and objective tests do correlate to each other when accounting for physiological torsional position of the fovea-ONH and temporal raphe. It was also found that the relationship between the subjective and objective tests and the Subjective Horizontal can be useful in determining the amount of cortical adaption that can be associated with the chronicity of a torsional strabismus.

5.6 Clinical Significance

The main research question of this thesis was: "To which of the objective measurements (fovea-optic nerve angle or temporal raphe) do the subjective measurements correspond more closely in cases of chronic torsional strabismus?" The results of this study indeed indicate that in normal individuals, subjective testing methods (Bagolini Lenses, DMR, Synoptophore, HTS) all correspond with objective testing methods (fundus photographs, OCT, and temporal raphe) when accounting for physiological variation. As well, the subjective and objective tests correspond to the Subjective Horizontal.

For patients with long-standing CN IV palsies, the relationship between subjective and objective testing methods represents the sensory adaption over time with long-standing deviations. This finding correlates with the theory of cortical adaption mentioned previously, including the concept of "progression of adaption" in patients with long-standing CN IV palsies. The results indicate that the participants in the current study are along the spectrum between acute acquired (having subjective and objective torsion with appreciation of image tilt) and congenital (only objective torsion with no subjective torsion or image tilt).

As mentioned previously, Sheeley and Arnoldi (2014) hypothesized that true

congenital CN IV palsy is a different entity than a long-standing one. There were three children (under 15 years old) included in this study whose lack of reportable torsion and no obvious precipitating factors strongly suggests a true congenital nature to their deviation, in keeping with the findings reported by Sheeley and Arondi (2014). Other older participants reported having their deviation "since childhood" in this study; however, it is difficult to fully rule out a precipitating factor in their history.

The small number of children enrolled in the study makes a comparison of "possibly congenital" to long-standing deviations challenging. Anecdotally, two of the children (OCT-T-17 and OCT-T-22) followed the same pattern as the reported trends, i.e. no appreciation for image tilt on the Subjective Horizontal, some subjective torsion comparable to their temporal raphe angle, and significant fovea-ONH torsion ($> 15\,^{\circ}$ excyclotorsion between both eyes). One child however (OCT-T-26), followed the true congenital pattern: no subjective torsion or appreciation of image tilt on Subjective Horizontal, significant fovea-ONH torsion; however, the temporal raphe angles were significantly different than all other measurements. Therefore, it is not reliable to judge the relationship between anatomical torsion and sensory responses, as seen with the general trend of the current study's results.

5.7 Practical Indications for Orthoptics, Ophthalmology, and Research

This study has a number of direct clinical indications:

1. It is important to understand the differences between different subjective torsional testing methods as well as the limitations of each. An accurate measurement and understanding of a patient's torsional deviation can change a treatment plan and prognosis.

2. It has been long understood that subjectively and objectively measured torsion are often not equivalent. When a patient presents with torsional diplopia, the comparison between their quantified subjective and objective results can aid confirming the longstanding nature of their problem. It is also important to consider the physiological positioning of the fovea, ON, and temporal raphe.

   Cortical adaptation has been postulated as one reason why subjective and objective measurements are different. Testing of the Subjective Horizontal is one method of assessing if cortical adaptation has occurred; the presence of which has implication on the possible surgical plan and outcome. For a patient with a longstanding CN IV palsy who has adapted to the tilted image, correction of their torsional deviation present by fundus orientation may not be a priority as subjectively, the patient is not aware of the torsion.

3. Imaging the temporal raphe is only in the preliminary stages with regards to strabismus. At the moment, the general lack of availability in clinics of this technology and the length of time involved for image capture further complicates the issue. There is also wide variability in both orientation and measurement of the raphe position. These limitations currently make this imaging process impractical for clinical use in assessing torsional strabismus. The information gained, however, will help to fill a gap in the literature regarding objective ocular torsional deviations and their relationship to perceived subjective torsion.

4. This study adds new information on the variability of subjective and objective torsion through the assessment of a normal population group.

