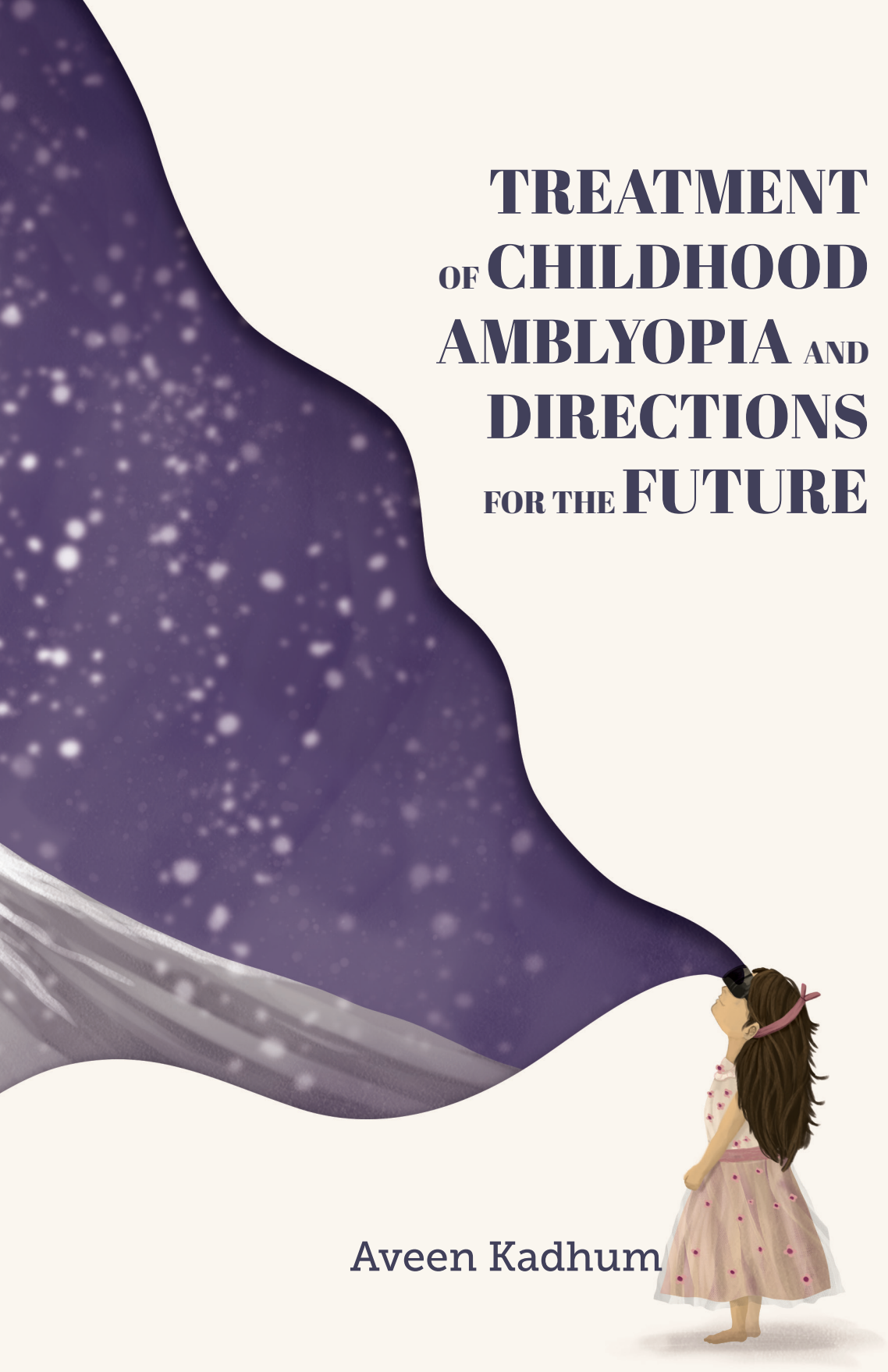
TREATMENT OF CHILDHOOD AMBLYOPIA AND DIRECTIONS FOR THE FUTURE



Aveen Kadhum

TREATMENT OF CHILDHOOD AMBLYOPIA AND DIRECTIONS FOR THE FUTURE

Aveen Kadhum

TREATMENT OF CHILDHOOD AMBLYOPIA AND DIRECTIONS FOR THE FUTURE

Behandeling van amblyopie bij kinderen en toekomstgerichte strategieën

Proefschrift

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

Prof.dr.ir. A.J. Schuit

en volgens besluit van het College voor Promoties.
De openbare verdediging zal plaatsvinden op

woensdag 19 november 2025 om 15.30 uur

door

Aveen Kadhum

geboren te Bagdad, Irak.

Erasmus University Rotterdam

This research was funded by: Uitzicht, Stichting Lijf en Leven, ODAS Stichting and Prof.dr. Henkes Stichting.

The publication of this thesis was financially supported by: Stichting Lijf en Leven, Landelijke Stichting voor Blinden en Slechtzienden, Oculenti, Stichting Blindenhulp, Thea Pharma, Bayer, Rotterdamse Stichting Blindenbelangen.

Cover design and layout: © evelienjagtman.com
Printed by: Ridderprint, Alblasserdam, The Netherlands

ISBN: 978-94-6522-600-2

Promotiecommissie

Promotor
Prof.dr. J.R. Vingerling

Overige leden
Prof.dr. K.F.M. Joosten
Prof.dr. N.E. Schalij-Delfos
Prof.dr. S.O. Dumoulin

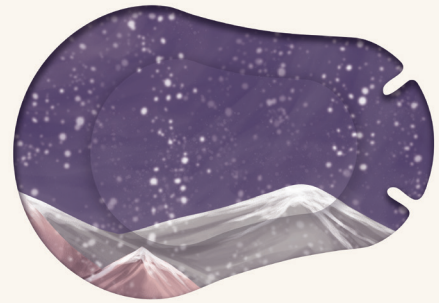
Copromotor
Dr. S.E. Loudon

To my parents

Paranimfen
Emily Tan
Shereen Kadhum

Table of contents

General introduction



General Introduction

Definition and causes of amblyopia

Amblyopia, a lazy eye, is derived from the Greek words ambly (dull) and ops (vision), meaning dullness of vision. It can be classified as a neurodevelopmental vision disorder due to a disturbance in early visual development. With a prevalence of approximately 2-4% it is the most common cause of vision loss in children, second to uncorrected refractive error.[1-3] It is defined as a unilateral or bilateral decrease in visual acuity with no structural abnormalities of the eye or visual pathway. Von Graefe once described it as 'a condition in which the observer sees nothing and the patient very little'.[4] Unilateral amblyopia is mainly caused by a difference in refractive error between the two eyes (anisometropia), leading to a blurred foveal image in one eye; by ocular misalignment (strabismus), resulting in two different foveal images; or by a combination of both, known as combined mechanism amblyopia. A high degree of refractive error in both eyes can lead to suboptimal bilateral visual input, resulting in bilateral amblyopia. A rare cause of unilateral amblyopia is deprivation, which is due to an obstruction in the visual axis preventing a clear retinal image, such as congenital cataract or ptosis. This rare form is also considered the most severe type of amblyopia. The severity of amblyopia appears to be associated with the age at which the normal visual development was disrupted, the amount of time spent with abnormal vision and the degree of imbalance between the two eyes.

Amblyopia is typically defined as a difference of two logMAR lines or more in best-corrected visual acuity between the two eyes. The severity is classified based on the visual acuity in the amblyopic eye, ranging from mild (≤0.2 logMAR), moderate (0.30-0.60 logMAR), to severe (0.70-1.30 logMAR) amblyopia.[5,6] It is important to note that many studies have demonstrated that visual loss due to amblyopia does not solely affect visual acuity, but rather involves a range of visual function deficits, including neural, oculomotor, perceptual and clinical abnormalities. One highly important factor determining the specific loss in visual function is whether binocular function is present.[7,8]

It is essential to detect and treat amblyopia early-on preventing permanent monocular visual impairment. Amblyopia has been shown to have a negative impact on school performance, fine motor skills, social interactions and self-image leading to a reduced quality of life.[9-12] In addition, persistent amblyopia doubles the life time risk of Bilateral Visual Impairment (BVI) and increases the duration of time spent with BVI with 6 months.[13]

Critical period of visual development and plasticity of the brain

At birth, children have not yet fully developed a range of different visual functions. During the first years of life, three essential conditions are needed for this visual development to take place: (1) adequate stimuli received from both eyes; (2) corresponding images due to ocular alignment; and (3) integrity of the visual pathways. If any of these conditions are disrupted, leading to an inadequate visual experience during the sensitive period, this could result in the development of amblyopia. The sensitive period in humans is considered to be from birth to approximately 8 years of age.[14]

Just as there is a time frame (i.e. sensitive period) during which amblyopia can develop, its treatment also needs to take place during this period. This concept was first proposed by Claude Worth. He stated that reduced vision in the amblyopic eye was due to the presence of a sensory obstacle, such as unilateral ptosis or strabismus, which led to halted visual development. Later, Hubel and Wiesel demonstrated, through their pioneering Nobel prize-winning experiments in cats and monkeys, that early monocular deprivation, created by suturing the eyelids of one eye, leads to substantial neural alterations. It induces a change in ocular dominance between the eyes in the visual cortex, causing profound visual loss in the sutured eye. These effects only occurred during the sensitive period. Furthermore, this visual loss could only be reversed by suturing the opposite eye and reopening the previously sutured eye within the sensitive period.

The effectiveness of amblyopia treatment decreases with age and this has been attributed to a decline in plasticity in the mature brain at the end of the sensitive period. Important structural changes occurring in the extracellular matrix towards the end of the sensitive period are thought to be partly responsible for this reduced plasticity. There is an increase in so-called cross-linked chondroitin sulphate proteoglycans (CSPGs), which contributes to the gradual elaboration of an insoluble matrix in the maturing brain. CSPGs form dense perineuronal nets, in particular around GABAergic parvalbumin-positive cells, thus inhibiting further axonal growth.[15]

Treatment of amblyopia

The established treatment for amblyopia includes correction of the refractive error, if necessary, and occlusion or penalisation of the fellow eye several hours per day, thus forcing the brain to use the input of the amblyopic eye. Occlusion treatment was first described by Thabit ibn Qurrah ibn Marwan al-Harrani (836-901) and dates back to as early as the 9th – 10th century AD. It has proven to be a

very successful treatment for amblyopia. However, its popularity has fluctuated over time, mainly due to problems with acceptance by children and parents. There have been arguments against occlusion therapy describing it as a burden for the child and their families, resulting in compliance issues. Furthermore, some have stated that it has a negative effect on the development of binocular vision. With this in mind, there has been a continuous search for alternative therapies to occlusion therapy and numerous non-occlusion treatments have been proposed and investigated.

Several studies have also suggested that amblyopia is not merely a monocular deficit, but rather a binocular problem caused by the disruption of binocular input in early childhood with suppression of the amblyopic eye.[16] This has led to a shift in amblyopia research from monocular to binocular therapies. In the last decade, new treatment methods have emerged that encourage cooperation between the two eyes during treatment, in contrast to traditional monocular approaches involving occlusion or penalisation of the fellow eye. These so-called behavioural treatment methods include perceptual learning, action video gaming and dichoptic training or dichoptic movie viewing. Publications regarding these new therapies have increased rapidly. Moreover, the prevailing consensus that amblyopia in adults is untreatable has been questioned with growing evidence for the possibility to remove the 'brakes' on plasticity.[17,18]

Figure 1 shows the meta-analysis of Tsirlin et al. and gives an overview of the mean visual acuity improvement with these different treatment methods, which is on average 1.7 logMAR line. Most of these studies have been performed in adults, older children or children who have received prior treatment with occlusion therapy.[19] Moreover, a valid comparison of these new treatment methods with the standard occlusion therapy was lacking in the literature. Therefore, we conducted our randomised clinical trial to allow for a valid comparison between dichoptic video gaming and standard occlusion therapy.

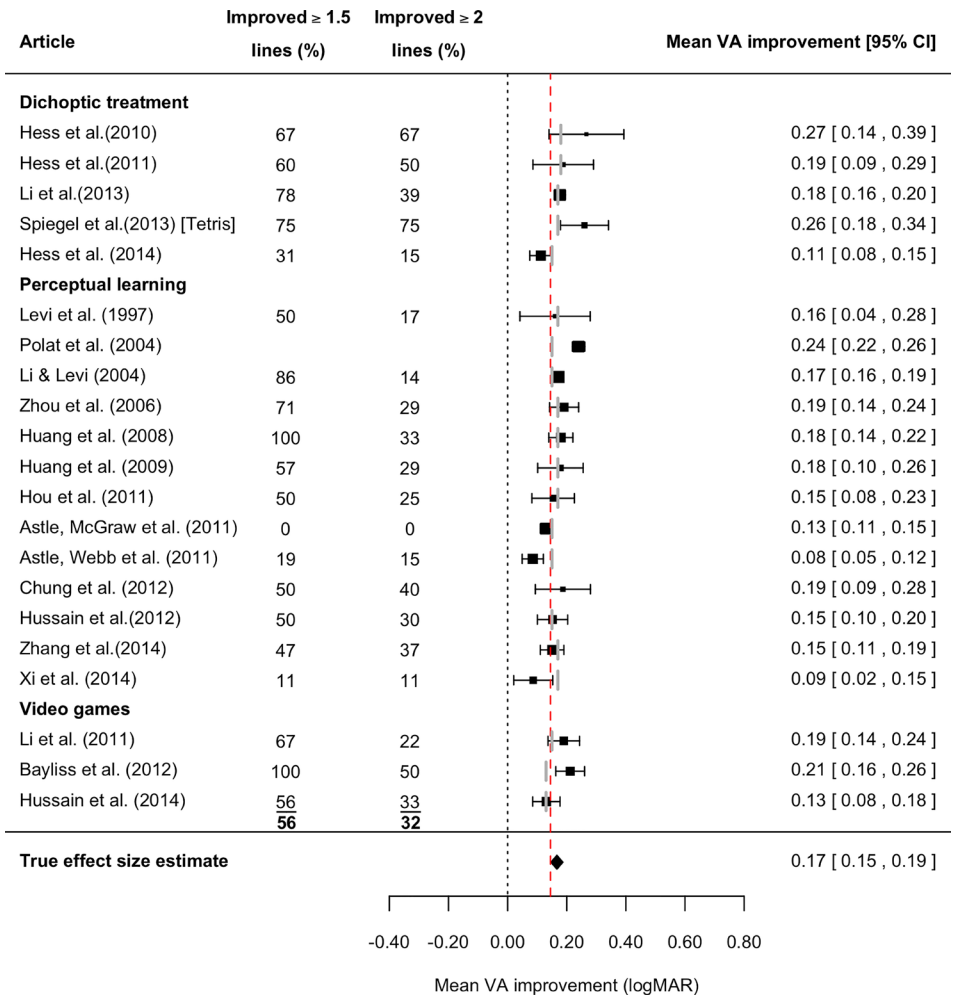


Figure 1. Means and 95% CI for visual acuity (VA) improvement in 21 studies used in the mixed-effects analyses. The red dashed line shows the mean test–retest reliability of 0.15 logMAR. The short gray lines show the test–retest reliability for the test used in each individual study. The size of the square symbols represents the relative weight given to each study in the model. The diamond symbol on the bottom row shows the estimated true effect size. The two middle columns show the percentage of participants who had visual acuity improved by 0.15 logMAR or higher and by 0.2 logMAR or higher.

From: Tsirlin I, Colpa L, Goltz HC, Wong AMF. Behavioral training as new treatment for adult amblyopia: A meta-analysis and systematic review. Invest Ophthalmol Vis Sci. 2015;56:4061-4075. Copyright holder: ARVO.

Aims and outline of this thesis

In this thesis, a newly developed dichoptic action video game using Virtual Reality (VR) goggles as a form of binocular treatment for amblyopia, is compared with the conventional occlusion treatment in children aged 4-12 years. The dichoptic action video game ('gaming treatment') was conducted by the researcher for 1 hour per week at the outpatient clinic (see Figure 2). The occlusion treatment was done by the parents at home for 2 hours per day. Compliance with the occlusion treatment was measured electronically using the Occlusion Dose Monitor (ODM; see Figure 3). In this randomised clinical trial (RCT) we investigated the effectiveness of both treatments, parental preferences and made an inventory of the barriers encountered while conducting this trial in order to assess the feasibility of this novel treatment in daily orthoptic practice.

Figure 2. Gaming treatment at the outpatient clinic.

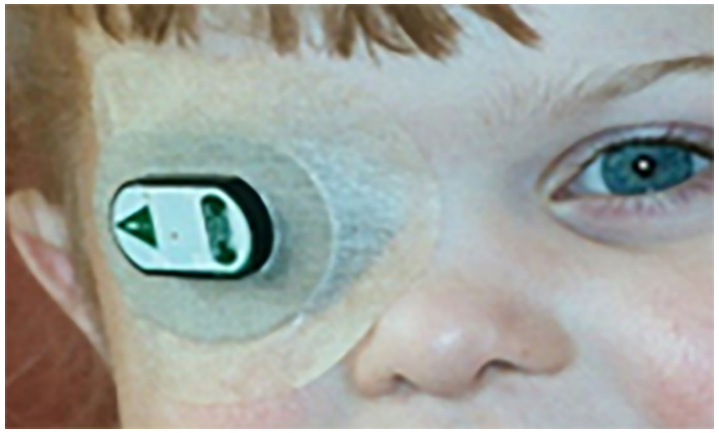


Figure 3. Occlusion patch with the Occlusion Dose Monitor.

As an introduction to binocular treatments for amblyopia, this thesis begins with a historical overview of non-occlusion treatments for amblyopia throughout history.

Occlusion therapy has been the mainstay treatment for centuries. Therefore, Chapter 3 reports on the long-term visual acuity outcomes observed in adolescents who were treated with occlusion therapy for amblyopia during childhood, approximately 15 years ago. This chapter also identifies potential risk factors for visual acuity deterioration after cessation of occlusion therapy.

The subsequent four chapters present data from our prospective RCT, in which we compared the effect of a binocular treatment, i.e. a dichoptic action video game using Virtual Reality (VR) goggles with standard occlusion therapy.

A proper optical treatment, or refractive adaptation phase, is an essential first step in the treatment of amblyopia. In Chapter 4, the outcomes of the refractive adaptation period prior to randomisation are evaluated and the use of the Occlusion Dose Monitor (ODM) for measuring compliance with spectacle wear is validated.

Chapter 5 presents the overall findings from our prospective RCT, in which the effectiveness of dichoptic video gaming is compared with occlusion therapy in an objective manner. This is followed by a systematic overview of the barriers encountered while conducting dichoptic gaming treatment using VR goggles (Chapter 6).

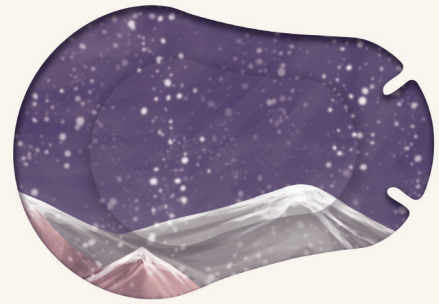
Chapter 7 provides further insight into parental experiences and preferences regarding dichoptic gaming and occlusion therapy. Semi-structured interviews were conducted with one or both parents after completion of the study period.

Finally, Chapter 8 discusses the significance of the findings presented in this thesis and explores the potential role of dichoptic video gaming in the future treatment of childhood amblyopia.

References

1. Brown SA, Weih LM, Fu CL, et al. Prevalence of amblyopia and associated refractive errors in an adult population in Victoria, Australia. Ophthalmic Epidemiol 2000;7(4):249-58.
2. Friedman DS, Repka MX, Katz J, et al. Prevalence of amblyopia and strabismus in white and African American children aged 6 through 71 months the Baltimore Pediatric Eye Disease Study. Ophthalmology 2009;116(11):2128-34 e1-2.
3. Burton MJ, Ramke J, Marques AP, et al. The Lancet Global Health Commission on Global Eye Health: vision beyond 2020. Lancet Glob Health 2021;9(4):e489-e551.
4. Mittelman D. Amblyopia. Pediatr Clin North Am 2003;50(1):189-96.
5. Holmes JM, Kraker RT, Beck RW, et al. A randomized trial of prescribed patching regimens for treatment of severe amblyopia in children. Ophthalmology 2003;110(11):2075-87.
6. Repka MX, Beck RW, Holmes JM, et al. A randomized trial of patching regimens for treatment of moderate amblyopia in children. Arch Ophthalmol 2003;121(5):603-11.
7. Levi DM. Visual processing in amblyopia: human studies. Strabismus 2006;14(1):11-9.
8. Levi DM. Rethinking amblyopia 2020. Vision Res 2020;176:118-29.
9. O'Connor AR, Birch EE, Anderson S, Draper H. Relationship between binocular vision, visual acuity, and fine motor skills. Optom Vis Sci 2010;87(12):942-7.
10. Birch EE, Castaneda YS, Cheng-Patel CS, et al. Self-perception of School-aged Children With Amblyopia and Its Association With Reading Speed and Motor Skills. JAMA Ophthalmol 2019;137(2):167-74.
11. Chua B, Mitchell P. Consequences of amblyopia on education, occupation, and long term vision loss. Br J Ophthalmol 2004;88(9):1119-21.
12. Webber AL, Wood JM, Gole GA, Brown B. The effect of amblyopia on fine motor skills in children. Invest Ophthalmol Vis Sci 2008;49(2):594-603.
13. van Leeuwen R, Eijkemans MJ, Vingerling JR, et al. Risk of bilateral visual impairment in individuals with amblyopia: the Rotterdam study. Br J Ophthalmol 2007;91(11):1450-1.
14. Zagui RMB. Amblyopia: Types, Diagnosis, Treatment, and New Perspectives. American Academy of Ophthalmology, 2019; v. 2024.
15. Sengpiel F. Plasticity of the visual cortex and treatment of amblyopia. Curr Biol 2014;24(18):R936-R40.
16. Hess RF, Thompson B. Amblyopia and the binocular approach to its therapy. Vision Res 2015;114:4-16.
17. Morishita H, Hensch TK. Critical period revisited: impact on vision. Curr Opin Neurobiol 2008;18(1):101-7.
18. Bavelier D, Levi DM, Li RW, et al. Removing brakes on adult brain plasticity: from molecular to behavioral interventions. J Neurosci 2010;30(45):14964-71.
19. Tsirlin I, Colpa L, Goltz HC, Wong AM. Behavioral Training as New Treatment for Adult Amblyopia: A Meta-Analysis and Systematic Review. Invest Ophthalmol Vis Sci 2015;56(6):4061-75.

From fusion exercises to a virtual reality game: a historical overview of binocular treatments for amblyopia



Introduction

The first mention of amblyopia dates back to the Greek Antiquity. Hippocrates described the term 'amblyopia', referring to reduced visual acuity in otherwise healthy eyes. Treatment for both amblyopia and strabismus involved a medicinal mixture comprising oil, vinegar, water, wine, honey and minerals. Additionally, specific diets and fresh vegetables were believed to enhance eye health, while regular physical exercise and a balanced lifestyle were also recommended.

Following this early description of amblyopia, there have been numerous attempts to unravel this condition and to find the appropriate treatment. Throughout history, apart from occlusion therapy, several non-occlusion treatment methods have been proposed, often involving both eyes. This is a trend that remains relevant to this day, with strikingly similar treatment approaches.

The following section presents a historical overview of these non-occlusion therapies.

Fusion exercises

The main purpose of fusion exercises is to enhance the ability to fuse two images into one, thereby improving binocular vision in the brain.

Charles de Saint-Yves (1667-1731), born in Maubert-Fontaine in northern France, studied general surgery and specialised in eye diseases at the General Hospital in Paris. He later established his own ophthalmology clinic in Paris. In 1722, he wrote his book 'Nouveau traité des maladies des yeux', in which he elaborates on 'des yeux louches'. He is one of the first to describe the cover test, now considered the hallmark of modern orthoptic practice for diagnosing strabismus. As a treatment for strabismus he recommended exercises: 'sit the child in front of a mirror so that each eye looks precisely at the pupil of the corresponding eye in the mirror. In addition, one must also read fine print and do handicrafts'.[1, 2]

In the United Kingdom, the physician and grandfather of Charles Darwin, Erasmus Darwin (1731-1802), modified Charles de Saint-Yves' exercises as a treatment for strabismus. He separated the two visual fields using a septum. Each eye was presented a small coloured piece of wood to improve fixation. After training and obtaining good fixation for each eye, the pieces of wood were presented simultaneously to each eye and the patient was instructed to superimpose them. He was a strong advocate of practising these exercises regularly. This treatment could be regarded as the first description of a dichoptic exercise.

Stereoscope and amblyoscope

Charles Wheatstone (1802-1875), a British professor of experimental philosophy, invented the first stereoscope in 1835, an instrument used for viewing objects binocularly. He established that presenting the eyes with two slightly different two-dimensional images through the stereoscope could lead to depth perception. Coming from a family that produced musical instruments, his interest in the study of vision was sparked by the visual expression of acoustic phenomena. In addition to the stereoscope, he developed other 'philosophical toys', such as the kaleidophone, instruments that combined science with entertainment.[3, 4]

David Brewster (1781-1868), a Scottish scientist, invented his own version a few years later in 1843, in which he replaced the mirrors with lenses to create the first portable 'lenticular stereoscope'.

Regarding the use of the stereoscope as a training tool for strabismus, this historical overview continues in France, where Louis Emile Javal (1839-1907) lived. Although his father was a wealthy businessman, he chose a scientific career and had an interest in strabismus. His family's medical history of strabismus may have contributed to this interest. His father had an esotropia and underwent strabismus surgery, which led to a consecutive exodeviation. Javal, affected by this tragic outcome, described it as 'le massacre des muscles oculaires'. He had a fascination for the stereoscope from a young age, at the time designed by Wheatstone and Brewster. When his younger sister Sophia also became affected by strabismus, he decided to train her with the stereoscope. Later, he developed his own version. He studied medicine and even wrote a dissertation entitled 'Manuel théorique et pratique du strabisme' (1896). Javal strongly opposed surgical treatment for any kind of ocular problem. He was committed to the re-establishment of binocular vision by means of occlusion therapy combined with orthoptic exercises and believed that long training sessions with the stereoscope would restore fusion. He sometimes conducted lengthy daily sessions of orthoptic exercises, on occasion causing children to miss school.[1, 2]

Fusion tubes

Priestley Smith introduced viewing through two independent 'fusion tubes ´ in 1891, which were later horizontally connected to form 'the heteroscope'.[5]

Following this development, Claud Alley Worth (1869-1936), a British ophthalmologist born in Holbeach, developed an improved version of the fusion tubes, which he called 'the amblyoscope', with movable tubes and illumination

(see Figure 1). He was a London-based ophthalmologist and also an accomplished mariner. He wrote books on both ophthalmology and sailing. He theorised that strabismus was caused by a congenital defect of the fusion mechanism and therefore proposed fusion exercises with active stimulation of the amblyopic eye using the amblyoscope. The amblyoscope was an instrument designed to improve fusion in patients with strabismus. Two paired images, for example a cage and a bird, were presented to either eye. Figure 2 shows two examples of fusion slides used in the amblyoscope. The right image is presented to the right eye and the left image is presented to the left eye. With fusion, the images are seen as one, for example a cat with the violin and a cow jumping over the moon.

