Effect of vision-based treatments on visual acuity and motor function in children with amblyopia

by

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Author's Declaration

This thesis consists of material all of which I authored or co-authored: see Statement of Contributions included in the thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

I understand that my thesis may be made electronically available to the public.

Statement of Contributions

Taylor Brin was the sole author for Chapters 1, 2, and 4-6. These chapters were written under the supervision of Dr. Ben Thompson and have not been published or submitted for publication.

Chapter 3 is a published manuscript, therefore Taylor Brin is not the sole author for that project. The contributions of each author in Chapter 3 is as follows:

Taylor Brin: literature screening, data analysis, writing manuscript, editing manuscript.

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William Bobier: project inception, developing search strategy, editing manuscript, guiding the project.

Ben Thompson: editing manuscript, guiding the project.

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Abstract

Purpose: To investigate existing as well as novel vision-based treatments in children with amblyopia and determine the utility of motor function as a potential outcome measure.

Methods: Three experiments were conducted. Experiment 1 was a meta-analysis that initially found 3346 articles through a comprehensive literature search in Ovid Embase, PubMed, the Cochrane Library, Vision Cite, and Scopus. The search was for randomized clinical trials (RCTs) from 1975 to June 2020 and investigated improvement in visual acuity (VA) of the amblyopic eye. The population was patients aged 4 – 17 years old with amblyopia undergoing vision-based treatment. Two independent reviewers narrowed the results to 36 articles. Meta-analyses and a meta-regression were conducted on a subset of these RCTs in order to determine if any one vision-based treatment was superior at improving VA of the amblyopic eye.

The goal of Experiment 2 was to characterize the types of motor function deficits seen in children (aged 3 - >7) with amblyopia and binocular vision problems (anisometropia without amblyopia, and strabismus without amblyopia), compared to controls. A total of 64 participants were recruited. Visual acuity (HOTV), stereopsis (Randot Preschool Stereoacuity Test), suppression (Worth 4 dot test) and motor function scores were assessed (Movement Assessment Battery for Children 2nd edition).

Experiment 3 involved developing a binocular video treatment for use in a multi-site RCT. This treatment aimed for children aged 3 – 6 with amblyopia was created by transforming an existing cartoon (Q Pootle 5, provided by the British Broadcasting Corporation) into a dichoptic format. The goal was to create a video treatment that inspired high adherence rates and could separate specific, key characters between the eyes.

Results: In Experiment 1, of the 3346 studies identified, 36 were included in a narrative synthesis. A random effects meta-analysis (five studies) compared the efficacy of binocular treatments versus patching: mean difference −0.03 logMAR; 95% CI 0.01 to 0.04 ($p<0.001$), favouring patching. An exploratory study-level regression (18 studies) showed no statistically significant differences between vision-based treatments and a reference group of 2–5 hours of patching. Age, sample size and pre- randomisation optical treatment were not statistically significantly associated with changes in amblyopic eye acuity. A network meta-analysis (26 studies) comparing vision-based treatments to patching 2–5 hours found one statistically significant comparison, namely, the favouring of a combination of two treatment arms comparing combination and binocular treatments, against patching 2–5 hours: standard mean difference: 2.63; 95% CI 1.18 to 4.09. However, this result was an indirect comparison calculated from a single study. A linear regression analysis (17 studies) found a significant relationship between adherence and effect size, but the model did not completely fit the data: regression coefficient 0.022; 95% CI 0.004 to 0.040 ($p=0.02$).

In Experiment 2, An ANCOVA did not find a significant main effect of patient group on total motor function standard scores $F(2, 51) = 1.59$, $p = 0.82$). None of the covariates (visual acuity

and stereopsis) were significantly associated with total motor function scores (lowest $p = 0.42$). When investigating the sub-categories of the MABC-2, one-way ANOVAs showed no significant effect of group for manual dexterity, catching and throwing, and balance scores.

A novel binocular treatment was developed from the ground up for Experiment 3. The resulting treatment separated key characters and/or items between the eyes, to ensure that the use of the amblyopic eye was essential for the patient to understand each scene. The cartoon was successfully ported to the New Nintendo 3DS XL, a handheld device that allows dichoptic videos to be shown without the need for glasses. This treatment is distinct from previous video treatments in the literature and we hypothesize that it will improve visual acuity of the amblyopic eye, stereopsis and fine and gross motor function skills in children with amblyopia.

Conclusion: Clinicians have many available options for treatment that are just as efficacious as patching for 2-5 hours. This includes the possibility of binocular treatments, which may also improve stereopsis. More research on symptoms other than just visual acuity, such as motor function, should be further investigated in patients with amblyopia in order to provide a complete healthcare plan.

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First and foremost, I would like the acknowledge all the encouragement and support I received from my supervisor, Dr. Ben Thompson. I could not have made it this far without his expert guidance. I thank him for believing in me and providing me with many opportunities to travel, present my work, and make life-long connections with like-minded researchers.

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Finally, I'm grateful towards my husband Alan Yee, who was always there to listen when I needed someone to talk to.

Dedication

This thesis is dedicated to Dr. Marty Steinbach, who got me started on this journey when he agreed to take me on as his last Master's student, despite being retired. May he rest in peace.

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List of Abbreviations

EHCO: Eye Health Council of Ontario

BCEA: bivariate contour ellipses area

BOT: Bruininks-Oseretsky Test

BRAVO: Binocular treatment of amblyopia using videogames

BVD: binocular vision disorder

I-Bit: Interactive Binocular Treatment

LTP: long term potentiation

logMAR: log of the minimum angle of resolution

MABC-2: Movement Assessment Battery for Children (2^{nd} edition)

NMA: Network meta-analysis

PEDIG: Pediatric Eye Disease Investigator Group

RCT: randomized clinical trial

rTMS: repeated transcranial magnetic stimulation

SD: standard deviation

SE: standard error

SMD: standard mean difference

TBS: theta-burst stimulation

tDCS: transcranial direct current stimulation

TMS: transcranial magnetic stimulation

VA: visual acuity

Chapter 1 – Introduction and Thesis Objectives

1.1 General Introduction

Unilateral amblyopia (also known as lazy eye) is a vision disorder that results in poor visual acuity in one eye. Visual acuity refers to the resolution of vision, and is typically measured using eye charts. The smallest angular size of critical detail at which a patient can correctly identify the optotype at a set distance represents their visual acuity. Therefore, visual acuity is crucial for any tasks requiring the perception of fine details, such as reading. Amblyopia also impairs stereopsis, which is the ability to use binocular vision to see in depth. Without binocular vision, only monocular depth cues such as relative size or motion parallax can be used (Tidbury, Brooks, O'Connor, & Wuerger, 2016). Poor stereoacuity has also been correlated with poor fine and gross motor skills (Buckley, Panesar, MacLellan, Pacey, & Barrett, 2010; Suttle, Melmoth, Finlay, Sloper, & Grant, 2011). The link between stereopsis and motor function has led to an area of research looking at how motor function is affected in patients with amblyopia. Motor function is typically assessed in terms of either fine or gross motor skills (Voelcker-Rehage, 2008). Fine motor function involves focused tasks that require high levels of dexterity and precision, such as writing something on paper while seated. Gross motor function tasks involve total body or multi-limb movements, such as walking in a straight line.

There are several treatment options to address the reduced visual acuity and stereopsis seen in amblyopia. Most are vision-based treatments, which we have defined as any treatment that alters visual input to the brain in some form, thereby changing how the brain interprets that information. For example, patching (wearing a patch over the fellow eye) and atropine (blurring the vision of the fellow eye by paralysing accommodation with eye drops) are monocular treatments that primarily aim to improve the poor visual acuity of the amblyopic eye. These treatments are effective and are commonly prescribed after a period of optical treatment (the prescription of spectacles). However, patching is unsuccessful in 15-20% of those treated, and even if it works initially, the relapse rate is around 25% (Holmes et al., 2004; Repka et al., 2003). In order to provide the best outcomes for patients, it is important to develop and thoroughly test new treatments that may be able to help patients who do not recover after receiving monocular treatments alone. This thesis will summarize the efficacy of current treatments in the literature, and propose a novel binocular treatment as well.

Treating amblyopia is not solely about improving the visual acuity of the amblyopic eye. As discussed above, stereopsis is impaired, which has been associated with motor function deficits in these patients (Suttle et al., 2011). It may be important to assess whether a treatment improves motor function as well, given how important it is for everyday tasks. Currently, motor function is rarely assessed in patients with amblyopia. In order to provide complete treatment for patients with amblyopia, all of their main symptoms should be addressed. This thesis will further investigate the link between motor function and amblyopia and the applicability of using motor function tests as an outcome measure. Furthermore, this thesis will test a new binocular treatment that may improve binocular vision, which could then lead to better motor function skills, as demonstrated by Webber et al. (Webber, Wood, & Thompson, 2016). Overall, this thesis has two main goals: 1) investigating current and new vision-based treatments, and 2) investigating motor function as a potential outcome measure for vision-based treatments.

1.1 Summary of Objectives and Hypotheses

This thesis includes three separate, but related experiments. All experiments were designed to test how vision-based treatments can affect young patients with amblyopia, in terms of visual acuity, motor function, or both. Our meta-analysis and systematic review (Experiment 1) examined vision-based treatments in the literature for children and young teens with amblyopia. Experiment 1 revealed two gaps in the literature that lead to the development of Experiment 2 and Experiment 3.

First of all, most RCTs screened in Experiment 1 used visual acuity of the amblyopic eye as an outcome measure. Other outcome measures such as stereopsis were rare, and no RCTs assessed motor function. It is now accepted that motor function is impaired in patients with amblyopia, and yet very few studies are investigating which types of available treatments could improve this. In Experiment 2, we used a standardized motor function tests in children with amblyopia to better understand which specific types of motor skills are impaired and why. Defining the extent and characteristics of these motor function deficits may aid future studies develop treatments that target the recovery of motor function and stereopsis.

Secondly, the results of Experiment 1 showed that it was unclear if visual acuity of the amblyopic eye improved significantly more after binocular treatments or patching (a monocular treatment). Therefore, we developed a new binocular treatment (Experiment 3) to further investigate this question that was not fully answered by the available literature in our meta-analysis. In order to extend our results from Experiment 2, we continued to use motor function as an outcome measure as well as visual acuity and stereopsis.

The following sections will detail the research objectives, summarize the literature, and describe all three experiments. Chapter 1 is the General Introduction. Chapter 2 reviews the literature on amblyopia treatments. Chapters 3 – 5 describe each specific experiment, presented as separate manuscripts. Chapter 6 summarizes all three experiments and comments on next steps in amblyopia research.

1.2.1 Experiment 1

This meta-analysis and systematic review was designed to review and analyze the literature on vision-based treatments in children with amblyopia aged 4- 17. The goal of this experiment was to perform a meta-analysis in order to determine which treatment was the most efficacious, and provide an updated summary of the published literature thus far to inform both clinicians and researchers on strengths and gaps in the literature.

1.2.2 Experiment 2

The purpose of this study was to determine the extent of motor function deficits and poor stereopsis in children with amblyopia. We hypothesized that motor function would be reduced in patients with amblyopia compared to those with healthy vision. Motor function was measured using a standardized motor function test and hand-tracking during a simple grasping task. We were interested in seeing if patients with anisometropia or strabismus (without amblyopia) also experienced motor function deficits, and if they were qualitatively and/or quantitatively different from patients with amblyopia.

1.2.3 Experiment 3

The goal of this study was to develop and test a novel binocular treatment for children with amblyopia. Previous binocular treatment studies used a binocular video game, but found that participants did not adhere to the treatment (Gao et al., 2018). Our solution was to switch from a game to an engaging cartoon (produced by the British Broadcasting Corporation), as the requirement for fine hand-eye co-ordination and puzzle-solving skills was no longer a potential barrier of entry for this treatment format. Our hypothesis was that this treatment would improve visual acuity of the amblyopic eye more than patching. Our secondary hypothesis was that this binocular treatment would also improve stereopsis and motor function (as measured by a standardized motor test) to a greater extent than patching. Ultimately, this new binocular treatment was developed to potentially provide more treatment options for patients, particularly for those who don't see any improvements after patching, or relapse once the patch is removed.

Chapter 2 – Literature Review

2.1 Amblyopia

2.1.1 Description

Amblyopia is a neurodevelopmental visual disorder that affects approximately 1 - 5% of the population (Chia et al., 2010; Fu et al., 2019). It is predicted that 221.9 million people will have amblyopia by the year 2040 (Fu et al., 2019). Considering that amblyopia is the number one cause of monocular vision loss in children, these numbers imply a huge impact on society, as well the individual.

Amblyopia can be caused by an abnormal binocular experience early in life such as strabismus (eye misalignment) or anisometropia (difference in refractive error between the eyes of 2 or more diopters). Mixed amblyopia (due to both anisometropia and strabismus) and more rarely, deprivation amblyopia (due to severe visual deprivation from birth, such as congenital cataracts) can occur. In these conditions, the images seen by each eye are highly disparate and difficult for the brain to fuse. In order to make sense of a scene, the signal from only one eye is processed by the brain. If this occurs during the critical period of visual development (Daw, 1998), generally thought to be before the age of 7 years old in humans, then abnormal neurodevelopment preferring the use of the fellow eye may occur. Since this is a period of high plasticity, there may be permanent changes in the visual cortex. For example, a reduction in both white and grey matter volume in the visual cortex has been seen for patients of amblyopia (Q. Li et al., 2013). This was specifically seen in regions responsible for spatial vision such as the inferior occipital gyrus, the bilateral parahippocampal gyrus and the left supramarginal/postcentral gyrus (for grey matter loss) as well as the left calcarine, the bilateral inferior frontal and the right precuneus areas (for white matter loss) (Q. Li et al., 2013). Structural abnormalities of white matter tracts in amblyopia have also been revealed using diffusion magnetic resonance imaging (and diffusion tensor imaging) with greater mean diffusivity in regions such as the anterior frontal corpus callosum, the right vertical occipital fasciculus (Duan, Norcia, Yeatman, & Mezer, 2015) and the optic radiation (Allen, Schmitt, Kushner, & Rokers, 2018). There is a particular decrease in the number of neurons responsible for binocular vision, as shown by primate models of amblyopia (E. L. Smith, 3rd et al., 1997).

Ocular dominance columns, which preferentially respond to the input from either the left or right eye, are also altered in amblyopia. Evidence suggests that there is a shift to prefer input from the fellow eye (Crawford & Harwerth, 2004; LeVay, Wiesel, & Hubel, 1980). For example, it was shown that most cells in the visual cortex of cats with strabismus could be activated solely by stimulating the dominant, fellow eye (Sengpiel, Blakemore, Kind, & Harrad, 1994; Wiesel & Hubel, 1965). In humans, it has been proposed that this shift in ocular dominance column activation pattern may only be seen in patients who develop amblyopia during early childhood, as those with late onset amblyopia did not show any shift in ocular dominance column activity (Goodyear, Nicolle, & Menon, 2002). The critical period of recovery is thought to be from the time of deprivation until approximately 19 years of age, after which it becomes very difficult to recover from amblyopia (Daw, 1998).

Patients with amblyopia suffer from a myriad of deficits affecting vision, motor function, and overall quality of life (see section 2.2). Our understanding of this complex visual disorder is constantly evolving as research uncovers new evidence for the potential mechanisms behind amblyopia and how to best treat it.

Amblyopia was originally considered a monocular disorder. In alignment with this theory, treatments were designed to focus on improving the "lazy" amblyopic eye. However, it was observed that even in cases where visual acuity of the amblyopic eye returned to normal, binocularity was not always restored alongside it (Levi, Knill, & Bavelier, 2015). It became apparent that amblyopia was not solely affecting the amblyopic eye, but that binocular systems were being affected as well. This is supported by animal studies observing the neuronal responses of macaques with experimental amblyopia, which discovered strong binocular suppression in V1 and V2 (Bi et al., 2011; Kiorpes, Kiper, O'Keefe, Cavanaugh, & Movshon, 1998). Amblyopia is now considered a binocular disorder, and new treatments are being developed to help improve both visual acuity and binocular vision in response to this paradigm shift.

Suppression of the amblyopic eye is a key contributing factor to the reduction in binocular vision. The exact nature of the suppression is not fully understood, although multiple theories exist. The current dominant theory proposes that there is a combination of active suppression of the neural activity of the amblyopic eye as well as passive suppression (Hess, Thompson, & Baker, 2014). Therefore, it appears that that the fellow eye cortical inputs suppress the activity of the amblyopic eye inputs and that there is also a reduction in the strength of amblyopic eye inputs (Hallum et al., 2017; Kiorpes, 2019). Suppression is a natural, adaptive response that allows the brain to reduce the chance of diplopia or binocular rivalry. This adaptative response becomes harmful when it persists to the point that neurological changes in the visual cortex occur, such as shifts in ocular dominance column activity and the alteration of binocular neurons in the visual cortex (LeVay et al., 1980; E. L. Smith, 3rd et al., 1997). Once these changes occur, suppression may remain even after the underlying anisometropia or strabismus is corrected. This theory is supported by studies showing that the strength of interocular suppression is positively correlated with the severity of amblyopia (as measured by visual acuity loss in the amblyopic eye) (Babu, Clavagnier, Bobier, Thompson, & Hess, 2013; Chima, Formankiewicz, & Waugh, 2016; L. Hamm et al., 2017; Hess et al., 2014; Kwon et al., 2014; J. Li et al., 2011; Mansouri, Thompson, & Hess, 2008; Narasimhan, Harrison, & Giaschi, 2012; Zhou, Huang, & Hess, 2013). Overall, our current understanding is that amblyopia is a binocular disorder that negatively affects multiple aspects of vision and can be caused by several different conditions.

2.2 Structures and Functions affected by amblyopia

2.2.1. Visual function

The primary deficits of amblyopia are reduced acuity in the amblyopic eye and reduced stereopsis. The level of visual acuity in the amblyopic eye is commonly used for both diagnosis and monitoring treatment success, where amblyopia is considered to be in remission if the difference in inter-ocular visual acuity is less than 0.2 logMAR (2 lines on a logMAR eye chart) (Wallace DK, 2018). It is important to improve visual acuity of the amblyopic eye to the same level as the fellow eye in order to reduce suppression sufficiently to allow for binocular vision. This also safeguards against a situation where the fellow eye is injured or becomes diseased, and the patient must rely on extremely poor vision in the unrecovered amblyopic eye. In cases of severe amblyopia, patients may be rendered legally blind if there is vision loss or damage to the fellow eye. Patients with amblyopia have a 18% risk of developing a bilateral visual impairment in their lifetime, compared to a 10% risk for a normal population (van Leeuwen et al., 2007).

There are differences in the types of acuity deficits seen in patients with strabismic amblyopia versus anisometropic amblyopia. Patients with strabismic amblyopia tend to have worse performance on optotype visual acuity and Vernier acuity tests than grating acuity tests, whereas those with anisometropic amblyopia perform poorly on all three (albeit with a less severe level of deficit than the patients with strabismic amblyopia) (Levi & Klein, 1982; Levi & Klein, 1985). Birch and Swanson found the same pattern of deficits in patients with infantile onset amblyopia (Birch & Swanson, 2000). The differences between these two subtypes of amblyopia may occur due to differences in pathophysiology between anisometropic and strabismic amblyopia. In anisometropic amblyopia, one image is blurred, but the eye is still correctly aligned. Animal studies show different resulting cortical changes: experimentally induced anisometropic amblyopia results in the loss of neurons sensitive to high spatial frequencies, but experimentally induced strabismic amblyopia particularly leads to the disruption of binocular connections in the brain (Kiorpes et al., 1998). Some suggest it may be that the level of remaining stereopsis predicts visual performance (such as on optotype acuity tests) moreso than etiology, and that patients with strabismus just have worse stereopsis in general (Bosworth RG, 2003).

Even if visual acuity is improved by treatment, other visual deficits may remain. Stereopsis is also greatly affected by amblyopia (Hess et al., 2014; McKee, Levi, & Movshon, 2003). If the patient is suppressing the signal from one eye, they are no longer able to process binocular disparity cues that allow for stereopsis to occur.

Some very specific aspects of contrast sensitivity are impaired in patients with amblyopia as well (Abrahamsson & Sjostrand, 1988). Patients with amblyopia require a greater level of contrast to be able to detect high spatial frequencies compared to controls, but this deficit is not seen for low spatial frequencies (Hess & Howell, 1977; Levi & Harwerth, 1977). Contrast sensitivity seems to only be impaired in the central visual field of patients with strabismic amblyopia (Hess & Pointer, 1985).

Visual function when using the fellow eye was historically assumed to be normal, but it has been suggested that the overall maturation of various visual functions may be delayed in amblyopia (see Figure 1) with deficits present when viewing with either eye (Meier & Giaschi, 2017). This is not due to any abnormality within the eye, but due to changes to visual processing. For example, deficits visual for perception of first and second order global motion that are equivalent to those observed during amblyopic eye viewing (Aaen-Stockdale, Ledgeway, & Hess, 2007). These abnormalities highlight the complex, binocular nature of amblyopia. We are only beginning to uncover the true extent of visual deficiencies present in amblyopia, and the underlying changes in the brain that cause them.