5.8 Potential Limitations and Future Directions

Research using temporal raphe scans for strabismus is still in preliminary stages which creates avenues for further research. A comparison of the temporal raphe before and after surgery could help to understand better the effects of the rotation of the globe on the fundus orientation during ocular excursions. Pre- and post-operative investigations may also help in the understanding of the relation between anatomical torsion and subjective perception due to a new globe position.

Comparison of longstanding and acutely acquired palsy deviations would also help to understand better the relationship between the temporal raphe, the Subjective Horizontal, and the subjective tests used in clinics. Assessing patients at different stages of their deviation would help to provide more evidence for changes to the "spectrum of effectiveness."

As with any research working with subjects, variability between subjects is common. The current study attempted to mitigate variability between participants by using the same lenses and trial frames for each participant. However, as previously described, there are inherent inaccuracies of the procedure; namely the difficulty of reading the torsion from the trial frame scale and position of the trial frames on the participant's face. As well, there can be differences between in participants interpretation of what is exactly parallel or horizontal.

Even though the angles obtained by fundus photography or temporal raphe scans were classified as objective testing, there is a subjective element from the examiner's perspective when measuring the torsional angles. Issues such as indistinct foveae or optic nerve head margins on fundus photos, and end points of the temporal raphe make determining where to create an angle more challenging. The current study attempted to reduce the subjectivity of measurements by comparing five clinicians to the PI. However, it does take practise to determine accurately both the fovea-ONH and temporal raphe angles; therefore, usage in the clinical setting would have to take this limitation into account.

Along with the subjectivity of assessing the angle of temporal raphe scans,

another limitation is the length of time for acquiring the scans for raphe imaging. On average, a fixation-steady participant takes approximately 3–4 minutes per eye. Participants who have poor fixation, dry eyes, inattention, or have trouble controlling a strabismic deviation, take longer to scan. Longer scan times can result in poorer fixation and more artifacts within the final image. Lower resolutions settings can be used to obtain a faster scan; however, these images are not as clear and therefore more difficult to determine the raphe orientation. With these limitations, scanning the temporal raphe may not be suitable for routine in a clinical assessment of patients with CN IV palsies.

Age was controlled for as previous research had shown changes to the appearance of the temporal raphe significant to aging (Huang et al., 2014); however, refractive error was not controlled for in this study. Higher myopic eyes have a number of structural differences than either emmetropic or hyperopic eyes. While the overall refractive errors from both groups were similar in the currently study, each group had three participants outside the normal range of spherical refractive errors. Therefore, future research should consider controlling for refractive errors between groups.

A last limitation of this study is the sample size. The ideal sample size for the study was determined from previous literature data that typically reported results from between 20 and 30 participants. A power calculation was completed to determine the number of participants needed for statistical significance and indicated that 50 participants were required. Due to clinical limitations, as well as time limitations for this study, recruitment of 25 participants was done.

CHAPTER 6: CONCLUSION

The purpose of this research was to investigate the relationship of subjective and objective ocular torsion in patients with CN IV palsies, and more specifically a potentially novel objective method using the retinal raphe imaged by OCT. Four common methods were used for assessing subjective torsion; namely, Bagolini Lenses, DMR, Synoptophore, the HTS and two methods for assessing traditional fovea-ONH torsional angles by fundus photography and OCT.

Previous literature has robustly supported a discrepancy between the torsional angles reported subjectively and anatomical fovea-ONH angles measured objectively in patients with long-standing CN IV palsies—a result further supported by results of this study. Therefore, the current study included a novel use of temporal raphe scans, and the limitations of the same technique, to assess the relationship between the raphe orientation and subjective torsion as well as the assessment of the Subjective Horizontal to determine possible cortical adaption.

The current study supports previous research in saying that a patient's subjective torsion is not equivalent to the fovea-ONH angle when the deviation is long-standing. This is because the physiological position of the retina is critical in determining the amount of true abnormal torsion. When the physiological retinal positioning is taken into account, the results of this study showed that the subjective tests correlate with the fovea-ONH angles as well as to the temporal raphe. The results also supported previous theories of cortical adaption, shown by the significant difference between the Subjective Horizontal and the subjective tests and fovea-ONH angles in participants with CN IV palsies.