The patient with strabismus was asked to make the images overlap by moving the tubes. The instrument could be adjusted to give a convergence up to 60° or a divergence up to 30°. Later, the possibility of vertical movement was added, allowing a vertical deviation of 20° upwards and 33° downwards, also known as the Worth-Black amblyoscope. The angle of strabismus could be read from a scale. Worth's amblyoscope was the forerunner of the synoptophore; the first model was designed in 1912 (Figure 3).[6]

Figure 1. Worth's amblyoscope. *Image from: Optometry museum and archive.*[7]

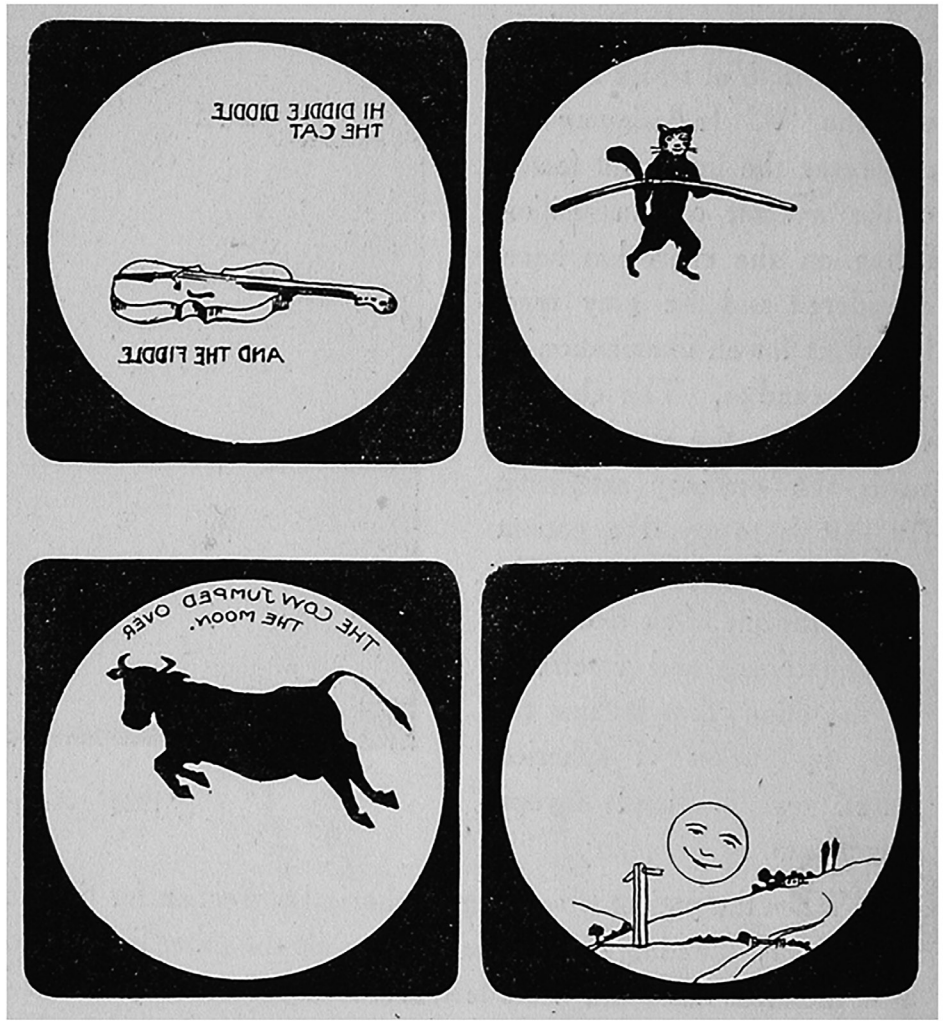


Figure 2. Fusion slides used in the amblyoscope.

Image from: The amblyoscope that was 'Worth' it. Keeler R, Singh AD, Dua HS. British Journal of Ophthalmology, 2013.[6]

Ernest Edmund Maddox (1863-1933) was a British surgeon and ophthalmologist renowned for inventing several devices, including the Maddox rod, double prism Maddox, red glass Maddox, Maddox cross and Maddox wing. He had a particular interest in Worth's amblyoscope and orthoptics, and, building on this work, he invented the cheiroscope – derived from the Greek 'cheir' ('hand') and 'skopio' ('I look'). He presented his invention in an article in 1929[8], in which he also paid tribute to Worth's amblyoscope. He explained that the cheiroscope approached the

problem from a different yet complementary angle, based on the simple principle of using the hand to educate the eye by rehearsing the process of training the hand and eye mutually to educate the squinting eye. The cheiroscope consisted of two lenses suspended over a drawing surface. He described several methods for using the cheiroscope; however, the principle remained the same (Figure 4). One eye viewed the picture, while the other saw the drawing surface. In one method, a line drawing was presented to the dominant eye, which the patient traced with a pencil in the field of view of the other, amblyopic, eye. Both fields of view were separated by a septum, and a mirror was used to reflect the line drawing.

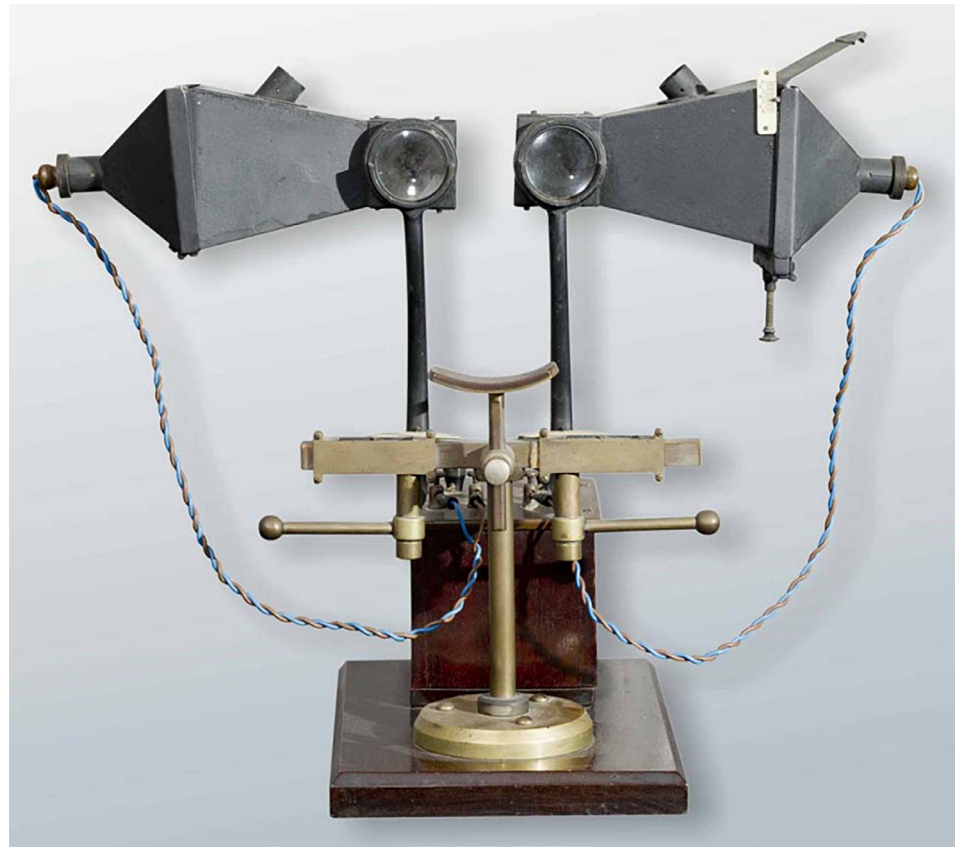


Figure 3. The first model of the synoptophore.

Image from: The amblyoscope that was 'Worth' it. Keeler R, Singh AD, Dua HS. British Journal of Ophthalmology, 2013.[6]

He emphasised that the drawing activity added another element of engagement, especially when the task was new, as children tended to lose interest when merely looking at pictures. Lastly, he proposed incorporating motion as a means of maintaining the attention of the child. For example, the teacher could move a picture of a cat, while the child attempted to place his own finger on the moving image, which appeared to the other eye.

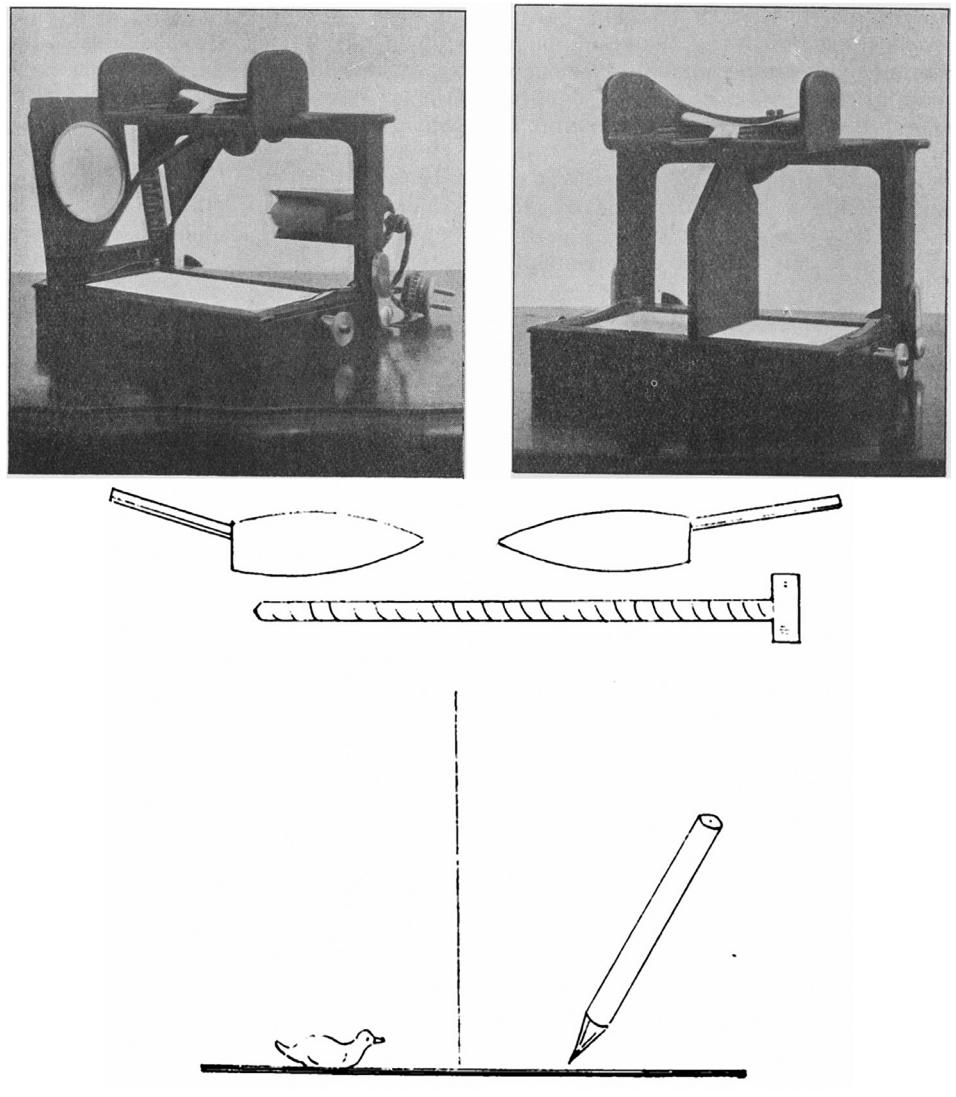


Figure 4. Different ways in using the cheiroscope. *Image from: Demonstration of the cheiroscope. By E.E. Maddox. By kind permission of the Royal Society of Medicine.*[8]

He was convinced that effort and concentration were crucial to achieve the desired effect. Because the training effect was thought to be cumulative, perseverance was deemed essential. Sometimes progress could appear negligible only for results to become suddenly apparent. He stated that these exercises were not a not a single-solution for strabismus, and should be combined with established therapies such as refraction, occlusion, prisms and surgery. Due to a lack of time to use the device himself, he taught his daughter Mary Maddox to use the device. She became a professional and opened the first orthoptic clinic at the Royal Westminster Ophthalmic Hospital in London. She is generally assumed to be the world's first orthoptist.

Pleoptics

As a result of medical neglect during WOII, there was a high prevalence of deep amblyopia in Europa, often in the presence of a steady, eccentric fixation. Many of these amblyopic patients were too old for standard occlusion therapy.

After the war, two centres existed in continental Europe focused on the treatment of strabismus and amblyopia. One in St. Gallen, Switzerland, led by Alfred Bangerter, and another in Giessen, Germany, under Curt Cüppers. Confronted with this new problem of older amblyopes, Bangerter and Cüppers led the development of a novel treatment approach: *'pleoptics'*, derived from the Greek words *'pleion'* ('more') and *'optikos'* ('eyesight').[9]

Comberg (1936)
Comberg was the first to propose direct stimulation of the fovea of the amblyopic eye. He stated: "The gaze-point of attention of the squinting eye does not correspond with the macula anymore and developed much too strong relationships with a new retinal locus. In such cases this eye will always fixate eccentrically, even when constantly and solely used, unless the macular region is forced to participate".[10] He suggested direct stimulation of the fovea of the amblyopic eye in cases of eccentric fixation using brightly illuminated objects, in order to train central fixation.

Bangerter and Cüppers both agreed with this principle of Comberg, whereby direct foveal stimulation in the amblyopic eye with eccentric fixation is used to induce central fixation.

Bangerter (1909-2002)
Professor Alfred Bangerter explained that amblyopia is an under-functioning caused by deprivation and considered amblyopia treatment as an education for seeing. The ordinary visual stimulation by the outside world often did not suffice, and only special, intensive and targeted stimuli could lead to improvement in vision. Creating as favourable viewing conditions as possible was emphasised by Bangerter´s treatment method. This involved: correcting optical errors, reducing larger angles of strabismus and eliminating other visual impairments. Applying adequate stimuli was also an important principle, whereby stimuli had to be adjusted according to the nature and degree of the amblyopia, for example, using strong stimuli was necessary in cases of deep amblyopia. Another principle was, including other sensory systems, such as touch or hearing, to assist in visual localisation during the exercises. He also emphasised that treating eccentric fixation was essential in order to succeed. The

periphery was 'switched off', including the pseudomacula, after direct stimulation of the macula, thereby enabling macular function.[11] He invented the so-called 'dazzling device', whereby the pseudomacula was intensively dazzled, creating a temporary scotoma. During this period, the actual macula was stimulated to induce central fixation. After central fixation was achieved, further training was undertaken using monocular exercises, occlusion of the better eye and binocular training.

In 1953, he published *Amblyopiebehandlung,* in which he presented the first textbook on functional therapy of amblyopia, which served as a foundation for amblyopia management at the time.[9, 11]

In 1947, he founded the 'School of Pleoptics and Orthoptics' in St. Gallen, where the prevailing idea was that there was not a single, uniform way of obtaining normal vision, but rather a variety of methods should be selected and combined for each patient. This approach allowed for optimal exercises in all cases. Based on these principles, Bangerter invented numerous instruments, such as the light-pointer cheiroscope, fusion cheiroscope, synoptophor and the stereoscope.[12]

Limitations
Interestingly, Bangerter also acknowledged the limitations of his exercises. For example, he stated that the exercises were difficult or impossible for children with a strabismus angle larger than 35°.[11] He further admitted that the exercises were time-consuming and demanded the full attention of the child and therefore advised a minimum age of five to six years.[14]

Cüppers (1910-1995)
Cüppers developed the Euthyscope, a special ophthalmoscope with a bright light source to dazzle the peripheral retina, while the fovea was protected by a black disc. This created a doughnut-shaped foveal afterimage, which was initially positive, i.e. a dark centre, but eventually became negative, i.e. a light centre. The transition from a positive to a negative afterimage was enhanced by flickering room illumination. The essence of this treatment was to make the patient with eccentric fixation aware of the visual direction of the fovea, which corresponded to the clear centre.[9,15] The device developed by Cüppers became commercially available, which led to concern on the part of Bangerter, who stated that some practitioners might attempt to treat deep amblyopia using the Euthyscope without having the skills to carry out the treatment correctly.

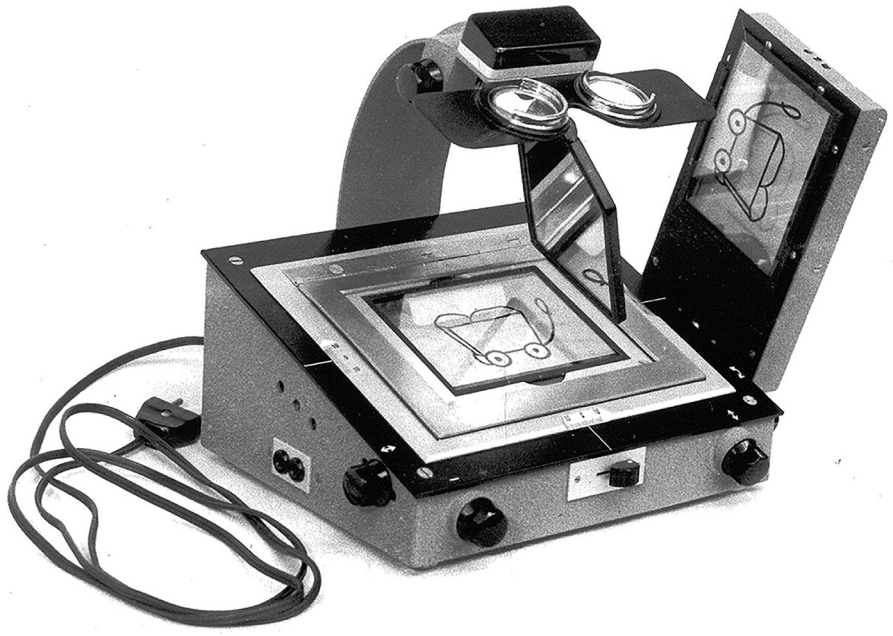


Figure 5. Fusion cheiroscope.

This is a modification of the original cheiroscope of Maddox. The object that can be traced, is presented to both eyes in whole or in part, stimulating fusion. *Image from: Bangerter A. Treatment of amblyopia: Part 3 Apparatus, exercise equipment and games (continued). Alfred Bangerter, Simonsz HJ. Strabismus. © copyright (2018), reprinted by permission of Informa UK Limited, trading as Taylor & Francis Group, https://www.tandfonline.com.*[13]

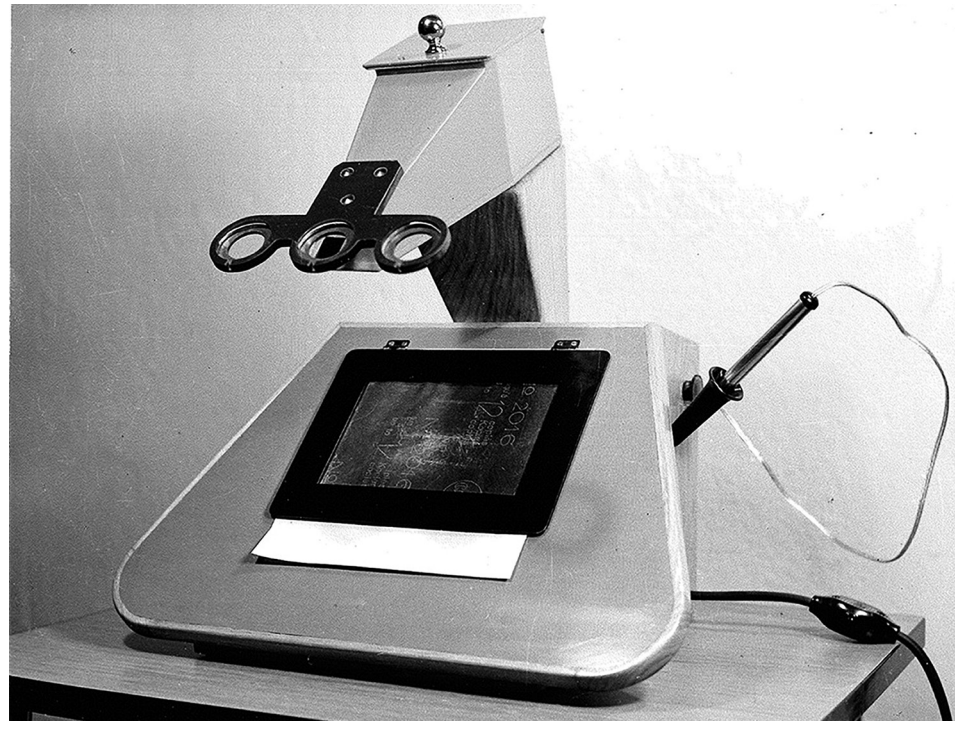


Figure 6. Light-pointer cheiroscope. A pointer containing a light tip is used to trace the contours of the diapositive presented to the other eye, which is projected onto the underlying paper. *Image from: Bangerter A. Treatment of amblyopia: Part 3 Apparatus, exercise equipment and games (continued). Alfred Bangerter, Simonsz HJ. Strabismus. © copyright (2018), reprinted by permission of Informa UK Limited, trading as Taylor & Francis Group, https://www.tandfonline.com.*[13]

Red-Filter Treatment

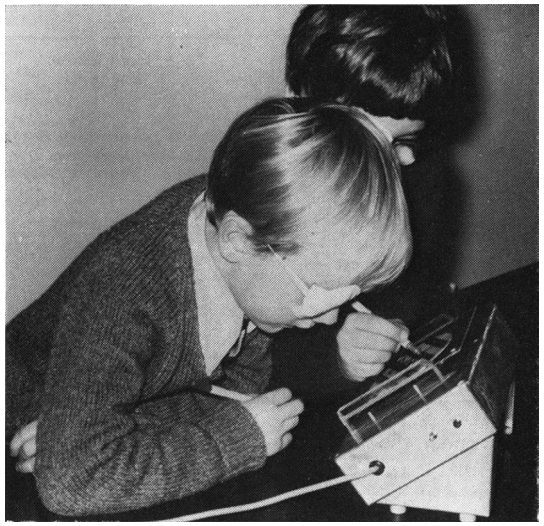
Brinker and Katz (1963)
The red-filter treatment was recommended to improve visual acuity and fixation in amblyopia. The idea was that red light selectively stimulates the cones of the retina. As the fovea exclusively consists of cones, it would be stimulated by the light passed through the red filter. The hypothesis was that in patients with eccentric fixation this could induce an impulse to use the fovea for fixation instead of the parafoveal fixation point.[1]

CAM treatment (1978)

The CAM treatment may be considered the first implementation of 'perceptual learning' in amblyopia.[16] The CAM treatment was developed and introduced as an alternative to occlusion therapy. It was an attempt to improve the acceptance of occlusion therapy and consisted of an apparatus in which high-contrast square-wave gratings were slowly rotated in front of the amblyopic eye, while the fellow eye was patched. The goal was to passively expose the amblyopic eye to a broad range of spatial frequencies and all orientations. The choice of contrast and spatial frequencies of these gratings was determined by assessing thresholds for low- and medium-frequency grating with simplified clinical plates.

During this exposure, children performed a task requiring visual concentration to maintain their interest. They played drawing games on a transparent Perspex plate positioned above the rotating grating, so that visual stimulation was maintained while they played. The duration of a treatment session was solely 7 minutes during weekly sessions with no need for occlusion between the sessions. The total duration of occlusion required to achieve the maximum level of visual acuity varied considerably between patients. The average number of treatments required was four, which was markedly shorter than conventional occlusion treatment. However, the effectiveness of the CAM treatment could not be confirmed in controlled studies. To investigate whether the rotating gratings of the CAM treatment were the determining factor responsible for improvement in the amblyopic eye, comparative studies with a control group were carried out. The control group also received occlusion of the fellow eye while playing games over a Perspex plate, but with no rotating gratings underneath. Both groups showed improvement, with no significant differences between them. It was concluded that the improvements may be attributed to the short-term occlusion of the fellow eye in combination with near visual activities, rather than exposure to the rotating gratings.[17]

A



B

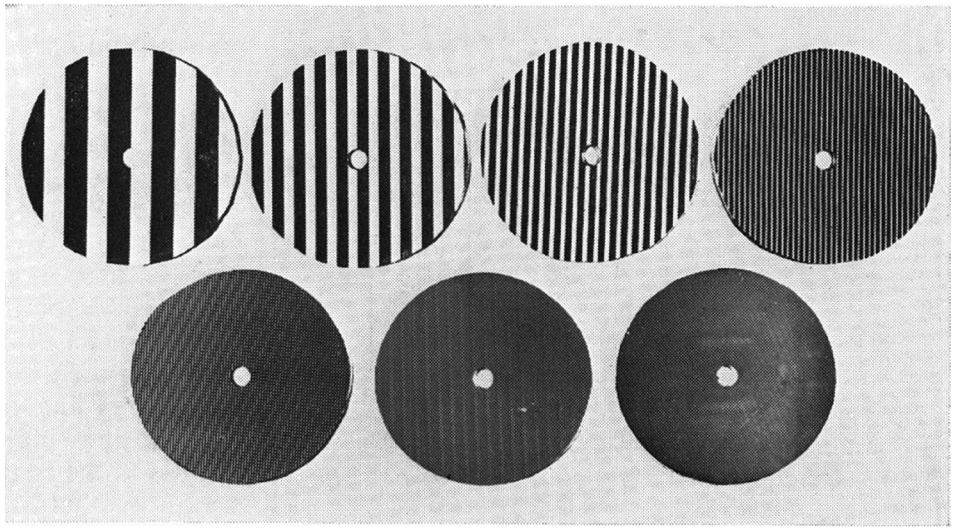


Figure 7 a. CAM treatment, b. Rotating gratings with different spatial frequencies

Images from: Preliminary results of a physiologically based treatment of amblyopia. Campbell FW, Hess RF, Watson PG, Banks R. British Journal of Ophthalmology, 1978.[18]

The present: Perceptual learning, dichoptic training, video games

Over the past decade, there has been a renewed interest in the use of games to treat amblyopia, accompanied by a rapid increase in publications concerning these new treatment methods. Interestingly, these modern treatment approaches bear a striking resemblance to the original visual exercises, sharing both advantages and limitations.

As discussed above, principles such as dichoptic training were already present in Priestly-Smith's fusion tubes, the amblyoscope and the synoptophore. The distinction lies in the application of modern technology, which provides new possibilities for dichoptic stimulation, for instance via Virtual Reality headsets.

Perceptual learning

Eleanor Gibson first defined perceptual learning as "Any relatively permanent and consistent change in the perception of a stimulus array following practice or experience with this array".[19] Nowadays, the definition of perceptual learning is broader and generally denotes "improvement on a perceptual or sensory task by practice or experience". Previous studies have shown improvement in performance on visual tasks after repeated practice, including improvement in visual search and texture discrimination.

In the past decade, perceptual learning as a treatment for amblyopia has been extensively researched, leading to the development of new treatment methods. Important to note is that it requires extensive training with thousands of trials on a perceptual task. Subjects generally improve through practice not only on that specific, trained task, but also demonstrate a transfer to the fellow eye and other tasks.

Dichoptic training

Dichoptic training is based on the theory that amblyopia should be viewed as a binocular disorder rather than a monocular one. Subsequently, binocular treatments have been proposed in the form of 'dichoptic training' as a promising new treatment for amblyopia. This approach consists of simultaneous and separate stimulation of both eyes. Some present the same image to each eye, with additional Gabor patches and suppression checks presented solely to the amblyopic eye[20], while others present different game elements to each eye, so that binocular viewing is necessary in order to see the complete image.[21]

This idea of dichoptic stimulation, whereby different images are presented to each eye independently was already present in earlier devices, such as Worth's amblyoscope, Maddox' amblyopcope and the synoptophore. However, modern technology permits more sophisticated implementation. In current approaches, the stimuli presented to the fellow eye are reduced in contrast/luminance to match the appearance of the stimuli presented to the amblyopic eye, thereby creating optimal conditions for binocular viewing. The aim is to reach a balanced contrast, promoting binocular summation. Dichoptic training has been investigated in multiple different forms. The original training was a motion coherence task by Hess et al., whereby subjects were presented signal dots to one eye and noise dots to the other eye.[22] Participants indicated the direction of motion of the signal dots among the noise dots. The contrast for the stimuli presented to the fellow eye was reduced and adjusted with training. The hypothesis was that the degree of contrast adjustment (signal imbalance) provided a measure for the degree of interocular suppression.

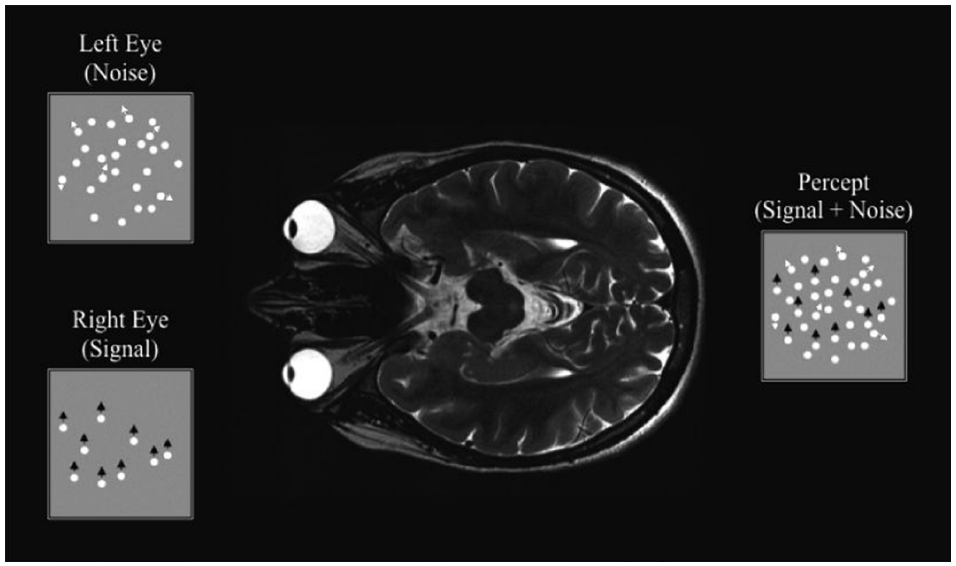


Figure 9. Illustration of the dichoptic motion coherence task.