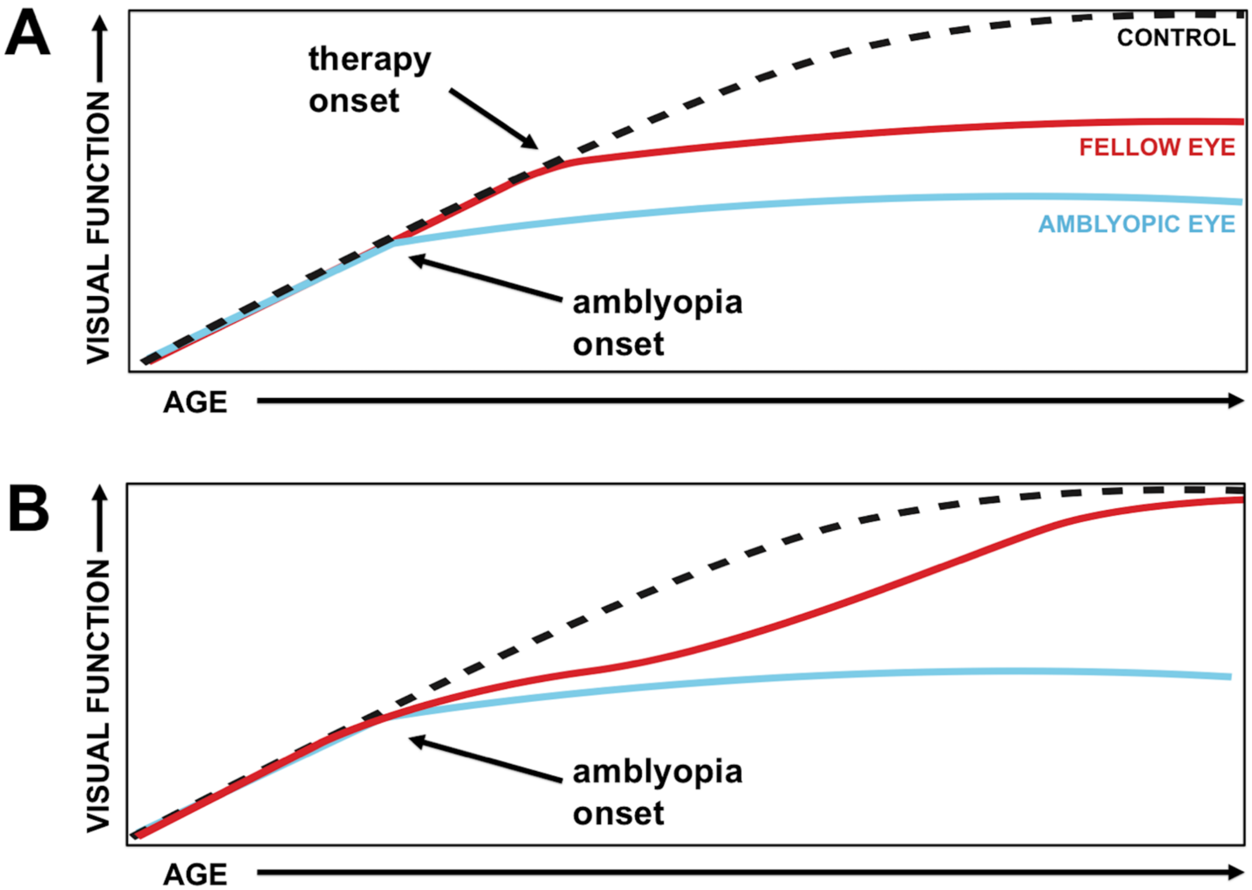

Figure 1. *Typical and abnormal maturation of visual function (Meier & Giaschi, 2017). Maturation of both the fellow and amblyopic eye are delayed compared to a control eye, whether a monocular treatment is pursued (A) or not (B). In fact, a monocular treatment may actually impede maturation of the fellow eye to the extent that it never reaches the normal level as controls.*

2.2.2. Neurology

In patients with amblyopia, the brain develops in such a way that one eye is perceptually dominant. The seminal experiments by Hubel and Wiesel revealed that early visual deprivation (a method of experimentally inducing amblyopia) in cats led to changes in the primary visual cortex, such as reduced neuronal responsiveness to visual stimuli (Wiesel & Hubel, 1963, 1965).

Cortical changes appear to be present not just in V1, where primary visual processing occurs, but in higher level processing areas as well (Kiorpes & Daw, 2018). For example, cortical thinning has been seen in patients with amblyopia bilaterally in V1 and unilaterally in V2, V3, V4, and the middle temporal (MT) area (Liang et al., 2019). Some animal studies have even shown greater visual processing deficits in V2 compared to V1 (Bi et al., 2011; Tao et al., 2014; Y. Wang et al., 2017). In macaques with strabismic amblyopia, the amblyopic eye showed a greatly reduced ability to drive V2 (but not V1) neurons (Bi et al., 2011). Furthermore, while both V1 and V2 show binocular suppression, only V2 shows below average spatial resolution and orientation bias (Bi et al., 2011).

Global motion processing is the ability to combine several local moving elements into an overall coherent perception. It is typically measured using a random dot kinematogram, where a certain subset of dots all move coherently in the same direction and another subset moves in random directions (Benjamin Thompson, 2017). In this test, global motion processing is the ability of an observer to accurately determine the direction of movement of the coherently moving dots. The middle temporal area (MT) is a region in the extrastriate visual cortex that preferentially responds to moving stimuli. Neuronal responses in MT revealed that macaques with induced amblyopia had less sensitivity to coherent motion indicating impaired motion integration mechanisms (El-Shamayleh, Kiorpes, Kohn, & Movshon, 2010). An fMRI study of humans with amblyopia showed large deficits in the extrastriate cortex as well as V1 when performing a contrast sensitivity task in the scanner (X. Li, Dumoulin, Mansouri, & Hess, 2007). The abnormalities in the extrastriate region are likely the cause of the global motion processing deficits in patients with anisometropic amblyopia (Bonhomme et al., 2006).

The implications of these findings are that the visual signal for the amblyopic eye is not just compromised at the V1 level, but that processing in high-level visual areas is also impaired. This explains why so many high-level vision deficits occur in patients with amblyopia, that could not be sufficiently explained with V1 dysfunctionality alone.

2.2.3. Motor function

Relatively recently, amblyopia has been shown to impair fine motor skills (Engel-Yeger, 2008; Grant & Moseley, 2011; Grant, Suttle, Melmoth, Conway, & Sloper, 2014). This is most likely due to the loss of binocular vision, which results in inaccurate depth perception. This is supported by the fact that fine motor skills in patients with amblyopia were shown to improve after completing a binocular, dichoptic video game treatment (Webber et al., 2016).

Experiments that track hand movements for reaching and grasping tasks have uncovered specific details of fine motor skill deficits in patients with strabismic and anisometropic amblyopia. This body of literature uses sophisticated hand-tracking devices to measure the position, velocity and acceleration of individual finger digits in the x, y and z axis of space.

Patients with strabismic or anisometropic amblyopia were found to take longer in the reach acceleration phase compared to controls (Niechwiej-Szwedo, Goltz, Chandrakumar, Hirji, Crawford, et al., 2011; Niechwiej-Szwedo, Goltz, Chandrakumar, Hirji, & Wong, 2011; Niechwiej-Szwedo, Goltz, Chandrakumar, & Wong, 2014b). This was found for all viewing conditions: amblyopic eye only, fellow eye only, and normal binocular viewing. Both patients with anisometropic and strabismic amblyopia appear to adopt a compensatory mechanism where they use online correction of their motor plan just before reaching their target in order to correct for misalignment that occurs at the initiation phase of the movement (Niechwiej-Szwedo, Goltz, Chandrakumar, Hirji, & Wong, 2011; Niechwiej-Szwedo et al., 2014b). In fact, children with amblyopia take almost double the amount of time as controls for the final approach when reaching for an object, with the worst performance being seen in those with the worst stereopsis (regardless of amblyopia type) (Suttle et al., 2011). The end result is precision and accuracy that matches controls, but in order to achieve this they need to make excessive corrections (Grant, Melmoth, Morgan, & Finlay, 2007; Niechwiej-Szwedo et al., 2014b). Unfortunately, patients with severe amblyopia are unable to make these corrections, and have worse endpoint precision compared to controls (Niechwiej-Szwedo, Goltz, Chandrakumar, & Wong, 2012). Patients with severe amblyopia are unable to adopt the same compensatory mechanisms as patients with moderate or mild amblyopia, and therefore may end up with the most compromised fine motor skills in a way that could affect everyday life.

Motor function has also been assessed in patients with amblyopia using standardized, age-appropriate motor function tests such as the Bruininks-Oseretsky Test of Motor Proficiency (BOT) and the Movement Assessment Battery for Children 2nd edition (MABC-2) (see Figure 2). Patients with strabismic amblyopia score significantly lower (worse) on the balance subtest tasks of the BOT2, compared to controls (Zipori, Colpa, Wong, Cushing, & Gordon, 2018). Similarly, patients with various types of amblyopia performed significantly worse than age-matched controls on 9 of the 16 fine motor subtests of the BOT1 (Webber, Wood, Gole, & Brown, 2008). Patients with strabismic amblyopia appear to have poorer motor function scores than those with anisometropic amblyopia, and stereopsis or visual acuity is uncorrelated with these scores (Webber et al., 2008; Zipori et al., 2018). This runs contrary to expectations, where poor motor function is explained by poorer stereopsis, as the two are usually strongly linked (Suttle et al., 2011). However, it becomes difficult to disentangle the input of stereopsis, visual acuity, and amblyopia subtype when they are not independent of each other.

Figure 2. *Examples of standardized motor function tests. The BOT2 kit is shown in the top image (a) and the MABC-2 is shown in the bottom image (b). Both tests involve fine and gross motor components that can be combined to calculate a total score of overall motor functioning. For example, some fine motor components of the BOT2 involve colouring in shapes and drawing*

shapes that copy an example shape. Some fine motor components of the MABC-2 involve posting coins in a slot and threading beads.

Being able to precisely and accurately interact with the world is important for a variety of everyday tasks. Kelly et al. have shown that patients with amblyopia and non-amblyopic strabismus take 28% longer to fill out multiple choice answer forms than those without amblyopia (Kelly, Jost, De La Cruz, & Birch, 2018). Multiple choice forms are common for university courses and many standardized tests, so patients with amblyopia that have to complete these under time constraints may be at a disadvantage compared to their peers. In the classroom, motor function deficits may be more of an issue than poor amblyopic eye visual acuity. Good fine motor skills have been positively linked to academic performance in general (Carlson, Rowe, & Curby, 2013; Sortor & Kulp, 2003).

Living with reduced motor skills can be emotionally taxing as well. This is particularly true for young children during their schooling years. Being seen as more clumsy and unco-ordinated than their peers can lead to a negative self-image and bullying. Peer acceptance and physical competence scores of children with amblyopia aged 3 – 7 were significantly lower than controls (Birch, Castaneda, et al., 2019a). Their physical competence scores were correlated with their aiming and catching subtest score on the MABC-2 (Birch, Castaneda, et al., 2019a). It is important to consider the emotional impact of amblyopia in order to understand which symptoms are the most detrimental to the everyday life of a patient, from their perspective.

2.2.4. Quality of life

As explained in the previous sections, amblyopia negatively impacts much more than just visual acuity. The constellation of visual and motor deficits have important functional consequences that can affect the daily lives of patients suffering from amblyopia. Since amblyopia tends to develop at a young age, it has been shown to have a negative impact on academic success (Carlton & Kaltenthaler, 2011). Most notably, amblyopia slows down reading. Patients with amblyopia read more slowly than their healthy peers under amblyopic eye viewing and binocular viewing conditions (Kelly, Jost, De La Cruz, & Birch, 2015; Stifter, Burggasser, Hirmann, Thaler, & Radner, 2005). Additionally, Kanonidou found that reading speed was slower than controls during a fellow eye viewing condition (Kanonidou, Proudlock, & Gottlob, 2010). Despite having functionally normal visual acuity during binocular and fellow eye viewing, performance is impaired. There seems to be something unique about amblyopia that leads to these reading deficits. For example, patients with anisometropic amblyopia read significantly more slowly than both controls and patients with anisometropia without amblyopia (Kelly et al., 2017). Slower reading in patients with anisometropic amblyopia was correlated with the frequency of both forward and regressive saccades, and fellow eye instability during binocular reading (Kelly et al., 2017). Poor fixation stability and saccadic control is well-known in patients with amblyopia (Steinbach, 2012). The amblyopic eye can have bivariate contour ellipse areas (BCEAs) up to 5 times larger than the fellow eye or normal controls (Subramanian, Jost, & Birch, 2013). The BCEA is a measure of fixation stability that calculates the area of the smallest ellipse possible that would enclose 68% of fixation points obtained from a perimeter, with larger values indicating worse fixation stability (Robert M, 1965). Considering that it has been shown that poor stereopsis was highly correlated with worse fixation stability in the amblyopic eye in patients with amblyopia (Birch EE, 2012), it may be that poor stereopsis is the root cause for slower reading speeds in these patients. In controls, poor stereopsis has been linked to poor reading ability, when controlling for IQ (Kulp & Schmidt, 1996).

Not all studies agree that amblyopia affects academic success, however. A large, 29 year prospective longitudinal birth cohort found that patients with amblyopia did not fare any worse in terms of motor development, self-esteem, or socio-economic status compared to those without amblyopia (Wilson GA, 2013). Over 1000 children were followed to see if they developed amblyopia based on either a "classic" (amblyopic eye VA equal or worse to 6/12 and a 2 line interocular difference in VA) or "modern" definition (amblyopic eye VA worse than 6/9, no interocular difference required). Children with amblyopia in this cohort performed just as well as peers on age-specific mathematics and reading comprehension tests (Wilson GA, 2013). They did not measure reading speed, which may explain why no differences were seen from the controls.

Treating amblyopia is difficult, and some patients may paradoxically suffer more from undergoing a treatment than the symptoms of amblyopia itself. Wearing an eye patch is seen as a social stigma, and many patients who wear a patch claimed to experience lower self-esteem, feelings of poor social acceptance, feelings of isolation, body image issues, and bullying from their peers (Carlton & Kaltenthaler, 2011). Most quality of life complaints from patients with amblyopia are actually targeted at issues with the treatment rather than the actual disease (Carlton & Kaltenthaler, 2011), especially during the first two months of treatment (Chen et al., 2016). However, another group found that quality of life was not significantly impacted by either patching or atropine (Steel, Codina, & Arblaster, 2019).

Amblyopia also limits the number of potential occupations that can be pursued, as strict standards for minimum visual acuity are set for pilots, certain military personnel, law enforcement, and any position that requires a commercial driver's license (Adams & Karas, 1999). With so many possible deficits – both functional and emotional – it is crucial that we develop effective treatments to improve patient outcomes.

2.3 Treatments

2.3.1 Optical treatment

According to the American Academy of Pediatric Ophthalmology, optical treatment is often the first treatment attempted in children with amblyopia (Wallace DK, 2018). It is a simple, non-invasive option that immediately improves uncorrected vision, and continual wear can result in further visual acuity improvements (Cotter et al., 2007; Cotter et al., 2006). A meta-analysis of studies that prescribed optical treatment to their study participants pre-trial found significant improvements in visual acuity of the amblyopic eye from optical treatment alone (Asper, Watt, & Khuu, 2018). In fact, some patients completely recover from optical correction alone. It was found that amblyopia was resolved in 32% of children undergoing at least 9 weeks of optical treatment (Writing Committee for the Pediatric Eye Disease Investigator et al., 2012).

Patients with anisometropic and strabismic amblyopia both show visual acuity benefits from optical treatment alone (Moseley et al., 2002; Writing Committee for the Pediatric Eye

Disease Investigator et al., 2012). Optical treatment allows for the correction of anisometropia, which is refractive in nature. By removing the difference in focal planes between the two eyes, both eyes can be in focus at the same time. However, it is less clear how optical treatment helps patients with strabismic amblyopia recover visual acuity (Writing Committee for the Pediatric Eye Disease Investigator et al., 2012). Even if the image in the strabismic eye is rendered in sharper detail from optical treatment, this does not fix the angle of deviation present. The patient may still not be foveating on targets with that eye, and therefore there will still be a difference in the corresponding retinal locations between the eyes. Surprisingly, the angle of deviation in patients with strabismus did not correlate with the efficacy of optical treatment (Writing Committee for the Pediatric Eye Disease Investigator et al., 2012). It was proposed that optical treatment allows for the usage of both eyes by correcting the optical blur of the amblyopic eye, which encourages the reduction of suppression (Writing Committee for the Pediatric Eye Disease Investigator et al., 2012). This is supported by Richardson et al.'s study showing that optical correction can improve stereopsis as well (Richardson, Wright, Hrisos, Buck, & Clarke, 2005). However, the actual mechanism behind how optical correction is so effective in patients with strabismic amblyopia is not known.

There are very few studies that use optical treatment as a planned treatment group in the literature. Most information on optical treatment comes from the period of time optical treatment is prescribed prior to the start of a trial designed to investigate a different amblyopia treatment. While this information is important and tells us that visual acuity improves significantly during this time (Asper et al., 2018), these data are not their primary objective and there is a lack of a control or comparison group. Despite the lack of formal literature on the subject, the use of optical treatment is considered to be an effective first treatment for patients with anisometropic and strabismic amblyopia (Wallace DK, 2018).

2.3.2. Monocular treatments

Occlusion therapy, Bangerter filters and atropine are the current types of monocular treatments used by clinicians for treating amblyopia (Wallace DK, 2018). Occlusion therapy (also known as patching) involves wearing a patch over the better eye for a minimum of 2 hours per day. The primary goal of patching is to improve the visual acuity of the amblyopic eye by forcing it to be used in isolation. Bangerter filters are not completely opaque like an eyepatch, but will still cause a large amount of blur to the fellow eye to reduce its acuity to less than that of the amblyopic eye. This will also force the amblyopic eye to be used. Atropine uses the same concept of monocular occlusion, but achieves this goal with the use of blurring eye drops instead of an eye patch or filter. The benefit of atropine is that once the drops are instilled in the fellow eye, the child has no choice but to wait for them to wear off, whereas a patch can be easily taken off in moments of frustration.

The effects of patching are well-known. Many studies have shown significant improvements in amblyopic eye visual acuity after a period of patching, although there is some debate over the ideal daily dosage (Gottlob, Awan, & Proudlock, 2004; Holmes et al., 2003; Pediatric Eye Disease Investigator et al., 2013). Atropine is considered to be just as efficacious as patching (Pediatric Eye Disease Investigator et al., 2008; Scheiman et al., 2008). In some cases, patching or atropine can even significantly improve stereopsis (S. Y. Lee & Isenberg, 2003). However, a review found that while visual acuity may return to normal levels from monocular treatments, stereoacuity remains impaired compared to that of age-matched children with normal vision (Wallace et al., 2011).

One potential downside of full time patching is the risk of inducing reverse amblyopia. There are cases where after wearing a patch for prolonged periods of time, visual acuity improves in the amblyopic eye but declines in the fellow eye so that now the eye defined as being amblyopic has switched sides. A retrospective review of patients under the age of 10 undergoing full time patching revealed that 19.3% developed reverse amblyopia (Longmuir, Pfeifer, Scott, & Olson, 2013). For part time patching, the rate is about 6% and considered to be more of a rare side effect (Hainline, Sprunger, Plager, Neely, & Guess, 2009).

Some studies have looked at the possibility of combining patching with other activities in order to potentially improve patient outcomes. For example, patching can be paired with perceptual learning, as a type of monocular training that repeatedly tests specific discrimination or detection tasks near threshold until an improvement is seen (Levi et al., 1997; Huang, Zhou, & Lu, 2008). This intensive training process has been shown to improve performance in related visual tasks, even in adults (Levi & Li, 2009). Perceptual learning does not always result in a transfer of skills however, and may result in the patient performing very well only on the specific stimuli they are trained on (Fahle, 2005). Another downside of perceptual learning is that it is time-consuming and can become tiring and repetitious for the patient.

2.3.3 Emerging Treatments

Brain stimulation as a treatment for amblyopia involves electric or magnetic stimulation of the brain, with the intention of increasing long term potentiation (LTP) of the visual cortex. This treatment is targeted primarily at adults, who are past the critical period of recovery (Daw, 1998). Research into brain stimulation techniques such as transcranial direct current stimulation (tDCS) and transcranial magnetic stimulation (TMS) may provide a new treatment option for older patients who are often deemed difficult to treat.

tDCS is a non-invasive treatment that uses electrodes to deliver a consistent, low intensity electric current. Stimulation can be positive (cathodal tDCS) to decrease neuronal excitability or negative (anodal tDCS) to increase neuronal excitability (Lefaucheur et al., 2017). Sham treatments (the device is turned off after about 30 seconds to make participants think they are receiving stimulation) are also often used in experiments as a control group. In the case of amblyopia treatment, a positive electrode is placed over the primary visual cortex for positive stimulation. The concept is that by stimulating the visual cortex, it may help the amblyopic eye overcome suppression by increasing the neuronal firing rate (Bocci et al., 2018). The intensity of the current and length of time spent undergoing tDCS determine the effect on excitability.

Adult rat models of amblyopia have shown that tDCS can improve depth perception to a level that matches control rats, with PET scans showing that the mechanism behind this was reorganization of the visual cortex (Castano-Castano et al., 2019). Anodal tDCS has also improved visual acuity to the point of an almost complete recovery in rats (Castano-Castano et al., 2017). These results have been replicated to some extent in adult humans. Cathodal stimulation of the primary visual cortex has resulted in improved visual acuity (Bocci et al., 2018) and reduced suppression (Bocci et al., 2018), while anodal stimulation resulted in improved contrast sensitivity (Ding et al., 2016; Spiegel, Byblow, Hess, & Thompson, 2013) and better stereopsis (Spiegel, Li, et al., 2013). A larger scale RCT has not yet been conducted on the effects of tDCS in patients with amblyopia.