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Appendix A Introductory Letter

Dear

We are writing to you because you/your child is a patient of Dr. LaRoche or Dr. Dahrab at the IWK Health Center Eye Clinic and may be eligible to participate in a research study. This study is being done as part of the Principle Investigators Master's thesis at Dalhousie University and the IWK Health Center. The study is aimed at better understanding the connection between measurements of rotations of the eyes by a variety of methods in patients with weakness of the fourth cranial nerve. Please find enclosed with this letter an Informed Consent Form. This document provides details of the study and what will be involved if you decide to participate/have your child participate. We would appreciate you taking the time to read through these documents.

The Principle Investigator (Rebecca Fels) will call you before your next appointment to follow up. They will be able to go over the consent documents and answer any questions you may have regarding the study or your/your childs participation. If you are interested at that time we will make arrangements to talk with you directly at you/your childs next appointment in the IWK Eye Clinic. If you would prefer, you can call or text the Principle Investigator directly at 902-789-3160 You can also email the Principle Investigator at Rebecca.Fels@iwk.nshealth.ca with any questions.

Participation in this study is voluntary. The quality of care you/your child will receive from the IWK Health Center will not be affected with either choice of participating or not participating in this study.

We appreciate your time in considering this option.

Sincerely,

Dr. G. R. LaRoche (study supervisor), IWK Health Center Eye Clinic
Rebecca Fels Orthoptist IWK Health Center Dalhousie University MSc candidate
Halifax, Nova Scotia

Appendix B Consent Form

Informed Consent

STUDY TITLE:	A Novel Use of Optical Coherence Tomography for Assessment of Axial Ocular Torsion in patients with Fourth Cranial Nerve Palsy
PRINCIPAL INVESTIGATOR:	Rebecca Fels Orthoptist IWK Health Centre 5980 University Ave. Halifax, NS, B3K 6R8 Canada **Email:** Rebecca.fels dal.ca
STUDY SPONSOR:	G. Robert LaRoche Professor of Ophthalmology Department of Ophthalmology and Visual Sciences, Dalhousie University Chief of Service, Pediatric Ophthalmology and Adult Strabismus IWK Health Centre
CONTACT	Rebecca Fels (902) 789–3160 Rebecca.fels dal.ca
FUNDER:	Funding will be provided by the Academic Enrichment fund, department of ophthalmology IWK health centre and an IWK Health Centre Category A Operating Grant.

If you are a parent or legal guardian of a child who may take part in this study, permission from you is required. When we say "you" in this consent form, we mean you or your child; "we" means the doctors and other staff.

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1. Introduction

You have been invited to take part in a research study. A research study is a way of gathering information on a treatment, procedure or medical device or to answer a question about something that is not well understood. Taking part in this study is voluntary. It is up to you to decide whether to be in the study or not. Before you decide, you need to understand what the study is for, what risks you might take and what benefits you might receive. This consent form explains the study.
The research team will tell you if there are any study timelines for making your decision. Please ask the research team to clarify anything you do not understand or would like to know more about. Make sure all your questions are answered to your satisfaction before deciding whether to participate in this research study.
The researchers will:

- Discuss the study with you
- Answer your questions
- Be available during the study to deal with problems and answer questions

You have one or both eyes that are misaligned along the visual axis. This is what we call "torsion."
You are being asked to consider participating in this study, because sometimes when we measure rotation of the eyes in clinic, these results so not correlate with what the patient actually sees. Some research suggests that measuring rotations of the eyes from a photograph of the layers in the back of the eye will give us new information, and may help us improve care.
We are currently involved in a research study to incorporate a new test which uses a camera that scans the layers of the back of the eye.
If you decide not to take part, or if you leave the study early, your usual health care will not be affected.

2. Why Is This Study Being Conducted?

Aim of the study and its significance:

- The aim of the study is to see if a new way of measuring the rotation of the eyes could be used as a standard method. The new method is called Optical Coherence Tomography (OCT) which is a sort of laser imaging of the back of the eye. We are going to compare the new method to standard methods of measurement that are currently used in clinics.