Image from: A new binocular approach to the treatment of amblyopia in adults well beyond the critical period of visual development. Hess RF, Mansouri B, Thompson B. Restorative Neurology and Neuroscience, 2010.[22]

Because of the tedious nature of the task, other forms of dichoptic training have been developed and introduced. Games such as *Tetris*, *Dig Rush* and a modified version of *Medal of Honour* as well as passive methods such as dichoptic movie watching, have also been investigated.[23-25]

The underlying rationale is that early disruption of the visual development prevents correlated binocular visual experience and induces suppression of the amblyopic eye by the fellow eye. Binocular treatment is thought to be able to alleviate this suppression leading to improved visual acuity and stereo acuity.

However, most studies have not been able to demonstrate an association between improvement in visual function and reduction in interocular suppression. Bossi et al. investigated 'balanced binocular viewing therapy' (BBV), which consisted of daily dichoptic movie and gameplay with adjusted contrast. They found visual acuity improvements that were not correlated with a reduction in suppression and concluded that a reduction in interocular suppression was not the basis of the observed improvements in visual acuity.[26] Vedamurthy et al. conducted a study using a dichoptic first-person shooter video game, with an imbedded perceptual learning task in adults with amblyopia. They also found similar improvements in visual acuity and stereopsis along with a reduction in suppression. However, they were also unable to demonstrate a relationship between improved visual function and suppression. Based on this apparent lack of association, they concluded that reduced suppression alone is unlikely to account for the observed improvements in visual function.[27] The exact mechanism by which binocular therapy improves visual function remains unclear.

Video gaming

Playing video games can have beneficial effects on vision, even in individuals without amblyopia. There is also growing evidence that intensive video game use, leads to significant, generalised improvements in cognitive function. Green et al. demonstrated that playing action video games can alter fundamental characteristics of the visual system, such as the spatial resolution of visual processing across the visual field. Action video game experience has been shown to increase the spatial resolution of vision as measured by crowding.[28]

Monocular stimulation

Contrary to the theory underlying a binocular approach to amblyopia therapy, studies have shown that monocular gaming treatment can also improve visual acuity and stereoacuity.[29] Levi et al. compared monocular gameplay of an action

video game with binocular gameplay. Both treatment groups improved in visual acuity, with the binocular group showing greater improvements, although a statistical significant difference could not be demonstrated due to the small sample sizes.[30] Overall, the reported effects of binocular versus monocular treatment in the literature appear comparable, with an average improvement of one to two lines in visual acuity, although there may be a beneficial effect on stereoacuity with the binocular approach.[31]

Comment

When reviewing the history of amblyopia treatment, it becomes clear that there has been a continuous search for alternative therapies to the occlusion patch, a pursuit that continues to the present day. Strikingly, there are notable similarities between more recent proposed non-occlusion therapies and historic non-occlusion therapies introduced in the past:

1. Focusing on amblyopia mainly as a binocular disorder requiring a binocular approach.
2. Using visual stimuli, sometimes with specific visual tasks, whereby one or both eyes are exposed to visual stimuli and exercises beyond normal daily visual challenges.
3. Comprising a structured training schedule, with a specific amount of training time prescribed for a defined period.
4. Being time-consuming in nature.
5. Often requiring a minimum age to be able to perform the exercises.
6. Generally excluding children with larger strabismus angles from performing the exercises.

These recurring characteristics suggest that many modern approaches share fundamental principles with earlier non-occlusion treatments.

Search strategy

Literature for this historic overview was based on information obtained from several databases including Medline, Embase, Web of Science, Cochrane and Google scholar.

Key words were used: amblyopia, non-occlusion, fusion exercises, pleoptics, amblyoscope, euthyscope, perceptual learning, binocular, cheiroscope, virtual reality, gaming, CAM.

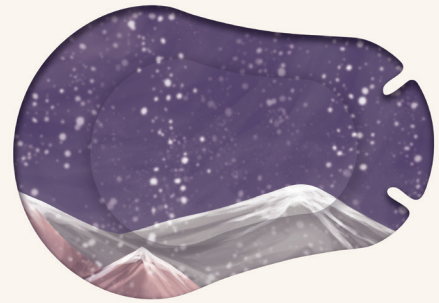
In addition, the book ‘Licht, kleur, ruimte. De leer van het zien in historisch perspectief’ by R.A. Crone was used.

References

1. Loudon SE, Simonsz HJ. The history of the treatment of amblyopia. Strabismus 2005;13(2):93-106.
2. Crone RA. Licht, kleur, ruimte: de leer van het zien in historisch perspectief: Bohn Stafleu Van Loghem, 1992.
3. Wade NJ. Charles Wheatstone (1802-1875). Perception 2002;31(3):265-72.
4. Wade NJ. Wheatstone and the origins of moving stereoscopic images. Perception 2012;41(8):901-24.
5. Keeler R, Singh AD, Dua HS. Scoping strabismus: stand-mounted synoptiscope. British Journal of Ophthalmology 2012;96(8):1051-.
6. Keeler R, Singh AD, Dua HS. The amblyoscope that was ´Worth´ it. Br J Ophthalmol 2013(97):1495-6.
7. archive Oma. Worth Amblyoscope. Optometry museum and archive, 1796; v. 2024.
8. Maddox EE. Demonstration of the Cheiroscope. Proc R Soc Med 1929;23(1):48-55.
9. Noorden GKV. The History of Strabismology: Wayenborgh Publishing, 2018.
10. Linksz A. THEORY OF PLEOPTICS. International Ophthalmology Clinics 1961;1(4):747-85.
11. Bangerter A. Treatment of Amblyopia: Part 1. Strabismus 2017;25(4):222-30.
12. Bangerter A. Treatment of amblyopia: part 4. Strabismus 2019;27(2):120-6.
13. Bangerter A. Treatment of amblyopia: Part 3 Apparatus, exercise equipment and games (continued). Strabismus 2018;26(2):106-9.
14. Bangerter A. Treatment of amblyopia: part 5. Strabismus 2019;27(3):191-7.
15. Mayweg S, Massie HH. Amblyopia ex-anopsia (suppression amblyopia); a preliminary report of the more recent methods of treatment of amblyopia, especially when associated with eccentric fixation in cases of strabismus. Br J Ophthalmol 1958;42(5):257-69.
16. Levi DM, Li RW. Perceptual learning as a potential treatment for amblyopia: a mini-review. Vision Res 2009;49(21):2535-49.
17. Tytla ME, Labow-Daily LS. Evaluation of the CAM treatment for amblyopia: a controlled study. Invest Ophthalmol Vis Sci 1981;20(3):400-6.
18. Campbell FW, Hess RF, Watson PG, Banks R. Preliminary results of a physiologically based treatment of amblyopia. Br J Ophthalmol 1978;62(11):748-55.
19. Gibson EJ. Perceptual learning. Annu Rev Psychol 1963;14:29-56.
20. Vedamurthy I, Nahum M, Huang SJ, et al. A dichoptic custom-made action video game as a treatment for adult amblyopia. Vision Res 2015;114:173-87.
21. Hess RF, Thompson B, Baker DH. Binocular vision in amblyopia: structure, suppression and plasticity. Ophthalmic Physiol Opt 2014;34(2):146-62.
22. Hess RF, Mansouri B, Thompson B. A new binocular approach to the treatment of amblyopia in adults well beyond the critical period of visual development. Restor Neurol Neurosci 2010;28(6):793-802.
23. Jost RM, Hudgins LA, Dao LM, et al. Randomized clinical trial of streaming dichoptic movies versus patching for treatment of amblyopia in children aged 3 to 7 years. Sci Rep 2022;12(1):4157.
24. Kelly KR, Jost RM, Wang YZ, et al. Improved Binocular Outcomes Following Binocular Treatment for Childhood Amblyopia. Invest Ophthalmol Vis Sci 2018;59(3):1221-8.

25. Li SL, Reynaud A, Hess RF, et al. Dichoptic movie viewing treats childhood amblyopia. J AAPOS 2015;19(5):401-5.
26. Bossi M, Tailor VK, Anderson EJ, et al. Binocular Therapy for Childhood Amblyopia Improves Vision Without Breaking Interocular Suppression. Invest Ophthalmol Vis Sci 2017;58(7):3031-43.
27. Vedamurthy I, Nahum M, Bavelier D, Levi DM. Mechanisms of recovery of visual function in adult amblyopia through a tailored action video game. Sci Rep 2015;5:8482.
28. Green CS, Bavelier D. Action-video-game experience alters the spatial resolution of vision. Psychol Sci 2007;18(1):88-94.
29. Tsirlin I, Colpa L, Goltz HC, Wong AM. Behavioral Training as New Treatment for Adult Amblyopia: A Meta-Analysis and Systematic Review. Invest Ophthalmol Vis Sci 2015;56(6):4061-75.
30. Gambacorta C, Nahum M, Vedamurthy I, et al. An action video game for the treatment of amblyopia in children: A feasibility study. Vision Res 2018;148:1-14.
31. Levi DM. Rethinking amblyopia 2020. Vision Res 2020;176:118-29.

Long-term follow-up of an amblyopia treatment study: change in visual acuity 15 years after occlusion therapy



Aveen Kadhum, Brigitte Simonsz-Tóth, Joost van Rosmalen, Sanne J.M. Pijnenburg, Bronte M. Janszen, Huibert J. Simonsz, Sjoukje E. Loudon

Acta Ophthalmologica 2021 Feb;99(1):e36-e42

Abstract

Purpose: To determine change in visual acuity (VA) in the population of a previous amblyopia treatment study (Loudon 2006) and assess risk factors for VA decrease.

Methods: Subjects treated between 2001 and 2003 were contacted between December 2015 and July 2017. Orthoptic examination was conducted under controlled circumstances and included subjective refraction, best corrected VA, reading acuity, binocular vision, retinal fixation, cover-uncover and alternating cover test. As a measure for degree of amblyopia, InterOcular VA Difference (IOD) at the end of occlusion therapy was compared with IOD at the follow-up examination using Wilcoxon's signed-rank test. Regression analysis was conducted to determine the influence of clinical and socio-economic factors on changes in IOD.

Results: Out of 303 subjects from the original study, 208 were contacted successfully, 59 refused and 15 were excluded because of non-amblyopic cause of visual impairment. Mean IOD at end of therapy (mean age 6.4 yrs) was 0.11±0.16 logMAR, IOD at follow-up examination (mean age 18.3 yrs) was 0.09±0.21 logMAR; this difference was not significant (p=0.054). Degree of anisometropia (p=0.008; univariable analysis), increasing anisometropia (p=0.009; multivariable), eccentric fixation (p<0.001; univariable and multivariable); large IOD (p<0.001; univariable and multivariable) and non-compliance during therapy (p=0.028; univariable) were associated with IOD increase.

Conclusion: Long-term results of occlusion therapy were good. High or increasing anisometropia, eccentric fixation and non-compliance during occlusion therapy were associated with long-term VA decrease. Subjects with poor initial VA had a larger increase despite little patching, but often showed long-term VA decrease.

3

Introduction

Amblyopia is the most common cause of monocular visual acuity loss in children with a prevalence varying from 1.6% to 3.5%.[1] It is mainly caused by strabismus and/or anisometropia or visual deprivation, which disrupts the equal input from both eyes to the visual cortex. Standard therapy is spectacle correction if necessary, and occlusion of the fellow eye several hours per day during the sensitive period.[2, 3]

Occlusion therapy is a very successful treatment, however, its success is hampered by non-compliance.[3-6] Long-term results of occlusion therapy vary widely.[7-16] Visual acuity deteriorated in 7-75% of the cases, largely depending on duration of follow-up and definition of outcome.[8, 17] Reported factors that negatively influenced the course of visual acuity after cessation of therapy included poor visual acuity at start of treatment, combined cause of amblyopia, eccentric fixation and age.[11, 13, 18] Almost all long-term studies were done retrospectively. Persistent amblyopia causes a significant burden on society, financially as well as a reduced quality of life.[19] It also nearly doubles the time an individual spends with bilateral visual impairment due to loss of vision in the non-amblyopic eye: this increases from 8 to 15.5 months, on average.[20]

In our previous randomized controlled trial (RCT; 2001-2003, N=303, NCT00131729) all newly diagnosed amblyopic children in four clinics in The Hague were registered. Included children received occlusion therapy, while compliance was measured electronically using the occlusion dose monitor (ODM). The purpose of the study was to determine whether compliance could be improved using an educational cartoon programme aimed at the child, and to identify risk factors for non-compliance. We found predictors for non-compliance to be a low initial visual acuity, poor parental fluency in the national language and low parental level of education. The educational programme significantly improved compliance throughout the study, limiting in particular the number of children who were not occluded at all.[5]

The purpose of this study was to determine the long-term course of the visual acuity after cessation of occlusion therapy for amblyopia and identify those at risk for visual acuity deterioration. At the time of this follow-up measurement all children were adolescents, most of them still living with their parents. They were contacted again for examination of their current visual acuity. Both the visual acuity measurement at end of occlusion therapy and at follow-up examination were performed under the same strictly controlled conditions by the same research orthoptist (BST). Compliance during occlusion therapy had been measured electronically and detailed clinical and socio-demographic data were readily available of all subjects.

Materials and Methods

Study population and orthoptic examination in amblyopia treatment study 2001-2004

Subjects were derived from a previous RCT, in which all newly diagnosed amblyopic children had been recruited from the four clinics in The Hague from 2001 until 2003.[5] The design for this prospective study has been reported in detail elsewhere.[5] Briefly, all amblyopic children were given standard orthoptic care with routine assessment every 3 to 4 months by the treating orthoptist. All measurements were conducted under controlled circumstances. Duration of occlusion (number of hours per day) for the first prescription was standardised according to the following formula: -6.63 x ratio acuity amblyopic eye/acuity better eye + 0.5 x age (years) + 4.97. Compliance was measured electronically using the ODM. Children were randomized to either the intervention group or the control group. The intervention group received an educational programme explaining to the child without words the reasons for patching. The control group received a picture to colour, without an educational message. The family's socio-economic status was ascertained using a 23-item questionnaire.

Occlusion therapy was completed when the interocular difference in visual acuity was one logMAR line or less on two consecutive visits to the orthoptist. From 2004 the research orthoptist (BST) assessed best corrected visual acuity with the Landolt-C chart 17.2' in children whose occlusion treatment was either 'completed' by the orthoptists or 'terminated' by the parents (i.e. parents who failed to attend the appointments in clinic). The research orthoptist tested the best corrected visual acuity with the Landolt-C chart 17.2' minutes of distance between optotypes at 5m distance. At least 3 out of 5 optotypes had to be answered correctly per line. The luminance of the chart was measured during the tests. This ranged from 160 cd/m2 to 320 cd/m2, which is in accordance with the ISO-8596 Standard.

Follow-up examination 2015-2017

All orthoptic and demographic data from the original 303 files were readily available and analysed. From these files, last known contact information was obtained. The subjects were contacted from December 2015 until July 2017 (Fig. 1). Eighty-nine (29%) could not be contacted using the available information from the original trial and six subjects had moved abroad. We were able to contact 208 subjects (69%), of whom 59 (19%) refused participation with a follow-up examination. Reasons for refusing participation included time or interest issues (N=33), not showing up for the appointment on multiple occasions (N=20), no

eye complaints (N=3) or had recently visited the ophthalmology department or optician (N=3). One subject could not be examined due to other disabilities. In total 148 subjects were examined, of these 14 were excluded. Reasons for exclusion were diminished visual acuity due to other ocular diseases (e.g. optic neuritis, mild oculocutaneous albinism) or brain damage (e.g. haemorrhage). In two subjects the visual acuity at the end of occlusion therapy was unknown and could not be obtained; in eight subjects the diagnosis of amblyopia could not be confirmed, in hindsight.

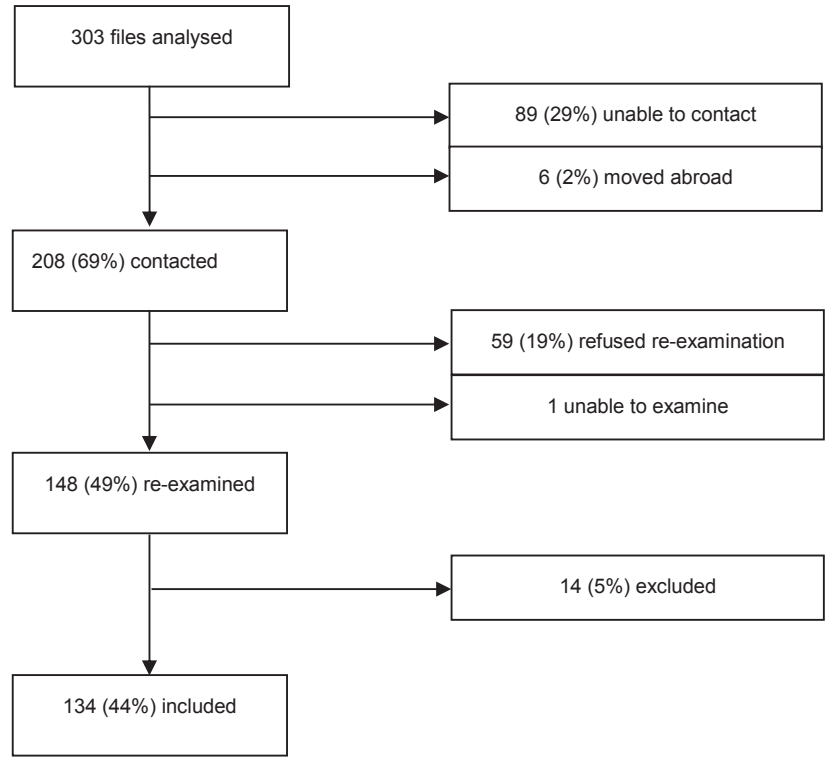


Figure 1. Recruitment procedure for re-examination.

The Ethical Committee of Erasmus University Rotterdam and the boards of the participating clinics approved the protocol and informed consent forms. Written informed consent was obtained from each subject and/or from his or her parents or guardians. The research adhered to the tenets of the Declaration of Helsinki.

The follow-up examinations were carried out at the outpatient clinic at Haaglanden Medical Center, Westeinde The Hague and conducted by the same research orthoptist (BST) who had examined the same subjects at the end of occlusion therapy, using the same protocol for measurement for visual acuity as in 2004. Examinations were performed through domiciliary visits if the subjects refused to visit the hospital. Binocular vision was assessed with Bagolini striated glasses, Titmus-Fly and TNO-test and expressed in five categories: (1) Bagolini negative; (2) Bagolini positive; (3) Bagolini and Titmus-Fly test positive; (4) TNO plate 480”-240”; (5) TNO plate 120”-15”. Retinal fixation and ocular alignment were investigated with the cover-uncover and alternating cover test at 30cm and 5m distance. Target for the cover test for fixation at near was a small object with detailed pictures to stimulate accommodation and to assess fixation. The target of the cover test at distance was a penlight. Reading acuity was tested using the Dutch version of the Radner Reading Chart.[21] Subjects were examined with their current spectacles. The best corrected visual acuity (BCVA) was determined using the Righton Retinomax handheld auto (kerato)-refractor together with subjective refraction in all subjects. Cycloplegic refraction was part of the original protocol, but most of the subjects refused participation if this was obliged. Therefore, to ensure for a reliable calculation of the refractive error we performed subjective refraction whereby the accommodation was eliminated with hypermetropic lenses. Degree of anisometropia was determined by calculating the difference in spherical equivalent between the two eyes based on the subjective refraction. Current degree of anisometropia was compared with the degree of anisometropia as measured with cycloplegic refraction at start of therapy: [Anisometropia follow-up] – [Anisometropia start of therapy]. Loss of 2 logMAR lines or more in visual acuity was defined as ‘severe deterioration’.

Statistics

Differences in characteristics, that is clinical and socio-economic data from the original study (N=303), between subjects who completed the follow-up examination (N=134) and those who did not, were investigated to assess for potential bias. These differences were tested using T-tests and Mann-Whitney tests for the following continuous variables: age at start of therapy, IOD at start, anisometropia at start, compliance during therapy, IOD at end of therapy. The chi-square test was used to investigate the following categorical variables: eccentric fixation, gender, randomisation group, fluency in the national language, level of education, number of working hours per week, country of origin and home-ownership.

As a measure for the degree of amblyopia we used the InterOcular VA Difference (IOD). The IOD at the end of occlusion therapy as measured by the research orthoptist (BST in 2004) was compared with the IOD as measured at the follow-up examination (BST in 2016). The main outcome measure was this change in IOD after cessation of occlusion therapy, calculated with the following formula: [VAae – Vafe]follow-up examination – [VAae – Vafe]end of occlusion treatment, with VAae the visual acuity of the amblyopic eye and VAfe the visual acuity of the fellow eye (logMAR). The Wilcoxon signed-rank test was used to assess any significant changes in IOD and binocular vision between end of occlusion treatment and at the follow-up examination. The Spearman correlation was used to determine the association between visual acuity and reading acuity. The influence of spectacle wearing on change in anisometropia was investigated with regression analysis.

In addition, we assessed risk factors for visual acuity deterioration. Univariable linear regression analysis was performed to investigate which clinical (i.e. age, gender, randomisation, diagnosis, visual acuity, anisometropia, retinal fixation, compliance, and duration of occlusion therapy) and socio-economic variables (i.e. parental fluency in the national language, parental level of education, number of working hours per week, country of origin and home-ownership) influenced the change in IOD (dependent variable). Potential confounding was corrected for in a multivariable linear regression analysis. Variable selection using a stepwise backward approach with a p-value cut-off of 0.20 was performed. All statistical tests were two-sided with a significance level of 0.05. Missing data were minimal, the variable “compliance” had five missing data points, and therefore complete case analyses were performed.

Results

Study population

Of the original cohort of 303 subjects, 208 were contacted successfully, 59 refused, 14 were excluded and we were unable to examine one subject. We included 134 (Fig. 1). Mean age at start of therapy was 4.7 (±2.0) years, 6.4 (±2.1) years at end of therapy and 18.3 (±2.1) years at follow-up examination.

Subjects who completed the follow-up examination and those who did not were comparable for the different baseline characteristics (p>0.05), except for gender. The follow-up group had significantly more females (p=0.006; 44% in the original cohort versus 53% in the follow-up group). Median compliance and interquartile range (IQR) in the original cohort (N=303) was 71% (IQR 37-91) with 150 (50%) subjects in the intervention group. Median compliance in the follow-up group (N=134) was 73% (IQR 42-91) with 73 (55%) subjects from the intervention group. In 18 subjects compliance was lower than 20%. Thirty-three subjects had strabismus amblyopia, 75 anisometropic amblyopia, 21 had a combined cause of amblyopia and 5 had deprivation amblyopia. Retinal fixation was determined as central in 124 subjects and as eccentric in 10 subjects.

Interocular Visual acuity Difference

Mean IOD at the start of treatment was 0.27 (±0.25) logMAR and 0.11 (±0.16) logMAR at end of therapy. Mean IOD at follow-up examination was 0.09 (±0.21) logMAR. There were 6 subjects who were prescribed occlusion treatment after their last examination, but failed to show up for their follow-up appointments. Patching might have continued, but this could not be confirmed. There was no significant difference between mean IOD at end of therapy and at follow-up examination (N=134; p=0.054). In 63 (47%) subjects the IOD had decreased, i.e. less amblyopia; in 36 (27%) subjects it remained stable. The IOD had increased, i.e. more amblyopia, in 35 subjects: 14 of the 75 (19%) anisometropic, 8 of the 33 (24%) strabismic, 10 of the 21 (48%) combined subjects and 3 of the 5 (60%) subjects with deprivation amblyopia. In five out of the 35 subjects the IOD had increased more than 2 logMAR lines. Subjects were categorised based on the initial depth of amblyopia according to the PEDIG criteria.[22, 23] Figure 2 shows the course of the IOD for each category. Subjects with severe amblyopia had improved most during occlusion therapy, but had deteriorated the most during follow-up examination.

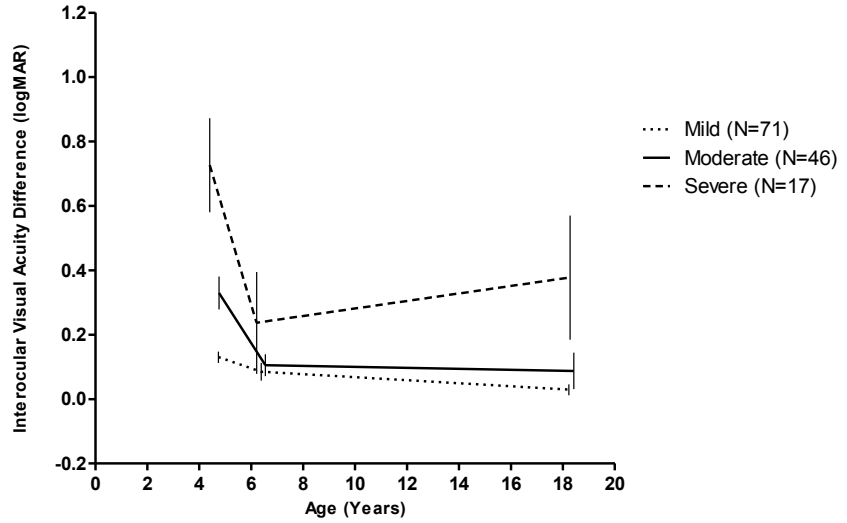


Figure 2. Mean Interocular Visual Acuity difference between the amblyopic eye and fellow eye at three points in time with 95% confidence intervals: at the start of occlusion therapy, at end of therapy and at the follow-up examination 12–15 years later. Subjects are categorized, based on the visual acuity of the amblyopic eye at start of occlusion therapy: mild (≤0.2 logMAR), moderate (0.30–0.60 logMAR) and severe (0.70–1.3 logMAR).

Factors influencing the course of IOD

Univariable analysis showed that a large IOD and high anisometropia at start of occlusion therapy were both associated with an IOD increase after cessation of therapy. Eccentric fixation and non-compliance during occlusion therapy were also significantly associated with IOD increase. Results of the univariable and multivariable analyses are listed in Table 1.

Multivariable analysis showed that a large IOD at start of occlusion therapy, eccentric fixation at start of therapy and an increasing anisometropia were associated with IOD increase after cessation of treatment. Of the socio-economic variables only parental level of education was borderline significant (p=0.054) in the multivariable analysis.

Table 1. Results of the univariable and multivariable analyses: the influence of clinical and socio-economic variables on the change in IOD between end of occlusion therapy and follow-up examination.