TMS uses an electric coil held above the scalp over the region of interest to either increase excitation (high frequency pulses) or decrease excitation (low frequency pulses of 1 Hz or less) (Fitzgerald, Fountain, & Daskalakis, 2006). The coil uses alternating magnetic fields to create electric currents. Repetitive TMS (rTMS) can improve contrast sensitivity in adults with amblyopia, which is retained up to 30 minutes after stimulation (Thompson, Mansouri, Koski, & Hess, 2008). The US Food and Drug Administration has approved rTMS as a treatment of depression (George, 2010). This form of stimulation has also been studied as a potential treatment for stroke patients (Hummel & Cohen, 2006) and Alzheimer's (X. Wang, Mao, & Yu, 2020). A more recent study used a subtype of TMS called theta-burst stimulation (TBS) over the right occipital lobe to significantly improve amblyopic eye visual acuity, stereopsis, and suppression moreso than a sham stimulation (Tuna et al., 2020). TBS may result in long-lasting improvements in contrast sensitivity in adults, which Clavignier et al. showed to potentially persist for up to 78 days post-treatment (Clavagnier, Thompson, & Hess, 2013). This subtype of TMS uses a different pattern of stimulation that uses periodic bursts instead of a continuous level of stimulation. Similar to tDCS, there have been no RCTs on TMS to date. These brain stimulation treatments are an area of emerging treatments that show promise, but more studies need to be done in order to develop stronger evidence.

2.3.4 Binocular Treatments

Binocular treatments are a relatively new type of treatment for patients with amblyopia. The concept behind binocular treatments is that they train both eyes with the goal of improving visual acuity in the amblyopic eye as well as binocular vision (Hess, Mansouri, & Thompson, 2010b). They are often dichoptic, in that they display different images to each eye that the patient has to fuse in order to perceive the overall scene. Although possible, it is rare for monocular treatments to improve stereopsis (Scheiman et al., 2008), so binocular treatments may provide additional benefits or be able to help patients who do not show any lasting improvements from monocular treatments.

There are several different types of binocular treatments that have been tested. One of the earlier ones was a dichoptic “Push-Pull” treatment, which used a signal and noise paradigm where the patient learned to identify the signal in the amblyopic eye (pull) and suppress noise in the fellow eye (push) (Ooi, Su, Natale, & He, 2013). The treatment is designed to reduce the dominance of the fellow eye to improve stereopsis. However, this was only tested in 3 participants (Ooi et al., 2013). Since then, binocular treatments have evolved to be more enticing to the patient and are often in the form of video games or movies.

The use of virtual reality is becoming more widespread, for both personal entertainment and emerging treatments. The technology has advanced to the point where virtual reality headsets are much lighter and the costs of owing one are no longer as exorbitant. The benefit of using virtual reality for treating amblyopia is that the headsets are built for dichoptic viewing. Furthermore, the patient is forced to be fully immersed in the treatment video or game without other visual distractions unless they remove the virtual reality device. One of the early binocular treatment systems to make use of virtual reality was the Interactive Binocular Treatment system (I-Bit) (Waddingham et al., 2006). The I-Bit used dichoptic videos and video games. For the videos, both eyes could see a surrounding frame, but the actual video footage was shown mostly to the amblyopic eye. For the games, specific elements were presented to each eye (e.g. a Pac-Man variant where Pac-Man and ghosts are seen by the amblyopic eye, and the maze walls and fruit are seen by the fellow eye). Pilot tests showed promising improvements to visual acuity of the amblyopic eye after only 3-4.4 hours of treatment, but the sample sizes were too small to perform any statistical analyses (Herbison et al., 2013; Waddingham et al., 2006). A larger sample was later established for an RCT. Visual acuity in the amblyopic eye improved by less than 1 line in the RCT for the dichoptic game and video treatment groups (Herbison et al., 2016a). The improvements seen for these treatments was not significantly different from the control group; a binocular game that was not dichoptic (i.e. all elements shown to both eyes). Although the I-Bit is an interesting direction for novel binocular treatments that could spark interest in children and adults alike, the actual improvements seen were quite modest. One of the limitations may be that the treatment dosage was only 30 minutes per week, which is very little compared to the usual minimum dose of 2 hours of patching per day.

Other groups have continued to investigate virtual reality as a delivery method for binocular treatments. Žiak showed that adults undergoing dichoptic treatment for anisometropic amblyopia using the Oculus Rift demonstrated significant improvements in both visual acuity and stereoacuity (Ziak, Holm, Halicka, Mojzis, & Pinero, 2017). Virtual reality games have also been successfully used on adult patients with poor or nil stereopsis (due to amblyopia or strabismus) to specifically train stereopsis (Vedamurthy et al., 2016). Virtual reality has many applications, and there is even the possibility of using augmented reality to allow patients to watch video content of their choosing, and then alter it to a dichoptic format in real time with a head-mounted display (Bao, Dong, Liu, Engel, & Jiang, 2018). All of these studies are smaller trials, so more larger studies using virtual reality for longer periods of time are needed.

Dichoptic viewing is a useful technique to try and promote binocular vision in patients with amblyopia. However, this can be difficult if suppression is too strong and the patient simply cannot see the stimuli presented to their amblyopic eye. In order to facilitate this, it is possible to balance interocular contrast levels in a way that allows the amblyopic eye to still perceive the image, resulting in normal binocular summation (Baker, Meese, Mansouri, & Hess, 2007; Mansouri et al., 2008). Hess et al. developed a technique where high contrast stimuli were shown to the amblyopic eye and low contrast to the fellow eye. After either a certain requirement was met (such as amount of total viewing time or number of days), the interocular contrast difference would decrease. (Hess, Mansouri, & Thompson, 2010a). This initial handicap of differing the contrast in each eye allows for a starting point to allow these patients to train binocular vision at a manageable level, until binocular fusion can occur with 100% contrast in both eyes.

A review of binocular contrast-balancing treatments combined the results of 192 adults and children with amblyopia across 8 studies determined that both visual acuity of the amblyopic eye and stereopsis showed significant improvements post-treatment (Hess & Thompson, 2015a). Compared to a monocular version, the binocular version of the same game was more effective at improving visual acuity of the amblyopic eye and stereopsis in adults (J. Li et al., 2013).

This contrast balancing technique was utilized for a binocular game treatment using Tetris, where the different blocks were shown dichoptically (see Figure 3). It was hypothesized that an interactive game would require the patient to focus more on the treatment, and be more engaging than traditional patching. This treatment was designed for an Apple iPod for portability and convenience. Results of small trials using this treatment were positive. An initial study on adults with amblyopia found that after just 3 weeks, both visual acuity of the amblyopic eye and stereopsis improved (Hess et al., 2012). This was surprising, as adults are often considered beyond the age at which patching would be effective.

Figure 3. *A screenshot of the Tetris game for the BRAVO trial (Gao et al., 2018). The high contrast blocks were shown to the amblyopic eye, while the low contrast blocks were shown to the fellow eye. The game could be paused at any time.*

Further studies on children found the treatment to significantly improve visual acuity of the amblyopic eye, while a sham game did not (Birch et al., 2015; S. L. Li et al., 2014). Stereopsis did not improve in these patients, however. Along a similar vein, when comparing a dichoptic video against patching, the binocular treatment was found to show significantly more gains in amblyopic eye visual acuity after 2 weeks (Kelly et al., 2016a). Interestingly, when the patching group crossed over to the binocular treatment group for an additional 2 weeks, they were able to catch up the same average visual acuity in the amblyopic eye as the binocular treatment group (who also continued for an additional 2 weeks). These preliminary results that a binocular treatment was superior to patching lead to the formation of largescale RCTs to fully test this theory. However, the same outcome was not seen for these RCTs. The Pediatric Eye Disease Investigator Group (PEDIG) is a network of over 300 researchers that conduct multi-site clinical studies in patients with eye disorders such as amblyopia and strabismus. A PEDIG study found the binocular Tetris game improved visual acuity of the amblyopic eye less than patching (Holmes et al., 2016a; Manh, Holmes, Lazar, Kraker, Wallace, Kulp, Galvin, Shah, Davis, et al., 2018). Similarly, the BRAVO RCT found that the binocular Tetris game was not significantly more efficacious than a placebo version of the game (Gao et al., 2018). Attempts to make more engaging games than Tetris by partnering with well-known video game companies such as Ubisoft have not shown success at the RCT level either, with improvements in amblyopic VA being significantly lower than those seen with optical treatment alone (see Figure 4) (Pediatric Eye Disease Investigator et al., 2019).

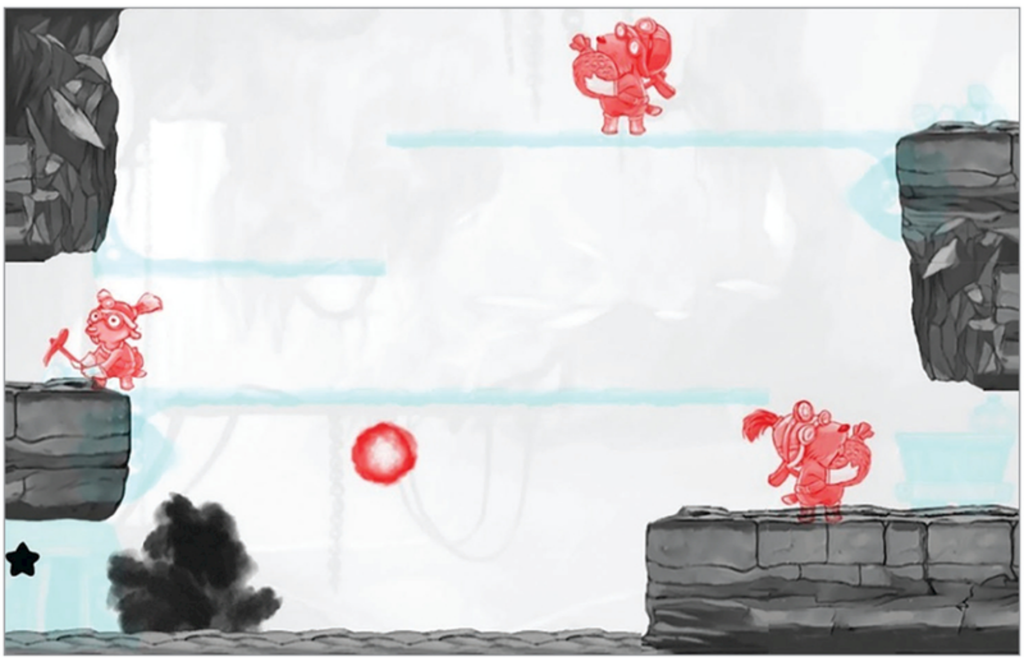

Figure 4. *A screenshot of the binocular game Dig Rush (Kelly et al., 2016a). Red, high contrast objects were shown to the amblyopic eye and blue low contrast objects to the fellow eye. This game was created to be more simple and child-friendly than Tetris.*

One potential explanation for the difference seen between the smaller trials and the RCT is adherence. Birch et al. found that adherence to a binocular treatment showed a significant positive correlation with the amount of improvement in amblyopic eye visual acuity (Birch et al., 2015). The smaller trials took place in the lab under supervision, while the RCTs allowed the patients to take the treatment home and record the time spent watching or playing. In the case of the BRAVO study, compliance was strikingly low. Thirty-six percent of participants in the treatment group completed under 25% of the prescribed overall dosage (Gao et al., 2018). Treatment adherence was poorest during the final 3 weeks, which matched up with patients self-reporting their increasing boredom with the repetitious nature of the game. Another potential reason for low adherence is that patients – especially young children - may not have been skilled enough to fully enjoy the game. Video games are an active treatment, and require the player to perform well in order for progress to be made. This format is likely not suitable for young children who do not possess the cognitive skills, hand-eye co-ordination, or attention span to complete these complex puzzles. Without progress, the task will remain at the same difficulty level (i.e. contrast balancing level). This poses as a problem considering the importance of treating amblyopia during the critical learning period to ensure the best outcomes (Daw, 1998).

It may not just be overall adherence rates, but how patients split up their attention as well. The Dig Rush trial had decent compliance rates, as 58% of participants in the treatment group completed 75% or more of the prescribed time. However, compliance is monitored using the reports of parents and the total amount of time recorded playing by the device. It may be that patients have the game running for the same duration as other patients, but are benefitting less from the treatment if they pause every 30 seconds to look at something else compared to someone who plays without any distraction. Objectively monitoring compliance is difficult, and requires extra tracking equipment included with the device in order to properly assess exactly how patients are interacting with the game or movie they are bringing home. However, this may be the key to understanding how to best administer binocular treatments if it is found that certain patterns of play are better than others.

Overall, small trials tend to show significant improvements from binocular treatments, but many RCTs do not. As such, the evidence for binocular treatments is highly heterogenous. The American Academy of Ophthalmology reported that binocular treatments should not replace patching yet, but more research is required to assess the usefulness of this option (Pineles et al., 2020). It's also possible that binocular treatments may be best as an additional treatment to be prescribed alongside of patching. An RCT by Yao et al. compared three separate treatments: patching, a binocular game, and a combination of the binocular game and patching (at a different time from the game) (Yao, Moon, & Qu, 2020). They found that the combined group had the largest improvements to amblyopic eye visual acuity and the binocular game alone had the smallest improvements (Yao et al., 2020). Adding a binocular treatment provided additional benefits to visual acuity as well as stereopsis, which were not achieved by patching alone (Yao et al., 2020). Overall, more research is required before binocular treatments can be effectively used in clinical practice, as there is still much to understand.

Chapter 5 will describe the development of a passive video treatment for children with amblyopia. The protocol will follow the outline of what was developed by Hess et al. as a patented binocular treatment method for patients with amblyopia (Hess et al., 2010b). This novel binocular treatment and its implications for motor function (Chapter 4) and visual acuity are explored in this thesis, as well as a comparison of all current vision-based treatments in the literature in Chapter 3.

Chapter 3: Efficacy of vision-based treatments for children and teens with amblyopia: a systematic review and meta-analysis of randomized controlled trials

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3.1 Introduction

Amblyopia is a neurodevelopmental visual disorder that affects between 0.34 to 3.9% of the population (Chia et al., 2010; Fu et al., 2019). Unilateral amblyopia is typically defined as visual acuity (VA) worse than 20/30 in an otherwise healthy eye, alongside a two-line interocular VA difference(Wallace et al., 2018). However, visual deficits caused by amblyopia extend beyond reduced VA and encompass broader deficits such as impaired contrast sensitivity, stereopsis, spatial localization, and global form and motion perception (Aaen-Stockdale & Hess, 2008; Abrahamsson & Sjostrand, 1988; L. M. Hamm, Black, Dai, & Thompson, 2014; Hess & Howell, 1977; Hess, Wang, Demanins, Wilkinson, & Wilson, 1999; Levi & Harwerth, 1977; Levi, Waugh, & Beard, 1994). These deficits may adversely impact everyday tasks such as reading or playing sports (Birch, Castaneda, et al., 2019a, 2019b; Kelly et al., 2015). Amblyopia also limits career opportunities in fields such as military service, law enforcement, aviation and surgery (Wallace et al., 2018), due to minimum standards of VA and binocularity in these professions.

Unilateral amblyopia results from abnormal visual experience early in life, typically caused by an eye misalignment (strabismus), a significant refractive difference between the eyes (anisometropia), or both (mixed). Deficits arise from impaired cortical processing of visual input from the eye that is chronically defocussed or misaligned (Barnes, Hess, Dumoulin, Achtman, & Pike, 2001). While the exact pathophysiology of amblyopia remains unknown, recent evidence suggests that it is a disorder of binocular vision where interocular suppression may play a key role in the resulting visual deficits.[18].

This systematic review considers vision-based amblyopia treatments that manipulate visual input to the brain, with the intention of changing cortical processing. Conventionally, vision-based amblyopia treatments targeting only the non-amblyopic fellow eye are referred to as monocular treatments. Examples include patching of the fellow eye and the use of atropine drops (Pediatric Eye Disease Investigator, 2003) or Bangerter filters (Pediatric Eye Disease Investigator Group Writing et al., 2010) to reduce fellow eye image quality. These treatments have been shown to effectively improve amblyopic eye VA when treatment adherence is maintained (Pediatric Eye Disease Investigator Group Writing et al., 2010; Repka et al., 2004; Scheiman et al., 2008). More recently, binocular approaches that rebalance the strength of visual input between the two eyes (Pediatric Eye Disease Investigator et al., 2019) have been developed to overcome interocular suppression and encourage simultaneous perception (Hess et al., 2010b; Hess & Thompson, 2015b). Binocular treatments are designed to improve both amblyopic eye VA and binocular visual function (Bossi et al., 2017; Hess et al., 2012; Kelly, Jost, Wang, et al., 2018; J. Li et al., 2013; Mitchell & Duffy, 2014; To et al., 2011; Vedamurthy et al., 2015).

A number of randomized controlled trials (RCTs) over the past two decades have evaluated the efficacy of monocular (e.g. patching, atropine and Bangerter filters) and binocular treatments for improving amblyopic eye VA. Comparisons of vision-based treatments for patients with amblyopia have been examined in systematic reviews comparing patching against atropine (T. Li, Qureshi, & Taylor, 2019; T. Li & Shotton, 2009; Osborne, Greenhalgh, Evans, & Self, 2018) or binocular treatments against patching (Pineles et al., 2020; Tailor, Bossi, Bunce, Greenwood, & Dahlmann-Noor, 2015; Carlos J. Hernández-Rodríguez, 2020). Only one review included a meta-analysis, which was limited to two studies and two treatments. Generally, published systematic reviews and meta-analyses find no significant differences between the various vision-based amblyopia treatments (Y. Li et al., 2020).

Treatment adherence, the time the participant spends engaged in the therapy, is a key factor that is often overlooked when assessing treatment efficacy. Poor adherence has been shown to lead to reduced treatment efficacy (Vagge & Nelson, 2017; Woodruff, Hiscox, Thompson, & Smith, 1994). Holmes et al. (Holmes et al., 2016b) attributed the lack of a treatment effect from their binocular approach to extremely poor adherence, as opposed to the method of the treatment itself. That is, the participants simply were not as engaged as expected. Studies of patching reveal that self-reported adherence rates are variable, ranging from 49% to

87% (Vagge & Nelson, 2017). Therefore, adherence rates can be quite low for children undergoing various types of amblyopia treatments, and this must be considered when determining the true effect of any given treatment.

We conducted this systematic review and meta-analysis to assess the comparative efficacy of vision-based treatments for improving VA of the amblyopic eye. Furthermore, we were interested in how treatment effect size may be impacted by adherence. Our study includes a large sample of RCTs in our systematic review and meta-analysis, with a sub-analysis of adherence rates.

3.3 Methods

3.3.1 Search Strategy

PRISMA guidelines were followed in conducting this review (Liberati et al., 2009). The research question and literature search keywords were devised following consultation with a team of clinical and research experts (see Supplementary Materials in published work). We used the Population, Intervention, Comparator, Outcome, Time, and Setting (PICOTS) framework (Cochrane Handbook for Systematic Reviews of Interventions (Higgins JPT, 2019)) to specify the parameters of the research question, develop the literature search strategy, and devise the eligibility criteria for inclusion of studies in the review (Table 1).

Table 1. *Population, Intervention, Comparator, Outcome, Time, Setting (PICOTS) framework*

PICOTS	**Criteria**
Population	Patients with amblyopia aged 4 – 17 years old (±1 year, to either the upper or lower end of that spectrum, but not both), caused by strabismus and/or anisometropia with no other ocular pathologies, mental illnesses, learning disabilities and/or systemic diseases. n > 5 participants in the study.
Intervention	Vision-based treatment conducted in a randomized clinical trial.
Comparator	Other types of vision-based treatments.
Outcome	Change in visual acuity of the amblyopic eye from baseline (logMAR) as the primary outcome.
Timing	Any duration.
Setting	Any environment (clinical or at home) and any country.

An information specialist (CC) used the PICOTS to build a comprehensive search strategy for the following databases: PubMed (Medline), Ovid Embase, The Cochrane Library, Scopus, and VisionCite. The initial search strategy was developed for PubMed (Medline) and the syntax and search terms were adapted to the other databases. Where available, controlled vocabulary such as medical subject headings (MeSH) were included in the search strategies. The database searches are updated as of June 17, 2020 and the search results were limited to English-language articles. The search strategy and PRISMA checklist are available as Supplementary Materials in the published work.

3.3.2 Screening

Retrieved citations were imported into RefWorks© (ProQuest LLC) for duplicate removal; remaining citations were transferred to DistillerSR© (Evidence Partners) for screening by two independent reviewers (AC, TB) at three levels: title, abstract and full text (Figure 5). A third independent reviewer (WB) resolved discrepancies at the abstract and full text levels. Citations generating discrepancies at title screening were advanced to abstract screening. Article eligibility criteria governing screening were:

Inclusion:

- Randomized controlled trials;
- Full-text published in English;
- Published between 1975 and June 17, 2020;
- Investigated one of the following vision-based treatments: patching or Bangerter filters, atropine, binocular treatments (any treatment using both eyes together, excluding optical treatment); combination treatments (any combined treatment that involved patching in addition to another intervention), or optical treatment.
- At least one group in the study included a vision-based treatment (e.g. the other group could be a placebo).

Exclusion:

- Grey literature, conference abstracts, letters, commentaries, review articles, or study designs other than RCTs; or
- Only investigated treatments that could be categorized as placebos (e.g., a monocular version of a video game as the control group for a binocular game) or that did not directly manipulate visual input to the brain (e.g., acupuncture).