- In a defined group (cohort) of people about to receive surgery for the treatment of torsion caused by a 4th cranial nerve weakness (palsy). The objective of this study to investigate the relationships between OCT-based and fundus photography-based measurements and compare them to those measurements based on patient perception of image torsion.

How your study intends to fill the gap of knowledge:

- In the eye clinic, we can measure rotation of the eye. We use that information to help us decide about treatments and see how well treatments are working.
- Sometimes what we measure in the clinic does not always correlate with what the patient sees. The importance of what the patient sees is primordial in the choice of the optimum treatment. We think (hypothesize) that by getting an image showing the layers of the retina in the back of the eye, we would understand the torsion seen by the patients better.

How it may contribute to care or education or research in the future:

- If the hypothesis is correct, and the OCT torsional measurements are the same as what the patient perceives, this could be a step toward a new standard for this measurement. The current methods of measurement are not always accurate, so the OCT could become the "gold standard" for torsional measures.
- A reliable, repeatable, and objective measure of ocular torsion would in turn, give surgeons more confidence in designing surgical treatment that address each patients real needs.
- As the OCT is already used in many eye clinics worldwide, this innovation could be readily applied to the benefit of countless patients.

3. How Long Will I Be In The Study?

This study will require two visits to eye clinics (one at the IWK Health Center, and one at the Victoria General Hospital). The first visit will be at the IWK Eye Clinic and will be part of your regularly scheduled appointment. This visit will take approximately two hours just like your regular appointment as the extra study tests will be completed during the regular wait time between seeing the orthoptist and Dr. LaRcohe or Dr. Dahrab.

The second visit will be at the VG Eye Clinic on the day of your surgery during the regular waiting period prior to going into the operating room. If this time is

inconvenient or the OCT machine is unavailable, another time will be scheduled. This second visit will last approximately 30 minutes in total. These visits will happen over an 8-month period depending on the surgery wait list. The entire study to collect all the data is expected to take about 1 year to complete and the results should be known in 1 to 1.5 years.

For participants in the normal cohort group, only two aspects of the study are required: a photograph of the back of the eye and a scan of the back of the eye. The photo will take approximately 15 minutes and is completed at the IWK Eye Clinic. The scan will take approximately 30 minutes and is completed at the VG Eye Clinic. Both can be done on the same day, or scheduled on different days if more convenient.

4. How Many People Will Take Part In This Study?

We predict that 50 people (25 with rotation of the eyes, 25 without) will participate in this study. Participants will be from the Maritime region.

5. How Is The Study Being Done?

The study is a prospective non-randomized, comparative test study. This means that all participants will complete the tests in the same order and the research team will compare the results of the tests to each other.

If you decide to participate, you will complete the majority of testing during your regularly-scheduled appointment at the IWK Health Center. Almost all of the tests done during this visit are part of your standard-of-care assessments. Two are added for research purposes, have no inherent risks, and take only a few minutes each.

For one of the tests, you will go to the eye clinic at the neighboring Victoria General Hospital for 1 visit. We will link this with your regular appointments. You will have a photo taken of the layers of the back of the eye, similar to the photo you will have at the IWK but with a different camera. The tests are painless, require eye drops, and do not have anything coming in contact with the eye. The test done at the VG is often used in eye care for other eye conditions. This will involve sitting in the exam chair, placing the chin in a chin-rest, looking at a small computer screen and having a technician take a photo. This test will take about 15 minutes.

Once all the tests are done, your participation in the study will end. No medicines or eye drops will be required and no follow-up visits are needed for the research.

This study will take about 2 to 3 hours: 2 hours for your regularly scheduled eye clinic visit, about 20 minutes for explanation of the research and answering questions, and another 30 minutes for the test at the VG Eye Clinic.

The results of the test will not be forwarded to your family doctor or optometrist.

Are There Risks To The Study?