Independent variables	**Univariable analysis**			**Multivariable analysis**		
	B	**95% CI**	**p-Value**	**B**	**95% CI**	**p-Value**
Age at start of therapy (years)	-0.016	-0,032, 0.000	0.055			
Gender**						
Boys	0.022	-0.044, 0.088	0.515	0.058	0.007, 0.108	0.026
Girls	reference					
IOD at start of therapy (logMAR)**	0.235	0.106, 0.363	<0.001	0.332	0.205, 0.458	<0.001
IOD at end of therapy (logMAR)**	-0.357	-0.557, -0.157	0.001	-0.647	-0.820, -0.473	<0.001
Anisometropia at start of therapy (D)*	0.042	0.011, 0.073	0.008	0.020	-0.009, 0.049	0.169
Diagnosis			0.052			
Strabismus	-0.110	-0.290, 0.070	0.227			
Anisometropia	-0.150	-0.323, 0.023	0.090			
Combined	-0.037	-0.223, 0.150	0.698			
Deprivation	reference					
Eccentric fixation**	0.279	0.163, 0.396	<0.001	0.220	0.121, 0.319	<0.001
Compliance (%)	0.000	-0.001, 0.001	0.575			
Duration of occlusion therapy (years)	0.011	-0.028, 0.049	0.579			
Change in anisometropia (D)**	0.025	-0.009, 0.059	0.155	0.037	0.009, 0.064	0.009
Intervention (educational programme)	0.045	-0.021, 0.111	0.177			
Parental fluency national language		-0.045, 0.126	0.618			
Excellent	0.040	-0.142, 0.107	0.353			
Good	-0.017	-0.115, 0.110	0.782			
Moderate	-0.003	-0.060, 0.211	0.964			
Poor	0.076		0.270			
None	reference					
Highest level of education			0.118			0.054
University	0.069	-0.096, 0.234	0.406	0.003	-0.120, 0.127	0.957
Higher education	0.094	-0.061, 0.250	0.233	-0.033	-0.152, 0.085	0.580
Secondary education	0.163	0.006, 0.320	0.041	0.051	-0.068, 0.169	0.398
Primary education	0.061	-0.098, 0.219	0.452	-0.051	-0.172, 0.069	0.401
None	reference					
Number of working hours per week	0.000	-0.003, 0.002	0.732			

Table 1. Continued

Independent variables	Univariable analysis			Multivariable analysis		
	B	95% CI	p-Value	B	95% CI	p-Value
Country of origin			0.131			
Natives	0.048	-0.039, 0.135	0.275			
Surinam	0.028	-0.102, 0.157	0.673			
Morocco	0.063	-0.045, 0.171	0.250			
Turkey	-0.074	-0.186. 0.037	0.188			
Other	reference					
Home-ownership						
Yes	-0.031	-0.099, 0.038	0.379			
No	reference					

* Variable significantly affecting change in IOD after univariable analysis (p<0.05)
** Variable significantly affecting change in IOD after multivariable analysis (p<0.05)

Increasing anisometropia and spectacle wearing

It has been suggested by Simonsz-Tóth that amblyopia in children with increasing anisohypermetropia is more likely to deteriorate as new spectacles are needed frequently to keep up with the changing refractive error.[11] Overall, the degree of anisometropia was stable or had decreased (N=91; 68%) with 0.09 (±1.0) dioptres (D): 0.90D (±1.0) at start of occlusion therapy and 0.80D (±1.2) at the follow up examination. Eleven (8%) of the 35 subjects in whom IOD had increased, also had an increase of their anisometropia. In the multivariable analysis (Table 1) an increase in anisometropia was significantly associated with an IOD increase after cessation of therapy (p=0.009). To determine whether this association could be explained by spectacle wearing, we inquired about spectacle wearing in daily life in all 134 subjects and divided them into three categories. Sixty subjects (45%) wore their spectacles at least more than 50% of all waking hours; 20 (15%) wore spectacles less than 50% and 54 (40%) never wore spectacle correction or did not have any. Using univariable regression a relationship could not be demonstrated (p=0.064). Of the 54 subjects who never wore spectacles or did not have any, 17 showed an improvement with additional correction. Interestingly, of the 11 subjects who had an IOD increase as well as an increase in anisometropia, 6 seldom or never wore spectacles.

Compliance

Mean compliance with occlusion therapy as measured electronically was not significantly associated with change in IOD (B=0.000; p=0.575). However, when comparing subjects who did not comply with therapy at all (i.e. compliance less than 20%) with subjects with compliance more than 20%, the non-compliers were at risk for IOD deterioration after therapy (p=0.028) in the univariable analysis. This cut-off point of 20% was chosen as the lowest point in the bimodal distribution of compliance, which separated the children who had not been occluded regularly or not at all from the children who occluded routinely.[24] These non-compliers had a mean IOD of 0.33 (±0.33) logMAR at start of therapy; 0.15 (±0.27) at end of their occlusion therapy and 0.23 (±0.32) at follow-up examination. The VA in the amblyopic eye increased even with little patching, but deteriorated after therapy: 0.42 (±0.33) logMAR at start, 0.21 (±0.29) logMAR at end of occlusion therapy and 0.14 (±0.32) logMAR at follow-up examination. Interestingly, of the 18 subjects with compliance less than 20%, 17 were in the control group; 1 in the intervention group who received the educational cartoon programme. The educational programme greatly reduced the number of non-compliers in the original study and significantly improved the rate of VA increase.[25]

Subjects with severe visual acuity deterioration after cessation of therapy

Of all 134 included subjects, five (4%) had visual acuity deterioration in the amblyopic eye of ≥0.2 logMAR lines (Fig. 3); visual acuity in the fellow eye was ≤0.0 logMAR. These five subjects all had a combination of microstrabismus, eccentric fixation and poor visual acuity of the amblyopic eye at start of occlusion therapy. In the first subject the amblyopia was caused by anisometropia and strabismus; anisometropia was 3.50D and had not increased. Compliance with therapy at the time was 59%. In the second subject the amblyopia was also caused by anisometropia and strabismus; anisometropia was 4.38D and increased with 1.4D, he ceased wearing his spectacles at age 12. Compliance was 0%. The third subject had a strabismus amblyopia; anisometropia was 0.25D and increased with 0.50D. She has never worn any refractive correction. Compliance was 99%. The fourth subject had strabismus and anisometropia amblyopia; anisometropia was 1.0D and increased with 5D, she did not wear adequate spectacle correction. Compliance was 98%. The fifth subject had strabismus and anisometropia amblyopia; anisometropia was 1D and had not increased. Compliance was 0% at the time. He wore adequate spectacle correction.

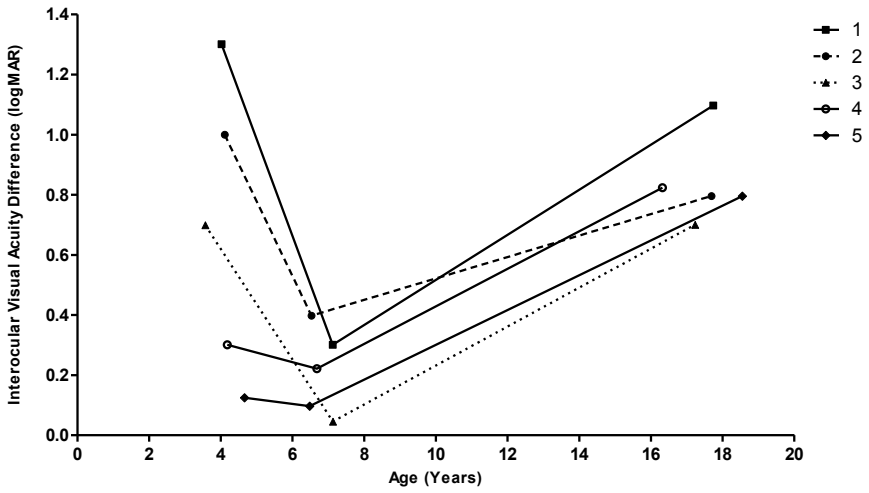


Figure 3. InterOcular VA Difference of the five subjects (number 1–5) with the largest VA deterioration measured at start of occlusion therapy, end of therapy and at follow-up examination. Four had a combined cause of amblyopia.

Binocular vision

In 34 (25%) subjects binocular vision at end of therapy was unknown and therefore, a comparison could not be made. Suppression as measured by Bagolini striated glasses was stable in the majority of the subjects (N=95; 71%). Three subjects scored a positive Bagolini test at end of therapy, but showed suppression on the Bagolini test at follow-up of whom two also showed profound deterioration in visual acuity of the amblyopic eye. Figure 4 shows the change in binocular vision of the 100 subjects at end of therapy and at the time of the follow-up examination; this change was not statistically significant (p=0.406).

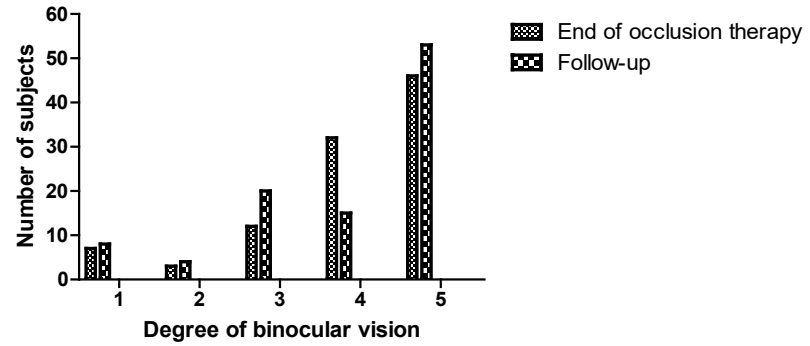


Figure 4. Binocular vision of the subjects at end of occlusion therapy and at the time of the follow-up examination. The degree of binocular vision was arranged into five categories: 1. Bagolini negative, 2. Bagolini positive, 3. Bagolini and Titmus-Fly positive, 4. TNO plate 480”-240”, 5. TNO plate 120”-15”.

Reading acuity

The mean reading acuity for the amblyopic eye was 0.19±0.26 logMAR and 0.05±0.14 logMAR for the fellow eye. Visual acuity at start of treatment was positively significantly correlated (Spearman correlation 0.377; p<0.001) with reading acuity at follow-up. Visual acuity at follow-up and reading acuity at follow-up were also significantly correlated (Spearman correlation 0.680; p<0.001).

Discussion

This study evaluated the long-term outcome of visual acuity in subjects who received occlusion therapy for amblyopia 12-15 years ago.[5] Visual acuity was measured under strictly controlled circumstances by the same orthoptist at end of therapy and at the long-term follow-up. Overall, we found good long-term results of occlusion therapy: 74% had stable or improved IOD.

Risk factors for IOD increase included degree of anisometropia, increasing anisometropia, eccentric fixation and non-compliance during occlusion therapy. A large IOD at the start of occlusion therapy was also significantly correlated with IOD increase after cessation of therapy. However, subjects with low initial VA also had worse compliance[5] with patch wearing, but increased the most during therapy even with little patching. Subjects who increased the most during occlusion therapy were the most at risk for loss of logMAR lines after cessation of therapy, explaining the found association between compliance and IOD increase after therapy.

Out of five subjects with severe deterioration (i.e. ≥2 logMAR lines) after cessation of occlusion therapy, four had a combined cause of amblyopia; three had increasing anisometropia and also had not worn their spectacles. One study comparable to ours was conducted by Simonsz-Tóth (N=137), who found 18 subjects (13%) with profound deterioration (>50% loss in visual acuity) in visual acuity 30 years after finishing occlusion treatment; 15 (11%) of these had an increase of anisometropia.[11] In that study the orthoptist who had examined the subjects during occlusion therapy also took part in the follow-up evaluation. In our study we found a lower percentage with severe visual acuity deterioration. This difference could be attributed to differences in length of follow-up time or improved spectacle wearing nowadays. We asked the subjects whether they had worn their spectacles, but on the basis of these data no statistically significant relationship was found.

Possible bias could be introduced to the analysis because of the 51% who either refused or could not be contacted. However, the statistical analysis showed that, except for gender, the subjects included for this study were a representative sample. We had more girls, maybe due to the fact that girls are more motivated to participate in a study. We also had missing data regarding the binocular vision, which could lead to a possible bias.

Another limitation in our study was that cycloplegic refraction was not performed. Our initial proposal did include cycloplegic refraction, but this was refused by most of the subjects. For calculation of the absolute refractive error, subjective refraction may not be ideal. However, for calculating the difference in refractive error between the eyes, i.e. the degree of anisometropia, it is expected that using subjective refraction is reliable. This is relevant as the degree of anisometropia and increasing anisometropia showed to be significantly correlated with IOD increase after cessation of occlusion therapy.

The Landolt-C 17.2” chart does not fulfil all the criteria of a ‘crowded’ chart and therefore visual acuity in the amblyopic eye may be over-scored. As primary outcome measure in the study we used visual acuity measured as much as possible according to ISO 8596 standard. The measurement of visual acuity with crowded optotypes is especially needed in the diagnosis and treatment of amblyopia, not so much in the final evaluation of the result of therapy. As we aimed to have comparable testing conditions for the follow-up measurements, we preferred to use the same chart as in 2004 and measurements were performed by the same orthoptist (BST).

Finally, it cannot be ruled out that there are other unknown factors that could cause changes in visual acuity as children grow older. Therefore, as a measure for amblyopia we used IOD as this would avoid part of the variability of the VA measurement.

We conclude that long-term results of occlusion therapy as a treatment for amblyopia were successful. High or increasing anisometropia, eccentric fixation and non-compliance during occlusion therapy were associated with increasing IOD and hence, with long-term visual acuity decrease.

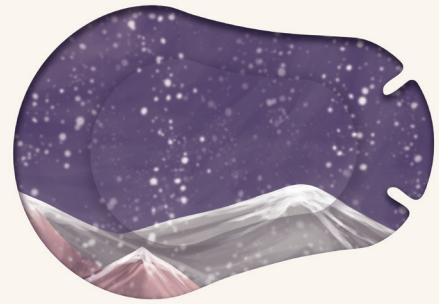
References

1. Reeves BC. Taxonomy and epidemiology of amblyopia. In: M.J. Mosely ARF, ed. Amblyopia: a Multidisciplinary Approach. London: Butterworth-Heinemann, 2002.
2. Stewart CE, Moseley MJ, Fielder AR, et al. Refractive adaptation in amblyopia: quantification of effect and implications for practice. Br J Ophthalmol 2004;88(12):1552-6.
3. Stewart CE, Moseley MJ, Stephens DA, Fielder AR. Treatment dose-response in amblyopia therapy: the Monitored Occlusion Treatment of Amblyopia Study (MOTAS). Invest Ophthalmol Vis Sci 2004;45(9):3048-54.
4. Loudon SE, Polling JR, Simonsz HJ. Electronically measured compliance with occlusion therapy for amblyopia is related to visual acuity increase. Graefes Arch Clin Exp Ophthalmol 2003;241(3):176-80.
5. Loudon SE, Fronius M, Looman CW, et al. Predictors and a remedy for noncompliance with amblyopia therapy in children measured with the occlusion dose monitor. Invest Ophthalmol Vis Sci 2006;47(10):4393-400.
6. Stewart CE, Stephens DA, Fielder AR, et al. Objectively monitored patching regimens for treatment of amblyopia: randomised trial. BMJ 2007;335(7622):707.
7. Repka MX, Wallace DK, Beck RW, et al. Two-year follow-up of a 6-month randomized trial of atropine vs patching for treatment of moderate amblyopia in children. Arch Ophthalmol 2005;123(2):149-57.
8. Hertle RW, Scheiman MM, Beck RW, et al. Stability of visual acuity improvement following discontinuation of amblyopia treatment in children aged 7 to 12 years. Arch Ophthalmol 2007;125(5):655-9.
9. Rutstein RP, Corliss DA. Long-term changes in visual acuity and refractive error in amblyopes. Optom Vis Sci 2004;81(7):510-5.
10. Leiba H, Shimshoni M, Oliver M, et al. Long-term follow-up of occlusion therapy in amblyopia. Ophthalmology 2001;108(9):1552-5.
11. Simonsz-Toth B, Loudon SE, van Kempen-du Saar H, et al. [Evaluation of visual acuity in a historical cohort of 137 patients treated for amblyopia by occlusion 30-35 years ago]. Klin Monbl Augenheilkd 2007;224(1):40-6.
12. Saxena R, Puranik S, Singh D, et al. Factors predicting recurrence in successfully treated cases of anisometropic amblyopia. Indian J Ophthalmol 2013;61(11):630-3.
13. Bhola R, Keech RV, Kutschke P, et al. Recurrence of amblyopia after occlusion therapy. Ophthalmology 2006;113(11):2097-100.
14. Scott WE, Kutschke PJ, Keech RV, et al. Amblyopia treatment outcomes. J AAPOS 2005;9(2):107-11.
15. Holmes JM, Beck RW, Kraker RT, et al. Risk of amblyopia recurrence after cessation of treatment. J AAPOS 2004;8(5):420-8.
16. Pediatric Eye Disease Investigator G, Repka MX, Kraker RT, et al. A randomized trial of atropine vs patching for treatment of moderate amblyopia: follow-up at age 10 years. Arch Ophthalmol 2008;126(8):1039-44.
17. Rutstein RP, Fuhr PS. Efficacy and stability of amblyopia therapy. Optom Vis Sci 1992;69(10):747-54.

18. Levartovsky S, Oliver M, Gottesman N, Shimshoni M. Factors affecting long term results of successfully treated amblyopia: initial visual acuity and type of amblyopia. Br J Ophthalmol 1995;79(3):225-8.
19. van de Graaf ES, van der Sterre GW, van Kempen-du Saar H, et al. Amblyopia and Strabismus Questionnaire (A&SQ): clinical validation in a historic cohort. Graefes Arch Clin Exp Ophthalmol 2007;245(11):1589-95.
20. van Leeuwen R, Eijkemans MJ, Vingerling JR, et al. Risk of bilateral visual impairment in individuals with amblyopia: the Rotterdam study. Br J Ophthalmol 2007;91(11):1450-1.
21. Maaijwee K, Mulder P, Radner W, Van Meurs JC. Reliability testing of the Dutch version of the Radner Reading Charts. Optom Vis Sci 2008;85(5):353-8.
22. Holmes JM, Kraker RT, Beck RW, et al. A randomized trial of prescribed patching regimens for treatment of severe amblyopia in children. Ophthalmology 2003;110(11):2075-87.
23. Repka MX, Beck RW, Holmes JM, et al. A randomized trial of patching regimens for treatment of moderate amblyopia in children. Arch Ophthalmol 2003;121(5):603-11.
24. Loudon SE, Passchier J, Chaker L, et al. Psychological causes of non-compliance with electronically monitored occlusion therapy for amblyopia. Br J Ophthalmol 2009;93(11):1499-503.
25. Tjiam AM, Holtslag G, Vukovic E, et al. An educational cartoon accelerates amblyopia therapy and improves compliance, especially among children of immigrants. Ophthalmology 2012;119(11):2393-401.

Effectiveness of optical treatment in amblyopia and validation of measuring spectacle compliance with the ODM

Spectacles resolve a third of amblyopia cases.



Aveen Kadhum, Emily T.C. Tan, Yaroslava Wenner,
Maurits V. Joosse, Sjoukje E. Loudon

Ophthalmic and Physiological Optics. 2024 Jul;44(5):945-953.

Abstract

Purpose: The improvement in visual acuity (VA) was determined during optical treatment in children with amblyopia before their participation in a randomised clinical trial comparing the effect of dichoptic video gaming using virtual reality goggles with occlusion therapy.

Methods: Children aged 4-12 years with an interocular VA difference ≥0.2 logMAR and an amblyogenic factor: strabismus <30Δ; ≥1.00D anisometropia, astigmatism ≥1.50D and/or hypermetropia ≥1.50D, were eligible for 16-weeks of optical treatment. Children with previous amblyopia treatment were excluded. Compliance with spectacle wear was measured electronically over 1 week using the Occlusion Dose Monitor (ODM). The reliability of these measurements was verified. The main outcome was an increase in amblyopic eye VA from baseline to 16 weeks.

Results: Sixty-five children entered the optical treatment period. Mean age was 6.0±2.2 years (range 4-12yrs; IQR 4.5–6.7yrs). Amblyopia was caused by anisometropia in 53 (82%) children, strabismus in 6 (9%) and combined mechanism in 6 (9%). After optical treatment, mean VA improved 0.20 logMAR (SD 0.28; p<0.001) and 0.07 in the amblyopic and fellow eye, respectively (SD 0.20; p=0.031). This resulted in 24 children (37%) with an interocular VA difference <0.20 logMAR; and in 17% of children with VA at the start of 0.30 logMAR or worse. Poor VA in the amblyopic eye at baseline (p=0.001) and high anisometropia (p=0.001) were associated with VA improvement. On average, spectacles were worn 9.7±2.4 hrs/day (range 2.3-13.6hrs); mean compliance was 73%±18% of estimated wake time. Only ambient temperature ≥31°Celcius, or when spectacles were worn on top of the head prevented a reliable ODM measurement.

Conclusions: VA improved by two lines resulting in more than a third of the children being treated sufficiently with spectacles alone and no longer being classified as amblyopic. The ODM proved to be a reliable method of measuring compliance with spectacle wear.

Key-points

- Spectacle correction during optical treatment is an important first step in amblyopia therapy, which results in sufficient treatment of amblyopia in approximately a third of the children.
- Even children with visual acuity ≥0.30 logMAR at baseline benefited from an optical treatment period, resulting in resolution of the amblyopia in 20% of cases.
- The occlusion dose monitor is a reliable method of measuring compliance with spectacle wear.

Introduction

Amblyopia is a neurodevelopmental vision disorder in children due to a disturbance in early visual development, and requires timely detection and treatment during the sensitive period.[1] Causes of amblyopia include strabismus (38%), anisometropia (37%) and both strabismus and anisometropia (24%).[2] Another less frequent cause is visual deprivation, which may be due to ptosis (2%).[3] Previous investigations have demonstrated that optical treatment, also called refractive adaptation, is a necessary and distinct component of amblyopia therapy.[4-6] Despite various studies showing the importance of spectacle wear as a first step in amblyopia treatment,[5, 7, 8] this is still not common practice. On occasion, spectacles are provided simultaneously with occlusion therapy or not prescribed at all, being replaced with extra hours of occlusion therapy. The beneficial effect of spectacles has not only been demonstrated in children, but also in adults.[9, 10] Prescribing a proper optical treatment prior to occlusion therapy may pre-empt the need for further occlusion therapy. Moreover, children who still need occlusion therapy will commence this treatment with improved visual acuity (VA) in the amblyopic eye, possibly leading to better compliance and a shorter occlusion period.[3, 7] Stewart et al. stated that the average number of weeks required to achieve optimum VA during the optical treatment period was 14–15 weeks.[5] We sought to highlight the need for optical treatment as a distinct component of amblyopia therapy.

In a randomised clinical trial (RCT; NCT03767985), we compared the effect of dichoptic video gaming using virtual reality goggles with occlusion therapy for newly diagnosed amblyopia in children after optical treatment. This 16 week optical treatment prior to enrolment was a prerequisite for participating in the study.[11] Compliance with spectacle wear was electronically monitored using the occlusion dose monitor (ODM). This device has been used in previous studies and proven to be a reliable device in measuring compliance with occlusion therapy.[12-15] The aim of this study was to investigate the VA increase during optical treatment, and to validate the use of the ODM for monitoring compliance with spectacle wear objectively under various conditions. In addition, we investigated the effect of VA at the start of treatment, as well as the effects of age, sex, refractive error, type of amblyopia and compliance with spectacle wear on the improvement in VA resulting from optical treatment.

Methods

Study population

Children aged 4-12 years with an interocular difference in VA (IOD) of ≥0.20 logMAR caused by anisometropia, strabismus or both anisometropia and strabismus were recruited for a prospective randomised control trial (RCT) comparing the effect of dichoptic gaming with occlusion therapy (NCT03767985).[16] Eligible children were recruited from five clinics in the Netherlands (Haaglanden Medical Center (The Hague), Tergooi Hospital (Hilversum, Blaricum), IJsselland Hospital, HU Clinics University of Applied Science Utrecht and Erasmus MC University Medical Center, Rotterdam) between December 2017 and June 2020. The majority of the participants were from The Hague, which comprises a multi-ethnical and -cultural population. Exclusion criteria were previous treatment for amblyopia, a neurological disorder, other eye disorders of diminished VA due to medication, brain damage or trauma. Children with strabismus >30Δ were also excluded as this prevented them from playing the dichoptic action video game and therefore entering the RCT. The Ethics Committee of the Erasmus University Medical Center and the boards of the participating clinics approved the protocol and informed consent forms. Written informed consent from the parents or guardians was a prerequisite for participation. The research adhered to the tenets of the Declaration of Helsinki.

Study design

Eligible children received a routine ophthalmic examination by the treating orthoptist and ophthalmologist. This included the following: (1) baseline, post-cycloplegic corrected VA using a tumbling E chart where possible. If they were too young, the Amsterdam Picture Chart, the Landolt C or Lea Hyvärinen charts were used; (2) ocular motility and (3) alignment using cover-uncover and alternating cover tests at 30 cm and at 5 m. Cycloplegic refraction was performed using 1% cyclopentolate eye drops. Children received spectacles in cases of anisometropia with ≥1D (spherical equivalent) difference between the two eyes, astigmatism with ≥1.5D difference between the eyes in any meridian, hypermetropia (spherical equivalent) ≥1.5D or ≥0.50D myopia. Children were prescribed 0.50D symmetrical undercorrection from the full cycloplegic refraction. Whenever possible, the cycloplegic refraction was confirmed subjectively. It was emphasised to the parents that wearing the spectacles was a prerequisite for participation in the RCT. Parents were instructed to let their child wear their spectacles during all waking hours and it was made clear that this was an important component of amblyopia treatment and may lead to VA improvement. All children were referred to the

research centre where the orthoptist (ET) carried out a standard orthoptic and ophthalmologic examination after 16 weeks of optical treatment. This included: (1) best corrected VA with their own spectacles using the crowded tumbling E chart (precision-vision.com), (2) stereo acuity using the Randot Stereotest Wirt circles (stereooptical.com) at 40 cm, (3) contrast sensitivity using the Pelli-Robson chart (precision-vision.com) in older subjects and CSV-1000 (vectorvision.com) in the younger children, (4) ocular motility and (5) alignment with the cover-uncover and alternating cover test at 30 cm and 5 m. The research orthoptist assessed whether the child fulfilled the criteria of amblyopia (i.e., interocular VA difference of 0.20 logMAR or more) and could be included in the RCT.

Families who had informed the treating orthoptist they would not wear the prescribed spectacles were not recruited as this was a prerequisite for the RCT. We retrospectively assessed how many families refused the spectacles by going through the clinical files during the study period.

Occlusion Dose Monitor

Compliance with spectacle wear was objectively monitored using the electronic recordings of the Occlusion Dose Monitor (ODM). The ODM is an investigational device used for study purposes only. Fielder developed the first prototype of this device in 1991, and this was modified by the Amsterdam University Medical Center.[17] In this study, the 2002 version of the ODM was used.[14, 17] This technique has proven to be reliable for the assessment of compliance with occlusion therapy.[14] The ODM was attached to the temple of the spectacles using a standard occlusion patch fromOrthopad (Trusetal Verbandstoffwerk GMBH, https://www.tshs.eu/en/index.html) or Opticlude™ (3M™, https://www.3mnederland.nl; Figure 1), in order to monitor compliance with spectacle wear for one week. It measures the temperature difference between the front and the back of the ODM every 3 minutes.[14] The families were instructed to keep the ODM attached to the glasses for one week, after which they could remove it, keep it in a provided container and return it at the next appointment. It was made clear to the families that the device measured the amount of time the spectacles were being worn. The battery duration was sufficient for at least 1 week. Within the expert group of orthoptists, it was decided to measure the compliance with spectacle wear directly after the 16 weeks of optical treatment, as we expected children to be more used to their glasses and compliance would be more stable, compared to the first few weeks. It was important that the timing of the compliance measurement was the same for all children.

The ODM measured the temperature difference between the front and the back of the monitor every 3 minutes. The sensitivity was set at 0.063° Celsius. After a period of recording, the data were saved on a computer by means of a docking system.

Figure 1. A 5-year-old girl wearing the occlusion dose monitor attached to the temple of the spectacles using an eye patch.

To investigate the reliability of these measurements, five members of the research group and their family members wore their spectacles with the ODM attached and kept diaries with time recordings of when the spectacles were worn. The ODM recordings and diaries were compared. In addition, measurements with the ODM attached to the spectacles were carried out under various conditions: (1) spectacles worn correctly; (2) spectacles on the table; (3) spectacles worn correctly but with ODM placed upside down on the patch; (4) spectacles on top of the head; (5) spectacles in the case and (6) ODM on an occlusion patch being worn

on the eye as a regular eye patch. Lastly, we investigated the influence of ambient temperature. We carried out measurements with the ODM on the spectacles, varying the room temperature from 18°C to 33°C to determine the temperature range preventing reliable measurements.

Outcome measure and statistical analysis

VA in both the amblyopic eye and the fellow eye were compared to the VA after 16 weeks of optical treatment. Wilcoxon signed-rank test was used to investigate if the observed change was statistically significant. The level of compliance was defined as the actual time spectacles were worn as measured by the ODM, divided by the number of waking hours. For the number of waking hours was, the systematic review of Galland et al.[18] was used, which was dependent on age, following the method of Maconachie et al.[19] This was expressed as a percentage. To determine the specificity of the ODM data when worn on the spectacles, the mean temperature difference and standard deviation were compared by means of Hotelling's-T2 test (comparing the averages of the variables, a method of multivariable analysis)[14] and the discriminant analysis. The relationship between the measured mean temperature difference and the ambient temperature was evaluated by means of the Pearson regression test.