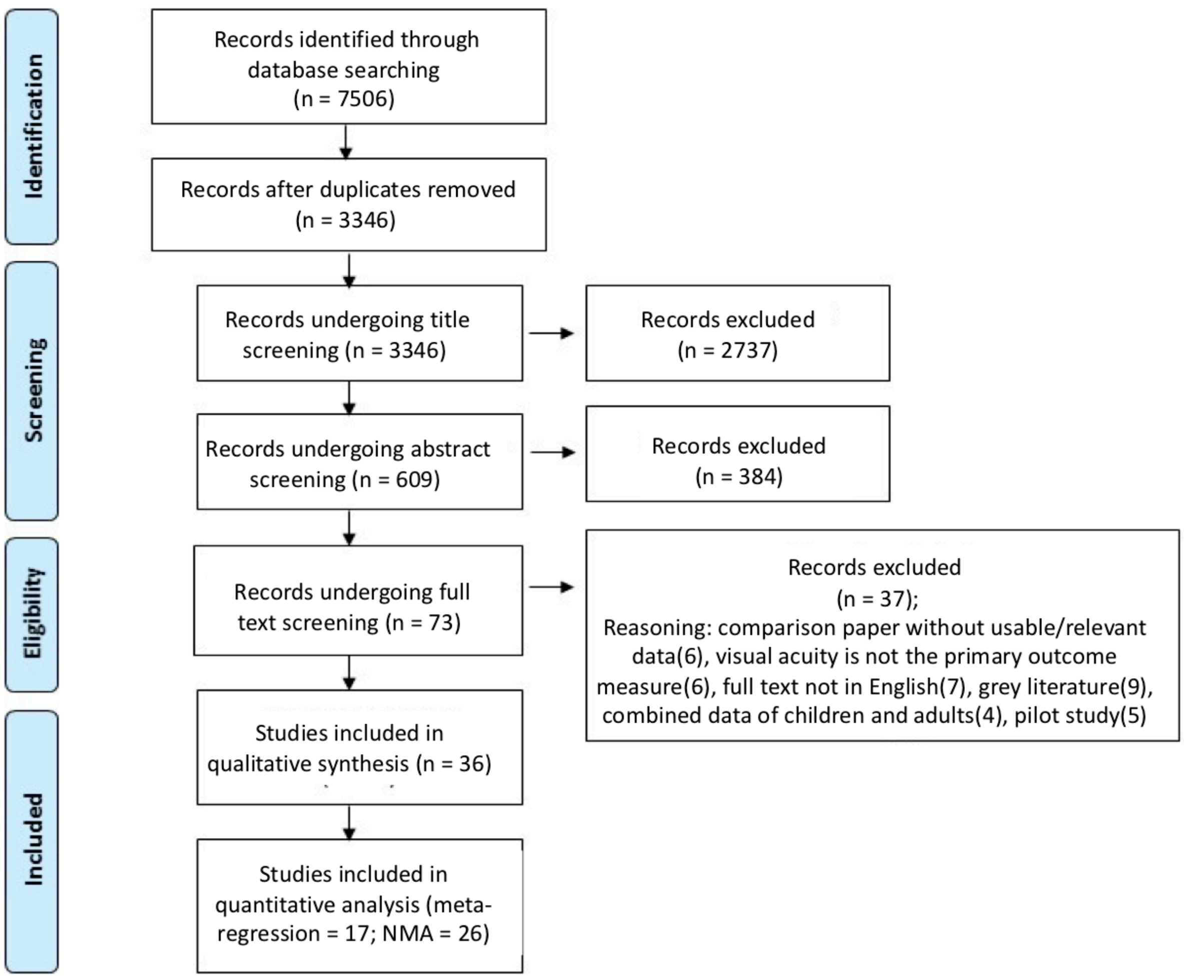

Figure 5. *Flowchart of article screening and selection. NMA, network meta-analysis.*

3.3.3 Data extraction

Two reviewers (AC, TB) independently performed double entry data to extract the following information from each study: starting and final sample sizes, mean and standard deviation (SD) of age in each group (or overall, if not available), treatment type, treatment dosage, mean and SD of change in VA of the amblyopic eye from baseline in logMAR, 95% confidence intervals (CI) of mean difference between treatments, study duration, setting (whether the treatment was prescribed for use at home or in-office), and treatment adherence rates.

3.3.4 Risk of Bias

AC and TB independently assessed the risk of bias (RoB) of the included RCTs at the study level using the Cochrane Risk of Bias 2 tool (August 22, 2019 version)(Higgins JPT, 2019). WB resolved all RoB disagreements. If information related to RoB was not reported, the authors of the study were contacted by e-mail for clarification. Some studies did not mask the outcome assessor, but the concern of it introducing bias was often mitigated through the use of well-validated and automated visual acuity systems. Since poor adherence is a well-documented issue with patching,(Vagge & Nelson, 2017) the risk of bias assessment included treatment adherence. For these studies, adherence was primarily based on participant reports.

To assess whether adherence affected the effect sizes (Hedges' g) of treatment comparisons, we regressed Hedges' g onto the adherence rates for 26 studies that reported adherence data for all treatment and comparator groups.

3.3.5 Meta-analysis

We conducted a meta-analysis (5 studies) comparing patching to binocular treatments(Holmes et al., 2016b; Kelly et al., 2016b; Y. H. Lee et al., 2020; Manh, Holmes, Lazar, Kraker, Wallace, Kulp, Galvin, Shah, & Davis, 2018; Yao et al., 2020). The inverse variance method, DerSimonian-Laird estimator for Tau^2, and a random effects model to obtain a pooled mean difference and 95% confidence interval for the study-specific mean differences were used to carry out the meta-analysis. There was a high degree of heterogeneity between the studies, with $I^2 = 80\%$; chi-sq = 19.74 ($p < 0.001$), and $Tau^2 = 0.0017$.We utilized the 'meta' package in R v4.0.2 (The R Foundation for Statistical Computing, Vienna, Austria) to conduct the meta-analyses. GRADEpro software (Hamilton, ON: Evidence Prime Inc.) was used to evaluate the overall certainty of evidence.

3.3.6 Study-level regression

We conducted an exploratory regression analysis at the study level to examine the relative effect of different treatments on VA. The dependent variable was the treatment-specific improvement in mean amblyopic eye VA from baseline to the end of the trial, as reported in each

RCT. The unit of measuring VA was the logarithm of the minimum angle of resolution (logMAR). We included patching 2-5 hours, patching 6-11 hours, patching 12 or more hours, atropine, binocular treatment, combination treatment, and intermittent patching (30 seconds on, 30 seconds off, using specialized glasses) in the regression analysis. Atropine, binocular treatments, and combination treatments did not have a sufficient number of studies to permit separation by dosage.

We modeled each treatment as a dummy variable and used patching 2-5 hours as the reference category. The regression coefficients represented the change in VA of the amblyopic eye for each treatment compared to patching 2-5 hours. Patching 2-5 hours was chosen as the reference because it was the most common treatment dosage employed across RCTs(Wallace et al., 2006; Yazdani et al., 2017). We controlled for patient mean age (or median age if the RCT did not report mean age), sample size, and whether participants were given optical treatment for four or more weeks prior to the start of the trial.

Since each RCT evaluated two treatments, we modelled 'study' as a group-level, random effects variable and fit a restricted maximum likelihood (REML) linear mixed model to the data. The other variables (age, sample size and whether spectacles were prescribed at least four weeks prior to the start of the trial) were treated as fixed effects. We used the 'lme4' package in R v4.0.2 to conduct the analysis.

3.3.7 Network Meta-Analysis

To infer relationships between a broader number of treatments beyond those that were directly investigated in head-to-head trials, we undertook a frequentist network meta-analysis (NMA). We used a random effects model to conduct the NMA and measured statistical heterogeneity using the X^2 test and I^2 statistic. For each direct treatment comparison, we extracted the treatment-specific mean changes in logMAR over follow-up and obtained a common effect size, namely Hedges' *g* (a type of standard mean difference [SMD]). Studies that were missing sufficient data to calculate Hedges' *g* were excluded from the analysis. Patching treatments were separated into four categories based on the daily prescribed dosage. Combination treatments were separated by daily prescribed dosage and whether the additional activities were performed at near or at distance. Three studies used a three-arm treatment design, with active therapies including two different binocular treatments (Herbison et al., 2016b) or a combination treatment and binocular treatment (Y. H. Lee et al., 2020; Yao et al., 2020). The active treatments were combined, and then the SMD was calculated for a combined active category and patching 2-5 hours.

Certainty of treatment efficacy was ranked using P-scores, which are analogous to SUCRA (surface under the cumulative ranking curve) scores (Rucker & Schwarzer, 2015). We generated plots to estimate the proportion of direct and indirect evidence contributing to each possible comparison, minimal parallelism, and mean path length. Further, we explored the possibility of publication bias using a comparison-adjusted funnel plot and Egger's test (see

Supplementary Materials in published work). We used the ‘esc’, ‘netmeta’, and ‘dmetar’ packages in R v4.0.2 to conduct the NMA.

It was not feasible to involve patients or the public in the design, conduct, reporting or dissemination of this project, as it is a meta-analysis on research that has already been conducted.

3.4 Results

Following duplicate removal, 3346 citations advanced to the screening phase. We ultimately included 36 RCTs (1%) in the narrative synthesis. From this 36, 5 RCTs (14%) were included in the meta-analysis, 18 in the regression analysis (50%), and 26 in the NMA (72%). The κ for the two screeners was 0.77 at the title and abstract levels (combined) and 1.00 at the full-text screening level.

3.4.1 Narrative synthesis of included studies

All types of vision-based treatments produced VA improvements ranging from 0.06 logMAR to 0.48 logMAR, except for two studies (Pawar et al., 2014; Lee et al., 2020) in which VA declined after patching (Pawar, Mumbare, Patil, & Ramakrishnan, 2014) or patching combined with perceptual learning (Y. H. Lee et al., 2020). While most treatments led to improved VA from baseline, less than half of the included RCTs (n = 17) reported clinically meaningful improvement, which is conventionally defined as a mean improvement in VA of > 2 lines (or 0.2 logMAR) (Chia et al., 2010). The most common treatments to achieve this threshold were patching or Bangerter filters (14 conditions), and combination treatments (9). In only 5 of these 17 studies, the active treatment showed a statistically significant difference in amblyopic eye VA improvement from the control group. Therefore, it is rare for studies to show both clinical (an improvement of at least 0.2 logMAR) and statistical significance.

Figure 6 shows the frequency with which each treatment category appeared in the 36 included RCTs, with patching being the most common therapy. Placebo treatments were the least common comparison, likely due to concerns over delaying treatment for young patients. The range of mean ages of participants in the included RCTs was 4.0 to 14.3 years. Only 10 RCTs had a mean age that was > 7 years.

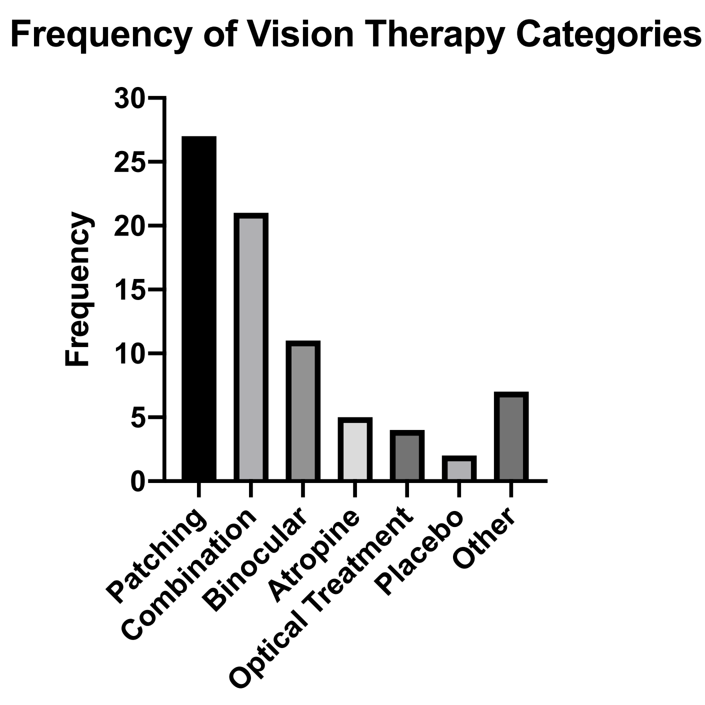

Figure 6. *Frequency of vision-based treatments in the literature.*

Of the 36 included studies, risk of bias was low in 17 and high in 12 (see Supplementary Materials in published work). The main reason for high risk of bias was poor adherence rates (7 studies). Adherence to amblyopia treatments was most commonly measured in the literature according to categories set by the Pediatric Eye Disease Investigator Group (PEDIG) (Glaser et al., 2002). PEDIG classifies adherence for individual study participants using a percentage score that is calculated by dividing the reported actual dose by the examiner's prescribed dose. These scores were grouped into 4 categories: "excellent" (76%–100%), "good" (51%–75%), "fair" (26%–50%), and "poor" (0–25%). Using these four categories, PEDIG reports the number or percentage of patients in a treatment arm that achieves "excellent" adherence.

Twenty-one of the 36 studies fully reported subjective adherence using the PEDIG classification standards. Over three-quarters of patients achieved "excellent" adherence in only 10 studies. Six studies reported less than half of patients reporting excellent adherence, with the lowest adherence score being a study by Manh et al., wherein only 13% of patients reported excellent adherence (Manh, Holmes, Lazar, Kraker, Wallace, Kulp, Galvin, Shah, & Davis, 2018). Given this variation, it was necessary to examine whether poor adherence influenced the published improvements in visual acuity.

Figure 7 shows the linear regression line between Hedges' *g* and adherence rates. When looking at the 17 studies that fully reported adherence rates, the linear regression was significant, demonstrating that treatments with high adherence rates showed larger effect sizes favouring the intervention treatment: regression coefficient 0.022; 95% CI 0.004, 0.040 ($p = 0.020$). However, the model does not fully explain the data. The regression line may exaggerate the relationship of adherence and effect size.

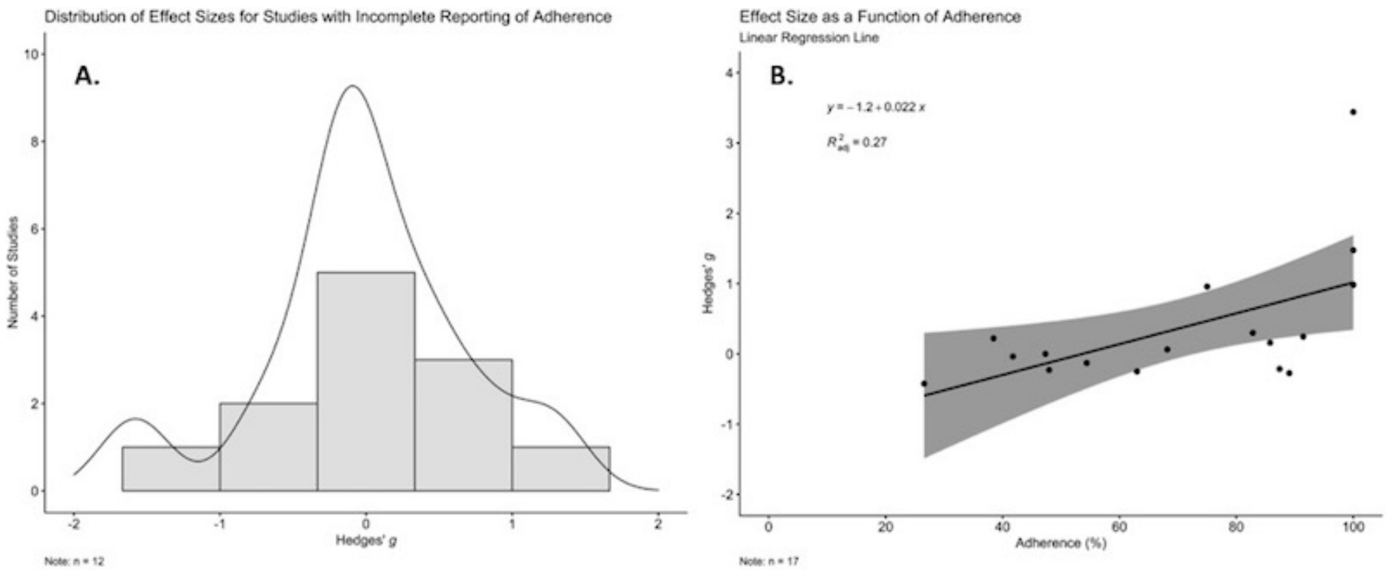

Figure 7. *Histogram (A) examined the Hedges' g of 12 studies with unreported or incomplete (eg, only reporting adherence rates for the active treatment) adherence data. The data for these studies do not appear to be biased. Scatterplot (B) shows the linear regression comparing effect size of each of the 17 studies as a function of reported adherence (with adherence defined as the percentage of patients achieving "excellent" adherence). Only studies with reported adherence data are included in this scatterplot.*

3.4.2 Meta-analysis: Binocular Treatment versus Patching

We performed a meta-analysis on five RCTs (Holmes et al., 2016b; Kelly et al., 2016b; Manh, Holmes, Lazar, Kraker, Wallace, Kulp, Galvin, Shah, & Davis, 2018; Yao et al., 2020) comparing the means of VA improvement for binocular treatments against patching. Figure 8 shows the difference between patching and binocular treatments was statistically significant at the 5% level (-0.03 logMAR; 95% CI: 0.01, 0.04). However, this difference is less than 2 letters, and is not clinically significant. There was a a high degree of heterogeneity between the studies, with I^2 = 80% and $X_4^2 = 19.74$ ($p < 0.001$). The overall GRADE certainty of evidence for these 5 studies was assessed, finding an overall low certainty of evidence. This rating was due to serious concerns with inconsistency (high heterogeneity) and low precision (the wide confidence intervals).

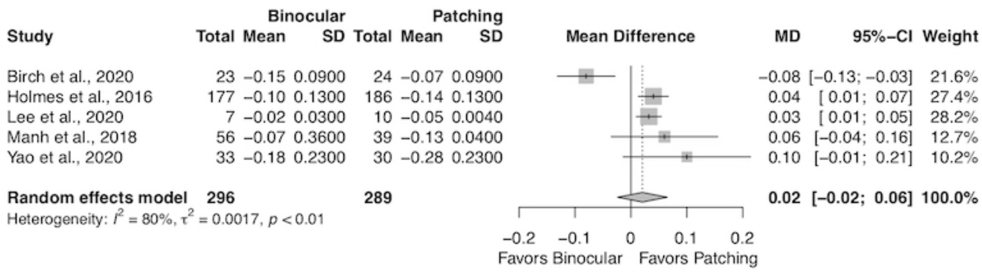

Figure 8. *Forest plot comparing patching to binocular treatments.*

3.4.3 Comparison of Multiple Vision-Based Treatments

The exploratory regression comparing any treatment to patching 2-5 hours contained 18 studies. None of the treatments showed a statistically significant difference relative to patching 2-5 hours per day (see Supplementary Materials in published work). Further, all treatments showed less than a 1 letter difference in VA compared to 2-5 hours of patching. Sample size, spectacle use, and mean (median) age were not associated with improvements in amblyopic eye VA from baseline in the included RCTs.

A NMA compared all treatments to patching 2-5 hours; the values in the Forest plot therefore represent the SMD of the treatment in question versus patching 2-5 hours. SMD > 0 favors the treatment in question; SMD < 0 favors patching 2-5 hours.

The high level of heterogeneity ($I^2 = 75.7\%$) in the NMA confirmed our decision to employ a random effects model. Twenty-six studies were included in the NMA, comparing 14 vision-based therapies to patching 2-5 hours and yielding 26 (direct and indirect) pairwise comparisons (Figure 9). Most treatment comparisons involved patching or combination treatments.

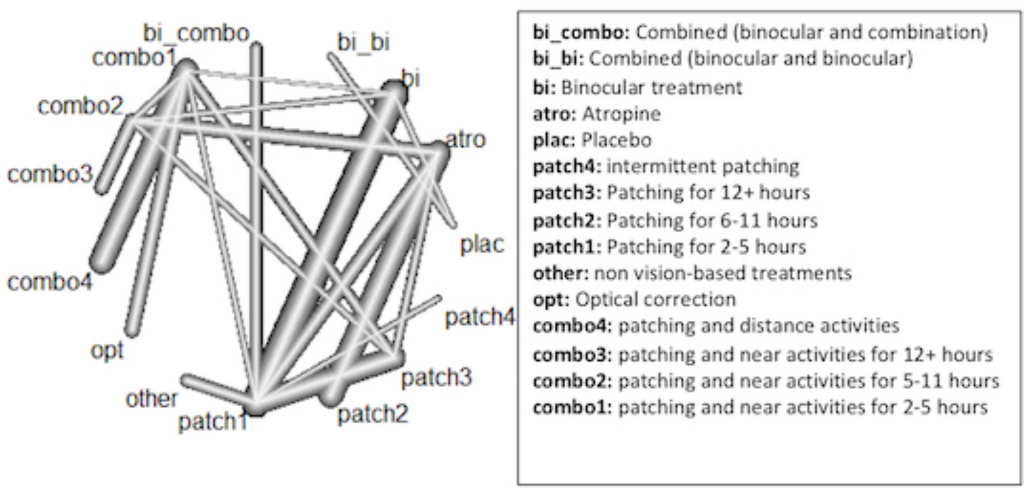

Figure 9. *Network graph of direct pairwise treatment comparisons. As the number of studies with a specific direct comparison increases, so does the thickness of the line.*

The only comparison of SMD between groups that reached statistical significance was found between the combined binocular and combination group and patching 2-5 hours with the combined binocular and combination group having a greater SMD (SMD = 2.63, 95% CI = 1.18, 4.09). The P-score for the combined binocular group was 0.9988, indicating a high level of certainty for the efficacy of this treatment (see Figure 10). However, the finding is from an indirect comparison, and only one of the included RCTs contains this type of therapy. The funnel plot did not show substantial evidence of asymmetry and Egger's test suggested publication bias was not present (p = 0.1151) (see Supplementary Materials in published work).