All of the tests for this research project have been demonstrated to be safe. There are no expected harms from participation.
There is a remote possibility that someone unintended may find out about your/your child's participation in the study. The researchers will try to make sure this doesn't happen. by ensuring that the records for the study will only be seen by the researchers and the IWK Research Ethics Audit Committee (see below).
As with any research, there is the possibility of unexpected risks. We do not anticipate any risks due to the nature of the tests, as there is never any direct contact with your eyes.

7. Are There Benefits Of Participating In This Study?

We cannot guarantee or promise that you will receive any direct benefits from this research. The photo may give us more compatible results with what you experience in your vision in everyday life.
Successful completion of this project will lay the groundwork for a better understanding of the rotation of the eye in IV cranial nerve weakness and what people really experience as opposed to what we currently measure. This would result in more comprehensive testing and hopefully better care for people with similar conditions. Results of this study will also add more specific knowledge on management and understanding of this type of strabismus condition.

8. What Alternatives to Participating are there?

You do not have to participate in the study. It is entirely your choice. If you choose not to participate, it will not affect the care you or your family members receive at the IWK Health Centre.

9. What Happens at the End of the Study?

It is anticipated that the results of this study will be published and or presented in a variety of forums. In any publication and/or presentation, information will be provided in such a way that you cannot be identified, except with your express permission.
An explanation of the results of your photo of the layers of the back of the eye will also be offered verbally at the time of the photo.

We may like to use information collected from you during this study for future research studies on eye rotation. If you agree to this, the confidentiality of your study records will be protected to the full extent provided by law.

10. What Are My Responsibilities?

As a study participant you will be expected to:

- Follow the directions of the research team;
- Report any changes in your health to the research team;
- Report any problems that you experience that you think might be related to participating in the study.

11. Can My Participation in this Study End Early?

Yes. If you chose to participate and later change your mind, you can say no and stop the research at any time. Should you wish to withdraw your consent, please inform the research team. If you choose to withdraw from this study, your decision will have no effect on your current or future medical treatment and healthcare. You can request that all your data be removed from the study.
Also, Dr. LaRoche, the Nova Scotia Health Authority Research Ethics Board, and the principal investigator have the right to stop patient recruitment or cancel the study at any time.
Lastly, the principal investigator may decide to remove you from this study without your consent for any of the following reasons:

- You do not follow the directions of the research team;
- There is new information that shows that being in this study is not in your best interest.

If you are withdrawn from this study, Rebecca Fels will discuss the reasons with you and plans will be made for your continued care outside of the study.
We would ask you to request in writing that you be removed from the study.

12. What About New Information?

You will be told about any other new information that might affect your health, welfare, or willingness to stay in the study and will be asked whether you wish to continue taking part in the study or not.

13. Will It Cost Me Anything?

There is no cost to you/your child participating in the study, other than your time to

attend the visit and possible parking expenses. As a compensation for your time, you will be given a $5 Tim Horton's gift card per visit (a total of $10).

Research Related Injury

If you become ill or injured as a direct result of participating in this study, necessary medical treatment will be available at no additional cost to you. Your signature on this form only indicates that you have understood to your satisfaction the information regarding your participation in the study and agree to participate as a subject. In no way does this waive your legal rights nor release the principal investigator, the research staff, the study sponsor or involved institutions from their legal and professional responsibilities.

14. What About My Privacy and Confidentiality?

Protecting your privacy is an important part of this study. Every effort to protect your privacy will be made. If the results of this study are presented to the public, nobody will be able to tell that you were in the study.

However, complete privacy cannot be guaranteed. For example, the principal investigator may be required by law to allow access to research records. If you decide to participate in this study, the research team will look at your personal health information and collect only the information they need for this study. "Personal health information" is health information about you that could identify you because it includes information such as your;

- Name,
- Address,
- Telephone number,
- Age or month/year of birth (MM/YY),
- ,New and existing medical records, or
- The types, dates and results of various tests and procedures.

The researchers in this study will be accessing your previous records only to ensure that you have the correct diagnosis to be eligible for this study. No data will be collected from past charts or hospital visits.

Access to Records

Other people may need to look at your personal health information to check that the information collected for the study is correct and to make sure the study followed the required laws and guidelines. These people might include:

- Dr. Robert LaRoche
- The Nova Scotia Health Authority Research Ethics Board (NSHA REB) and people working for or with the NSHA REB because they oversee the ethical conduct of research studies within the Nova Scotia Health Authority.