Wilcoxon signed-rank test was used to compare VA changes from baseline until 16 weeks. The effect of VA at the start, age, sex, refractive error, type of amblyopia and compliance with spectacle wear on VA changes during optical treatment was assessed using linear regression models. Statistical analysis was performed using SPSS statistics version 28 (ibm.com) and BiAS 11.10 (Epsilon 2019, https://www.bias-online.de).

Results

Study population

Ninety-six children were recruited for the RCT; two were excluded because of legal issues. Participation in the RCT was discussed with 94 families, of whom 29 refused to participate. Sixty-five entered and completed the 16-week optical treatment, see Figure 2. Mean age was 6.0±2.2 years; 30 were female (46%). The mean spherical equivalent refractive error in the amblyopic eye (AE) and fellow eye (FE) was 2.55±3.14D and 2.08±2.03D, respectively, see Table 1. After the 16-week optical treatment period, eight participants dropped out, three refused further participation due to the time-consuming nature of the weekly visits to the clinic, three due to stopping of recruitment caused by the COVID-19 pandemic and two withdrew their participation.

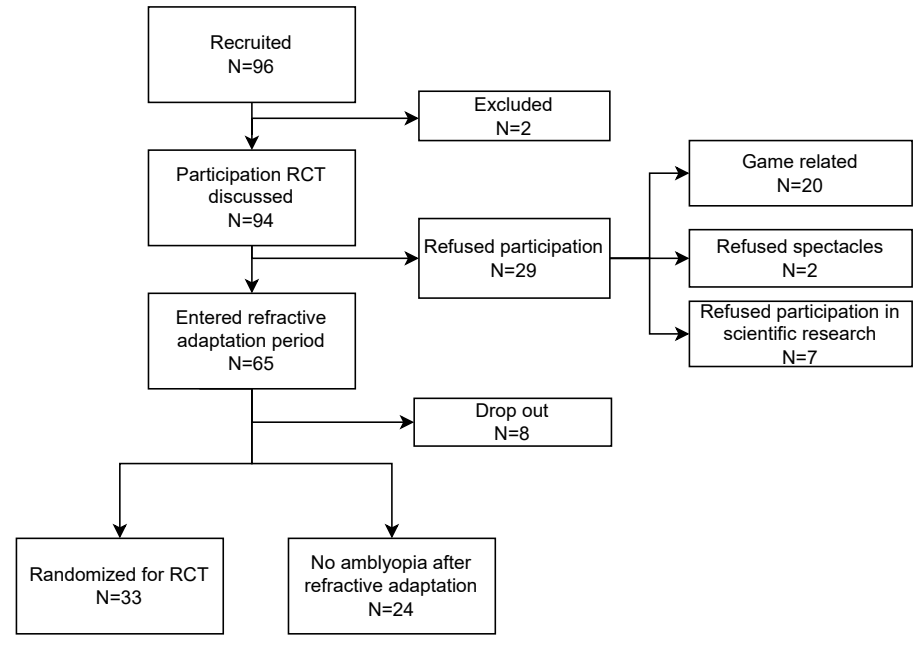


Figure 2. Flow chart of patient recruitment. RCT, randomised clinical trial.

Table 1. Baseline characteristics.

	All participants (N=65)
Gender, female (N, %)	30 (46%)
Age (years, mean, ±SD)	6.0 ± 2.2
Visual acuity amblyopic eye (logMAR, mean ±SD)	0.51 ± 0.39
Visual acuity fellow eye (logMAR, mean, ±SD)	0.15 ± 0.19
Amblyopia cause (N, %)	
Anisometropia	53 (82%)
Strabismus	6 (9%)
Combined	6 (9%)
Spherical equivalent amblyopic eye (diopters, mean ±SD)	2.55 ± 3.14
Spherical equivalent fellow eye (diopters, mean, SD)	2.08 ± 2.03
Anisometropia (diopters, mean, SD)	1.40 (1.70)

Visual Acuity

The mean VA, recorded under cycloplegia with optical correction at baseline was 0.51±0.39 logMAR in the amblyopic eye, which improved on average by two lines after 16 weeks to 0.31±0.31 logMAR (p<0.001). Mean VA in the fellow eye at baseline was 0.15±0.19 logMAR, which improved by almost one line to 0.08±0.13 logMAR (p=0.03).

The VA in children with anisometropic amblyopia (N=53) improved by 0.23±0.20 in the amblyopic eye and 0.07±0.19 logMAR in the fellow eye (p<0.001 and p=0.03 respectively). For children with strabismus (N=6), there was a mean change in VA for the amblyopic eye of -0.03±0.43 logMAR (three improved and three deteriorated). The fellow eye improved by 0.17±0.32 logMAR (p=0.92 and p=0.16 respectively). In children with both anisometropia and strabismus (N=6), a change of 0.16±0.32 logMAR and -0.07±0.15 logMAR was observed in the amblyopic and fellow eye, respectively (p=0.28 and p=0.29, respectively). The interocular difference decreased on average by 0.14±0.28 logMAR.

Overall, 24 (37%) children improved such that they no longer met the criteria for amblyopia (i.e., < 0.20 logMAR interocular difference); thus making them ineligible for the RCT. Of these children, 21 had anisometropia, two strabismus and one had both anisometropia and strabismus.

Of the 35 children with VA at the start of therapy of 0.30 logMAR or worse, (28 with anisometropia, two with strabismus, five with both anisometropia and strabismus), six (17%) were considered sufficiently treated after optical treatment (an interocular difference in VA ≤0.20 logMAR). Of these, five had anisometropia and one both anisometropia and strabismus.

Of the 30 children with VA at the start of therapy of 0.30 logMAR or better (25 with anisometropia, four with strabismus and one with both anisometropia and strabismus), 18 (60%) were considered treated after optical treatment (N=16 anisometropia, N=2 strabismus).

Retrospectively we investigated how many new patients visited the recruiting orthoptists, required spectacles but refused to purchase them. There was only one child who refused the required spectacles and therefore was not referred to the research centre. VA in the amblyopic eye was 0.40 logMAR, which had not changed at the next visit, some 3-4 months later.

Compliance with spectacle wear with the ODM

Figure 3 shows an example of a one-week of ODM recording, while Figure S1 shows the study population categorised by compliance. The mean compliance with spectacle wear was 73%±18% (range 16–100%). Poor uncorrected VA in both the amblyopic and fellow eye at baseline were associated with a better spectacle compliance (Spearman correlation: 0.29 p=0.047; 0.32 p=0.03, respectively).

Only five children wore their spectacles less than 50% of all waking hours, with a mean compliance of 34%±13%. All five had anisometropic amblyopia. Their mean VA before spectacle wear in the amblyopic and fellow eye was 0.40±0.51 and 0.01±0.04 logMAR, respectively. This improved to 0.24±0.33 and 0.02±0.08 logMAR, respectively, after optical treatment.

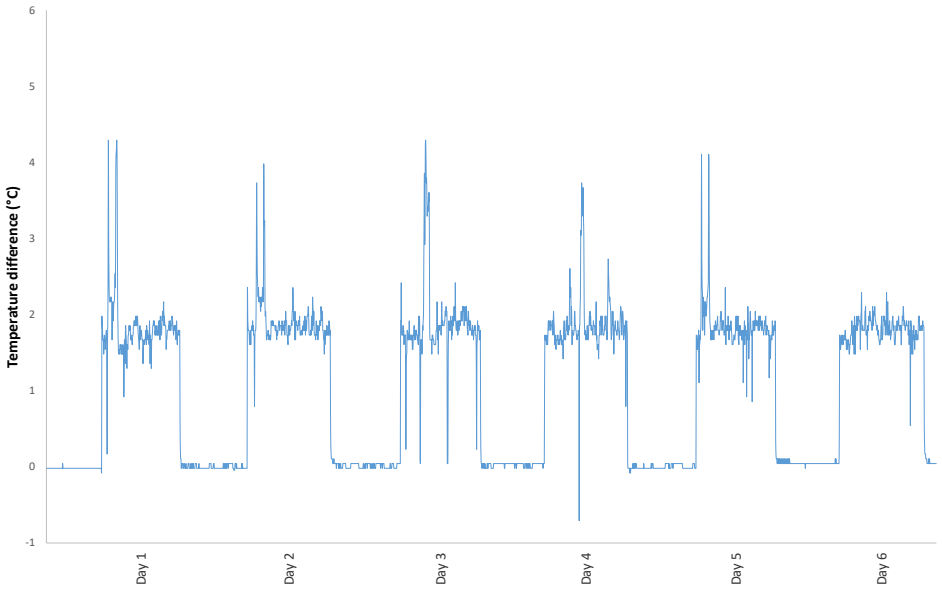


Figure 3. Example of a 1-week recording of spectacle wear with the occlusion dose monitor (ODM). The x- and y-axis show the day of the recording and the temperature difference between the front and back of the ODM in °C, respectively. The temperature difference when the spectacles were not worn was approximately 0°C.

Factors influencing outcome

Univariable analysis showed that poor VA in the amblyopic eye at baseline (p=0.001) and high anisometropia (p=0.001) were associated with VA improvement. In contrast, age (p=0.14), sex (p=0.41), amblyopia aetiology (p=0.09) and electronically monitored compliance with spectacle wear (p=0.84) were not associated with the change in VA. The multivariable analysis showed that poor VA in the amblyopic eye at baseline was associated with VA improvement during the optical treatment (p=0.001); children with strabismic amblyopia had less VA improvement compared with the anisometropic and combined children (p=0.003). High anisometropia (p=0.54), age (p=0.21), compliance with spectacle wear (p=0.74) and gender (0.86) were not significantly associated with VA improvement.

Compliance with spectacle wear and VA improvement

Figure 4 shows the relationship between VA improvement in the amblyopic eye and compliance with spectacle wear.

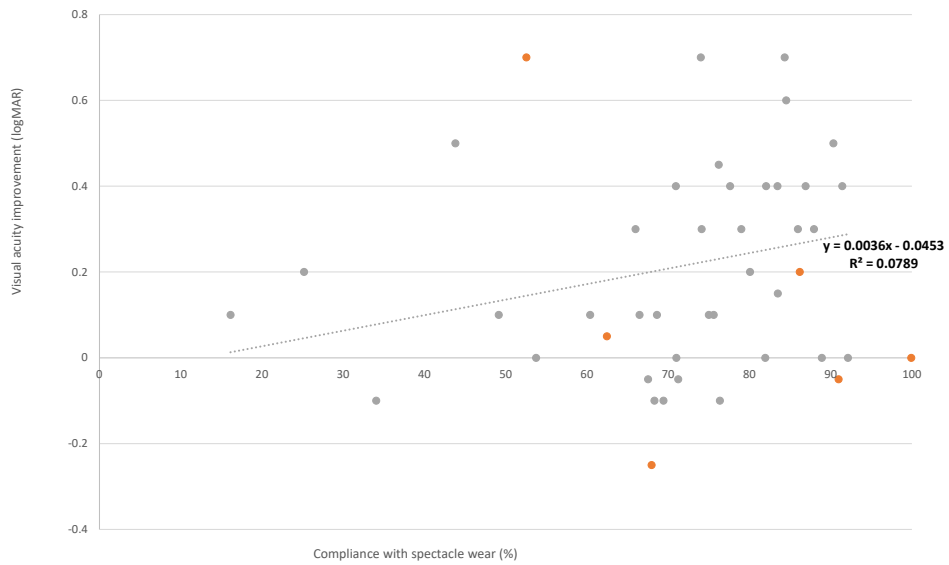


Figure 4. Scatterplot showing compliance with spectacle wear and visual acuity improvement with optical treatment. Each dot represents one subject. Note that some data points may (partially) overlap. Orange dots represent the children with strabismus.

Strabismus

There were 14 children in the study with strabismus: two with fully accommodative esotropia, seven with partially accommodative esotropia, two with micro esotropia (N=2), one intermittent exotropia and one with secondary exotropia. Of the two children with fully accommodative esotropia, one was considered treated after optical therapy and the other was not. All seven children with partially accommodative strabismus were *not* sufficiently treated with optical treatment (see Table 2).

Table 2. Subtype of strabismus with result of optical treatment.

Subtype strabismus	N	Sufficiently treated after optical treatment	Insufficiently treated after optical treatment
Fully accommodative esotropia	2	1	1
Partially accommodative esotropia	7	0	7
Micro esotropia	2	2	0
Intermittent exotropia	1	0	1
Secondary exotropia	1	0	1

Validation of measuring spectacle compliance with the ODM

Correspondence between the ODM measurements and diaries

Correspondence between the spectacle wearing times as measured by the ODM and the recorded diaries was 93%. The duration of measurements lasted > 11 hours. The mean time difference between the ODM measurements and the researchers' diary was 2±1 minutes with a maximum of 5 minutes. This was due to a sampling rate for the ODM of 3 minutes.

Influence of ambient temperature

The ambient temperature influenced the temperature difference measured by the ODM following this formula: y = -0.1496x + 4.678 (y is the measured temperature difference by the ODM and x equals the actual temperature in the room). As expected, high ambient temperatures (≥31°C) prevented reliable measurements with the ODM (Figure S2). The temperature difference was zero when the ambient temperature approached 31°C.

Different locations

Several locations were tested to investigate whether the monitoring system could be deceived (Table 3; Figure S3 Appendix). ODM measurements were carried out while the spectacles were worn correctly, with the spectacles in the spectacle case, while the spectacles were worn on top of the head and with the spectacles worn correctly but with the ODM upside down in the patch and while the eye was patched. These measurements are presented in Table 3.

Undesired situations as spectacles in the case or on the table could be distinguished from spectacles worn correctly with a low rate of false classification. The temperature difference measured from the patch worn on the eye was generally higher than on the spectacles. It was not possible to distinguish between spectacles worn correctly versus on top of the head.

Table 3. Mean temperature differences (°C) with standard deviations (SD) measured by the occlusion dose monitor (ODM) in different locations.

	spectacles worn correctly	In spectacle case	On top of the head	On the table	Worn correctly with ODM patched reversed	Eye patched
Number of tests	28	8	6	19	4	15
Mean temperature difference (°C, SD)	1.455 (SD 0.480)	0.067 (SD 0.064)	1.505 (SD 0.538)	0.039 (SD 0.056)	-1.327 (SD 0.548)	2.552 (SD 0.579)
Discriminant analysis: rate of false classification	-	p=0.03	p=0.37	p=0.01	p=0.0002	p=0.11
Hotelling's T2 test	-	p<0.00001	p=0.335	p<0.00001	p<0.00001	p<0.00001

Note: Results of the discriminant analysis (rate of classification) and Hotelling's T2 test for comparison between measurements with the spectacles worn correctly are also displayed.

Discussion

This study highlights the necessity for optical treatment as an essential first step in the management of not only refractive amblyopia but also for amblyopia associated with strabismus and both anisometropia and strabismus. We found that VA improved on average by 0.20 logMAR in the amblyopic eye and 0.07 logMAR in the fellow eye, resulting in more than a third of the children being treated sufficiently with spectacles alone. The study population included a large number of children with mild amblyopia, a group often excluded from clinical trials. Some 37% of this group were treated sufficiently with optical treatment alone, emphasising the importance of spectacles, even in these mild cases. In addition, the results showed that the use of an objective monitor to measure compliance with spectacle wear is a reliable method.

These findings are comparable with the available literature. Stewart et al. (n=65) found a significant improvement in VA of 0.24 logMAR in the amblyopic eye of children with anisometropia and/or strabismic amblyopia during optical treatment. In 13.8% (n=9), no further amblyopia treatment was necessary.[5] Cotter et al. (n=84) showed that the mean VA improvement during optical treatment in children with anisometropic amblyopia was 0.29 logMAR, with 27% (n=23) having resolution of their amblyopia.[7] Additionally, the PEDIG group (n=146) demonstrated that even in children with strabismus or a combined cause of amblyopia, optical treatment resulted in a clinically meaningful improvement in the amblyopic eye, with a mean improvement of 0.26 logMAR and 32% (n=41) having resolution of their amblyopia.[8] However, in these studies, there was no electronic monitoring of compliance with spectacle wear.

The electronically monitored compliance with spectacle wear found in the present study was relatively good, with an average of 73%. Compliance was monitored for one week. Spectacle compliance was measured directly after the 16 weeks of optical treatment, as we expected children to be more used to their glasses and compliance would be more stable, when compared with the first few weeks. We considered the most important aspect was that the timing of the compliance measurement was the same for all children.

Parents were told that spectacle wear was compulsory for participation in the trial. This statement alone could have resulted in better spectacle wear. The children who refused to wear the spectacles a priori were excluded from the trial. However, we determined the number of children who were missed following refusal to

wear spectacles by retrospectively studying all newly diagnosed amblyopic children. We found that only one patient was not referred. VA did not improve in this child at their second visit to the orthoptist. Nevertheless, these findings were comparable with Maconachie et al., who reported an average compliance of 70%.[19] They observed a moderate correlation between compliance with spectacle wear and the percentage improvement in VA during the optical treatment phase. We were not able to demonstrate this correlation, possibly because the present population represented a select group with a higher level and less variance in compliance.

Further, we found that children with poor VA in the amblyopic eye and high anisometropia at baseline showed more improvement in VA during optical treatment, according to the univariable analysis. Children with strabismic amblyopia improved less during optical treatment than the children with anisometropia or both anisometropia and strabismic amblyopia. Maconachie et al. also found that individuals with anisometropic amblyopia improved more during optical treatment than those with strabismic amblyopia.[19]

The results showed that the ODM positioned on the temple of the spectacles is a reliable method for measuring the duration of spectacle wear. The recorded diaries were in agreement with the objective recordings, which is in accordance with previous findings.[19] Indeed, the results were comparable with a validation study showing that use of the ODM for monitoring compliance with occlusion therapy is reliable.[14] The likelihood of misclassification was minimal for spectacles placed on a table or in their case. However, it was not possible to distinguish between spectacles worn correctly versus on top of the head. On the other hand, a child refusing to wear spectacles typically removes them entirely, rather than placing them on their head.

In conclusion, these results emphasise the necessity for optical treatment for all types of amblyopia, leading to sufficient therapy in more than a third of the children. When baseline VA in the amblyopic eye was 0.30 logMAR or worse, it represented adequate treatment in one out of six children. In addition, the ODM proved to be a reliable device for measuring spectacle wear compliance.

References

1. Miller NP, Aldred B, Schmitt MA, Rokers B. Impact of Amblyopia on the Central Nervous System. J Binocul Vis Ocul Motil. 2020;70(4):182-92. Epub 2020/11/19.
2. Pediatric Eye Disease Investigator G. The clinical profile of moderate amblyopia in children younger than 7 years. Arch Ophthalmol. 2002;120(3):281-7. Epub 2002/03/15.
3. Loudon SE, Fronius M, Looman CW, Awan M, Simonsz B, van der Maas PJ, et al. Predictors and a remedy for noncompliance with amblyopia therapy in children measured with the occlusion dose monitor. Invest Ophthalmol Vis Sci. 2006;47(10):4393-400. Epub 2006/09/28.
4. Moseley MJ, Neufeld M, McCarry B, Charnock A, McNamara R, Rice T, et al. Remediation of refractive amblyopia by optical correction alone. Ophthalmic Physiol Opt. 2002;22(4):296-9. Epub 2002/08/07.
5. Stewart CE, Moseley MJ, Fielder AR, Stephens DA, Cooperative M. Refractive adaptation in amblyopia: quantification of effect and implications for practice. Br J Ophthalmol. 2004;88(12):1552-6. Epub 2004/11/19.
6. Scheiman MM, Hertle RW, Beck RW, Edwards AR, Birch E, Cotter SA, et al. Randomized trial of treatment of amblyopia in children aged 7 to 17 years. Arch Ophthalmol. 2005;123(4):437-47. Epub 2005/04/13.
7. Cotter SA, Pediatric Eye Disease Investigator G, Edwards AR, Wallace DK, Beck RW, Arnold RW, et al. Treatment of anisometropic amblyopia in children with refractive correction. Ophthalmology. 2006;113(6):895-903. Epub 2006/06/06.
8. Writing Committee for the Pediatric Eye Disease Investigator G, Cotter SA, Foster NC, Holmes JM, Melia BM, Wallace DK, et al. Optical treatment of strabismic and combined strabismic-anisometropic amblyopia. Ophthalmology. 2012;119(1):150-8. Epub 2011/10/01.
9. Vedamurthy I, Nahum M, Huang SJ, Zheng F, Bayliss J, Bavelier D, et al. A dichoptic custom-made action video game as a treatment for adult amblyopia. Vision Res. 2015;114:173-87. Epub 2015/04/29.
10. Gao TY, Anstice N, Babu RJ, Black JM, Bobier WR, Dai S, et al. Optical treatment of amblyopia in older children and adults is essential prior to enrolment in a clinical trial. Ophthalmic Physiol Opt. 2018;38(2):129-43. Epub 2018/01/23.
11. Kadhum A, Tan ETC, Levi DM, Colpa L, Fronius M, Simonsz HJ, et al. Barriers to successful dichoptic treatment for amblyopia in young children. Graefes Arch Clin Exp Ophthalmol. 2021. Epub 2021/06/01.
12. Fielder AR, Irwin M, Auld R, Cocker KD, Jones HS, Moseley MJ. Compliance in amblyopia therapy: objective monitoring of occlusion. Br J Ophthalmol. 1995;79(6):585-9. Epub 1995/06/01.
13. Simonsz HJ. Occlusion dose monitor available for electronic recording of compliance in patch wearing for amblyopia. Strabismus. 2012;20(1):42. Epub 2012/03/07.
14. Chopovska Y, Loudon SE, Cirina L, Zubcov A, Simonsz HJ, Luchtenberg M, et al. Electronic recording of occlusion treatment for amblyopia: potential of the new technology. Graefes Arch Clin Exp Ophthalmol. 2005;243(6):539-44. Epub 2005/06/21.
15. Stewart CE, Moseley MJ, Stephens DA, Fielder AR. Treatment dose-response in amblyopia therapy: the Monitored Occlusion Treatment of Amblyopia Study (MOTAS). Invest Ophthalmol Vis Sci. 2004;45(9):3048-54. Epub 2004/08/25.

16. Kadhum A, Tan ETC, Fronius M, Baart SJ, Levi DM, Joosse MV, et al. Supervised dichoptic gaming versus monitored occlusion therapy for childhood amblyopia: Effectiveness and efficiency. Acta Ophthalmol. 2023. Epub 2023/04/20.
17. Simonsz HJ, Polling JR, Voorn R, van Leeuwen J, Meester H, Romijn C, et al. Electronic monitoring of treatment compliance in patching for amblyopia. Strabismus. 1999;7(2):113-23. Epub 1999/07/27.
18. Galland BC, Taylor BJ, Elder DE, Herbison P. Normal sleep patterns in infants and children: a systematic review of observational studies. Sleep Med Rev. 2012;16:213–22.
19. Maconachie GD, Farooq S, Bush G, Kempton J, Proudlock FA, Gottlob I. Association between adherence to glasses wearing during amblyopia treatment and improvement in visual acuity. JAMA Ophthalmol. 2016;134:1347–53.

Appendix

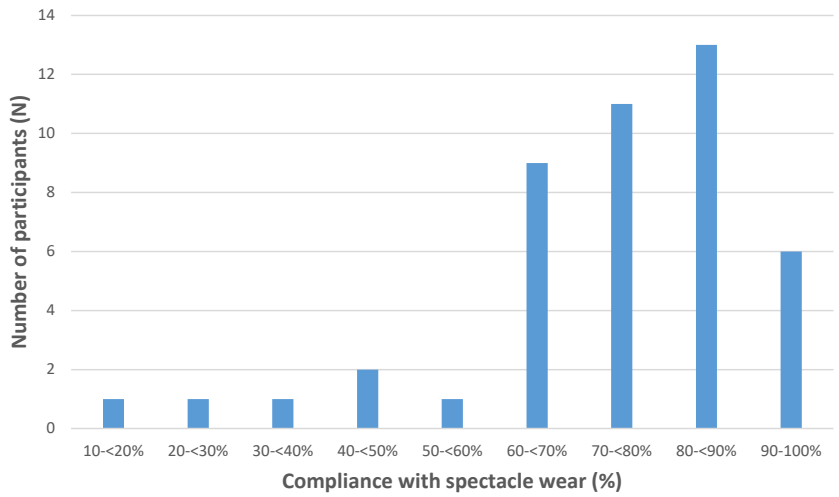


Figure S1. Compliance with spectacle wear in categories, calculated with duration of spectacle wear in hours, based on the average sleep duration for age.

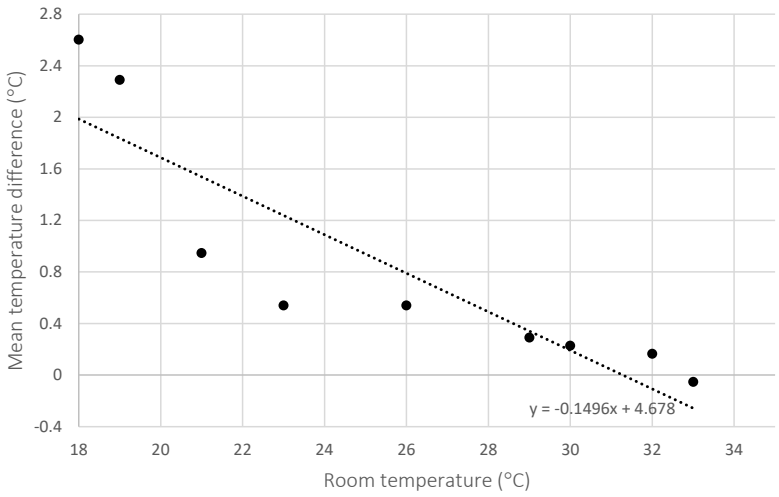
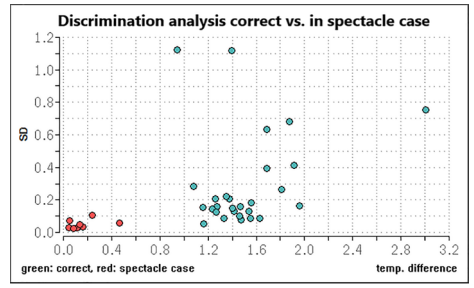


Figure S2. Influence of ambient temperature on ODM measurement. Room temperature is shown on the x-axis; mean temperature differences measured by the ODM are shown on the y-axis. Room temperature ≥31°C prevented reliable measurements.

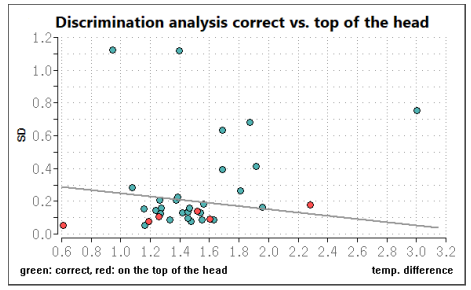
A



Chance for a false classification: p=0.026140

Hotelling's T^2 p<0.00001

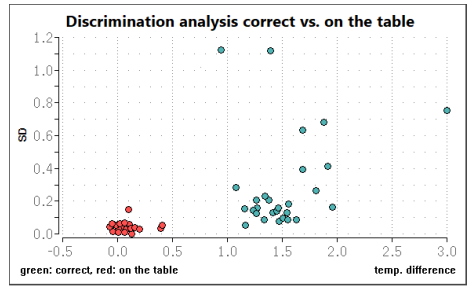
B



Chance for a false classification: p=0.365327

Hotelling's T^2 p=0.334548

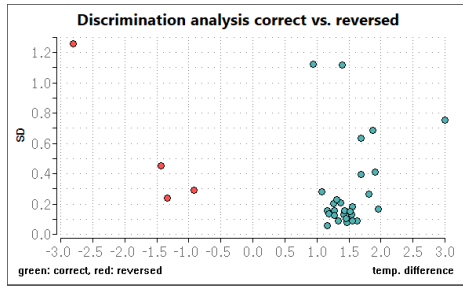
C



Chance for a false classification: p=0.010192

Hotelling's T^2 p<0.00001

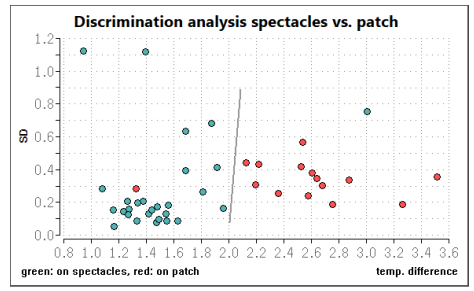
D



Chance for a false classification: p=0.000236

Hotelling's T^2 p<0.00001

E

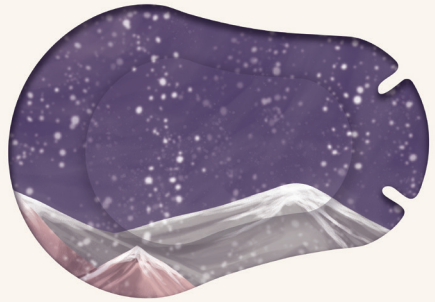


Chance for a false classification: p=0.114087

Hotelling's T^2 p<0.00001

Figure S3. Discrimination analysis of spectacles worn correctly compared with different circumstances: a Comparison with spectacles in spectacle case; b Comparison with spectacles worn on top of the head; c Comparison with spectacles on table; d Comparison with spectacles worn upside down in the patch; e Comparison with ODM on patch on the eye. Abscissa: mean temperature difference measured by the ODM; ordinate: SD of temperature differences measured by the ODM.