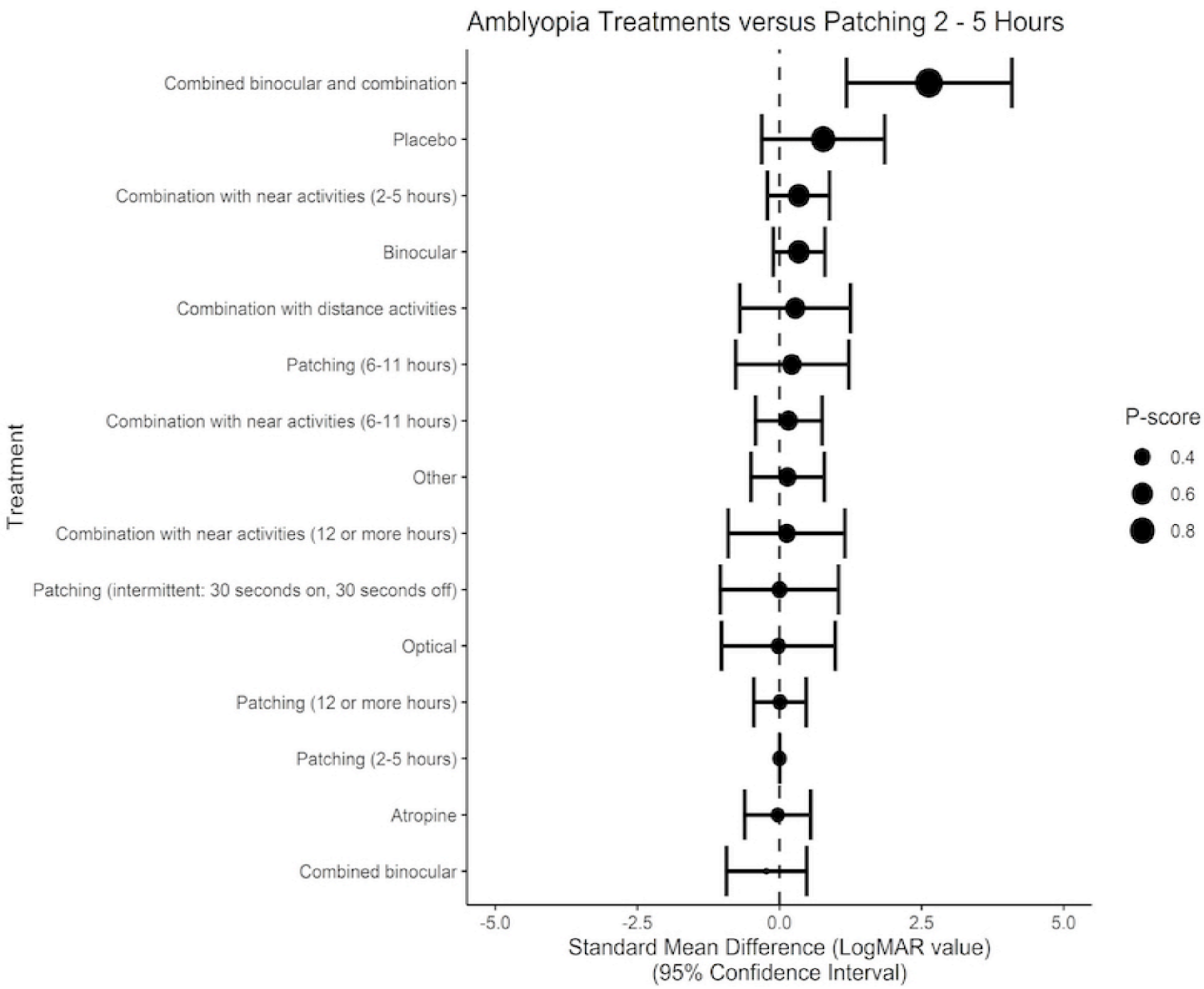

Figure 10. *Forest plot of SMD and P-scores of treatments. The treatments are ranked from highest P-score (most efficacious) to lowest. SMD, standard mean difference.*

The results of the NMA should be interpreted with caution. Out of 105 total unique network estimates (treatment comparisons), only 20 contained some proportion of direct evidence (median proportion = 0.69; interquartile range [IQR] = 0.60). The remaining 85 estimates were based entirely on indirect evidence. For 90 of 105 estimates, the minimum number of independent paths contributing to the effect size estimate on an aggregated level (minimal parallelism) was 1; larger numbers of paths support more robust estimates, with the median number of paths being 2.1 (IQR = 0.76) in the 15 comparisons with > 1 minimum path. For mean path length, which characterizes the degree of indirectness of an effect size estimate, values > 2 indicate the need to interpret the estimate in question with caution. We found mean path lengths > 2 in 80 of the 105 network estimates (plots available from the authors upon request).

3.5 Discussion

The objective of this systematic review and meta-analysis was to identify an optimal vision-based treatment for improving amblyopic eye VA in 4 to 17 year olds. Our analyses uncovered no clinically important differences between any of the treatments included in our analyses and patching 2-5 hours. Our adherence analysis revealed that poor adherence may be a factor in reducing treatment efficacy and may have affected our results. With high or unclear risk of bias in almost half the included RCTs, the findings of this review should be interpreted with caution.

Our results are similar to a previous network meta-analysis showing no significant difference between various amblyopia treatments, and that more research is needed (Y. Li et al., 2020). Several literature reviews have specifically compared the efficacy of binocular treatments to patching. A review by Pineles et al. (2020) did not recommend the use of binocular treatments (Pineles et al., 2020), while other systematic literature reviews concluded that more research was required before making any conclusions about binocular treatments (Carlos J. Hernández-Rodríguez, 2020; Tsirlin, Colpa, Goltz, & Wong, 2015). More RCTs were available at the time of our literature search than these studies, but the overall strength of evidence for this comparison was low which implies that further research is still required.

For the NMA, although it was not a significant result, we did not expect placebos to be considered more efficacious than patching 2-5 hours. This result may have arisen because the comparison was indirect and only 2 studies used a placebo group. Furthermore, the adherence rate for the treatment group of one of the studies was very poor (Gao et al., 2018), which may explain why the placebo group is ranked as the second best treatment in the NMA. Nonetheless, it is interesting to see how similar all vision-based treatments appear to be in terms of improving amblyopic eye VA. This implies that clinicians may have multiple treatment options. However, amblyopic eye VA improvements in general were small, as fewer than half of the studies reported an improvement greater than 2 LogMAR lines.

3.5.1 Strengths and Limitations of the Literature

One of the limitations of the literature is that the relatively small number of RCTs prevented us from conducting sub-analyses by age or by dosage.

Our exploratory regression analysis showed that optical treatment prior to instituting another form of vision-based treatment was not significantly related to VA improvement. Since the studies that used optical treatment prescribed spectacles to patients in every group, it was impossible to directly compare the effect of optical treatment to no optical treatment. Additionally, optical treatment durations were variable across many RCTs, with some employing a defined length of time (ranging widely from 4-18 weeks) and others waiting until the VA improvement reached a plateau.

Although our exploratory regression did not find an effect for age, it should be noted that 73% of the included RCTs featured a mean age of < 7 years. It is possible we did not have a sufficiently wide enough range of ages to discern an effect.

Our meta-analyses revealed a high level of imprecision in the included studies, evidenced by wide confidence intervals passing through the null value. A likely explanation for this variability is poor treatment adherence. It is critical to consider how low treatment adherence can negatively affect treatment efficacy (Vagge & Nelson, 2017; Woodruff et al., 1994). Poor adherence was the largest source of potential bias in studies, as identified in the RoB ratings. Of the studies that reported adherence rates, fewer than half had what would be considered good treatment adherence. It is also important to note that adherence data were almost entirely subjective. Many treatments took place at home, unsupervised by the experimenters and in uncontrolled environments. Adherence was reported by parents in the form of diaries or calendars. Subjective reports regularly over-estimate adherence rates when compared to objective measures (Vagge & Nelson, 2017; J. Wang, 2015),(Stewart, Stephens, Fielder, &

Moseley, 2007). For example, Holmes et al. prescribed a binocular video game treatment to be played at home and found that the average of parent-reported adherence was 66.7% of the total prescribed treatment time, while the game data revealed adherence to be 22.2% (Holmes et al., 2016b). Since the subjective adherence rates reported are likely higher than the actual adherence rate, this limits our ability to assess the true impact of adherence. However, these potentially inflated adherence rates were still poor, implying that the problem is more pronounced than what is reported here. Our linear regression showed a significant relationship between effect size and subjective adherence rates. However, the model does not fully explain the data, so this relationship may be exaggerated.

Where possible, robust objective measures should be used to ensure accuracy. Patching adherence can be objectively measured using occlusion dose monitors, which are modified eye patches that contain a battery and the ability to log data about the amount of time the patch is in contact with the skin around the eye (Fronius, Cirina, Ackermann, Kohnen, & Diehl, 2014). Some video game treatments can measure the amount of time a game is turned on or the number of log-ins, but there is no guarantee that the patient is actually looking at the screen while the game is powered on. The simplest option for ensuring adherence objectively is to administer treatment under supervised laboratory conditions, however cumbersome it may be for caregivers.

3.5.2 Strengths and Limitations of the Review

The major strength of this review is the comprehensive analysis of multiple vision-based therapies drawn from 5 different databases (Guyatt et al., 2008; Wallace et al., 2018). We also included studies that couldn't be meta-analyzed (due to insufficient data reported) in our systematic review to piece together a complete look at the relevant literature. Our results suggest that practitioners have a variety of equally effective treatments at their disposal and should be able to consider both patient and caregiver preferences in the management of amblyopia.

Another strength is the analysis of adherence rates. Previously, Li et al. (2020) performed a network meta-analysis examining various vision-based treatments in patient with amblyopia, and concluded that there was no clinically significant difference in the efficacy of these treatments (Y. Li et al., 2020). However, this study did not assess adherence rates, which we found to greatly impact the risk of bias rating. The goal of our adherence analysis was to control for adherence as much as possible when assessing treatment efficacy.

3.6 Conclusion

Vision-based treatments for amblyopia produce improvements in amblyopic eye VA for patients aged 4 to 17 years, but these improvements are not clinically significantly different from 2-5 hours of patching. Adherence must be considered when interpreting this result because many studies had poor or unreported adherence. One critical factor to consider for future studies is objective adherence monitoring, which may explain low treatment effects and high variability in a number of studies.

New vision-based treatments - such as binocular games – continue to be developed (Pediatric Eye Disease Investigator et al., 2019) and may change the landscape of available treatment options for clinicians in 5-10 years time. It is imperative that the literature continues to be surveyed as new studies arise and our understanding of amblyopia evolves.

Chapter 4 – MOCHA: Motor Function in Children with Amblyopia

4.1 Chapter Summary

Chapter 3 focused on improvement in amblyopic eye VA as an outcome measure, however, there are other symptoms of amblyopia that should also be considered when assessing treatment efficacy. For example, visuomotor skills are an outcome measure often overlooked in patients with amblyopia despite the importance of these abilities for everyday tasks. The goal of this study was to characterize the specific visuomotor deficits seen in patients with amblyopia, as well as other binocular vision disorders, compared to controls. This information could help clinicians to more easily recognize and address motor function deficits in their patients.

Fine and gross motor skills were assessed using the Movement Assessment Battery for Children 2nd edition (MABC-2) to allow for standardized comparisons across different ages. Another goal of the study was to determine the cause of any motor deficits seen so that they may be addressed by a novel binocular treatment (see Chapter 5). If poor stereopsis negatively affects aspects of motor function, a binocular treatment that improves stereopsis may present additional benefits other than VA improvements.

ACKNOWLEDGEMENTS: Dr. Krista Kelly trained Taylor Brin to perform the MABC-2. Dr. Amy Chow and Dr. Melanie Mungalsingh conducted the cover test for all participants tested at the Waterloo site. Participant recruitment and the remaining visual and motor testing at the Waterloo site was completed by Taylor Brin. Taylor Brin also designed the study, completed all regulatory documentation, analysed and interpreted the data. Due to COVID-19 safety restrictions that prevented face-to-face research from continuing at the Waterloo site, a second data collection site was necessary. Dr. Zixuan Xu conducted full testing of the remaining participants at the Guangzhou site, supervised by Dr. Jinrong Li. Taylor Brin trained Dr. Xu.

4.2 Introduction

4.2.1 Characterizing motor function deficits

Previous studies have demonstrated that visuomotor skills are impaired in patients with amblyopia (Grant & Moseley, 2011; Grant et al., 2014) as well as those with strabismus without amblyopia (Caputo et al., 2007; Niechwiej-Szwedo, Goltz, Chandrakumar, & Wong, 2014a). Specifically, patients with amblyopia exhibited reduced accuracy, speed, or both on everyday visuomotor tasks such as grasping objects or walking compared to controls (Grant & Moseley, 2011). Children with strabismus or anisometropia (with and without amblyopia) were 3-6 times more likely than controls to have a total score that is below the 15th percentile on the MABC-2 (Kelly et al., 2020). This level of scoring would be severe enough to indicate that the child is at risk for having a motor function disorder, and the scoring guide recommends continued monitoring.

There may be differences in motor deficits between patients with amblyopia and those with strabismus and anisometropia without amblyopia. Kelly et al. (2020) found that patients with strabismus or anisometropia without amblyopia were not significantly different from controls in terms of aiming and catching and balance scores. However, patients with amblyopia were significantly worse than controls in all components of the test. There appears to be a relationship whereby patients who have amblyopia in addition to strabismus or anisometropia are more likely than controls to have more abnormal motor function scores for certain tasks.

The exact cause of reduced motor function in patients with amblyopia and binocular vision disorders is still unknown. It has been theorized that the reduction of stereopsis is what leads to poor visuomotor skills. The rationale for this is that binocular vision provides advantages such as vergence, processing binocular disparity, and depth perception. Fine motor tasks in particular require precise target localization, and certain gross motor tasks such as throwing or catching a ball also involve these skills. However, patients with amblyopia also struggle in tasks related to stability and locomotion, which require less specific target localization (Sa, Luz, Pombo, Rodrigues, & Cordovil, 2021). This was found to be related to visual acuity. In controls, stereopsis is crucial for gross motor skills such as catching a ball (Mazyn, Lenoir, Montagne, Delaey, & Savelsbergh, 2007) and gait during obstacle navigation (Buckley et al., 2010), as well as performing fine motor tasks such as the Purdue pegboard and bead-threading (O'Connor, Birch, Anderson, Draper, & Group, 2010). Suttle et al. (2011) found that poorer stereopsis was significantly associated with the worst performance during the final approach phase of reaching for an object (Suttle et al., 2011). Grant et al (2014) also found that nil stereopsis was associated with more frequent reaching and grasping errors (Grant et al., 2014). The link between stereopsis and both fine and gross motor skills is well-defined in the literature. However, this correlation between stereopsis and motor function deficits is not always found for patients with amblyopia and binocular vision disorders (Ibrahimi, Mendiola-Santibanez, & Gkaros, 2021; Webber et al., 2008; Zipori et al., 2018).

Another theory is that motor function deficits are caused by the abnormal neural development seen in patients with amblyopia (Webber et al., 2008). Patients with amblyopia have reduced binocularity and exhibit abnormal signaling in V1 as well as high-level visual areas (Kiorpes & Daw, 2018). This could explain why motor function deficits are often more severe in patients with amblyopia compared to those with only strabismus or only anisometropia. For example, when performing reach-to-touch movements, negative stereopsis reduced the precision of patients with strabismic amblyopia, but did not affect patients with strabismus only (Niechwiej-Szwedo et al., 2014a). Both patients had strabismus and negative stereopsis, but the end result was different. This is further supported by the finding that motor dysfunction seems to be the most pronounced in patients with more severe amblyopia, as defined by a worse visual acuity of the amblyopic eye (Grant et al., 2014; Sa et al., 2021). Ultimately, more research is required to fully understand the cause or causes of these motor function deficits.

4.2.2. Motor function rehabilitation

Visuomotor deficits are an important symptom associated with amblyopia and binocular vision disorders and should be considered when evaluating treatments that aim to provide the highest quality of life possible for a patient. In particular, we may be able to develop novel treatment approaches that aim to improve motor function alongside visual acuity of the amblyopic eye. Binocular treatments that may improve stereopsis are a potential avenue. Furthermore, virtual reality is a possible delivery method, as it has a history of use in training fine motor skills and improving locomotion in other patient groups (Coco-Martin et al., 2020). Even virtual reality experiences that don't require full body immersion and only use a joystick can improve certain motor functions, such as balance and gait (Coco-Martin et al., 2020; Maggio et al., 2019; Mohammadi, Semnani, Mirmohammadkhani, & Grampurohit, 2019).

Webber et al. (2016) found that a binocular game treatment improved fine motor scores in patients with amblyopia (Webber et al., 2016). Improvements in VA of the amblyopic eye, stereopsis, and fine motor skills persisted 12 weeks after treatment had ceased. This finding demonstrates that a single treatment may be able to improve multiple symptoms associated with amblyopia at once, without the need for a separate treatment just for motor function deficits. However, this is the only binocular treatment study that included motor function as a primary outcome measure. Future studies using binocular treatments may consider including motor function tests in order to determine if there are any improvements in motor skills (see Chapter 5).

Visuomotor function may also be a crucial outcome measure for both clinicians and researchers to consider when providing treatment to a patient because poor motor skills negatively impact self-esteem, perceptions of physical competence, and are associated with slow reading speeds in children with amblyopia (Birch, Castaneda, et al., 2019b; Kelly et al., 2015). A child could recover their vision in the amblyopic eye, but still struggle with motor tasks. In fact, patients with corrected and non-corrected amblyopia exhibited the same degree of locomotion and stability-related impairments on the Motor Competence Assessment battery (Sa et al., 2021).

In order to efficiently treat visuomotor deficits in patients with amblyopia, there are several outstanding questions in the field that need to be addressed. Firstly, more information is needed to determine how different subtypes of amblyopia may affect visuomotor skills. If patients with strabismus tend to exhibit more severe deficits than those with anisometropia (Webber et al., 2008; Zipori et al., 2018), for example, this would provide valuable information about the mechanism causing those specific visuomotor deficits. Clinicians may also use this information to foster awareness of the specific patient types that may need more visuomotor function monitoring and testing. Secondly, more research is needed regarding how visuomotor skills differ between patients with amblyopia and those with binocular vision disorders. While there are numerous studies that focus on just one group, there are few that include both to draw direct comparisons. Comparing the visuomotor deficits of a patient with anisometropia to a patient with anisometropic amblyopia may reveal what additional issues are associated with amblyopia itself. Finally, the role stereopsis plays in visuomotor deficits in patients with amblyopia is still unclear. If poor stereopsis predicts poor visuomotor deficits, then treatments that specifically target improvements in stereopsis would be a useful area to explore. The more that is known about the underlying reason behind visuomotor dysfunction, the more pointed our efforts can be in creating a treatment that targets the source of the issue.

To answer these questions, a study comparing patients with amblyopia, binocular vision disorders, and controls was developed. This allowed for a comparison between amblyopia and binocular vision disorders, with the ability to further sub-divide patients based on whether they had anisometropia or strabismus. The link between stereopsis and visuomotor skills was also explored to determine if poor stereopsis was a predictive factor of poor visuomotor skills. Given the importance of both gross and fine motor function for everyday tasks, raising awareness of the specific visuomotor deficits in these patients is a priority.

4.2.3. Purpose

The objective of this study was is to explore the type and extent of motor function deficits in children aged 3-<7 years old with amblyopia or abnormal binocular vision. Identifying the type of visuomotor deficits was of particular interest, as this information would allow for specific sub-categories of motor function to be targeted as outcome measures in the next generation of randomized clinical trials. Determining the associated visual dysfunction of these deficits was also important for mapping the motor domains affected by binocular vision loss and amblyopia to inform the development of new treatments.

4.2.4 Hypothesis

We hypothesize that patients with amblyopia and binocular vision disorders will have significantly lower overall motor function scores on the MABC-2 compared to controls. Particularly, patients with amblyopia will have the most severe deficits compared to those with binocular vision disorders. We also predict that total motor function scores will be significantly affected by stereopsis, such that poor stereopsis will predict lower total motor function scores. Furthermore, having unmeasurable stereopsis will be a predictor of lower total motor function scores than those with measurable stereopsis.

4.3 Methods

4.3.1 Participants

Nine participants were tested at the University of Waterloo School of Optometry & Vision Science (Ontario, Canada) prior to cessation of in-person research throughout the province due to COVID-19. Of these nine participants, 7 were in the control group, 1 was in the amblyopic group and 1 was in the BVD group. Fifty-five participants were subsequently tested at the Zhongshan Ophthalmic Centre (Guangzhou, China). T.B. provided virtual training sessions to instruct Z.X. how to conduct the experiment in the same manner as the Waterloo site. The protocol was filmed and reviewed by TB to further aid with standardization.

Children aged 3 to <7 years old were recruited across three different groups. Group one had a confirmed diagnosis of amblyopia (anisometropic or strabismic only). Group two had anisometropia or strabismus without amblyopia. Group three was a control group with measurable stereopsis, no previous history of amblyopia (or BVDs), and no currently diagnosed eye problems. The patient's chart was referenced in order to ensure eligibility before contact. Participants with amblyopia were required to have a best-corrected visual acuity of 0.3 – 1.0 logMAR (inclusive) in the amblyopic eye and an age-dependent normal visual acuity in the fellow eye (0.3 logMAR for 3-4 years of age, 0.2 logMAR for 5 years of age). The interocular difference in visual acuity had to be 0.3 logMAR or greater for the amblyopia group. Anisometropia was defined as an interocular difference in spherical equivalent refraction of 1 diopter or more. Participants were not included if they had a diagnosed eye disease or visual disorder other than amblyopia, strabismus, or anisometropia. Patients who were born prematurely (>8 weeks premature) or diagnosed with a systemic disease, developmental delay, or vestibular disorder were also excluded. Eligible participants visited the lab for a single visit to complete all the tests.

4.3.2 Motor function test

The MABC-2 is a collection of tests aimed to assess motor skill dysfunction in children aged 3-16, with the tasks vary depending on the age of the child being assessed. The 3 – 6 years age band was used for this study. The tasks measured manual dexterity, aiming and catching, and balance. Participants were scored on their performance in each of the tasks, and assigned an age-standardized score and percentile rank. A full explanation of each task for the relevant age band is given in Table 2.