Use of Your Study Information

Any study data about you that is sent outside of the Nova Scotia Health Authority will have a code and will not contain your name or address, or any information that directly identifies you.
De-identified study data may be transferred to Regulatory authorities within and outside Canada. The research team and the other people listed above will keep the information they *see* or *receive* about you confidential, to the extent permitted by applicable laws. Even though the risk of identifying you from the study data is very small, it can never be completely eliminated.
The research team will keep any personal health information about you in a secure and confidential location for 7 years and then destroy it according to IWK policy. Your personal health information will not be shared with others without your permission.
After your part in the study ends, we may continue to review your health records for safety and data accuracy until the study is finished or you withdraw your consent.
You have the right to be informed of the results of this study once the entire study is complete.
The REB and people working for or with the REB may also contact you personally for quality assurance purposes.
Your access to records

You have the right to access, review, and request changes to your study data.

15. Declaration of Financial Interest

Your doctor / nurse practitioner is also a researcher on this project. However, he will not receive any payments from the study. Whether you participate or not will not change the way your doctor / nurse practitioner takes care of you.
This study is not anticipated to be involved in any commercialization resulting in sales or products. None of the researchers involved in this study has financial interests to disclose.

16. What About Questions or Problems

For further information about the study you may call the principal investigator, who is the person in charge of this study and/or any other research team member listed below.

Rebecca Fels	Principle Investigator; rebecca.fels dal.ca
Jayme Dannrath	Admin Assistant; (902) 470–2742
Dr. Robert G. La Roche	Research Coordinator; (902) 470–8731
Mr. Steve Van Iderstine:	Research Associate: (902) 470–2741 steve.van-iderstine@iwk.nshealth.ca

17. **What Are My Rights?**

> *You have the right to all information that could help you make a decision about participating in this study. You also have the right to ask questions about this study and your rights as a research participant, and to have them answered to your satisfaction before you make any decision. You also have the right to ask questions and to receive answers throughout this study.*

Your signature on this form indicates that you have understood to your satisfaction the information regarding participation in the research project and agree to participate. In no way does this waive your legal rights nor release the investigators or the IWK Health Centre from their legal and professional responsibilities.
If you become ill or injured as a direct result of participating in this study, necessary medical treatment will be available at no additional cost to you. You are free to withdraw from the study at any time without jeopardizing the health care you are entitled to receive.
If you have any questions at any time during or after the study about research in general you may contact the Research Office of the IWK Health Centre at (902) 470–8520, Monday to Friday between 8:00 a.m. and 4:00 p.m.

18. Consent Form Signature Page

I have reviewed all of the information in this consent form related to the study called:

A Novel Use of Optical Coherence Tomography for Assessment of Axial Ocular Torsion in patients with Fourth Cranial Nerve Palsy

I have been given the opportunity to discuss this study. All of my questions have been answered to my satisfaction.

I authorize access to my personal health information, and research study data as explained in this form.

This signature on this consent form means that I agree to take part in this study. I understand that I am free to withdraw at any time without affecting my future care.

Name of Participant: (print) _____

Participant or parent/guardian's Signature _____

Date(dd/mm/yyyy): _____ **Time:** _____

Future Research Studies: Do you agree that the information collected from you during the study may be used for future research studies on eye rotation? ☐ Yes ☐ No

STATEMENT BY PERSON PROVIDING INFORMATION ON THE STUDY

I have explained the nature and demands of the research study and judge that the participant named above understands the nature and demands of the study.

Name: (print) _____ **Position:** _____

Signature: _____ **Date(dd/mm/yyyy):** _____ **Time:** _____

STATEMENT BY PERSON OBTAINING CONSENT

I have explained the nature and demands of the consent process and judge that they understand that participation is voluntary and that they may withdraw at any time from participating.

Name: (print) _____ **Position:** _____

Signature: _____ **Date(dd/mm/yyyy):** _____ **Time:** _____

I will be given a signed copy of this consent.