Supervised dichoptic gaming versus monitored occlusion therapy for childhood amblyopia: Effectiveness and efficiency



Aveen Kadhum, Emily T.C. Tan, Maria Fronius, Sara J. Baart, Dennis M. Levi, Maurits V. Joosse, Huib J. Simonsz, Sjoukje E. Loudon

Acta Ophthalmologica. 2024 Feb;102(1):38-48

Abstract

Purpose: To compare the effectiveness and efficiency of supervised dichoptic action-videogame play to occlusion therapy in children with amblyopia.

Methods: Newly diagnosed children with amblyopia aged 4-12 years were recruited, excluding strabismus >30PD. After 16 weeks of refractive adaptation children were randomised to gaming 1 h/week supervised by the researcher, or electronically monitored occlusion 2 h/day. The gaming group played a dichoptic action-videogame using virtual reality goggles, which included the task of catching a snowflake presented intermittently to the amblyopic eye. Contrast for the fellow eye was self-adjusted until 2 identical images were perceived. The primary outcome was visual acuity (VA) change from baseline to 24 weeks.

Results: We recruited 96 children, 29 declined and 2 were excluded for language or legal issues. After refractive adaptation, 24 of the remaining 65 no longer met the inclusion criteria for amblyopia, and 8 dropped out. Of 16 children treated with gaming, 7 (6.7 years) completed treatment, whereas 9 younger children (5.3 years) did not. Of 17 treated with occlusion, 14 (5.1 years) completed treatment and 3 (4.5 years) did not. Of 5 children with small-angle strabismus, 3 treated with occlusion completed treatment, 2 treated with gaming did not. Median VA improved by 0.30 logMAR (IQR 0.20–0.40) after gaming, 0.20 logMAR (0.00–0.30) after occlusion (p=0.823). Treatment efficiency was 1.25 logMAR/100 hours (range 0.42–2.08) with gaming, 0.08 (-0.19–0.68) with occlusion (p<0.001).

Conclusion: Dichoptic gaming seems a viable alternative for older children with refractive amblyopia after glasses adaptation. Treatment efficiency with gaming under continuous supervision was 15 times higher than with occlusion at home.

Introduction

Amblyopia is the main cause of unilateral visual acuity loss in children, with a prevalence of 2%–4% of the population.[1-3] The long established treatment has been occlusion of the better eye for several hours per day.[4] Occlusion therapy has proven to be a successful treatment, even over the long-term, with 74% having stable or improved visual acuity 12–15 years post-treatment.[5] However, its success is hampered by poor compliance, on average 50%–60%.[4, 6] Compliance has been shown to be associated with parental fluency in the national language, country of origin, level of education and initial visual acuity of the child. Using an educational program aimed at the child explaining the rationale for treatment significantly improved compliance.[6] Primarily, compliance is highly dependent on the level of understanding of the rationale of therapy.

The dose-response of occlusion therapy has been investigated using the occlusion dose monitor. The number of occlusion hours required to achieve 1 logMAR line in visual acuity gain was 120 hours.[4] Occlusion therapy has been shown to result in up to 7 logMAR lines of visual acuity improvement. It is most effective within the first few weeks of treatment with on average 58 hours of required occlusion to achieve 1 logMAR line in visual acuity gain after 1 month; after 4 months, this is on average 169 hours.[7] In addition, the age of the child plays a significant role in the efficiency of treatment: the number of required occlusion hours for younger children is less than for older children to achieve the same visual acuity gain.[4, 6] The recently introduced measure 'treatment efficiency'[7] is not based on the dose-response calculation and, hence, permits inclusion of patients with no change in visual acuity in the calculation (no division by zero). This reduces bias in comparisons where patients with poor compliance or older children are included in study samples.[7]

In the past decade there has been a particular interest in behavioural training therapies for amblyopia. These include perceptual learning, video gaming or movie watching. Viewing conditions are either monocular, using only the amblyopic eye, or dichoptic, using two eyes. Perceptual learning is the ability to improve performance on sensory tasks as a result of repeated practice.[8] Playing video games with the amblyopic eye has been shown to generate similar changes as perceptual learning: a reduction of noise and an increase in sampling efficiency.[9] Dichoptic gaming or movie watching is based on the idea that amblyopia is a binocular disorder and is caused by suppression. With dichoptic viewing conditions, different information is presented to the two eyes,

with the amblyopic eye receiving a more intense stimulus than the fellow eye, by reducing the contrast of the image presented to the fellow eye. The goal is to reduce suppression and/or improve fusion.[9, 10] Most of these studies have reported a positive effect on visual acuity in children as well as in adults.[9, 10]

The results of behavioral training therapies such as perceptual learning, video gaming and dichoptic therapies are on average 1 to 2 logMAR lines of improvement in visual acuity in children as well as in adults.[9, 10] The number of treatment hours varies across studies from 10 to 112 hours. No clear dose-response relationship has been demonstrated, however, the number of required treatment hours seems to be less as compared to occlusion therapy.[9, 10]

Previous studies comparing gaming with occlusion therapy in children have not monitored compliance electronically.[11-15] Some studies have investigated only the effectiveness of gaming or dichoptic movie watching and did not compare with occlusion therapy.[16-27] Other studies compared a combination of treatments, making it difficult to identify the contribution of gaming therapy.[28-31] [32-34] Furthermore, many of these studies included children who were previously occluded, whereby treatment was either incomplete or ineffective.[11, 13, 15-19, 21, 22, 24, 25, 27] It is unclear whether previous occlusion therapy acts as a barrier to improvements from subsequent dichoptic gaming therapy, or actually makes it more likely to be successful.

Therefore, we designed this randomized clinical trial to compare for the first time the effectiveness of supervised dichoptic video gaming using Virtual Reality (VR) goggles with electronically monitored occlusion therapy for children with newly diagnosed amblyopia.

Materials and Methods

The study was conducted at 5 clinics in the Netherlands: Haaglanden Medical Center (The Hague), Tergooi Hospital (Hilversum, Blaricum), IJsselland Hospital, HU Clinics University of Applied Science Utrecht and ErasmusMC University Medical Center Rotterdam. From December 2017 until June 2020, 10 treating orthoptists referred eligible children to the research centre. The Ethics Committee of the ErasmusMC University Medical Center Rotterdam and the Boards of the participating clinics approved the protocol and informed consent forms. Written informed consent was obtained from each subject's parents/legal guardians. The study adhered to the tenets of the Declaration of Helsinki. The study is listed on www.clinicaltrials.gov under identifier NCT03767985.

Orthoptic examinations

The treating orthoptist referred all newly diagnosed amblyopic children aged 4 to 12 years; i.e. no previous treatment for amblyopia. Amblyopia was associated with a refractive error, strabismus or a combination of the two, with an interocular visual acuity difference of at least 0.2 logMAR. Exclusion criteria were non-comitant or large angle strabismus >30 prism diopters (PD), a neurological disorder, nystagmus, other eye disorders and diminished visual acuity due to medication, brain damage or trauma. Cycloplegic refraction was performed by the treating orthoptist using retinoscopy, 30 minutes after cyclopentolate 1% in both eyes. Spectacles were prescribed in those with anisometropia ≥1.00 D difference between the eyes in spherical equivalent, astigmatism ≥1.50 D difference between the eyes in astigmatism in any meridian and/or a hypermetropia (spherical equivalent) ≥1.50 D. Children were prescribed 0.5D undercorrection from the full cycloplegic refraction. Whenever possible, the cycloplegic refraction was subjectively confirmed. Prior to randomization a refractive adaptation period of 16 weeks was incorporated. Eligible children were referred to the research orthoptist (ET) who performed a baseline standard orthoptic examination. This included: (1) best corrected visual acuity using the crowded tumbling E chart (Precision Vision®), (2) stereo acuity using the circles Randot Stereotest at 40cm, (3) contrast sensitivity using the Pelli-Robson chart in older subjects and CSV-1000 in the younger children, (4) ocular motility and (5) alignment with the cover-uncover and alternating cover test at 30cm and 5m distance.

Randomization and treatment

Children in whom amblyopia persisted after refractive adaptation were randomized to either the occlusion group: 2 hrs/day or the gaming group: dichoptic action video game using the Oculus Rift VR goggles once a week for 1

hour at the outpatient clinic. The randomize R package version 1.3 was used for generating the randomization list using a permuted block design with R version 3.3.2. Treatment was prescribed for 24 weeks. Compliance in the children in the occlusion group was monitored using the Occlusion Dose Monitor (ODM) for 1 week every 6 weeks[6, 35], i.e. 4 measurements. Parents were instructed to attach the ODM to the front of the patch with double sided Scotch tape. It thus measured the temperature difference between the front and the back every 3 minutes, enabling exact determination of when and for how long the patch was worn. Parents were asked to use the ODM the week following the visit to the clinic. Compliance (%) was calculated by dividing the number of monitored occlusion hours by the prescribed occlusion hours, multiplied by 100.

The principles of the game have been reported in detail elsewhere.[36] In short, it was a dichoptic action video game using the Oculus Rift VR goggles, custom-made and based on the previously reported games described elsewhere.[37] Snowmen appeared and the child was instructed to throw snowballs at them to gain points. A red snowflake appeared every 30 seconds for 10 seconds solely to the amblyopic eye; the child was instructed to catch the snowflakes to gain extra points. This was to ensure that the amblyopic eye was still engaged during game play. The software included settings for perceptually balancing the images seen by the two eyes by attenuating the contrast of the image seen by the fellow eye. Contrast setting began by presenting the image with full contrast to the amblyopic eye and a black screen to the fellow eye. The image (Fig.1a) for the fellow eye was gradually increased in contrast by steps of 10% until the child perceived two equally balanced images. This procedure was repeated four times and the average of these outcomes was used to play the game. The game also included settings to correct for misalignment. Two nonius lines were presented dichoptically, which had to be aligned until a full cross was perceived. Both the perceptual balance and alignment tasks were adjusted at the start of each game session and they were based on the input of the child. In the gaming group compliance was registered by the researcher, who supervised the gaming session and used a stopwatch to determine the exact game duration. Figure 1b shows a 6-year-old boy playing the game in the clinic.

a. An image with attenuated contrast for the fellow eye (left eye) in order to match the image perceived by the amblyopic eye (right eye).

b. A child playing the dichoptic action video game using VR goggles at the outpatient clinic. On the right side of the figure you can see the laptop displaying the image the child sees in the headset.

Figure 1

During the 24 weeks of occlusion therapy or gaming therapy all children were examined every 6 weeks by the same research orthoptist (ET) using the same strict protocol to prevent any bias. During these orthoptic examinations at the clinic the ODM was given to the parents in the occlusion group with instructions how to attach the ODM to the patch. Treatment was completed if equal visual acuity was measured on 2 consecutive visits. If no further treatment was required (i.e. no standard occlusion therapy necessary) VA was measured 3 months after completion of the study trial. After 24 weeks children were referred back to their treating orthoptist for further treatment if necessary.

Statistical analysis

We hypothesized that there would be no significant difference in visual acuity improvement after 24 weeks of treatment between the gaming group and the occlusion group. We performed an equivalence trial.

Based on the literature, the number of required treatment hours for gaming seems to be less, as compared to occlusion therapy: 10-20 hours of gaming seems comparable to 100-120 hours of occlusion.[4, 9] Hence, we compared 2 hours of prescribed occlusion per day, 7 days per week (336 total hours) to 1 hour of gaming per week (24 total hours).

Differences in clinical characteristics between the gaming group and occlusion group were investigated using Mann-Whitney U tests for the following continuous variables: age at start of therapy, visual acuity of at start of therapy, stereo acuity, spherical equivalent of both eyes and anisometropia. The chi-square test was used to investigate the categorical variable sex.

A mixed model with time as factor and an interaction with treatment was used to compare visual acuity in the amblyopic eye at the start and after 24 weeks within the dichoptic game and occlusion groups and to compare the improvement in visual acuity between the two groups. Random effects for patient and time were included to account for the clustered structure of the data within patients. Within the mixed model, we used an intention-to-treat analysis for all included children to correct for any drop-out during the study. In addition, a per-protocol analysis was conducted including only the children who completed the therapy. A p-value of <0.05 was considered statistically significant. Visual acuity was log transformed to meet the criteria of normally distributed values for mixed model.

As mentioned, children in the occlusion group were prescribed 2 hours of occlusion per day. Compliance was electronically monitored for one week every 6 weeks. The number of occlusion hours was calculated by prescribed occlusion hours multiplied with the monitored percentage of compliance. Treatment efficiency was calculated by dividing VA improvement by occlusion hours. In the gaming group children came once a week at the outpatient clinic to play the dichoptic video game for 1 hour. Treatment efficiency was calculated by dividing VA improvement by the number of supervised gaming hours at the outpatient clinic.

To calculate treatment efficiency (expressed as acuity gain in logMAR per 100 h of treatment) the measured visual acuity gains were divided by the hours of treatment and multiplied by 100.[7] We used the following formula:

$$\frac{visual\ acuity\ gain\ (logMAR) * 100}{number\ of\ treatment\ hours}$$

Difference in treatment efficiency between the treatment groups was investigated using Mann-Whitney U test.

Stereo acuity was converted to the logarithm (base 10) of the stereo acuity values and participants who failed the stereo acuity test were arbitrarily assigned a value of 800 arcsec (2.90 logarcsec), similar to Gambacorta, which corresponds to double the maximum testable disparity in the circles Randot Stereotest.[21] A mixed model was used to compare stereo acuity at the start of therapy and after 24 weeks within the dichoptic game and occlusion groups and to compare the improvement in stereo acuity between the two groups. Stereo acuity was log transformed to meet the criteria of normally distributed values for mixed model.

To investigate any correlation between change in the contrast balance setting and change in visual acuity in the amblyopic eye and change in stereo acuity, we used Spearman rank correlation.

Results

Ninety-six newly diagnosed amblyopic children were recruited; two were excluded due to language problems or legal issues. Participation in the study was offered to 94 families. Twenty-nine refused participation. Reasons for not participating with the game therapy are listed in a previous publication 36. Mostly, these were for reasons directly related to the game therapy because they were either unwilling or unable to comply with the weekly game sessions.[36] Sixty-five were eligible for the study. Children were first prescribed glasses when necessary. After the refractive adaptation period, amblyopia was sufficiently treated in 24 children and these therefore did not meet the inclusion criteria. Another eight participants dropped out: due to the time- consuming nature of the weekly visits to the clinic three refused further participation, three due to the inclusion-stop caused by the COVID-19 pandemic and two withdrew their participation. Thirty-three children were randomized: 17 to the occlusion group and 16 to the gaming group (Figure 2). During the study three (18%) children dropped out of the occlusion group and nine (56%) out of the gaming group. Reasons for dropout are listed in a previous publication.[36] Twenty-one completed the full 24-week study period: 14 in the occlusion group and 7 in the gaming group.

Study population

Median age was 5.4 (IQR 4.5-6.7) years; 16 were girls (49%) for the two groups together. There was no significant difference in baseline characteristics between the two groups (Table 1). Median age of the children in the gaming group was 0.9 years older than the occlusion group (not statistically significant). Twenty-eight children had amblyopia associated with anisometropia. Three children had strabismus amblyopia with mean age 5.8 (SD 0.8) years, mean strabismus angle was 10 (SD 7) PD, mean visual acuity at start was 0.47 (SD 0.31) logMAR and stereo acuity was 2.25 (SD 0.57) logarcsec. Visual acuity at the end was 0.20 logMAR in the amblyopic eye in one child; the other two children dropped out after 1 game session. There were two children with combined mechanism amblyopia with mean age 4.5 (SD 1.3) years, strabismus angle in both children was 8PD, mean visual acuity at start was 0.65 (SD 0.64) logMAR; stereo acuity was nil in one child, the other child did not have a stereo acuity measurement at start; mean visual acuity at the end was 0.25 (SD 0.35) logMAR.

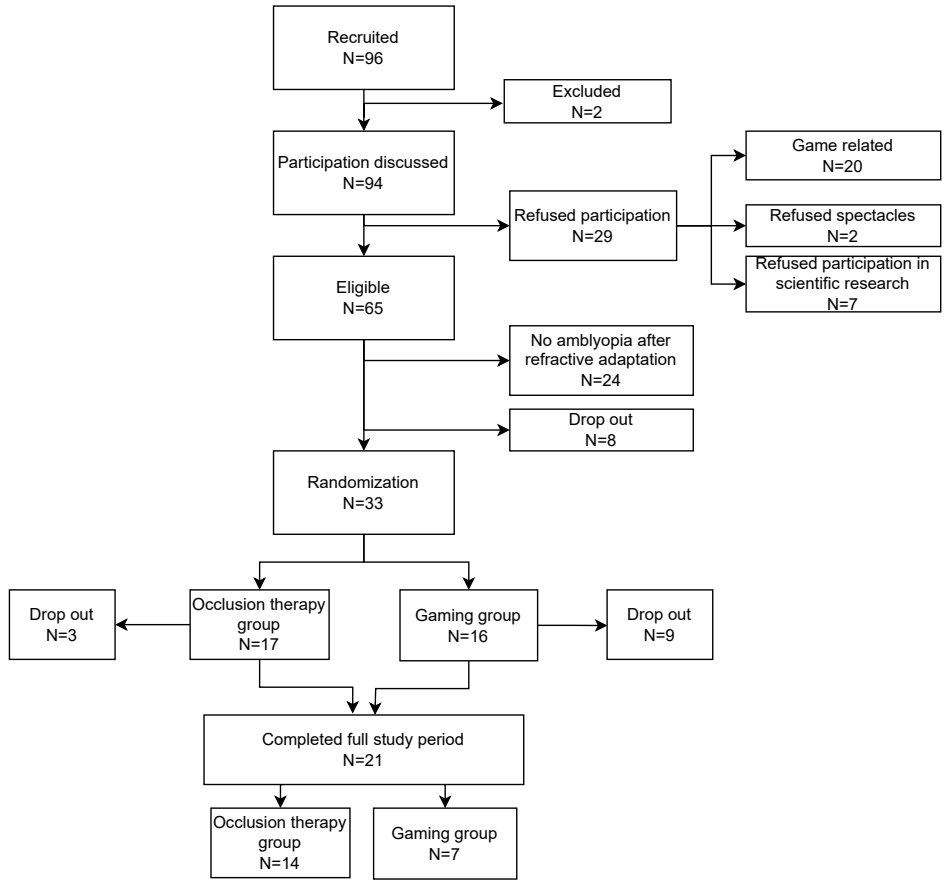


Figure 2. Study flowchart with the number of participants.

Table 1. Baseline Characteristics for all randomized participants (N=33). Differences between the two groups are analyzed with Mann-Whitney U test (continuous variables) or Chi Square test (categorical variables)..

	Occlusion therapy group (N=17)	**Gaming group (N=16)**	***p* Value**
Gender, female	10 (59%)	6 (38%)	0.221
Age at baseline (years, median, IQR)	4.9 (4.3–6.3)	5.8 (4.9–7.2)	0.127
Visual acuity amblyopic eye at baseline (logMAR, median, IQR)	0.40 (0.20–0.45)	0.40 (0.30–0.50)	0.698
Visual acuity fellow eye at baseline (logMAR, median, IQR)	0.00 (0.00–0.18)	0.03 (0.00–0.10)	0.614
Stereoacuity at baseline (log seconds of arc, median, IQR)	2.00 (1.70–2.30)	1.77 (1.35–2.30)	0.163
Amblyopia cause			a
Anisometropia	14	14	
Strabismus	1	2	
Combined	2	0	
Spherical equivalent amblyopic eye (diopters, median, IQR)	3.3 (0.7–4.7)	3.5 (1.0–5.3)	0.769
Spherical equivalent fellow eye (diopters, median, IQR)	1.5 (0.5–2.8)	2.1 (0.2–3.4)	0.769
Spherical equivalent anisometropia (diopters, median, IQR)	1.0 (0.4–2.6)	1.1 (0.3–2.1)	0.810

[a]Groups smaller than 3 were not tested for significance.

Occlusion vs dichoptic gaming

Visual acuity

Median visual acuity in the amblyopic eye improved 0.30 logMAR (IQR 0.20 - 0.40) in the gaming group and 0.20 logMAR (IQR 0.00 - 0.30) in the occlusion group after 24 weeks of treatment. See Figure 3.

An intention-to-treat analysis using a mixed model with time as factor was conducted with all included children (N=33). This analysis showed that visual acuity in the amblyopic eye improved significantly after 24 weeks in both the gaming as well as in the occlusion group (p<0.001). There was no statistically significant difference in improvement between the two groups after 24 weeks (p=0.823). On all measurements there was no significant difference between the two groups: at 6 weeks (p=0.115), at 12 weeks (p=0.453) and at 18 weeks (p=0.719).

A per-protocol analysis was conducted including only the children who completed the full study (N=21), this showed comparable results with the intention-to-treat analysis: a significant improvement after 24 weeks for both groups (p<0.001), and no significant difference in visual acuity improvement between the two groups after 24 weeks (p=0.837). On all measurements there was no significant difference: at 6 weeks (p=0.131), 12 weeks (p=0.461) and at 18 weeks (p=0.710).

The intention-to-treat analysis was repeated without the five children with strabismus/combined cause of amblyopia. This analysis also showed no significant difference between the two groups after 24 weeks (p=0.511). There was no significant difference on all measurements: at 6 weeks (p=0.211), at 12 weeks (p=0.965) and at 18 weeks (p=0.977).

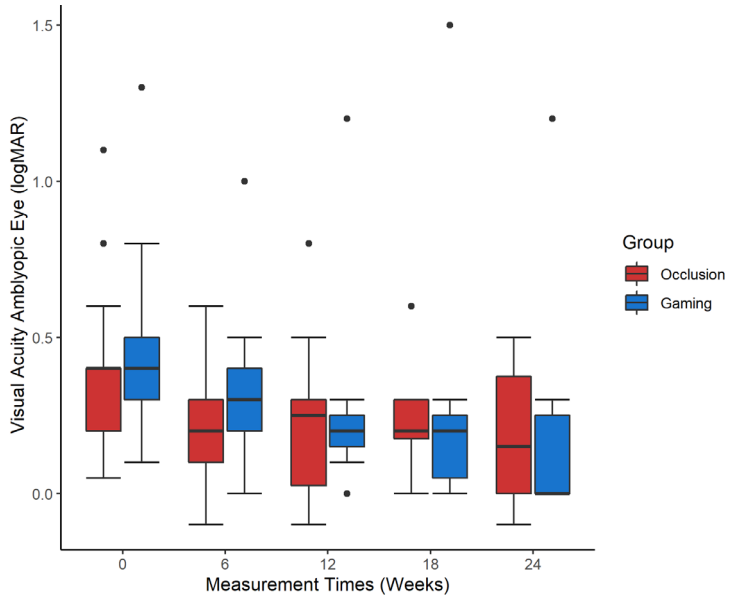


Figure 3. Visual acuity in the amblyopic eye (logMAR) from baseline to 24 weeks of treatment (N = 33). The boxplots represent the 25th and 75th percentiles of the data and the line in the box is the median value. Whiskers represent the 5th and 95th percentiles. The circles represent the outliers. Red is the occlusion group; blue is the gaming group.

Compliance with therapy

Of the 17 children in the occlusion group, 2 had unknown measurements as they dropped out prior to the 6-week appointment. Mean compliance with occlusion therapy for the remaining 15 children was 81% (min 13, max 100, SD 42%), i.e., the mean daily dose rate was 1.62 ± 0.84 h/d.

Compliance with gaming was observed by the researcher during each game session ensuring each child completed the full treatment. If a child could not attend the scheduled appointment for whatever reason, or if there was a no-show, a new appointment was made as soon as possible to make up for the missed treatment hours. All children who completed the study achieved the 24 hours of required game time.

Treatment efficiency

Treatment efficiency was calculated for both treatment groups using the following formula: (acuity gain (logMAR) * 100 hours) / cumulated measured treatment hours. For the occlusion group we calculated this based on the monitored occlusion hours (Table 2).

Table 2. Median treatment efficiency: acuity gain (logMAR) per 100 h of treatment for both groups including the range with minimum and maximum values. Electronically monitored hours were used in the calculation for the occlusion group.

	Occlusion therapy group	**Gaming group**
After 6 weeks	0.23 (–0.73–0.59)	3.33 (0.00–5.00)
After 12 weeks	0.12 (–0.10–0.42)	1.67 (–0.83–3.33)
After 18 weeks	0.10 (0.00–0.47)	1.11 (–1.11–2.78)
After 24 weeks	0.08 (–0.19–0.68)	1.25 (0.42–2.08)

Treatment efficiency after 6 weeks (p=0.001) and 24 weeks was significantly higher for gaming compared to occlusion therapy (p<0.001).

There was a decrease in treatment efficiency with both gaming and occlusion therapy over time, with the most rapid decrease occurring during the first 12 weeks. A maximum of VA recovery was reached after approximately 14.6 (SD 6.8) hours of gaming.

Stereo acuity

Median stereo acuity in the occlusion group at start of treatment was 2.00 log arc sec [min 1.48 – max 2.90] and improved to 1.40 [min 1.30 – max 2.90] log arc sec after 24 weeks. In the gaming group stereo acuity improved from 1.70 [min 1.30 – max 2.90] to 1.40 [min 1.30 – max 2.90]. Stereo acuity improved significantly after 24 weeks of treatment (mixed model; p<0.001) with no significant difference in between the two groups (p=0.609). On all measurements there was no significant difference between the two groups: at 6 weeks (p=0.172), at 12 weeks (p=0.661), or at 18 weeks (p=0.601). The correlation between visual acuity and stereo acuity gain was significant (Spearman correlation 0.565; p<0.001).

Contrast sensitivity

In the occlusion group 13 children were examined using the CSV-1000; 3 children could not be tested due to equipment failure and one child had a missing CSV-1000 at baseline. In the gaming group 6 children were examined using the CSV-1000, 5 children with the Pelli-Robson chart; data of 5 children were missing. Overall, in the occlusion group contrast sensitivity at start of treatment was on average 1.22 [min 0.70 – max 1.63] and 1.51 [min 0.70 – max 2.08] at end of therapy using the outcome of the 3 cycles/degree line. In the gaming group this was 1.30 [min 1.17 – max 1.63] at the start of treatment and 1.52 [min 1.34 – max 1.78] at end

of therapy. Overall, we could not demonstrate a significant difference between the two groups at start as well as after 24 weeks (Mann-Whitney U test; p>0.05). In addition, the Wilcoxon Signed Rank Test showed no significant improvement within the groups (p>0.05).

Of the 5 children examined using the Pelli-Robson chart in the gaming group, two finished the treatment: they started with 1.73 (min 1.65 – max 1.80) and measured 1.95 (min 1.95 – max 1.95) after 24 weeks of therapy for the amblyopic eye.

Visual acuity follow-up after treatment

Of the 14 children from the occlusion group, 7 (50%) achieved equal visual acuity during or after 24 weeks of the study period. Five (71%) of the 7 children from the gaming group achieved equal visual acuity. Fisher's exact test showed no statistically significant difference between these two proportions (p=0.64). Visual acuity was assessed 3-4 months after the cessation of treatment to determine the stability of visual acuity. Three of the five in the gaming group maintained their achieved visual acuity and two had a slight decrease in visual acuity in the amblyopic eye of 0.10 logMAR. The median visual acuity at the follow-up examination was 0.00 (min 0.00 - max 0.30) logMAR.

Of the 12 children with anisometropia amblyopia in the occlusion group who finished the 24 weeks, 6 (50%) achieved equal visual acuity during or after 24 weeks of the study period.