Category	Task	Scoring Dimension
Manual Dexterity 1	Posting coins (preferred hand); posting coins (non-preferred hand)	Time to completion (seconds)
Manual Dexterity 2	Threading beads (bimanual)	Time to completion (seconds)
Manual Dexterity 3	Drawing a trail within the lines (preferred hand)	Number of errors
Aiming and Catching - Catching	Catching a beanbag	Number of successful catches (out of 10)
Aiming and Catching - Throwing	Throwing a beanbag onto a target mat	Number of successful throws onto the target (out of 10)
Balance – Static Balance	Balancing on preferred leg; balancing on non-preferred leg	Time spent balancing (seconds) (max score = 30s)
Balance – Dynamic Balance 1	Walking along a straight line with heels raised	Number of steps without a mistake (max score = 15)
Balance – Dynamic Balance 2	Jumping on mats consecutively	Number of hops without a mistake (max score = 5)

Table 2. *Individual tasks from each category of the MABC-2 for the age band of 3 – 6.*

4.3.3 Visual function tests

The PEDIG ATS-HOTV was used to test visual acuity in patients with amblyopia from ages 3-<7. The full protocol for this test is described elsewhere (Moke et al., 2001). The optotypes H, O, T, and V were displayed on a screen, one at a time in random order, surrounded on all sides by crowding lines. The patient either held up a card that matched the letter they saw or reported it verbally, depending on their letter recognition ability.

Suppression was measured with the Worth Four Dot test at far and near distances. An abnormal result was classified as seeing less than 4 dots. For example, seeing only 2-3 dots would indicate that suppression is occurring. The cover test was used to determine the direction and magnitude of tropia (eye deviation), particularly for patients with strabismus. This test was always performed by an optometrist. Finally, the Randot® Preschool Stereoacuity Test (RPST) was used to measure stereopsis.

4.4 Results

4.4.1 Patient characteristics

A total of 64 participants were tested. Eight controls were excluded from the study for having nil stereopsis (3) or reporting previous amblyopia treatment (5). The remaining 56 participants were separated into 3 groups: amblyopia (21), BVD (21), and controls (14). Nil stereopsis was given a value of 10,000 arc sec. This value was chosen arbitrarily in order to conduct the analysis (O'Connor et al., 2010). All analyses were conducted using JASP (JASP Team 2020, Version 0.14.1).

The clinical characteristics of each group are summarized in Table 3. Binocular function (BF) was calculated by taking the log of the RPST result (in arc sec) (Webber, Wood, Thompson, & Birch, 2019). Those with nil stereopsis had a BF score assigned based on their Worth 4 Dot test results. Those with normal fusion were given a score of 4 and those with suppression were given a score of 5. The worst value possible is 5, indicating nil stereopsis and suppression.

	Control (N = 14)	BVD (N = 21)	Amblyopia (N = 21)
Aetiology			
Anisometropia, No., (%)	0 (0%)	7 (33%)	9 (43%)
Strabismus, No., (%)	0 (0%)	14 (66%)	12 (57%)
Mean age (months)	57.2 (SD = 10)	63.8 (SD = 9.5)	65.3 (SD = 9.2)
Females, No., (%)	5 (36%)	11 (52%)	10 (48%)
Abnormal Worth Four Dot (near or far), No., (%)	3 (21%)	8 (38%)	20 (95%)
Median near stereopsis (arc sec), (interquartile range)	100 (50 – 100)	100 (47.5 – 250)	10,000 (400 – 10,000)
Mean BF score	1.8 (SD = 0.3)	2.2 (SD = 0.9)	3.8 (SD = 1.0)
Nil near stereopsis, No., (%)	0 (0%)	2 (10%)	15 (72%)
Amblyopic eye visual acuity (logMAR), No., (%)			
≤0.1	13 (93%)	13 (62%)	1 (5%)
0.2 - 0.3	1 (7%)	6 (29%)	4 (20%)
0.4 – 0.5	0 (0%)	0 (0%)	12 (57%)
0.6 – 0.7	0 (0%)	2 (9%)	3 (14%)
>0.7	0 (0%)	0 (0%)	1 (5%)
Mean visual acuity of amblyopic eye (logMAR)	0.01 (SD = 0.08)	0.15 (SD = 0.20)	0.45 (SD = 0.15)
Fellow eye visual acuity (logMAR), No., (%)			
-0.1	4 (29%)	3 (14%)	0 (0%)
0	7 (50%)	8 (38%)	6 (29%)
0.1	3 (21%)	7 (33%)	9 (43%)
0.2	0 (0%)	1 (5%)	5 (24%)
0.3	0 (0%)	1 (5%)	1 (5%)
≥0.4	0 (0%)	1 (5%)	0 (0%)
Mean visual acuity of fellow eye (logMAR)	0 (SD = 0.07)	0.07 (SD = 0.15)	0.1 (SD = 0.09)
Mean inter-ocular VA difference (logMAR)	0.05 (SD = 0.05)	0.07 (SD = 0.11)	0.34 (SD = 0.14)

Table 3. *Clinical characteristics of patients separated by group. For controls and patients with BVDs, the worse eye was used to calculate "amblyopic eye visual acuity."*

A one-way ANOVA showed a significant effect of group on stereopsis ($F(2,53) = 25.83$, $p < 0.001$). A Tukey post-hoc analysis revealed that stereopsis was significantly worse in the amblyopia group compared to the BVD group as well as the control group ($p < 0.001$). Measurable stereopsis was not present in fifteen out of twenty-one (72%) patients with amblyopia. There was no significant difference in stereopsis between the BVD group and the control group ($p = 0.60$). The same pattern of results was found when using the BF Score as well.

Similar results were found for visual acuity of the worse eye (logMAR). A one-way ANOVA revealed a significant effect of group on visual acuity of the worse eye ($F(2,53) = 34.41$, $p < 0.001$), with only the amblyopic group showing significantly worse scores than the other groups.

4.4.2 Motor function: Percentile Scores

When examining the total motor function scores (percentile), the mean score was highest in controls (58.3, SD = 20.5) followed by BVD patients (53.7, SD = 29.8), then patients with amblyopia (49.9, SD = 29.9). A Kruskal-Wallis test revealed no significant effect of group on total motor function percentile scores ($H(2) = 0.68$, $p = 0.71$).

The motor function percentile scores were also separated into 3 categories. Three separate one-way Kruskal-Wallis tests found there was also no significant effect of group on percentile scores in the manual dexterity (H(2) = 0.21, p = 0.90) aiming and catching (H(2) = 1.23, p = 0.54), and balance (H(2) = 0.02, p = 0.99) categories. The MABC-2 performance in each category as well as the total score is summarized in Figure 11.

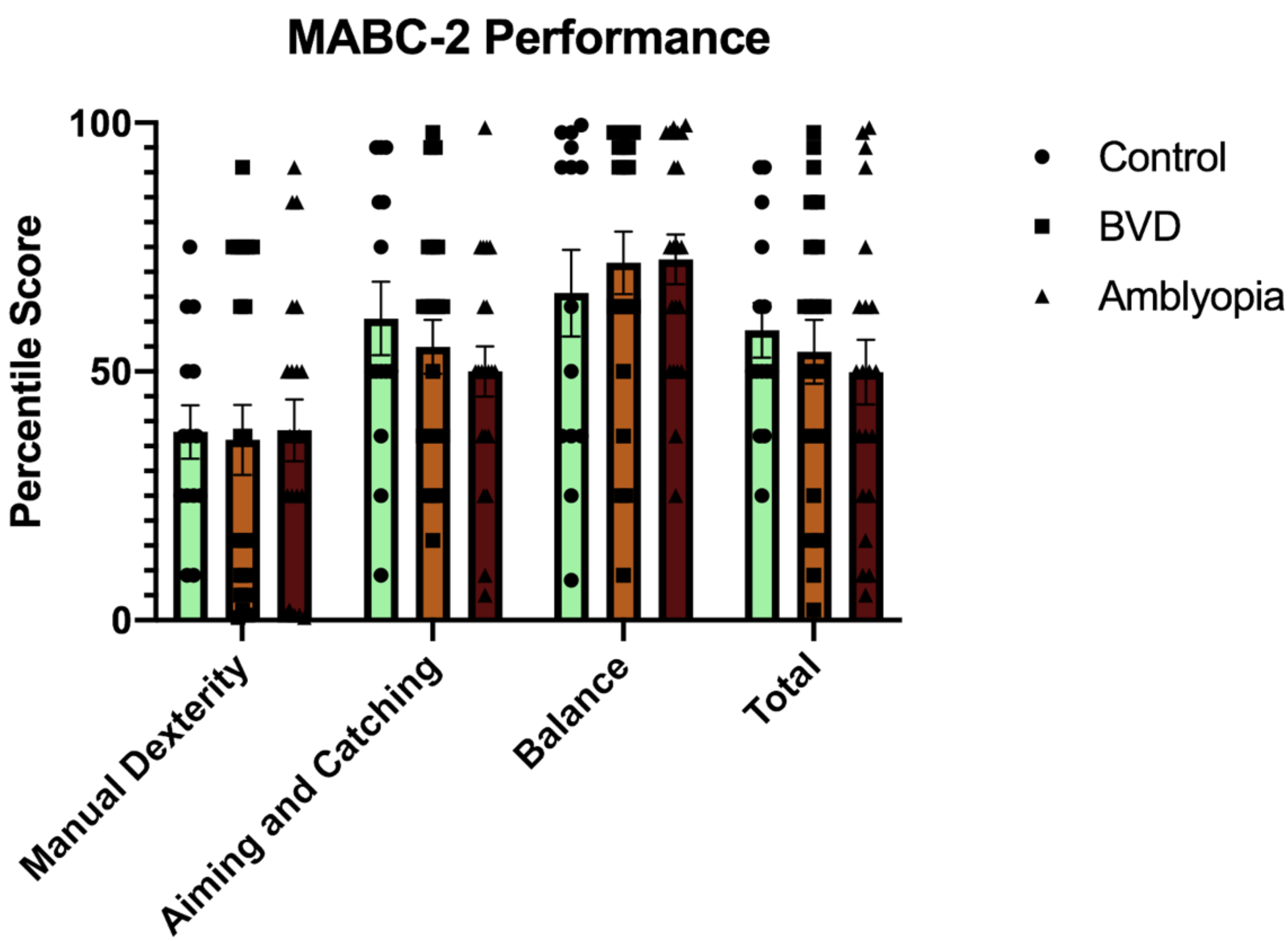

Figure 11. *Bar graph showing performance on each component of the MABC-2 in terms of percentile scores, as well as the overall test score. Higher scores represent better performance. The SE bars show a high level of variability for all groups. The large range of scores obtained can be seen in the individual data points.*

It was observed that some patients fell below the 15th percentile for total motor function score, indicating a potential motor function disorder. Overall, 0 controls, 2 patients with BVD and 3 patients with amblyopia met this criterion. A chi-square test showed no significant association between the number of participants with motor function scores below the 15th percentile and group ($\chi 2(2)= 0.28$, $p = 0.87$).

4.4.3. Motor function: Standard Scores

A summary of the standard scores obtained for each individual task and category is shown in Table 4. A one-way ANOVA showed no significant effect of group on total MABC-2 standard score ($F(2.53) = 0.37$, $p = 0.70$). Three additional one-way ANOVAs also did not find an effect on group for manual dexterity, aiming and catching or balance standard total scores.

	Mean Standard Score in each Task, (SD)											
	Manual Dexterity				Aiming and Catching			Balance				Total
	Coins	Beads	Trail	Total	Catch	Throw	Total	One-foot	Heels Raised	Jumping	Total	Total
Controls	8.4 (1.9)	9.7 (2.3)	8.8 (3.3)	8.9 (1.8)	10.6 (4.3)	10.8 (2.4)	11.1 (2.8)	11.4 (2.8)	11.4 (2.8)	11.3 (1.7)	12.8 (3.3)	10.9 (1.9)
BVD	8.9 (3.3)	10.1 (3.7)	8.8 (4.1)	8.2 (3.4)	8.9 (2.1)	11.4 (3.2)	10.6 (2.5)	11.9 (2.3)	10.8 (3.0)	11.9 (0.4)	12.5 (3.2)	10.2 (2.9)
Amblyopia	7.5 (2.8)	9.4 (3.8)	7.7 (4.1)	8.4 (3.5)	8.0 (2.7)	11.3 (3.3)	10.0 (2.4)	11.7 (3.0)	11.2 (2.2)	11.8 (0.4)	12.3 (3.0)	10.1 (3.2)

Table 4. *Mean standard scores for each individual task and overall category of the MABC-2. Higher scores indicate better performance, with a minimum score of 1 and a maximum standard score of 19.*

Multiple independent samples t-tests were run to determine if standard scores in each category (4 categories) and task (8 tasks) were significantly different between patients with amblyopia and controls. The BVD group was not included as their stereopsis and visual acuity was not significantly different from controls, and therefore they may have been too similar to the control group. Patients with amblyopia did not perform significantly differently in any of the domains, except for the catching task where they were significantly worse than controls $t(33) = -2.13$, $p = 0.041$. However, with a Bonferroni correction to account for the multiple t-tests, the finding was no longer significant. Stereoacuity was not significantly correlated with catching performance $r = 0.20$, $p = 0.38$.

4.4.4 Relationship between vision tests and motor skills

An ANCOVA comparing different mean total motor function standard scores did not find a significant main effect based on the patient group ($F(2, 51) = 1.59$, $p = 0.82$). Mean visual acuity of the worse eye and stereopsis were included as covariates, and were also not significantly associated with total motor function scores (lowest $p = 0.42$).

Amblyopia is a very heterogeneous condition, so an analysis separating multiple clinical covariates was conducted. Namely, presence or absence of stereopsis, type of amblyopia and inter-ocular acuity difference were considered. Presence of stereopsis was recorded as “measurable” or “nil.” A logistic regression comparing total motor function standard scores to these three covariates in patients with amblyopia was run. None of these factors significantly predicted total motor function scores $\chi2(17)= 2.01$, $p = 0.57$. The details of the regression are summarized in Table 5.

Coefficients

					Wald Test		
	Estimate	**SE**	**Odds Ratio**	**z**	**Wald Statistic**	**df**	**p**
(Intercept)	0.124	1.994	1.132	0.062	0.004	1	0.950
Total MABC-2 Score	-0.003	0.176	0.997	-0.016	0.0003	1	0.987
Inter-ocular VA	0.917	4.367	0.400	-0.210	0.04	1	0.834
Type (strabismus)	-1.299	1.049	0.247	1.779	1.78	1	0.182

Table 5. *Coefficients of the logistic regression examining presence or absence of stereopsis. VA indicates inter-ocular visual acuity difference. SE stands for standard error.*

Finally, an independent t-test was run to determine if patients with amblyopia who were undergoing perceptual learning as a treatment (in conjunction with a patching regiment) had significantly different mean total MABC-2 standard scores than those treated with patching alone. Ten patients with amblyopia were undergoing perceptual learning. However, there was no significant difference between the total motor function standard scores based on which treatment they were undergoing ($t(19) = -1.37$, $p = 0.188$).

4.5 Discussion

Our findings run contrary to what would be expected based on the current literature. It was expected that patients with BVD and amblyopia would have worse scores on the MABC-2 compared to controls. While the total scores are in the expected direction (controls having the highest scores and patients with amblyopia having the lowest), this finding does not reach statistical significance for percentile scores or standard scores.

Our results go against previous findings of significantly worse scores in children with amblyopia on the MABC-2 in those aged 3-7 (Birch, Castaneda, et al., 2019a) and 3-13 (Kelly et al., 2020). The first edition of the MABC similarly showed worse scores in patients with amblyopia between the age of 4 and 7 compared to controls (Engel-Yeger, 2008). For example, the standard scores obtained in our sample for controls (10.9 (SD = 1.9)) were comparable to those found by Kelly et al. (9.8 (SD = 2.3)). Considering the average score would be a 10, both values are around what would be expected for a control group. However, the mean total standard score for patients with amblyopia was 10.1 (SD = 3.2) in our sample, but 7.2 (SD = 2.7) in Kelly et al.'s sample. The mean standard scores for Manual Dexterity, Aiming and Catching and Balance are all lower in our sample of amblyopic patients compared to their results.

There are several potential explanations for these findings. These results may be because the BVD group did not have significantly worse stereopsis than controls. This may be that because we used the patient's chart to screen for eligibility that the patients had improved since their last visit. As a result, the BVD group may have had more mild binocular impairments than expected. However, this does not explain why there is no significant difference in the amblyopia patient group, as their stereopsis and visual acuity was significantly worse than both the BVD and control group.

A possible explanation is that cultural differences played a role in the motor development of the patients assessed. The amblyopic group was largely composed of children from China (20 from Guangzhou, 1 from Waterloo) whereas the control group contained a more even distribution (7 from Guangzhou, 7 from Waterloo). The reason this heterogeneity may have influenced the results is that both fine and gross motor function has been reported to be significantly better in Chinese children compared to Western children (Pang & Fong, 2009). For the MABC-2 in particular, Chinese children aged 3-10 performed significantly better on manual dexterity than children from the UK (Ke et al., 2020). On the MABC-1, children from Hong Kong performed significantly better on both manual dexterity and balance compared to American children (S. M. Chow, Henderson, & Barnett, 2001). Furthermore, an interaction between age and country was found, suggesting that different cultures develop skills at different ages. It was proposed that manual dexterity in particular is more advanced in children growing up in China and Hong Kong due to various factors such as learning to use chopsticks by the age of 2 as well as mandatory, highly academically-oriented preschool programs before the age of 7 (A. Chow, Giaschi, & Thompson, 2018; S. M. Chow et al., 2001). By the age of 4, children are able to write at least 30 Chinese characters as well as the entire English alphabet (S. M. Chow et al., 2001). All this is to say that early life experiences are very different in Western children versus those growing up in China. Therefore, the Chinese children in our sample (mainly the patient groups) may have a sped-up motor development process, compared to the Canadian children in our sample. This may have acted as a buffer or protective factor that helped patients with amblyopia attain more normal results on the MABC-2. Therefore, a limitation of this study is that culture was not considered as a possible confounding variable at the outset.

The only task where patients with amblyopia appeared to perform worse than controls was the catching task. Kelly et al. also found that patients with amblyopia had significantly worse performance in catching, but not throwing (Kelly et al., 2020). It was proposed that catching is a more difficult task, as it involves complex calculations to intercept the beanbag and coordinate the actual catching motion (Carnahan & McFadyen, 1996). However, for our sample, the difference in performance did not maintain significance after a Bonferroni correction to account for the multiple t-tests.

It was predicted that stereopsis would predict total motor function scores, however this was not seen. As explained previously, not all studies show a link between stereopsis and abnormal motor function scores in patients with amblyopia (Ibrahimi et al., 2021; Webber et al., 2008; Zipori et al., 2018). Furthermore, our age group was very young and included children who are still in the phase of motor development where they utilize a feedforward approach that relies heavily on ballistic motion. Children under the age of 5 do not rely on their visual system as much to make corrections to their movements, and therefore may not rely on stereopsis as heavily as older children (Suttle et al., 2011). It is still unclear what the exact cause is of these dysfunctions. However, since there was no significant difference in total motor function scores by group, a strong link between stereopsis and motor function scores is not expected.

Some potential limitations of this study are the large variabilities. For patients with amblyopia, the total motor function score (percentile) ranged from 5-99 – almost spreading the entire possible range of values. The total standard scores ranged from 5-17 (the possible range is from 1-19). This is another possible explanation for not finding a significant effect of group on total motor function scores. Having more patients may have helped with the large variability.

4.6 Conclusion

No differences in MABC-2 scores were found. The MABC-2 may not be sensitive enough to consistently detect visuomotor deficits in patients with amblyopia and BVDs, particularly when the culture of the patients being tested differs from the normative data the test is based upon. Future work will look into replacing all the controls with patients from China and comparing them to a Canadian dataset to further investigate potential cultural differences in motor development.

It is still important to comprehend the nature of motor function deficits in patients with BVD and amblyopia. There is a lot left to understand about which patients are affected and why. Poor visuomotor skills may cause impediments in a patient's everyday life that can be just as intrusive as those related to poor acuity. Both patients with amblyopia and BVD demonstrate lower physical competence and perception of peer acceptance scores compared to controls, and these scores were significantly related to the throwing and catching category of the MABC-2 (Birch, Castaneda, et al., 2019a). This implies that patients are conscious of their motor deficits, and the way these deficits differentiate them from their peers. Fine motor skills are essential for any task that requires high levels of manual dexterity, which are common in day-to-day life. Fine motor skills are also significantly related to academic performance (Carlson et al., 2013), and in particular, patients with amblyopia with lower fine motor scores on the MABC-2 take longer than controls to fill out multiple choice scantrons (Kelly, Jost, De La Cruz, et al., 2018). Patients with binocular vision disorders are at a significantly higher risk of sustaining a fall, fracture or musculoskeletal injury (Pineles, Repka, Yu, Lum, & Coleman, 2015). Therefore, by targeting gross motor function deficits at an early age, we may be able to help prevent falls and fall-related injuries in the future where the outcome may be more damaging.

Current treatments for amblyopia such as patching focus on improving VA of the amblyopic eye. However, these treatments do not aim to improve stereopsis. Based on studies showing that stereopsis is linked to motor function, this implies that a monocular-only approach will not help with motor function deficits. Adults who have been treated for amblyopia and have normal visual acuity but lingering stereoacuity deficits demonstrate prehension deficits (Grant et al., 2007).

Chapter 5 proposes a novel binocular treatment that will be used in future studies to examine if motor function scores improve post-treatment.