Appendix C Child Assent Form

A Novel Use of Optical Coherence Tomography for Assessment of Ocular Torsion

Or

A New Way to Measure How Our Eye Rotates

Information for Children

Researchers

Rebecca Fels, OC(C)

Dr. G Robert LaRoche,

Pediatric Ophthalmologist, IWK Health Centre

Why are we doing this study

You are being asked to participate in a research study. Before you decide whether you want to be in it, we want to tell you about it so you can understand what you are saying yes to. A research study is like a science project at school. When doctors want to learn more about how and why our eyes rotate in kids like you, they do a research study. This study will collect information to see if a new way of measuring how your eyes rotate is better than how we already measure.

What will happen during this study?

You are going to come to the IWK eye clinic for your normal visit and during this time you're going to have many different tests done to see how your eyes move. To get as much information as possible you will also do two more new tests. For the first test, you will look at a big board with a line of light. Using a controller, you will turn the light until you think it is straight. This will take just a few minutes. The second test will be done at a new location in the Victoria General Hospital Eye Clinic. This test will take a scan (like a picture) of the back of your eye. The scan takes a few minutes for each eye so the whole test will take 15 minutes. You will not need any eye drops and nothing will touch your eye for any of the study tests.
The second test may be done on a different day than on the day you are coming to the IWK. We expect the whole study to take 2 to 3 hours.

Are there any good or bad things about this study?

The information we get from this study will not help you directly, but it will help

other people trying to understand the same problem. This will help people with rotated eyes in the future. No bad things are expected to happen during your time in the study because there will be nothing touching your eyes and nothing should be uncomfortable.

Who will know about what I did in this study?

No one except the researchers will know you are taking part in this study unless you want to tell them. Your name, your study forms and your hospital chart will only be seen by people involved in the study. The people investigating in this study will look at your previous visits only to make sure that you have the right eye condition to be in this study. They will not take any data or other information from your past visits.

Do I have to be in this study?

You do not have to be in this study. No one will be mad at you and it will not affect how your doctors look after you if you decide not to be in the study. If you don't want to be in this study, tell us. Even if you say yes now, you can change your mind later. Being in this study is totally up to you.

What if I have any questions

You can ask questions about the study any time, now or later. You can talk to your parents about things in the study you don't understand. You can also ask your doctor or our research coordinator, Mandy, about the study. You can call them or email them:

Rebecca Fels	rebecca.fels dal.ca or (902) 789–3160
Dr. G Robert LaRoche	(902) 470–8731

Appendix D General Population Recruitment Poster

Department of Health Professions: Clinical Vision Science
Dalhousie University

PARTICIPANTS NEEDED FOR RESEARCH IN STUDY OF TORSIONAL ROTATIONS OF THE EYE

We are looking for volunteers to take part in a study of the accuracy of different measurements for eye rotations
As a participant in this study, you would be asked to have a picture taken as well as a scan of the back of both eyes.
Your participation would involve 2 sessions lasting approximately 1 hour total. This can be done in one day or split over two separate days.
In appreciation for your time, you will receive $10 in gift cards to Tim Hortons

For more information about this study, or to volunteer for this study, please contact:
Rebecca Fels
(MSc Student, Clinical Vision Science, Dalhousie University)
at
Email: rebecca.fels@dal.ca **or**
Call/text: 902–789–3160

This study has been reviewed by and received REB approval through IWK Health Centre Research Ethics Committees.

Appendix E Data Collection Sheet

A Novel Use of Optical Coherence Tomography for Assessment of Ocular Torsion

Participant ID:	Assessment Date: (yyyy/mm/dd)	Investigator:
Age (year/month):	Gender:	Lensometry:
Palsy Lateralization:	Fixing Eye:	Onset:
Bagolini:	DMR:	
Synoptophore:	Harms:	
Subjective Horizontal	RE Light:	LE Light:
	RE Dark:	LE Dark:
Fundus RE:		OCT RE:
LE:		LE
Visual Acuity RE:		
LE:		

Appendix F Scatter plot of non-adjusted data for the CN IV Palsy Group