Contrast balance task for the game

In our study the contrast-balance task was determined subjectively by the child rather than using arbitrary values. In the children who completed treatment (N=7), the contrast balance setting was, on average, 57±17% at the first game session and improved to 78±14% at 24 weeks. In Figure 4 visual acuity of all children from the game group is displayed with the contrast balance setting for the game on the same day. There was no significant correlation found between change in visual acuity in the amblyopic eye and change in contrast balance setting (Spearman correlation -0.122; p=0.484). There was also no significant correlation found between change in stereo acuity and change in contrast balance setting (Spearman correlation -0.216; p=0.212), consistent with previous studies.[37, 38]

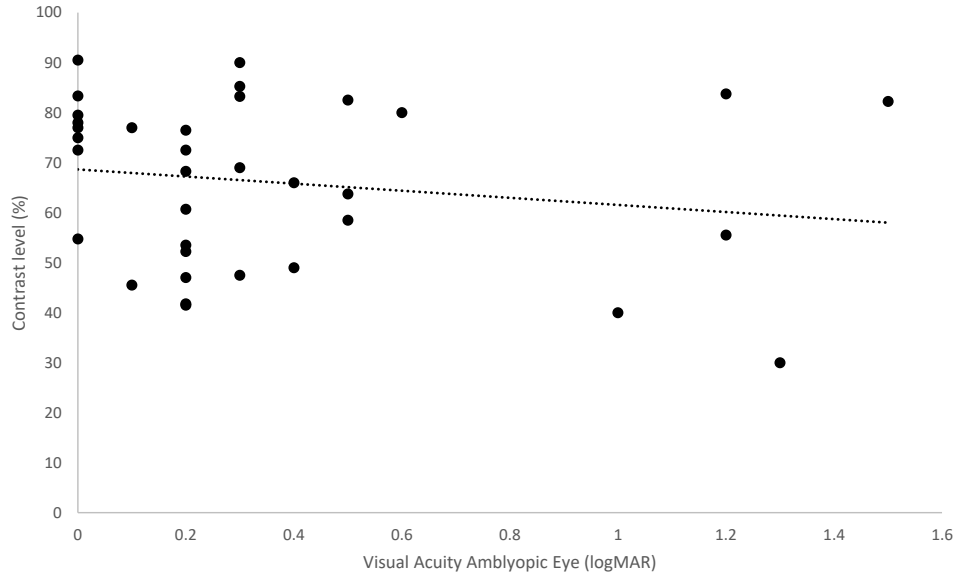


Figure 4. Scatterplot representing the relationship between visual acuity in the amblyopic eye (logMAR) and the level of contrast (%) setting in the game. Each dot represents one child with their contrast balance % and visual acuity measured on the same day.

Discussion

This is the first study to measure and compare the efficacy and efficiency of supervised outpatient dichoptic action video gaming using VR goggles to objectively monitored occlusion therapy in 4–12-year-old children with newly diagnosed amblyopia. While several published studies.[11, 13, 15, 18, 19, 21, 22, 24, 25, 27, 39] included subjects with a history of occlusion for amblyopia, it is unclear whether previous treatment could be a hindrance or an aid to acuity improvements subsequently gained through dichoptic therapy. Although we started with 96 recruited children, only 33 could be randomized: after 16 weeks of glasses adaptation, a third of the originally recruited children no longer had an interocular VA difference ≥0.20 logMAR and no longer qualified as amblyopic. This highlights the necessity to carefully select and refractively manage patients participating in any amblyopia treatment protocol. At the end of the 24-week treatment period visual acuity had improved by 0.30 logMAR (IQR 0.20-0.40) in the gaming group and 0.20 logMAR (IQR 0.00-0.30) in the occlusion group; this difference between the two treatment groups was not statistically significant. Considering that more than half of the children from the gaming group failed to complete treatment, mostly children of young age including 2 with small-angle strabismus, our impression is that VR gaming is a viable alternative for older children with refractive amblyopia after glasses adaptation.

Evaluation of our methods and results

Compliance with gaming was ensured by direct supervision of the game sessions and the researcher made sure that treatment was completed. Compliance with occlusion therapy was monitored electronically for 1 week every 6 weeks, that is four measurements. It is possible that compliance was higher in the week it was measured than for the ensuing weeks, as the compliance measurement was done in the first week following orthoptic examination (Hawthorne effect). With 81% it was higher than in our previous studies, whereby overall mean compliance was 55-57% after 4 months.[6, 40] An important difference was that in our previous studies the ODM was distributed by researchers via home visits ensuring separation of researchers measuring compliance and treating orthoptists. In the current study the ODM was distributed in the clinic by the researcher during the visual acuity measurement, instructing parents to use the ODM immediately in the first week of the coming 6 weeks. The research orthoptist (ET) who measured the visual acuity and performed the orthoptic examinations was initially masked for randomization of the children. However, in practice this could not be guaranteed. Every effort was made to ensure that every participant received the same amount of time for the orthoptic examination. ET was not aware of treatment compliance.

Treatment efficiency with gaming was 15 times higher than with occlusion therapy, despite that the children in the gaming group were slightly older. The efficiency was calculated by dividing the VA gain by the prescribed occlusion hours corrected for by the monitored compliance for a week (on average 81%). Even when assuming that compliance with occlusion was comparable to our previous studies (55-57%), treatment efficiency with gaming would still be higher. Assuming compliance with occlusion therapy to be 55%[6], calculated treatment efficiency would be 0.13 logMAR per 100 hours of treatment for occlusion and 0.22 for gaming after 16 weeks[11] (see Table 3). Calculating this for Kelly et al. resulted in a treatment efficiency of 1.50 logMAR per 100 hours of treatment for gaming and 0.25 for occlusion therapy after 2 weeks.[12] Treatment efficiency of amblyopia therapy with the I-BiT games was 3.33 logMAR per 100 hours of gaming after 3 weeks and 2.00 after 6 weeks.[18] Gambacorta et al. calculated treatment efficiency after 10 hours of gaming, which resulted in 1.0 logMAR VA gain per 100 hours of gaming. When calculating this after 20 hours of gaming, they found a decrease in treatment efficiency to 0.70 logMAR VA gain per 100 hours of gaming. In this study gaming was done in sessions of 1 hour, 1-3 times per week; after 10 and 20 hours VA was assessed.[21]

Treatment efficiency with gaming was higher than with occlusion in all studies. It is notable that treatment efficiency for gaming at home was lower than for supervised gaming. Efficiency decreased rapidly with duration of treatment with a maximum of VA recovery occurring after approximately 15 hours of gaming. Opting for at-home gaming treatment comes with its own limitations and significantly low levels of compliance.[11, 13, 33]

Table 3. Calculated treatment efficiency (VA improvement logMAR/100 h of therapy) for gaming and occlusion therapy for children in previous studies.

Studies	Efficiency supervised gaming	Efficiency gaming at home	Efficiency occlusion therapy
This study (median)	3.33 after 6 weeks (6 h) 1.25 after 24 weeks (24 h)		0.23 after 6 weeks (≈68 h) 0.08 after 24 weeks (≈272 h)
Kelly et al. 2016 (mean)		1.50 after 2 weeks (10 h)[a]	0.25 after 2 weeks (28 h)[a]
Holmes et al. 2016 (mean)		0.22 after 16 weeks (112 h)[a]	0.13 after 16 weeks (224 h)[a]
Herbison et al. 2016 (mean)	3.33 after 3 weeks (1.5 h) 2.00 after 6 weeks (3 h)		
Gambacorta et al. 2018 (mean)	1.00 after 10 h of dichoptic gaming 0.70 after 20 h of dichoptic gaming 0.60 after 10 h of monocular gaming 0.30 after 20 h of monocular gaming		
Fronius et al. 2014 (median)			0.19 after 4 weeks (117 h) 0.11 after 16 weeks (469 h)
Stewart et al. 2004 (mean)			0.08[b]

Note: Treatment hours for occlusion therapy for this study are based on the found 81%; in reality treatment hours and TE were calculated for each child separately based on his/her compliance data.

[a]There was no electronic monitoring of occlusion therapy and no supervised gaming therapy. We have calculated treatment efficiency based on the provided mean or median visual acuity improvement and prescribed treatment hours. Treatment efficiency calculations for the study of Holmes in this table were done using the data from the subgroup age 5 to <7 years with no prior treatment.

[b]The study of Stewart did not have a fixed treatment duration for occlusion, but dose-response was provided.

The number of children who completed the study was low, mainly due to young age, logistical challenges and loss of interest in the game. Therefore, for the interpretation of the mixed-model, the age-dependent drop-out needs to be taken into account. The children in the gaming group were slightly older, although not significantly, this could influence treatment efficiency. A third of all originally 96 recruited children no longer had amblyopia after glasses adaptation. Furthermore, only 44% of the children in the gaming group completed the treatment period. Notably, all 3 young children with small-angle strabismus in the occlusion group completed treatment, whereas the 2 in the gaming group did not. We had expected that poor VA may influence the ability to perform the game settings. However, this was not the case. We found that younger children had difficulties applying the game settings, i.e. they did not understand the contrast balance task and alignment task and could not communicate properly what they perceived in the goggles.[36] In addition, these children were also unable to comprehend the task of throwing snowballs at the approaching snowmen and would often just look around in the goggles. Overall, we found that children younger than 5.5 years of age had too much difficulty with the game and 1 hour of gaming was too tedious for them. On the other hand, older children (and their parents) were unwilling to attend the weekly game sessions. Losing interest in the game was apparent at all ages.[36] As such, gaming seems unsuited as a standard treatment for amblyopia in countries with an extensive vision screening program where amblyopia is diagnosed and treated by age 4 or 5.[41]

Relationship between contrast balance input and VA improvement

For this study, the contrast balance setting was assessed subjectively by the child prior to each game session. We found that for younger children this task was very difficult. In other studies, a fixed level of contrast of 15-20% was used as starting level, or a dichoptic task to set the level of contrast.[12, 22, 26, 33, 42] They integrated this process in the software, whereby contrast was adjusted after completing a certain number of hours of gaming and/or after a certain amount of points

were gained. We could not demonstrate a correlation between the contrast balance setting with either visual acuity or stereo acuity throughout the study period. The literature shows subjects with improved contrast after therapy but no changes in visual acuity and stereo acuity.[23] Bossi found that acuity gains were not correlated with suppression.[20] Moreover, Gambacorta published no significant relationship between decreased suppression as measured by increased in-game interocular suppression and improved visual acuity and stereo acuity.[21] The theory being that contrast information acts as a (proxy) measure of suppression, and thus contrast balance ratios, visual acuity and stereoacuity outcomes should all be interdependent. However, our data was unable to support this relationship, despite improvements in visual acuity and stereo acuity being strongly correlated.

Possible mechanisms for increased efficiency in gaming?

Visual acuity improvement with gaming was 0.30 logMAR with 1 hour of gaming per week over 24 weeks. Visual acuity improved with occlusion by 0.20 logMAR with 2 hours per day of occlusion, prescribed over the same time period. More rapid VA improvement may reflect greater plasticity in the visual cortex. Could this difference in efficiency be explained by different modes of action of occlusion therapy as compared to that of dichoptic game therapy? It is possible that occlusion and gaming influence plasticity at different anatomical locations. Attention may increase cortical plasticity and 'speed up the treatment of amblyopia'. In mice, it has recently become apparent that the degree of modulation in the Lateral Geniculate Nucleus (LGN) determines cortical plasticity, i.e. the ability to either develop amblyopia or to be cured from it.[43 44] During occlusion therapy, little to no modulation takes place in the LGN unlike with gaming therapy.

In human subjects with amblyopia, functional connectivity of higher visual areas and frontal cortical areas are altered.[45] Whether plasticity in these brain regions is induced by different types of visual stimulation, as in occlusion versus gaming, remains unknown. Several pathways in the brain can enhance plasticity in the visual cortex. From mouse models, it is known that plasticity in the visual cortex induced by monocular deprivation requires a temporary reduction of inhibition which is provided by the parvalbumin-expressing basket cells.[46] In addition, a cortical mechanism exists that also reduces inhibition and thereby enhances plasticity in the visual cortex.[47] This involves interneurons that express vasoactive intestinal peptide (VIP) which selectively inhibits other inhibitory neurons. These VIP interneurons are highly sensitive to neuromodulation and are activated during behavioral states in which learning is required, like dichoptic training. This disinhibitory circuit is activated by signals such as reward, punishment,

arousal or attention, signals that are present during gameplay.[48] Interestingly, this latter pathway remains active in adulthood, while modulation of parvalbumin-expressing basket cells only occurs during a critical period of development. It is thus possible that these pathways are (i) recruited differently by occlusion and gaming therapy, (ii) influence cortical plasticity differently at different ages and, presumably, (iii) with different periods of decay. Future research could shed further light on which pathways are involved and whether the effect of gaming treatment persists into adulthood.

In summary, treatment efficiency for dichoptic gaming treatment is higher and can be considered a viable alternative for occlusion therapy. However, the applicability is hampered by practical implications and in countries that have an extensive vision screening program where amblyopia is diagnosed and treated by age four, dichoptic treatment seems better suited for older children as they are able to understand the settings and game more easily.

Acknowledgements

Professor Christiaan N. Levelt, Netherlands Institute for Neuroscience, Amsterdam
Marieke Telleman, Erasmus Medical Centre, Rotterdam
Brigitte Simonsz-Tóth, Haaglanden Medical Centre, The Hague
Ellen van Minderhout, Haaglanden Medical Centre, The Hague
Marleen Vermeulen-Jongen, Haaglanden Medical Centre, The Hague
Patty Lindeboom, Haaglanden Medical Centre, The Hague
Carine Kuit-Baaij Tergooi Hospital, Blaricum/Hilversum
Chantal van den Bosch St. Antonius Hospital, Utrecht/Nieuwegein
Danielle Hamers, Tergooi Hospital, Blaricum/Hilversum
Inez Calis, Tergooi Hospital, Blaricum/Hilversum
Danielle van Gemert, IJsselland Hospital, Capelle aan den Ijssel

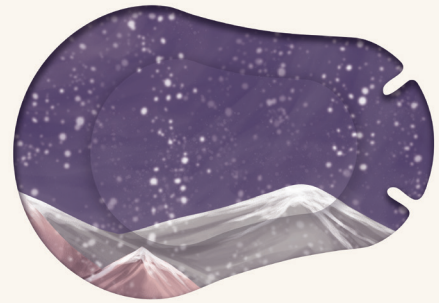
References

1. Attebo K, Mitchell P, Cumming R, et al. Prevalence and causes of amblyopia in an adult population. Ophthalmology 1998;105(1):154-9.
2. Friedman DS, Repka MX, Katz J, et al. Prevalence of amblyopia and strabismus in white and African American children aged 6 through 71 months the Baltimore Pediatric Eye Disease Study. Ophthalmology 2009;116(11):2128-34 e1-2.
3. Brown SA, Weih LM, Fu CL, et al. Prevalence of amblyopia and associated refractive errors in an adult population in Victoria, Australia. Ophthalmic Epidemiol 2000;7(4):249-58.
4. Stewart CE, Moseley MJ, Stephens DA, Fielder AR. Treatment dose-response in amblyopia therapy: the Monitored Occlusion Treatment of Amblyopia Study (MOTAS). Invest Ophthalmol Vis Sci 2004;45(9):3048-54.
5. Kadhum A, Simonsz-Toth B, van Rosmalen J, et al. Long-term follow-up of an amblyopia treatment study: change in visual acuity 15 years after occlusion therapy. Acta Ophthalmol 2020.
6. Loudon SE, Fronius M, Looman CW, et al. Predictors and a remedy for noncompliance with amblyopia therapy in children measured with the occlusion dose monitor. Invest Ophthalmol Vis Sci 2006;47(10):4393-400.
7. Fronius M, Cirina L, Ackermann H, et al. Efficiency of electronically monitored amblyopia treatment between 5 and 16 years of age: new insight into declining susceptibility of the visual system. Vision Res 2014;103:11-9.
8. Bavelier D, Levi DM, Li RW, et al. Removing brakes on adult brain plasticity: from molecular to behavioral interventions. J Neurosci 2010;30(45):14964-71.
9. Tsirlin I, Colpa L, Goltz HC, Wong AM. Behavioral Training as New Treatment for Adult Amblyopia: A Meta-Analysis and Systematic Review. Invest Ophthalmol Vis Sci 2015;56(6):4061-75.
10. Pineles SL, Aakalu VK, Hutchinson AK, et al. Binocular Treatment of Amblyopia: A Report by the American Academy of Ophthalmology. Ophthalmology 2020;127(2):261-72.
11. Holmes JM, Manh VM, Lazar EL, et al. Effect of a Binocular iPad Game vs Part-time Patching in Children Aged 5 to 12 Years With Amblyopia: A Randomized Clinical Trial. JAMA Ophthalmol 2016;134(12):1391-400.
12. Kelly KR, Jost RM, Dao L, et al. Binocular iPad Game vs Patching for Treatment of Amblyopia in Children: A Randomized Clinical Trial. JAMA Ophthalmol 2016;134(12):1402-8.
13. Manh VM, Holmes JM, Lazar EL, et al. A Randomized Trial of a Binocular iPad Game Versus Part-Time Patching in Children Aged 13 to 16 Years With Amblyopia. Am J Ophthalmol 2018;186:104-15.
14. Jost RM, Hudgins LA, Dao LM, et al. Randomized clinical trial of streaming dichoptic movies versus patching for treatment of amblyopia in children aged 3 to 7 years. Sci Rep 2022;12(1):4157.
15. Rajavi Z, Soltani A, Vakili A, et al. Virtual Reality Game Playing in Amblyopia Therapy: A Randomized Clinical Trial. J Pediatr Ophthalmol Strabismus 2021;58(3):154-60.
16. Mansouri B, Singh P, Globa A, Pearson P. Binocular training reduces amblyopic visual acuity impairment. Strabismus 2014;22(1):1-6.

17. Li SL, Reynaud A, Hess RF, et al. Dichoptic movie viewing treats childhood amblyopia. J AAPOS 2015;19(5):401-5.
18. Herbison N, MacKeith D, Vivian A, et al. Randomised controlled trial of video clips and interactive games to improve vision in children with amblyopia using the I-BiT system. Br J Ophthalmol 2016;100(11):1511-6.
19. Barollo M, Contemori G, Battaglini L, et al. Perceptual learning improves contrast sensitivity, visual acuity, and foveal crowding in amblyopia. Restor Neurol Neurosci 2017;35(5):483-96.
20. Bossi M, Tailor VK, Anderson EJ, et al. Binocular Therapy for Childhood Amblyopia Improves Vision Without Breaking Interocular Suppression. Invest Ophthalmol Vis Sci 2017;58(7):3031-43.
21. Gambacorta C, Nahum M, Vedamurthy I, et al. An action video game for the treatment of amblyopia in children: A feasibility study. Vision Res 2018;148:1-14.
22. Gao TY, Guo CX, Babu RJ, et al. Effectiveness of a Binocular Video Game vs Placebo Video Game for Improving Visual Functions in Older Children, Teenagers, and Adults With Amblyopia: A Randomized Clinical Trial. JAMA Ophthalmol 2018;136(2):172-81.
23. Kelly KR, Jost RM, Wang YZ, et al. Improved Binocular Outcomes Following Binocular Treatment for Childhood Amblyopia. Invest Ophthalmol Vis Sci 2018;59(3):1221-8.
24. Mezad-Koursh D, Rosenblatt A, Newman H, Stolovitch C. Home use of binocular dichoptic video content device for treatment of amblyopia: a pilot study. J AAPOS 2018;22(2):134-8 e4.
25. Portela-Camino JA, Martin-Gonzalez S, Ruiz-Alcocer J, et al. A Random Dot Computer Video Game Improves Stereopsis. Optom Vis Sci 2018;95(6):523-35.
26. Birch EE, Li SL, Jost RM, et al. Binocular iPad treatment for amblyopia in preschool children. J AAPOS 2015;19(1):6-11.
27. Huang YT, Lin HJ, Liao WL, et al. Effects of Vision Therapy on Bilateral Amblyopia Unresponsive to Conventional Treatment: A Retrospective Comparative Study. Children (Basel) 2022;9(2).
28. Dadeya S, Dangda S. Television Video Games in the Treatment of Amblyopia in Children Aged 4-7 Years. Strabismus 2016;24(4):146-52.
29. Singh A, Sharma P, Saxena R. Evaluation of the Role of Monocular Video Game Play as an Adjuvant to Occlusion Therapy in the Management of Anisometropic Amblyopia. J Pediatr Ophthalmol Strabismus 2017;54(4):244-9.
30. Birch EE, Jost RM, Wang SX, Kelly KR. A pilot randomized trial of contrast-rebalanced binocular treatment for deprivation amblyopia. J AAPOS 2020;24(6):344 e1- e5.
31. Rajavi Z, Sabbaghi H, Amini Sharifi E, et al. The role of Interactive Binocular Treatment system in amblyopia therapy. J Curr Ophthalmol 2016;28(4):217-22.
32. Hsieh YC, Liao WL, Tsai YY, Lin HJ. Efficacy of vision therapy for unilateral refractive amblyopia in children aged 7-10 years. BMC Ophthalmol 2022;22(1):44.
33. Pediatric Eye Disease Investigator G, Holmes JM, Manny RE, et al. A Randomized Trial of Binocular Dig Rush Game Treatment for Amblyopia in Children Aged 7 to 12 Years. Ophthalmology 2019;126(3):456-66.
34. Xiao S, Angjeli E, Wu HC, et al. Randomized Controlled Trial of a Dichoptic Digital Therapeutic for Amblyopia. Ophthalmology 2022;129(1):77-85.
35. Simonsz HJ, Polling JR, Voorn R, et al. Electronic monitoring of treatment compliance in patching for amblyopia. Strabismus 1999;7(2):113-23.

36. Kadhum A, Tan ETC, Levi DM, et al. Barriers to successful dichoptic treatment for amblyopia in young children. Graefes Arch Clin Exp Ophthalmol 2021.
37. Vedamurthy I, Nahum M, Huang SJ, et al. A dichoptic custom-made action video game as a treatment for adult amblyopia. Vision Res 2015;114:173-87.
38. Knox PJ, Simmers AJ, Gray LS, Cleary M. An exploratory study: prolonged periods of binocular stimulation can provide an effective treatment for childhood amblyopia. Invest Ophthalmol Vis Sci 2012;53(2):817-24.
39. Li J, Spiegel DP, Hess RF, et al. Dichoptic training improves contrast sensitivity in adults with amblyopia. Vision Res 2015;114:161-72.
40. Tjiam AM, Holtslag G, Van Minderhout HM, et al. Randomised comparison of three tools for improving compliance with occlusion therapy: an educational cartoon story, a reward calendar, and an information leaflet for parents. Graefes Arch Clin Exp Ophthalmol 2013;251(1):321-9.
41. Groenewoud JH, Tjiam AM, Lantau VK, et al. Rotterdam AMblyopia screening effectiveness study: detection and causes of amblyopia in a large birth cohort. Invest Ophthalmol Vis Sci 2010;51(7):3476-84.
42. Hess RF, Thompson B, Black JM, et al. An iPod treatment of amblyopia: an updated binocular approach. Optometry 2012;83(2):87-94.
43. Sommeijer JP, Ahmadlou M, Saiepour MH, et al. Thalamic inhibition regulates critical-period plasticity in visual cortex and thalamus. Nat Neurosci 2017;20(12):1715-21.
44. Stephany CE, Ma X, Dorton HM, et al. Distinct Circuits for Recovery of Eye Dominance and Acuity in Murine Amblyopia. Curr Biol 2018;28(12):1914-23 e5.
45. Wang T, Li Q, Guo M, et al. Abnormal functional connectivity density in children with anisometropic amblyopia at resting-state. Brain Res 2014;1563:41-51.
46. Kuhlman SJ, Olivas ND, Tring E, et al. A disinhibitory microcircuit initiates critical-period plasticity in the visual cortex. Nature 2013;501(7468):543-6.
47. Fu Y, Kaneko M, Tang Y, et al. A cortical disinhibitory circuit for enhancing adult plasticity. Elife 2015;4:e05558.
48. Zhang S, Xu M, Kamigaki T, et al. Selective attention. Long-range and local circuits for top-down modulation of visual cortex processing. Science 2014;345(6197):660-5.

Barriers to successful dichoptic treatment for amblyopia in young children



Aveen Kadhum, Emily T.C. Tan, Dennis M. Levi, Linda Colpa, Maria Fronius, Huib J. Simonsz, Sjoukje E. Loudon

Graefe's Archive for Clinical and Experimental Ophthalmology. 2021 Oct;259(10):3149-3157

Abstract

Purpose: In an ongoing randomised clinical trial comparing dichoptic videogames with patching for amblyopia, we evaluated any barriers of this novel amblyopia treatment method.

Methods: From December 2017, all newly diagnosed amblyopic children were recruited. Excluded were children under age four, with strabismus exceeding 30PD or with neurological disorder. The videogame was exercised for one hour per week at the outpatient clinic under direct supervision. Record was kept of difficulties encountered during treatment and categorized into domains. Factors influencing the successful completion of this treatment were identified and related to patient characteristics.

Results: Ninety-one children were recruited for the trial, 20 parents refused participation before randomization, because of the logistic difficulties the outpatient dichoptic treatment would cause them. Of the 17 children who commenced dichoptic treatment (median age 6.2 yrs; IQR 4.9-8.4 yrs), 10 did not complete treatment. All children under age 5.5 years were unable to comprehend the game settings or the game itself. Older children (N=7; 41%) were less willing to comply with the videogame. Loss of interest in the game (N=8; 47%) was found to be a limiting factor at all ages.

Conclusion: Half of the children failed to complete dichoptic treatment, mainly due to young age. In countries with nationwide screening where amblyopia is detected before age six, the applicability of dichoptic treatment is limited.

Key message

- Dichoptic video gaming as a possible alternative to patching treatment for amblyopia is widely researched and seems to result in 1 to 2 logMAR lines of improvement in visual acuity.
- During our study comparing these two treatments, several barriers to successful dichoptic treatment became apparent.
- Children <5.5 years were unable to understand the game settings (i.e. perceptual balance task and alignment task) and perform the game adequately; older children were unwilling or unable to attend the dichoptic game sessions.
- In countries with nationwide vision screening the applicability of dichoptic treatment is limited.

Introduction

The past decade has seen a rise in the use of dichoptic training[1 2] as a possible alternative or supplement to the standard patching therapy for amblyopia.[3, 4] The new dichoptic therapies are often presented as video games: stimulating the brain by repeating a set of simple tasks.[5] They are based on the theory that amblyopia is an intrinsically binocular problem: disruption of binocular vision in early childhood leads to amblyopia with suppression of the amblyopic eye[1]. Since playing a video game is expected to be enjoyable for children, it was assumed that this approach would be less of a burden for the child, than patching. In addition, it has been suggested that these therapies may be more effective in improving stereoacuity[6,7] and contrast sensitivity.[8]

A number of studies have reported favourable results not only in children, but also in adults with on average 1 to 2 logMAR lines of improvement.[9, 10] However, studies comparing the effectiveness of behavioural training with patching were incomplete because the actual gaming time was compared to prescribed or reported patching time.[11-13] Patching times noted by parents are often overestimated whereas compliance with patching measured electronically is poor (on average 50%), making a valid comparison difficult.[3, 14] In addition, studies on dichoptic treatment often compare 1hr of gaming to 1hr of patching. However, the treatment efficiency of gaming is reported to be higher than patching: 100–120 h of patching for each line of visual acuity (VA) gain in young amblyopes[3] and more than 200 h in older than 7 year olds[15] seems to be equivalent to 10–20 h of gaming therapy.[2, 16-18] This encouraged us to design the first trial (NCT03767985) in which we compare the effectiveness of dichoptic video gaming with electronically monitored patching therapy for amblyopia. For this study we recruited children newly diagnosed with amblyopia. A dichoptic action video game (1 h/week) using virtual reality (VR) goggles was played under direct supervision of the researcher at an outpatient clinic in the Netherlands. During the trial it quickly became apparent that this treatment method brought along several unexpected challenges. Thus, in this report, our main focus was to present our experiences working with dichoptic action video gaming as an amblyopia treatment for children; the patching group is not discussed in this report and overall results of the randomised clinical trial (RCT) will be presented elsewhere. We present the first report describing our experiences with this new game therapy and its feasibility in orthoptic practice.

Materials and methods

For the RCT (NCT03767985), children were recruited from four clinics between December 2017 and April 2020. The majority of the participants were from The Hague, which consists of a multi-ethnic and -cultural population with 45% being of Dutch origin and 55% of non-Dutch origin. The treating orthoptist in the clinic referred the child with newly diagnosed amblyopia to the research centre. The research orthoptist examined the child according to the study protocol, using the crowded tumbling E-chart. Amblyopia was defined as an interocular visual acuity (VA) difference of 2 or more logMAR lines caused by refractive error, strabismus or a combination of the two. The decision to include the child was made by the research orthoptist, following the inclusion and exclusion criteria of the study protocol.