Chapter 5 - Development of a binocular video treatment on the Nintendo 3DS for children with amblyopia

5.1 Chapter Summary

Binocular treatments for patients with amblyopia have become a rapidly evolving area of research. These treatments may be in the form of dichoptic games or movies; often designed with the goal of being entertaining in order to keep the patient engaged. A binocular treatment is defined as a prescribed regimen involving the repeated exposure to dichoptically presented images that need to be combined binocularly. This creates an environment where both eyes are used co-operatively in order to properly play a game or watch a movie. This may lead to improvements in stereopsis as well visual acuity of the amblyopic eye. However, more research is needed to determine the efficacy of binocular treatments. One of the main obstacles for understanding the efficacy of binocular treatments are the strikingly low adherence rates sometimes seen in studies that take place outside of a controlled laboratory setting. Binocular video treatments that do not require high levels of dexterity and interactivity (as opposed to binocular video games) may help increase adherence, but a formal RCT has not yet been conducted. The binocular video treatment we have developed is unique in that particularly salient aspects of the cartoon are separated between the eyes to ensure that the child cannot make sense of the scene without relying on their amblyopic eye. This differs from other video treatments that typically split dynamically changing random patchwork patterns between the eyes. In this chapter, the development process of a novel binocular treatment is described.

Dr. Ben Thompson and Taylor Brin hold a patent for the binocular treatment of amblyopia discussed in this chapter.

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Birch, Dr. Ann Webber and Dr. Robert Hess. Its progress was delayed by COVID-19, therefore this Chapter focused on the methodological innovations that enabled the trial's commencement.

5.2 Introduction

As described in Chapter 3, it is detrimental for patients with amblyopia to neglect their prescribed treatment regimen, as this can reduce the potential for improvement in visual acuity of the amblyopic eye (L. K. Smith, Thompson, Woodruff, & Hiscox, 1995; Vagge & Nelson, 2017). A prospective study showed that if young patients are left untreated due to non-adherence, that amblyopia persists or worsens (Simons & Preslan, 1999). Other treatment options may be required for children with amblyopia who cannot be convinced to comply with their prescribed treatment.

Binocular treatments may be an alternative or complementary option to standard approaches. Binocular treatments display either a movie or video game dichoptically so that binocular fusion is required to perceive the entire scene. Binocular treatments may use techniques such as contrast-balancing to minimize suppression of the amblyopic eye (Hess et al., 2010a). The goal of these treatments is to improve stereopsis as well as visual acuity.

In addition to improving visual acuity of the amblyopic eye, binocular treatments are also uniquely designed with the intention to improve stereopsis. Amblyopia is considered a binocular disorder that is caused, in part, by suppression of the amblyopic eye. Plasticity of the visual cortex can allow for long term changes in binocular vision following regular training (Hess et al., 2010a). In contrast, monocular treatments rarely improve stereopsis (Scheiman et al., 2008). It has been theorized that these changes to binocular vision can lead to improvements in fine motor skills as well (Webber et al., 2016). However, since motor function is rarely used as an outcome measure for patients with amblyopia, there is little information on how these skills change post-treatment.

In theory, binocular treatments have several advantages over monocular treatments such as patching. Binocular treatments can be more inviting to try than patching, and they have the potential to improve stereopsis (and subsequently, fine motor skills). However, the efficacy of binocular treatments is still unclear and requires more research. Until then, these advantages remain theoretical. As explained in Chapter 3, RCTs that took place at home showed markedly lower adherence rates compared to those that took place in the lab. There are numerous unknown factors that may affect adherence when the child is in an environment that the experimenter cannot control or directly observe. A binocular treatment that inspires higher rates of adherence when taken out of the lab is required to truly understand its impact on visual acuity, stereopsis and fine motor skills.

The objective of this study was to create a binocular treatment that would achieve high levels of adherence outside of the lab, while improving visual and motor function. The binocular treatment developed in this Chapter was a contrast-balanced dichoptic animation. The final version of this treatment was created after planning various ways to avoid the pitfalls of previous binocular treatments while maintaining the benefits. To overcome the issue of low adherence, we chose an engaging cartoon that does not require the same dexterity and skill as a video game.

Our technique was created to be unique from other video treatments in the literature, as the video editor can specifically pick out the most salient characters and separate them between the eyes. Many other video treatments randomly separate different areas of the screen between the eyes, and these areas can dynamically change throughout the video (Birch, Jost, et al., 2019; S. L. Li et al., 2015). However, the random nature of this separation means that in certain scenes the patient may be able to rely on just their fellow to see what is going on, such as if the face of the main character happens to be visible only in that eye. The constant shifting that can happen abruptly in the middle of a scene can be disruptive to the viewing experience. This Chapter will explain the development of a manual process for creating different videos for each eye to ensure that the use of the amblyopic eye is necessary to appreciate the resulting dichoptic animations. The porting of the dichoptic animations to a handheld treatment device will also be explained.

5.3 Development Process

5.3.1. User Engagement

Amblyopia treatments are shown to be most effective when prescribed during the period of visual development (often estimated to be before the age of 7 years in humans) (Daw, 1998). Unfortunately, young children may not fully understand the consequences that refusing treatment will have on their future. Poor adherence rates also make it more difficult for researchers and clinicians to accurately determine if the reason for a treatment failing to significantly improve visual acuity of the amblyopic eye is due to the treatment itself or poor adherence.

In order to try and ameliorate this issue, we have designed a binocular video treatment that is more likely to be engaging to children. We chose a passive, video treatment (as opposed to a video game treatment) so that it would not be possible for children to fail and that progression through the treatment would be the same for everyone. Dichoptic video games required a certain level of hand-eye co-ordination and problem-solving skills in order to progress to more visually demanding inter-ocular contrast thresholds. This presents an additional barrier to entry for children who may become frustrated if they are not good at the game.

The treatment uses 52 episodes of the cartoon Q Pootle 5 (Blue-Zoo Productions, Snapper Productions) provided to us in a collaboration with the British Broadcasting Corporation. This show is specifically targeted at children under the age of 7, which overlaps with our ideal patient population. We are testing children aged 3-6 within the ongoing RCT.

Another potential barrier that could hinder adherence is the convenience of the treatment. Some binocular treatments involve shutter glasses, virtual reality headsets, or complicated computer apparatus. To remove any added piece of equipment that may be inconvenient or uncomfortable for children, we have chosen a digital display that doesn't require any additional glasses or a headset to enable dichoptic stimulus presentation. The cartoon is displayed on the New Nintendo 3DS XL (Nintendo Company, Ltd.), which is able to show dichoptic images in its upper screen (see Figure 12). This device uses carefully placed parallax barriers that completely block light coming from the back of the screen in such a way that only certain pixels are seen by each individual eye. The system is also able to track head position in order to make slight adjustments to the position of the parallax barrier in order to maintain dichoptic viewing, evening if the child is moving around.

Figure 12. *An example of the Nintendo 3DS system. The movie is displayed in the upper screen while the bottom touch screen can be used to control the device.*

This lightweight portable device may help with at-home treatment. Its portability means that a child has more flexibility with when they are able to watch the videos. They could watch the videos in the car, while waiting at a restaurant, or while lying down in a comfortable position at home. This level of freedom is not present for larger systems. Although sitting still in a well-lit room is the ideal situation, this portable system provides secondary options for patients who may struggle to focus. It may be better for them to complete the treatment in sub-optimal conditions than being unable to watch the video at all if the instructions are too strict. Furthermore, the dichoptic presentation would not be compromised in these alternate viewing conditions. The patient would still be forced to use binocular fusion to perceive the scene, no matter where they chose to watch the videos.

5.3.2 Dichoptic Presentation

The plan was to display a video dichoptically in a way that specifically separated key characters and objects to the amblyopic eye. This differs from currently existing binocular video treatments. For example, Li et al. used a method that split random areas of the video between the eyes, and dynamically changed those areas over time (see Figure 13) (S. L. Li et al., 2015). The I-Bit system shows the outside frame of the video to both eyes and the inner rectangle containing most of the action of the video predominantly to the amblyopic eye (Foss et al., 2013). The convenience of these methods is that they can be applied to any video. However, this convenience means that it is not entirely ensured that the patient must use their amblyopic eye to understand the scene. Therefore, we manually selected and deleted key characters in the video shown to the fellow eye to be certain that the patient needs to use the amblyopic eye (see Figure 14). An animation using computer-generated images was chosen so that when a character is deleted from a scene, the background scenery remains since it is a fully rendered, computer-generated environment.

Figure 13. *Dichoptic movie format used by Li et al. The amblyopic eye sees the higher contrast image on the left while the fellow eyes sees the lower contrast image on the right. Note that in this example, the fellow eye can see the face of the main character, and therefore may not find it necessary to focus on the video shown to the amblyopic eye.*

Figure 14. *In the current binocular video treatment on the Nintendo 3DS XL, the amblyopic eye is shown the image on the left: a full contrast video with all characters present. The fellow eye is shown the image on the right: a low contrast video with the main character missing. The fellow eye is missing the key information needed to understand the scene, and therefore the patient will be unable to perceive the main character without use of the amblyopic eye.*

To aid with binocular fusion, the contrast was lowered for the fellow eye video. Within our ongoing RCT, all participants begin with a fellow eye contrast of 20%, which was the lowest starting level in the PEDIG trial (Birch, Jost, et al., 2019). This contrast level was chosen so that the video was unlikely to be above anyone's threshold for binocular fusion. Following procedures from a previous PEDIG video treatment (Birch, Jost, et al., 2019), (Birch, Jost, et al., 2019), contrast increases by 10% of the previous day's value each day. With each day, the increase in contrast makes it more difficult for the patient to suppress the fellow eye. Over time, the patient has to tolerate smaller inter-ocular differences in contrast.

Within the RCT, on day one, all participants watch the same 6 episodes that were edited to have 20% contrast in the fellow eye. Another set of 6 episodes are edited to 22% contrast for day 2. The process is continued up until the maximum 4 week mark when 84% contrast is reached. In order to adjust the overall contrast in the fellow eye, the colours present in the video were averaged. This was done by first converting the pixels from RGB colour space to CIE LAB colour space. Using all the pixels in a given scene, the mean of the luminance value as well as the a (red-green) and b (blue-yellow) co-ordinate values on the colour plane was calculated to determine the output. This output was a single frame that was entirely made up of a solid colour. This was repeated for every single frame of the video, creating a resultant video that shifted from the average colour of one frame to the next. During the final video editing phase in Adobe Premier, this video was placed as a layer in front of the fellow eye video. The opacity of the solid colour layer was adjusted to change the contrast. For example, an opacity of 80% corresponded to a contrast of 20%.

5.3.3 Optimizing User Experience

It was important that the video was as comfortable to watch as possible, despite the dichoptic format. Steps were taken to minimize binocular rivalry, which would make binocular fusion more difficult. A third video file called a “mask” file was used during development to try and address the potential issue of rivalry (see Figure 15). To create a mask video file, everything in the video was removed (creating an entirely black background), leaving only the key character or object that was absent in the fellow eye video. This character was filled in with a solid colour to give it a flat appearance, like a silhouette. This file could then be used to reduce the background contrast in the specific area where the character was missing in the fellow eye. This was done the same way as adjusting the contrast in the fellow eye video, but for a smaller area. The average colour of each frame was calculated and then that solid colour was placed over the silhouette of the character. Opacity was adjusted to alter the background's contrast. The amblyopic eye would still see the 100% contrast video with all characters present. We hypothesized that this would reduce binocular rivalry, particularly in scenes where the background may have a lot of details or colours that were not analogous to those in the amblyopic eye. For example, removing the character may reveal a distracting, detail-rich background that could make it difficult for patients to focus on the character shown to the other eye. Patients with high levels of suppression may report being unable to see the character at all in these situations. The mask also provides a reference for where the amblyopic eye should focus, alerting the patient to the location where something is missing

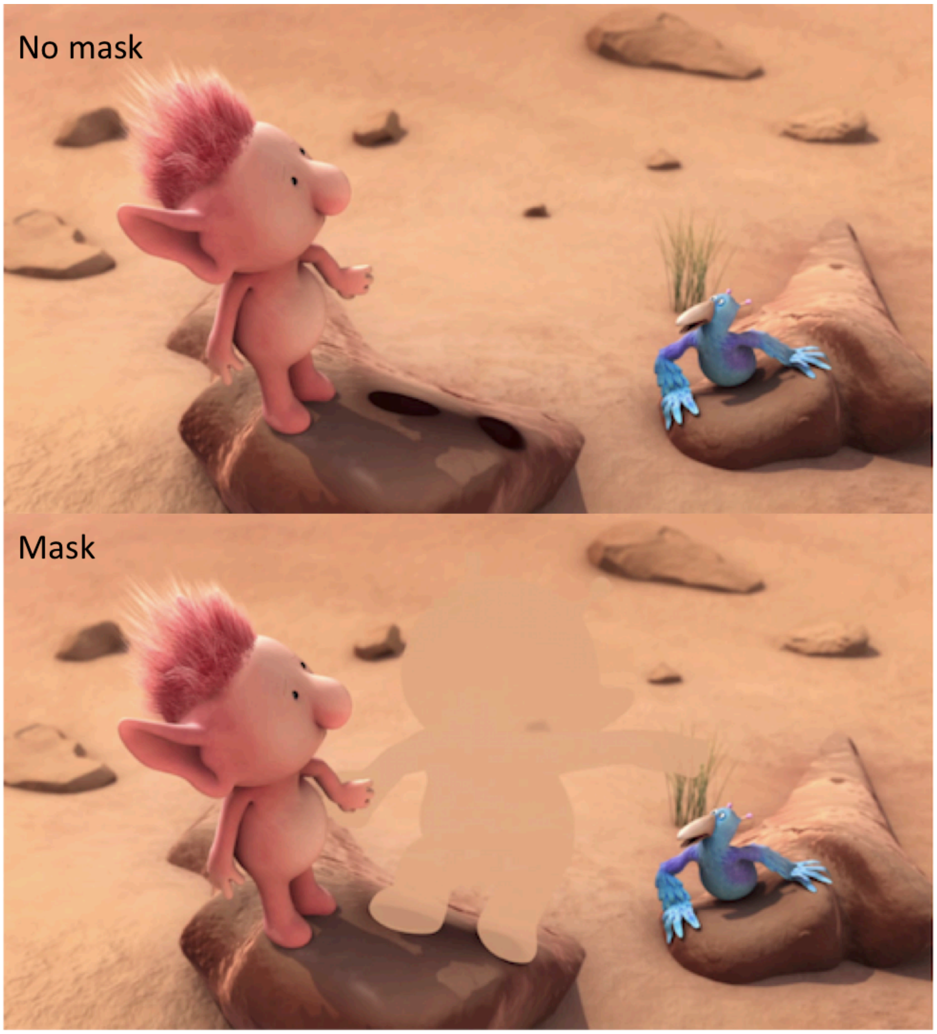

Figure 15. Top image: no mask applied. Bottom image: a background mask of 25% contrast and 51 pixel blur.

In order to test the theory that a mask would reduce suppression and improve the viewing experience, two pilot studies were conducted. The aim of the first pilot study was to determine which background contrast level for a mask would result in the smallest rivalry ratings. The purpose was to identify optimal mask parameters for use in the treatment itself, so there was not a condition without a mask. The aim of the second pilot study was to determine whether rivalry ratings were affected by whether a mask was present or not. Ethics approval for the pilot studies was obtained from the University of Waterloo Ethics Committee. All participants provided informed consent and met our inclusion criteria of having no self-reported vision problems or diagnosed visual disorder.

For the first pilot test, 14 healthy adults (age range: 20 – 30 years old) with normal or corrected-to-normal vision were recruited. Dichoptic screenshots of the cartoon were shown using a 3D computer monitor at 30cm. Nvidia Stereo-shutter glasses separated two images: an image with all characters present, and an image with the character missing and a mask. The mask was presented at 12%, 25%, 50% and 100% background contrast. A control condition showed the same picture (all characters present) to both eyes. The images were shown for 2 seconds each.

Before beginning the actual experiment, participants were shown 5 example images (different from the test images). Four were at 100% contrast and one was a control image. This was to give them a better understanding of binocular rivalry. Binocular rivalry was explained as a phenomenon where if each eye is shown a disparate image, the brain will not be able to continuously fuse the two percepts and will alternate between them. They were allowed to look at the images as long as they wanted. However, since the images in the actual trial were shown briefly, alternation would be minimal or absent. Instead, the image was described as appearing unstable or ghost-like. Once the participant confirmed they understood what to look for when rating binocular rivalry, the experiment began. Participants also provided informal descriptions of what they experienced after the experiment was over.

Trials within a block randomly showed either the control scene or one of the contrast mask levels, so there were two possible conditions in each block. The next block would repeat but with a different scene, for a total of four scenes (4 blocks X 100 trials = 400 total). Participants were asked to rate rivalry on a scale of 1-4 for each image using a keyboard, with 4 indicating the most binocular rivalry.

A one-way mixed model ANOVA was used with the different contrast levels as factors and the rivalry rates as the outcome measure. There was no significant effect of mask contrast on binocular rivalry ratings ($p > 0.05$). We found a ceiling effect where the range of the mean ratings for the non-control images was 3.2 – 3.5. These results did not support the initial hypothesis that a mask would improve the viewing experience for patients through reducing rivalry. We performed a second pilot study to determine if keeping the mask was necessary.

The second pilot study recruited and tested 6 healthy adults (age range: 19-30), using the same inclusion criteria. In order to improve the performance of the masks, we introduced Gaussian blur. The sigma for the low pass filter that created the blur was set to 51 pixels. The reasoning behind this was to soften the high spatial frequency details of the background area behind the removed character. The background shown to the fellow eye should not distract from the amblyopic eye's view of the character. A 0% background contrast level with no blur (i.e. no mask at all) was introduced to test our hypothesis that a mask would produce less rivalry than no mask. Therefore, we tested mask contrast at 0% (no blur), 0% (with blur), 12%, 25%, 50%, and 100%. All the contrast levels from 12%-100% contained blur.

A trial block involved a random presentation of either the control scene or any of the contrast masks for an image, until all conditions were shown. The next block repeated, but with a different scene (4 blocks x 480 trials = 1920 total). Once again, we found no significant difference in ratings between any of the conditions ($p > 0.05$). A similar ceiling effect was seen as well, as the mean for all treatment conditions ranged from 3.5 – 3.7 (see Figure 16).

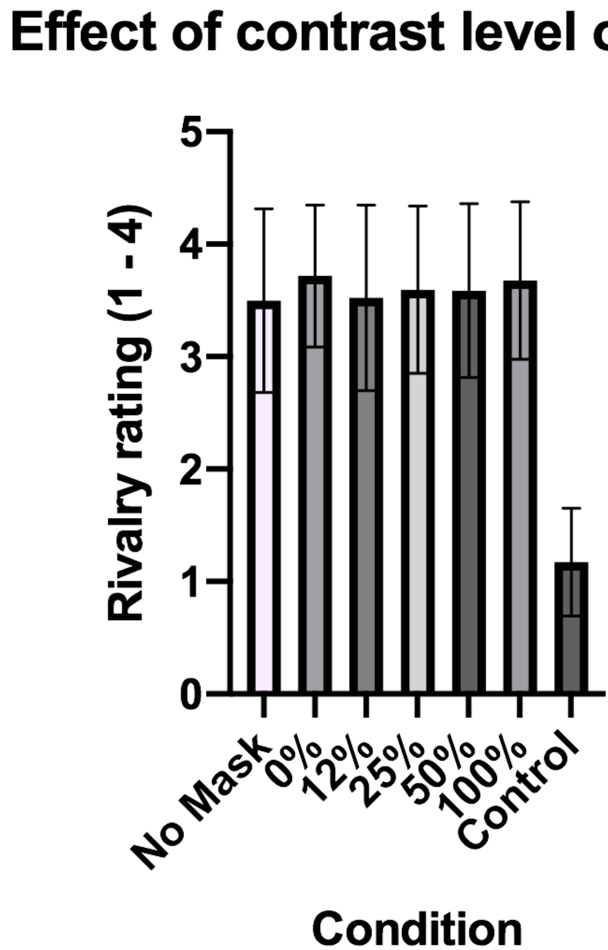

Figure 16. *Bar graph showing the binocular rivalry ratings for different contrast levels. The error bars show standard deviation. The "No Mask" condition is at 0% contrast without any blur and does not differ from any of the mask conditions. The control image (non-dichoptic) was consistently reported to produce minimal or no rivalry, as expected.*

Since the presence of a mask did not affect an observer's perception of the cartoon, the decision was made to remove the mask from the final binocular treatment paradigm in order to greatly speed up the workflow.

5.3.4 Workflow

Given the amount of manual labour required for creating the dichoptic animations, workflow optimization became essential for completing the editing in a timely manner (see Figure 17). Each section of a 10-minute episode was split into multiple clips that ranged from approximately 3 – 20 seconds. The files were edited in Adobe After Effects CS6 (Adobe Systems Incorporated, California, US). Two videos were exported: one for the fellow eye and one for the amblyopic eye. The amblyopic eye video was the default video and did not require any adjustments at this stage. To create the video for the fellow eye, key characters or objects (e.g. a spaceship) were deleted from the scene. In scenes with more than one character, the video editor qualitatively chose which character to remove by assessing the criteria outlined below. The character or object that met the most of these requirements was chosen. In the case of a tie, the video editor used their judgement to select one.

Main character or object selection criteria:

- The character or object is in the centre of the screen
- The character or object is facing the viewer
- The character is speaking in the scene
- The character or object took up the largest area of all other characters or objects in the scene

These videos were then placed in a queue to render overnight, as even a 3 second video could take up to 10 minutes to render. The next day, the rendered video files output from overnight underwent a quality check to ensure that there were no rendering errors.

Once all the clips in any given episode were completed, they were batch imported, in order, to Adobe Premier. Each eye had its own layer to check that the timing was perfectly synchronized. The final audio cut from the official episode was available for us to overlay with the clips. However, the timing and content of the final audio cut did not always match up with the clips, which were rendered from files at an earlier stage of development. This resulted in some scenes being slowed down or sped up to match the timing of the audio file.

After the editing in Premier was complete, the amblyopic eye video was exported as is while the contrast was lowered to a pre-specified level for the fellow eye video. The order that the patient watched the videos was pre-determined, so all videos planned for day 1 had the fellow eye contrast set to 20%, with contrast increasing by 10% each day. The amblyopic eye was always set to 100% contrast. These two videos were then combined into a stereoscopic video format using a Python script. This format is immediately recognizable by the Nintendo 3DS, and the animation is automatically presented dichoptically when played. The files were too large to store internally on the Nintendo 3DS, so they were uploaded to Amazon Web Services (Amazon Web Services Inc.) to be accessed by any Nintendo 3DS system that is given the web links and password.

A team of part-time (2) and full-time (3) video editors were hired and trained to speed up the process. Each editor was assigned to a computer and a set of episodes to complete from start to finish. It took approximately 2 weeks of full time work for one episode to be completed from start to finish.

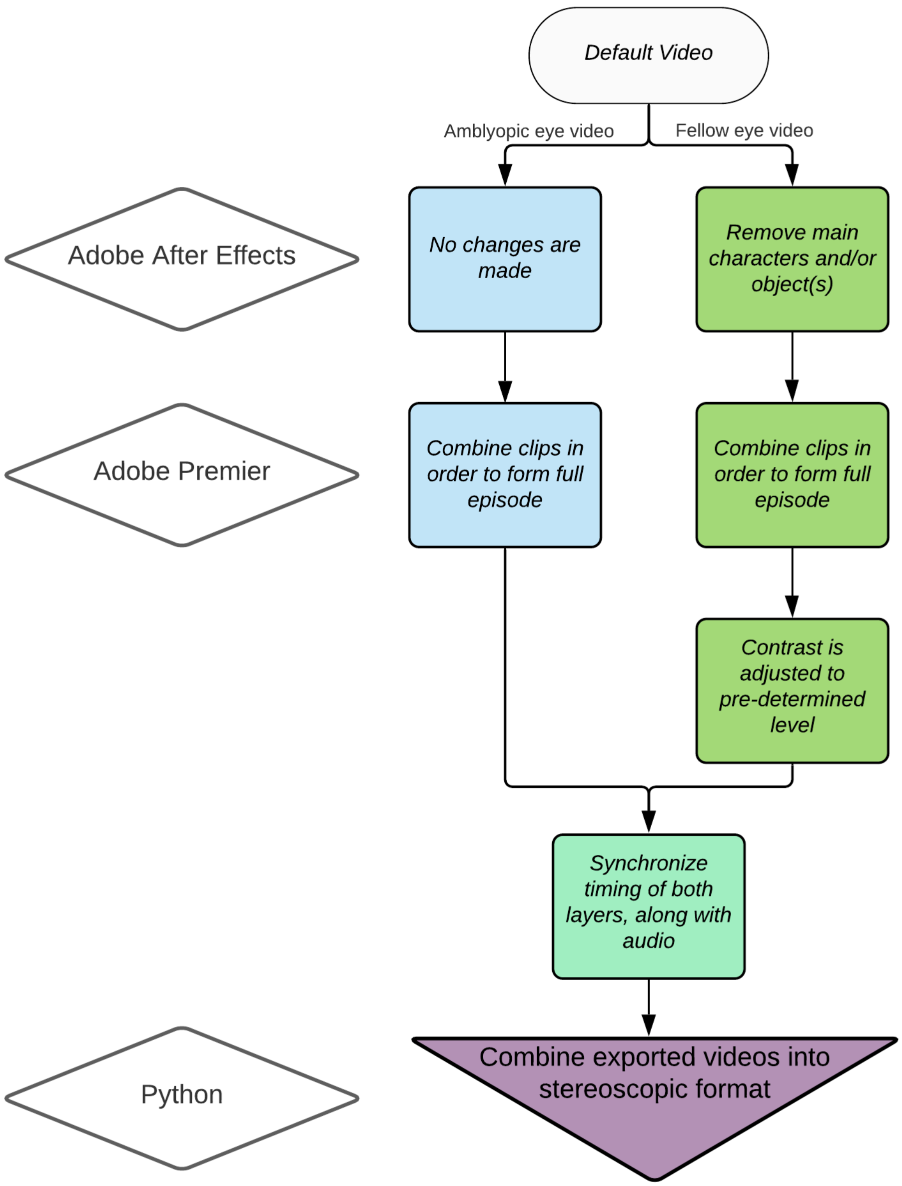

Figure 17. *Flow chart of the editing process.*

5.3.5 Missing data

Blue-Zoo Productions Ltd. (London, UK), the animation studio responsible for making Q Pootle 5, provided work-in-progress Adobe Aftereffects files that were saved in their archives. However, considering the cartoon was at least 7 years old, all of the in-progress files required to fully render an episode were not archived. As a result, certain scenes were incomplete (missing characters, backgrounds, animations etc.). In the case of missing assets in any given scene, it was recreated as well as possible. For example, if the sky was missing it would be replaced with a solid blue background. Some scenes unfortunately had too many errors to be salvaged, unless an expert completely re-animated the scene from scratch. In this case, these scenes had to be replaced with the official, final cut video of that scene. Since the final cut is not dichoptic, both eyes would see all the characters in this situation. The contrast would still be reduced in the fellow eye video. This was rare, occurring in only 5 out of 52 episodes (<10%) and lasted for a maximum of 10 seconds in any given episode where this problem was found.

5.4 – Discussion

We have successfully developed a technique for creating a dichoptic treatment for children with amblyopia. Over two years of development were spent streamlining this process, which could be applied to other cartoons that use similar graphics in the future. This method specifically selects the most prominent character or object in a scene and displays it only to the amblyopic eye.

The results of the pilot tests led us to abandon the use of masks in the fellow eye for the treatment. However, these results were unexpected, as a mask was predicted to reduce binocular rivalry ratings. There are a few possible explanations for this. The four-item scale may not have been sensitive enough to detect small differences in binocular rivalry ratings between the different mask conditions. However, based on participants' incidental reporting, they only were able to distinguish the images into two categories: the control images and the mask images. This is reflected in their scoring where the means can be separated into two categories: a mean score of around 1 (control images) and a mean score of around 3.5 (mask conditions). Therefore, it is more likely that binocular rivalry ratings are not strongly affected by the presence or absence of a mask.

It is possible that binocular rivalry ratings were unaffected by changes to contrast and blur due to the small region of focus. The dominance of certain images during binocular rivalry is strongly driven by global effects, as opposed to just one area of an image (S. H. Lee & Blake, 2004). So although reducing contrast and introducing blur were thought to decrease the stimulus strength for the mask image during binocular rivalry, (Brascamp, Klink, & Levelt, 2015; Mueller & Blake, 1989; Wolf & Hochstein, 2011) the size of the stimulus itself may have prevented this from happening. In this situation, everything about the two images shown to each eye is the same except for one element (the character that is removed from the scene). It has been shown that if there is some extent of binocular similarity between the eyes, then rivalry will not occur – even if there are incongruent elements present (Blake & Boothroyd, 1985). In this experiment, participants were shown horizontal contours to one eye and both horizontal and vertical contours to the other. Their reaction time to reporting changes in contrast matched their values for binocular fusion (trials with horizontal contours shown to each eye), but not binocular rivalry (trials with a horizontal contour in one eye and a vertical contour in the other). In other words, the horizontal contour that was shared between the eyes allowed for fusion to occur. The adjustments to the background contrast and blur are in a small area, which does not necessarily fall in the central, foveal region. The majority of the scene is then the same between the eyes. Therefore, participants do not notice any difference between the presence of a masks and no mask, as there is no binocular rivalry.

Participants likely did not use the rivalry rating scale to report binocular rivalry, but to report the presence of a dichoptic image or not. Therefore, control images received lower ratings to indicate normalcy while all masks were detected as being different from the control image in some way that was not overtly binocular rivalry. After the experiment, participants reported that the dichoptic images appeared "shimmery" compared to the control image, but did not describe alternating between two different images or mixed percepts. Furthermore, the brief presentation time may have reduced or entirely removed any switching between percepts, as there was simply not enough time to experience binocular rivalry.

Another possibility is that the face of the character present in one of the eyes drew more attention than the featureless background mask image. For example, when showing a face to one eye and a pattern (that was matched for contrast, luminance and spatial frequency) to the other, there was a predominance tending towards the face (Yu & Blake, 1992). A higher predominance indicates a larger percentage of time spent exclusively perceiving the face. Participants may have also exhibited a preference for perceiving the image with faces. Therefore, any changes to the mask would not be perceived, as that image was constantly suppressed in favour of perceiving the face. This would also occur for the image without the mask where the character is missing and just an unaltered background remains.

5.5 Conclusion

We have developed a unique binocular treatment that is currently being tested in a multi-site RCT. Recruitment has begun at The Retina Foundation (Dallas, United States of America) with 11 patients with amblyopia (5 in the patching group and 6 in the treatment group). In this RCT, patients are randomized to either a treatment group or a patching group. The child is asked to watch the cartoons 1 hour a day, 4 days a week. The patching group patches at home for 2 hours everyday. After 2 weeks of either patching or watching the cartoon, the parents or guardians will be asked if they want to continue the study for an optional, additional 2 weeks. Those in the treatment group will continue watching the cartoon and those in the patching group will have the opportunity to crossover to the treatment group. This gives every patient an equal chance to try the treatment if they are interested. Outcomes are measured at baseline, after 2 weeks, and after 4 weeks (if applicable). Preliminary results show that after 2 weeks of watching the cartoon, improvements in the visual acuity of the amblyopic eye are greater than those seen in the patching group. After crossing over, the patching group is able to “catch up” to the binocular treatment group.

The treatment is a promising option for children with amblyopia, particularly those who fail to adhere to patching regimens. As this RCT continues to expand recruitment, we will be able to assess what effect this treatment has on visual acuity, stereopsis and motor function in young children with amblyopia.

Chapter 6: Summary, Conclusions, and Future Directions

6.1 Summary of Findings

Amblyopia can be a difficult visual disorder to treat, particularly in young children where treatment adherence is a formidable challenge (L. K. Smith et al., 1995). The goal of constantly pushing the boundaries of knowledge to improve the implementation of existing treatments and to create new ones was the impetus for many of the experiments in this thesis. As a result, Chapter 3's in-depth summary of the literature may now serve as a reference for clinicians when determining the most beneficial treatment for their patients. The binocular treatment developed in Chapter 5 may become another treatment option for clinicians to have at their disposal. Finally, exploring motor function deficits in patients with amblyopia was also expected to further inform clinicians as well as future binocular treatment RCTs. The aim of this thesis, through multiple experiments, was to explore the effect of vision-based treatments on visual and motor outcome measures. The specific results of each experiment and how they relate to this aim is summarized in this chapter.

6.1.1 Efficacy of vision-based treatments

The purpose of Experiment 1 was to evaluate the efficacy of vision-based treatments in young patients with amblyopia. This was achieved with a systematic review of all relevant published RCTs after careful screening. The narrative synthesis included 36 studies, screened from an initial 3346 studies.

Binocular treatments were created as an alternative or supplement to monocular treatments for patients with amblyopia. The results in RCTs comparing binocular treatments to monocular treatments such as patching have been inconsistent; showing mixed success. This variability has made it difficult to determine the true efficacy of binocular treatments and where they stand in relation to patching. We ran a random effects meta-analysis assessed 5 studies that compared binocular treatments to patching for 2-5 hours. The mean difference (improvement of visual acuity of the amblyopic eye) was −0.03 logMAR; 95% CI 0.01 to 0.04 ($p<0.001$), favouring patching. This difference was less than 2 letters on an acuity chart, and not considered a clinically significant finding. Similarly, our network meta-analysis (26 studies) did not find any clinically significant differences between vision-based treatments and patching for 2-5 hours.

An exploratory meta-regression with 18 studies showed no significant association of age, sample size or pre-randomisation optical treatment with changes in visual acuity of the amblyopic eye. Possible reasons for this are explained in depth in Chapter 3's Discussion. We expected that older patients would show less improvements in amblyopic eye visual acuity. Upon examining the ages included in this analysis, it appears that the data does not span the entire range of 4-17 years old that was thought to be captured in this analysis. Considering that over 73% of the RCTs had a mean age of under 7 years old, the majority of the children in our sample were within the age range where treatment was predicted to be the most efficacious. If a wider range of ages that included older children was available, an effect may have been seen.

Pre-randomisation optical treatment was difficult to measure accurately, as patients were prescribed anywhere from 4-18 weeks of optical treatment. Some studies did not report the exact duration either, instead choosing to cease treatment on a case-by-case basis once the individual patient had reached a plateau.

Finally, a linear regression analysis (17 studies) found a significant association between adherence and RCT effect size: regression coefficient 0.022; 95% CI 0.004 to 0.040 (p=0.02). Studies with worse adherence rates tended to have smaller effect sizes. The data did not completely fit the model, so these results must be interpreted with caution. Adherence may impact treatment efficacy. Future studies should take adherence into account when measuring the effect of their treatment.

Our findings were comparable to what was found in a recent systematic review by Li et al. (Y. Li et al., 2020). Ultimately, they conclude from a network meta-analysis of RCTs that all vision-based treatments were comparable. Some differences in methodology include the fact that they conducted a literature search of 3 databases (versus the 6 examined in ours) and that they applied a Bayesian approach (ours was a frequentist approach).

The findings all address the primary goal of our study, finding that there is no significant clinical difference between vision-based treatments in young children with amblyopia. Clinicians should be aware of the variety of options at their disposal outside of patching and optical treatment.

6.1.2 Visuomotor function as an outcome measure

This experiment was devised to answer certain research questions regarding visuomotor deficits in patients with amblyopia. The specific types of visuomotor deficits (and the severity of those deficits) may vary by type of amblyopia. Patients with amblyopia may also face different visuomotor challenges compared to those with BVD. Finally, in order to better understand one of the potential causes of visuomotor deficits, stereopsis was examined and compared to MABC-2 scores.

Ultimately, we did not find a significant link between different types of amblyopia and total motor function scores. A logistic regression showed that stereopsis, type of amblyopia and inter-ocular visual acuity difference did not predict total motor function standard scores.

When looking at all 3 groups, we did not find a significant effect of group on total motor function scores. Stereopsis and visual acuity of the worse eye were not significant covariates either. Splitting the motor function scores by each sub-category led to the same result: none of the groups performed significantly differently from one another.

These results were surprising given that the literature suggests motor impairments in both patient groups. The BVD group may have been more mild than expected, as their stereopsis was not significantly worse than controls. The results from the amblyopia group are more difficult to disentangle. It may be due to cultural differences, as scores on the MABC-2 and other motor function tests are higher in Chinese children compared to Western children. The more advanced motor development may have helped children with amblyopia to overcome potential deficits brought about by poor or absent stereopsis.

6.1.3 Development of a novel binocular treatment

After finding no significant difference between binocular treatments and patching (in terms of improving visual acuity of the amblyopic eye) in the systematic review of the literature, a novel binocular treatment was developed. A multi-site, international RCT was planned where the primary outcome measure was the improvement of visual acuity of the amblyopic eye from baseline after 2 weeks of treatment. The secondary outcomes were improvement in stereopsis after 2 weeks and improvement in total motor function score (Movement Assessment Battery for Children, 2nd edition) after 2 weeks. The treatment aimed to inspire high adherence rates and improve functions other than just visual acuity. However, due to research delays directly caused by COVID-19, Experiment 3 described the stages of development of the treatment itself.

Two pilot studies were run in order to empirically determine the ideal treatment settings to reduce the amount of binocular rivalry. However, both pilot studies found that a mask was not helpful at reducing rivalry ratings. The first pilot study showed no significant difference between four different contrast levels and a control image (same image shown to each eye). The second pilot study included a condition that had no mask and also introduced background blur to all the masks. This additional blur was thought to help further reduce rivalry and help with the ceiling effect seen in the first pilot study where all the images produced high binocular rivalry ratings. Despite this attempt, no significant difference was found between any of the masks and no mask. A ceiling effect was observed again, where all the mean binocular rivalry ratings for the masks ranged from 3.5 – 3.7. Following this result, masks were no longer used in the final treatment.

It was proposed that the participants simply divided the images into two categories: control images and everything else. This theory is in alignment with that participants reported seeing. All the images that had different images shown to each eye – regardless of whether the other image contained a mask or not – were seen as being different from the control images. Furthermore, participants did not report alternations between percepts, suggesting that the difference between the two images was so minor they did not experience actual binocular rivalry/ Therefore, the binocular rivalry rating scale instead measured how aware participants were that the dichoptic images were different from one another.

This experiment summarized the process involved for creating a binocular treatment that separates prominent characters between the eyes to encourage binocular fusion. The RCT remains in-progress. The results from this study will provide valuable information about the efficacy of this treatment and, in general, the effect of binocular treatments on motor function.

6.2 Dissertation and Conclusions

These three studies were all conducted to better understand how to treat young patients with amblyopia. Experiment 1 provided a qualitative and quantitative overview of the literature, finding that existing strategies show no significant difference between various vision-based treatments and patching for 2-5 hours. This finding gave us confidence in our venture in Experiment 3, wherein a novel binocular treatment was developed. Experiment 1 found no clinically significant difference between binocular treatments and patching (2-5 hours) in the current literature. Similar findings were reported in a 2020 meta-analysis (Y. Li et al., 2020). The finding that adherence rates were very low in many studies informed the design of the binocular treatment in Chapter 5, namely the decision to make it a video format. maximize adherence rates, we chose a video treatment that would not demand any physical skills or input from the patient. It was theorized that this would make the treatment more accessible to a wider audience of patients (such as younger children) and help improve adherence rates.

Experiment 2 was designed to better understand the types of motor function deficits in patients with amblyopia before starting the binocular treatment in Experiment 3. We did not find a significant difference in total motor function score in patients with amblyopia or BVD compared to controls. However, these results may be due to the fact that the patients recruited did not have severe amblyopia and were therefore able to adapt compensatory mechanisms to perform motor tasks as well as controls.

That being said, a binocular treatment can still be beneficial for patients with amblyopia. We plan to assess visual acuity of the amblyopic eye and stereopsis (as well as motor function). It may be that the few patients that have total scores below the 15^{th} percentile are those who show the most improvements. This is based on our results in Experiment 2 where only patients with BVD or amblyopia had total scores that were flagged as being highly abnormal, suggesting a higher probability of motor function deficits in this population. So while not every patient may exhibit motor function deficits, those that do may benefit the most from binocular treatments. Therefore, these findings in Experiment 2, while unexpected, still provided a clue for how to proceed with the binocular treatment.

The primary objective of determining how vision-based treatment affect visual acuity and motor function in patients with amblyopia was addressed in various ways over the course of this thesis. Experiment 1 can be used to help clinicians make evidence-based decisions about the ideal treatment options for their patients, and provided more information to the on-going binocular versus monocular treatment debate. In Chapter 5, we developed a binocular video treatment that was designed to inspire high adherence rates, improve functions other than just visual acuity of the amblyopic eye, and differ from other currently available binocular treatments. Future work, described more in section 6.3, will involve testing this treatment in the currently running RCT.

6.3 Limitations and Future Work

The limitations and suggestions for future work are explained in depth in the discussion of each chapter. These points are now summarized here. In Experiment 1, there were several studies assigned a high risk of bias due to low adherence rates. A high risk of bias indicates that a certain level of caution is required when assessing the results of these studies, as they may be biased by uncontrolled factors. Some studies with high risk of bias were included in the analyses, which may have altered the results of those analyses. This is a limitation of the literature that is a challenge to overcome, as young patients with amblyopia have notoriously low adherence rates. Future studies should make sure to report adherence using the most objective measures available, as poor adherence may negatively impact the efficacy of their treatment. Another limitation is the fact that the patients included in our study were only occupying a very narrow age range skewed towards younger children.

In Experiment 2, our sample population of patients may have been too mild. Patients with BVDs did not have significantly worse stereopsis compared to controls. This may explain why we did not find any significant difference between the three groups in their motor function scores.

Future studies should still examine visuomotor function in patients with amblyopia and BVD to better understand the relationship. For example, patients with more severe amblyopia should be assessed in future work, as they may be at the highest risk of also having a motor function impairment. Another option is to use hand-tracking cameras to assess specific grasping and reaching strategies used by patients during the manual dexterity portion of the test. This may be able to assess if any motor compensatory strategies are being employed. Although their final performance may be the same as controls, we would be able to look for compensatory mechanisms such as having more online corrections during the endpoint (e.g. making more adjustments than controls right before placing the coin into the slot). However, this would increase the amount of time it would take to complete time-based tasks, which would result in a worse score.

Moving forward, this study will investigate the cultural differences in motor function skills by obtaining a sample that is completely from China. This can then be compared to a Canadian sample. The hypothesis is that Canadian patients with amblyopia will have more impaired motor skills than Chinese patients with amblyopia. The results of such a study will help us to better understand why our findings differ, and provide important information for the motor development profiles of children with amblyopia in different countries.

The limitations of the video-editing method in Experiment 3 are that it can only be applied to cartoons that allow for specific animation layers to be deleted independently. As such, the child is unable to choose the cartoon they want to watch, as seen in other treatments that apply a filter over any pre-existing footage (Bao et al., 2018). Compared to an automatic program, the editing process for this binocular treatment is time-consuming, with a single 10-minute episode taking 2-3 weeks of full-time work to complete. However, the result is a video where the main character is carefully cut out of every scene. This is a unique method for binocular treatments.

Following the results of Chapter 3 regarding the important of adherence reporting, the Waterloo site is developing a system to track the gaze of children in the treatment group to ensure they are watching the cartoon. This will also provide information about their specific pattern of watching, such as if they look away every couple of seconds or watch the videos in small chunks rather than all at once. Patching could also be assessed with occlusion dose monitors to maximize objectivity.

This RCT is ongoing and future work will involve completing data collection and analysis for this project. Overall, a novel binocular treatment that is the culmination of four years of research and video-editing has been created. This project may one day be a part of a future meta-analysis looking at binocular versus monocular treatments in the years to come. If effective in children, it may also be a potential option for adults as well if it is customized with more age-appropriate content.

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