Based on the literature, an age range of 4–12 years was applied.[11, 13] Exclusion criteria were previous treatment for amblyopia, strabismus angle more than 30 PD, neurological disorder, other eye disorders and diminished acuity due to medication, brain damage or trauma. Cycloplegic refraction was performed using 1% cyclopentolate. In our study all children who required spectacles first underwent a 16-week refractive adaptation period according to a standardised protocol. This was a prerequisite for the study. If visual acuity difference was less than 2 logMAR lines after refractive adaptation, hence not meeting the criteria for amblyopia, they were not eligible for randomisation. Other parameters, i.e. age, gender, diagnosis, were also documented. The socio-economic and demographic variables were assessed using a questionnaire.

The Ethics Committee of Erasmus University Rotterdam and the Boards of the participating clinics approved the protocol and informed consent forms. Written informed consent was obtained from each subject and/or from his or her parents or guardians. The research adhered to the tenets of the Declaration of Helsinki.

We kept records of all difficulties encountered during the study and created a diagram representing the factors that influenced the success of dichoptic game treatment. We created a focus group, consisting of the research team, two independent orthoptists and two paediatric ophthalmologists as experts in the field. During multiple sessions with our focus group these factors were discussed, evaluated and categorised into three domains: (1) equipment and usage, (2) child and parental adherence with therapy and appointments; and (3) costs. All factors weighed equally and were systematically scored per child; each domain will be discussed separately below.

Equipment and usage

Hardware

The devices used to perform the dichoptic game were the Oculus Rift and the laptop Asus ROG Strix SCAR Edition GL503VS-EI012T. This was a fixed set-up located at the outpatient-clinic (Fig.1).

Figure 1. A 6-year-old boy playing the game. He is wearing the VR goggles and using the controllers to play the game. The laptop on the desk shows the split screen with the left eye being the fellow eye and hence displaying a reduced contrast/luminance.

The game

The software included an active and engaging game for children with settings for perceptually balancing the images seen by the two eyes (by attenuating the contrast/luminance of the image seen by the dominant eye), and the ability to correct for alignment at the start of each game session. The video game was custom-made, based on the principles of the dichoptic game developed by

Levi et al.[4, 17] and modified by Alting (Dfab). The game consisted of two different game surroundings (market place and cave), with difficulty increasing during game play. The child, wearing the VR goggles and holding the controllers, was standing in the marketplace. Snowmen appeared and the child was instructed to throw snowballs at the approaching snowmen. Points were awarded for hitting the snowmen. A suppression check was incorporated in the form of a snowflake, which was presented every 30 seconds for 10 seconds solely to the amblyopic eye. The child was instructed to catch the snowflake before it disappeared to gain extra points. More importantly, successfully catching the snowflake would confirm that the amblyopic eye was still engaged.

Prior to each game session, a perceptual balance and alignment task was performed. Firstly, for the perceptual balance task, two images were presented dichoptically and the contrast/luminance presented to the fellow eye was modulated in order to match the appearance of the high-contrast image perceived by the amblyopic eye. The researcher adjusted the contrast/luminance based on the feedback of the child. The task was repeated four times and the mean contrast/luminance level was applied (Fig. 2a). Balancing the perceptual input to the two eyes is purported in the literature to reduce suppression and is believed to be a key factor in dichoptic therapy effects on visual acuity and stereoacuity.[1, 19] The primary goal of the perceptual balance task was to reduce suppression and facilitate fusion. We chose to base the level of contrast/luminance subjectively on the patient's feedback as opposed to randomly assigning a contrast level to ensure genuine conditions.

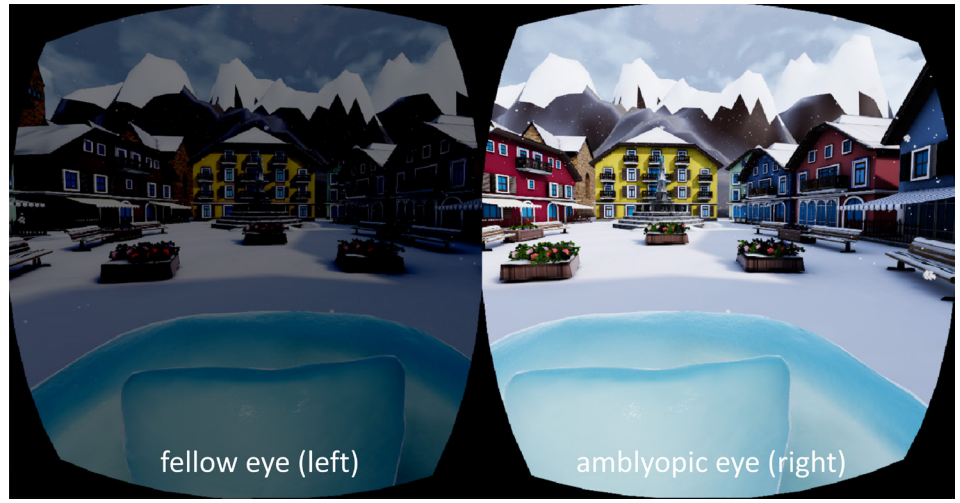
Secondly, the alignment task was performed according to the principles used in previous studies in both adults and children.[4, 17, 20] This included the presentation of two nonius lines dichoptically (Fig. 2b). These two images had to be aligned properly until a full cross was perceived. Both the perceptual balance and alignment tasks were based on the patient's subjective responses.

Child and parental adherence with therapy and appointments

Children who did not bring their spectacles to a game session had to be rescheduled. Dichoptic gaming treatment in our study was conducted once a week at the outpatient clinic and comprised of a total of 24 sessions. This meant weekly trips to the clinic by the patient with at least one parent or supervisor. Each game session commenced with the perceptual balance and alignment settings followed by 1 h of game play with breaks in between. All sessions were directly supervised by the

researcher enabling objective monitoring of compliance. Compliance during each game session was recorded with a stopwatch. Compliance with the scheduled weekly game session appointments during the total therapy duration was also recorded.

a Dichoptic presentation with attenuated contrast/luminance for the fellow eye (left eye) in order to match the image perceived by the amblyopic eye (right eye).



b Alignment task with two nonius lines to fuse into one full cross. The image on the right shows the full cross perceived when the two images are fused.

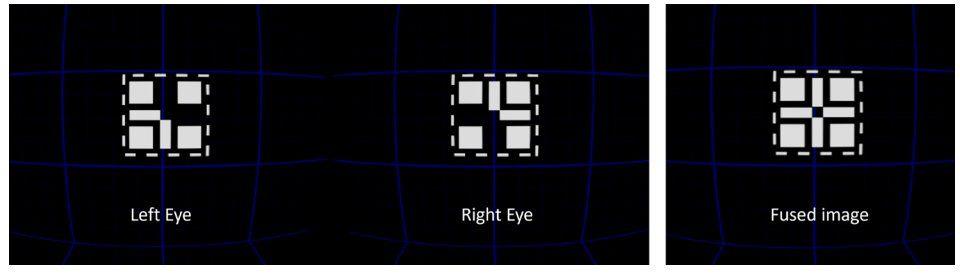


Figure 2

Costs

We assessed all costs involved for the health care provider as well as the patient. This included the following: equipment, software and maintenance/updates, personnel supervising the game sessions, treatment room rent, overhead and travel costs.

Results

For the RCT 91 children (age 4-12 years) were recruited by the treating orthoptists; all records were analysed (Fig. 3). Two children were excluded based on linguistic problems and legal issues. The parents of 29 children refused participation before randomisation, 20 for reasons directly related to the dichoptic game treatment: 18 were unwilling or unable to comply with the weekly game-sessions, one parent refused participation as he thought the game treatment would be harmful for his child's eyes and one child was frightened by the prospect of the game. After the refractive adaptation period, amblyopia was sufficiently treated in 25 children, i.e. visual acuity difference between both eyes resolved to less than 2 logMAR lines. Thirty-five were randomised into the two arms of the study: 18 to patching and 17 to the dichoptic gaming group. The 17 children assigned to the game group were included in this study and are the subject of this paper.

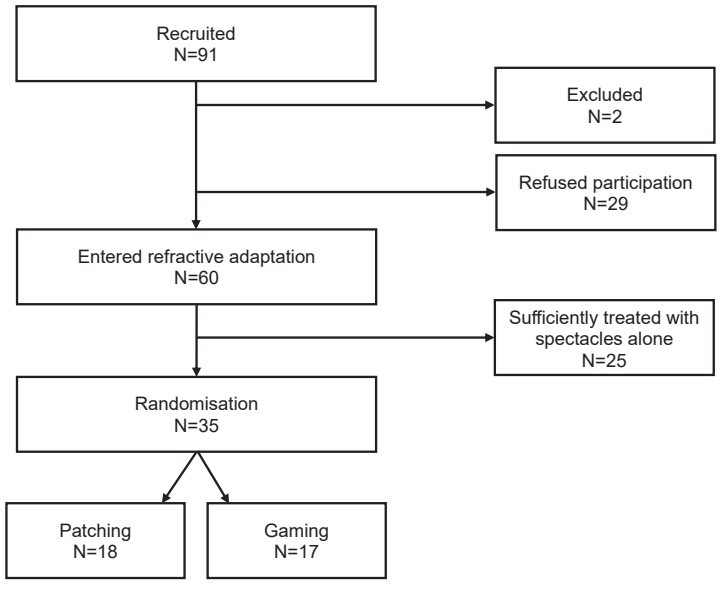


Figure 3. Flowchart with recruitment of children for randomised controlled trial.

Visual acuity

No children were excluded based on their visual acuity as it did not limit the ability to conduct the treatment. No apparent relationship could be found between visual acuity in the amblyopic eye at start of treatment and the ability to perform the dichoptic game treatment."

Strabismus

Based on the literature, patients with a strabismus angle >30PD were excluded.[4] In our study in the gaming group, there were only two subjects with strabismus: the first patient had 10PD partial accommodative esotropia, hypermetropia with dubious binocular single vision; the second patient had 12PD fully accommodative esotropia, hypermetropia with demonstrable binocular single vision. These subjects with strabismus did not complete the game treatment; however, their angle of strabismus was not the main reason for them being unable to conduct the therapy.

Age

Median age of the gaming group was 6.2 years (IQR 4.9–8.4 yrs). Median age of those who dropped out was younger, 5.4 years (IQR 4.8–7.3) compared to 6.7 years (IQR 5.4–12.3) in the children who completed the game treatment; however, this was not significant (P=0.27; Mann-Whitney U Test).

Equipment and usage

Hardware

Initially, the dichoptic video game was played using Zeiss 3D OLED goggles. In practice we experienced difficulty fitting the subjects' own spectacles underneath these 3D goggles. Moreover, during game play, there was no external screen for the researcher to verify the image seen in the OLED goggles by the child, therefore making it impossible to track the game progress during game sessions. To correct these obstacles, we changed to the Oculus Rift VR goggles (see Fig. 1).

The laptop together with the Oculus Rift had to be set up adequately for the space where the game sessions were conducted. This set-up was intended for use at the outpatient clinic and was not easy to transport as it was bulky and heavy (Fig. 4).

The Oculus Rift was more appropriate for older children due to the size and weight of the headset and controllers. However, in 24% the spectacles would become foggy underneath the headset during active game play, resulting in a blurry image. If children reported this, the game session was interrupted in order to clean the spectacles. Foggy spectacles could not be directly observed by the supervisor, so it is possible that this occurred more often than was reported. Keeping the spectacles clean was essential as presenting a clear and sharp image to both eyes during game play was a critical element of the therapy and had to be maintained at all times. These breaks led to frustration by the child and loss of concentration.

The game

As depicted in Table 1, children younger than 5.5 years had difficulties applying the game settings, i.e. they did not understand the perceptual balance task and/or could not communicate properly whether they perceived a full cross with the alignment setting. In addition, these children were also unable to comprehend the task of throwing snowballs at the approaching snowmen and would often just look around in the VR goggles. Overall, 7 children did not complete the treatment due to difficulties with the game settings.

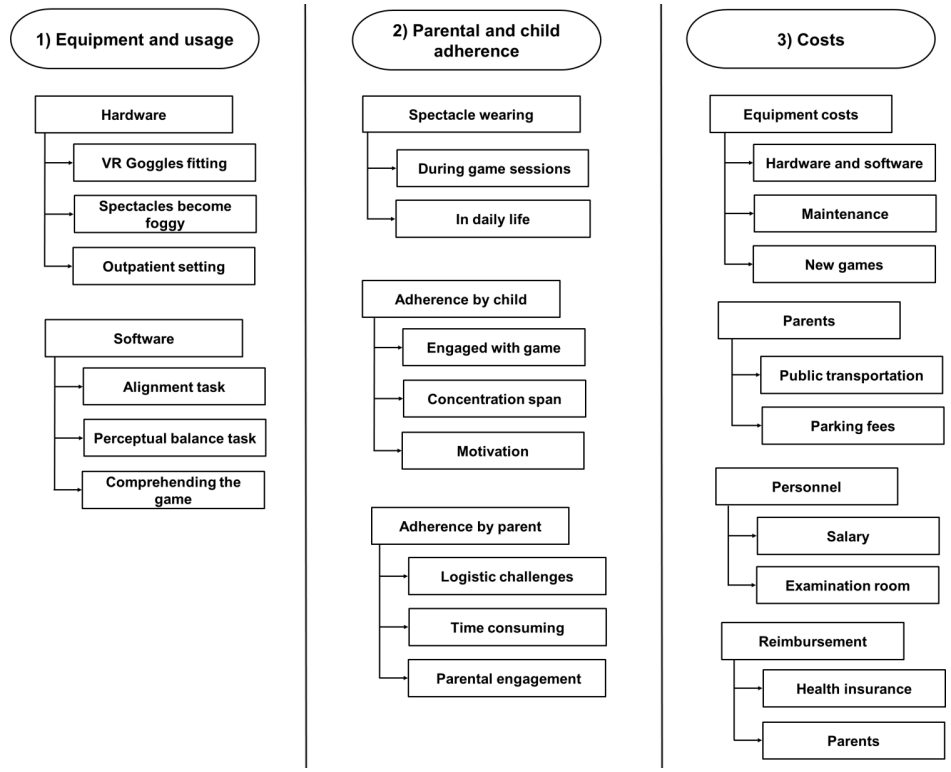


Figure 4. Overview of the challenges for each domain.

Child and parental adherence with therapy and appointments

Children who refused to wear their spectacles were excluded from participating, as this would preclude optimal treatment. In addition, optimal spectacle correction is essential for obtaining or improving binocular vision; for example, a patient with a fully accommodative esotropia. Two eligible children were excluded due to refusal to wear spectacles.

During the trial, on occasion some children would forget to bring their spectacles. Children who showed up at the appointment without their refractive correction had to be rescheduled. This occurred in 3% of the scheduled appointments.

Table 1. This table shows the scoring sheet used to tabulate the challenges for each child. The sheet is arranged according to age. Some patients had more than one challenge. Seven children completed the dichoptic treatment. T time of drop out in weeks during the trial. T0 refers to drop-out during the first game session trial, T2 refers to drop-out after 2 game sessions (2 weeks) and T6 after 6 game sessions (6 weeks).

Patient	Time of drop-out	Age	Difficulties with game settings	Difficulty comprehending the game	Lost interest in the game	VR goggles and controllers too large	Foggy glasses	Forgot to take spectacles to game session	Unable/unwilling to attend game appointments
No 16		4.06	X	X	X	X			X
No 1	T0	4.51	X			X			
No 5	T0	4.67	X	X	X	X			
No 15	T0	4.87	X	X					
No 9	T2	5.00			X	X			
No 14	T6	5.34	X	X	X	X			X
No 3	T0	5.37	X						
No 8		5.41			X			X	
No 11		6.16			X		X	X	X
No 2	T0	6.27	X						
No 13		6.66				X	X		
No 4	T6	6.67			X	X			X
No 10		7.41				X			
No 12	T0	9.37							X
No 17	T0	10.55							X
No 7		12.33			X		X		X
No 6		12.46					X		
TOTAL			7/17=41%	4/17=24%	8/17=47%	8/17=47%	4/17=24%	2/17=12%	7/17=41%

Table 1 shows that boredom with the game was apparent in the younger, but also in older children. During the lengthy sessions or whenever they lost interest in the game they would simply stop throwing snowballs and refuse to continue. On consecutive appointments, the child would become increasingly reluctant to come in and play the game. In our study each game session lasted a minimum of 1.5 h: one h for gaming and 30 min for doing the settings and breaks in between.

Table 1 shows that approximately half of the children (41%) were unwilling or unable to comply with the weekly game-sessions. Parents had to implement the weekly 1.5-hour game session into their schedule; this excluded travel time to and from the clinic. For this reason, 18 eligible subjects refused participation a priori, because they found the game treatment too much of a burden and difficult to incorporate into their daily life. In addition, within the gaming group there were 3 children who dropped out due to these same logistic challenges. In addition, many families had both working parents and siblings having other commitments (e.g. sports), which often resulted in limited time to attend the clinic. Another

type of non-compliance was found during the study: parents of children in the game group frequently cancelled their appointments often mentioning that their child was not interested in playing the game anymore. Overall adherence was not related to age.

Costs

Several costs were identified (Fig. 4). Firstly, the required *hardware* to perform the game including the laptop and virtual reality headset. Secondly, the *software*: the development and modifications of an engaging child friendly dichoptic video game with two different game environments, including settings for perceptual balance and alignment and a suppression check. In addition, in our study the game sessions were conducted under direct supervision once a week at the outpatient clinic. This resulted in personnel costs: an orthoptist needed to supervise the game session. Then, there are the travel expenses, parking fees and the cost of time off work for the parents to be taken into account.

Discussion

We recorded factors that influenced the applicability of dichoptic video gaming with VR goggles in young children. These factors ranged from recruitment of an eligible patient up until successful completion of dichoptic treatment. Almost all parents who refused to participate prior to inclusion were unable or unwilling to engage in outpatient dichoptic treatment; and half of the included children did not complete the treatment. Overall, we found that children younger than 5.5 years of age had too much difficulty with the game settings, difficulty comprehending the game and 1 h of active gaming was too tedious for them. Older children (and their parents) were unwilling to adhere to the weekly game schedule. Losing interest in the game was apparent at all ages.

Age turned out to be a key factor in determining eligibility and success of dichoptic treatment in practice. In the literature, the age of children undergoing these therapies mostly range from 4 to 17 years.[10] We note that the subjects from the study of Gambacorta et al., which used the same gaming principles, had older subjects with an age range of 7 to 17 years.[17] We found that young children, with limited language skills and cognitive ability, had more difficulty comprehending the game as well as understanding and articulating feedback concerning for example the perceptual balance and alignment settings. In countries such as the Netherlands, with an extensive vision screening program, children with strabismic amblyopia are detected at 2.5 years of age and those with refractive amblyopia at 4.5 years of age.[21] This raises the question as to whether this type of therapy would be feasible. Children with a large strabismus angle (>30PD) were excluded; we only had two children with a strabismus angle up to 12PD who were able to fuse the images. The reason for these children to drop out was their inability to fully understand the game settings (ocular alignment and contrast settings). However, one could hypothesise that the second child especially, based on her small-angle strabismus and some degree of demonstrable binocular single vision, would have been able to conduct the game. From clinical experience, we would expect children with a larger strabismus angle to have more difficulty fusing the images. Several studies based on dichoptic iPad treatment using anaglyphic glasses applied an even smaller strabismus angle as exclusion criteria, excluding all patients with deviations ≥10PD or even ≥4PD.[11, 18] As children with strabismic amblyopia are detected at an earlier age, treatment should commence as soon as possible rendering them ineligible, not only because of the angle of strabismus, but also their age. This would indicate dichoptic treatment in children would be at best feasible for small angle strabismic/combined amblyopes or anisometropic amblyopes that are first diagnosed at an older age, or in countries with less successful early detection and treatment programs for amblyopia.

In our study the game was played under direct supervision of the researcher. This design was chosen to ensure the game therapy was conducted correctly and to monitor compliance. However, this set-up revealed its own challenges. Due to a fixed game set-up at the outpatient clinic, parents had to incorporate this into their daily routine and maybe even take time off work—the costs of which needs to be considered by all parties. Ideally, a home-based alternative would be offered; however, Holmes et al. reported poor compliance with iPad games at home.[11, 12] In addition, moving to a home-based setting would require more parental responsibility and supervision to ensure the sessions are performed correctly and, with VR, avoiding injury if children move around with the goggles on.

Patient motivation with the game therapy is essential. Unlike adults with amblyopia, who are generally intrinsically motivated to improve their eyesight and therefore to comply with treatment, children have to be kept engaged. Young children, especially, have more difficulty comprehending the reasons for treatment. Moreover, these young children in general have a shorter concentration span and get more easily distracted during the game. Therefore, games should be aimed at keeping children engaged according to their age group. Young children need a gaming environment with minimal stimuli and simplistic objects; older children need a more complex and varied gaming environment with more stimuli to keep them engaged. Ideally there should be a variety of different highly engaging games with rich environments for different age categories. This would come with high costs. Important to note is that the video game industry is a whole separate branch developing rapidly with large teams set up specifically to develop games. Games developed by research groups cannot match the quality of games developed by the industry, due to their expertise and experience, so ideally researchers should work together with the game industry to produce compelling video games. However, regardless of offering a broad range of games suitable for different age categories, we cannot overlook the psychological factor that assigning a child to play a video game as a therapy is not the same as when a child voluntarily chooses to play a game; therefore compliance rates should not be overestimated.

The costs of conducting dichoptic treatment with VR goggles were considerable. This raises the question who will pay for these costs: the national or private health insurance, or out of pocket of the families. Our set-up in the clinic made it labour intensive and therefore more expensive.

The VR goggles used in this game therapy were not primarily designed for young children. New inexpensive consumer VR headsets such as the Oculus Go, that can be operated via a cell phone, may help to offset some of these issues. Offering dichoptic therapy for amblyopia in other forms, such as using an iPad or dichoptic movie watching, may be more suitable for younger children.[22] Nevertheless, there were several other aspects limiting the success of this type of treatment that would still be present with these alternative forms, such as issues with compliance and logistics.

As awareness of these new therapies rises this has its effect on daily orthoptic practice. With this inventory, we hope to provide treating orthoptists guidelines for informing parents about these new treatment methods.

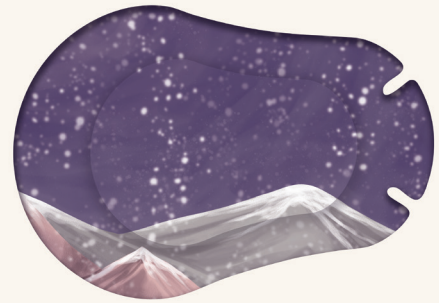
References

1. Hess RF, Thompson B (2015) Amblyopia and the binocular approach to its therapy. Vision Res 114:4–16. https://doi.org/10. 1016/j.visres.2015.02.009
2. Levi DM (2020) Rethinking amblyopia 2020. Vision Res 176:118–129. https://doi.org/10.1016/j.visres.2020.07.014
3. Stewart CE, Moseley MJ, Stephens DA, Fielder AR (2004) Treatment dose-response in amblyopia therapy: the Monitored Occlusion Treatment of Amblyopia Study (MOTAS). Invest Ophthalmol Vis Sci 45:3048–3054. https://doi.org/10.1167/iovs.04-0250
4. Vedamurthy I, Nahum M, Huang SJ, Zheng F, Bayliss J, Bavelier D, Levi DM (2015) A dichoptic custom-made action video game as a treatment for adult amblyopia. Vision Res 114:173–187. https://doi.org/10.1016/j.visres.2015.04.008
5. Jaeggi SM, Buschkuehl M, Jonides J, Shah P (2011) Short- and long-term benefits of cognitive training. Proc Natl Acad Sci U S A 108:10081–10086. https://doi.org/10.1073/pnas.1103228108
6. Levi DM, Knill DC, Bavelier D (2015) Stereopsis and amblyopia: a mini-review. Vision Res 114:17–30. https:// doi. org/ 10. 1016/j. visres.2015.01.002
7. Hess RF, Thompson B, Baker DH (2014) Binocular vision in amblyopia: structure, suppression and plasticity. Ophthalmic Physiol Opt 34:146–162. https://doi.org/10.1111/opo.12123
8. Li J, Spiegel DP, Hess RF, Chen Z, Chan LY, Deng D, Yu M, Thompson B (2015) Dichoptic training improves contrast sensitivity in adults with amblyopia. Vision Res 114:161–172. https:// doi.org/10.1016/j.visres.2015.01.017
9. Tsirlin I, Colpa L, Goltz HC, Wong AM (2015) Behavioral training as new treatment for adult amblyopia: a meta-analysis and systematic review. Invest Ophthalmol Vis Sci 56:4061–4075. https://doi.org/10.1167/iovs.15-16583
10. Pineles SL, Aakalu VK, Hutchinson AK, Galvin JA, Heidary G, Binenbaum G, VanderVeen DK, Lambert SR (2020) Binocular treatment of amblyopia: a report by the American Academy of Ophthalmology. Ophthalmology 127:261–272. https:// doi. org/ 10. 1016/j.ophtha.2019.08.024
11. Holmes JM, Manh VM, Lazar EL, Beck RW, Birch EE, Kraker RT, Crouch ER, Erzurum SA, Khuddus N, Summers AI, Wallace DK, Investigator PED, G, (2016) Effect of a binocular iPad game vs part-time patching in children aged 5 to 12 years with amblyopia: a randomized clinical trial. JAMA Ophthalmol 134:1391 1400. https://doi. org/10.1001/jamaophthalmol.2016.4262
12. Manh VM, Holmes JM, Lazar EL, Kraker RT, Wallace DK, Kulp MT, Galvin JA, Shah BK, Davis PL, Investigator PED, G, (2018) A randomized trial of a binocular iPad game versus part-time patching in children aged 13 to 16 years with amblyopia. Am J Ophthalmol 186:104–115. https://doi.org/10.1016/j.ajo.2017.11. 017
13. Pediatric Eye Disease Investigator G, Holmes JM, Manny RE, Lazar EL, Birch EE, Kelly KR, Summers AI, Martinson SR, Raghuram A, Colburn JD, Law C, Marsh JD, Bitner DP, Kraker RT, Wallace DK (2019) A randomized trial of binocular dig rush game treatment for amblyopia in children aged 7 to 12 years. Ophthalmology 126:456–466. https://doi.org/10.1016/j.ophtha.2018. 10.032

14. Loudon SE, Fronius M, Looman CW, Awan M, Simonsz B, van der Maas PJ, Simonsz HJ (2006) Predictors and a remedy for non-compliance with amblyopia therapy in children measured with the occlusion dose monitor. Invest Ophthalmol Vis Sci 47:4393–4400. https://doi.org/10.1167/iovs.05-1428
15. Fronius M, Cirina L, Ackermann H, Kohnen T, Diehl CM (2014) Efficiency of electronically monitored amblyopia treatment between 5 and 16 years of age: new insight into declining susceptibility of the visual system. Vision Res 103:11–19. https:// doi. org/10.1016/j.visres.2014.07.018
16. Birch EE, Li SL, Jost RM, Morale SE, De La Cruz A, Stager D Jr, Dao L, Stager DR Sr (2015) Binocular iPad treatment for amblyopia in preschool children. J AAPOS 19:6–11. https:// doi. org/10.1016/j.jaapos.2014.09.009
17. Gambacorta C, Nahum M, Vedamurthy I, Bayliss J, Jordan J, Bavelier D, Levi DM (2018) An action video game for the treatment of amblyopia in children: a feasibility study. Vision Res 148:1–14. https://doi.org/10.1016/j.visres.2018.04.005
18. Kelly KR, Jost RM, Dao L, Beauchamp CL, Leffler JN, Birch EE (2016) Binocular iPad game vs patching for treatment of amblyopia in children: a randomized clinical trial. JAMA Ophthalmol 134:1402–1408. https:// doi. org/ 10. 1001/ jamaophthalmol. 2016. 4224
19. Vedamurthy I, Nahum M, Bavelier D, Levi DM (2015) Mecha nisms of recovery of visual function in adult amblyopia through a tailored action video game. Sci Rep 5:8482. https://doi.org/10. 1038/srep08482
20. Ding J, Levi DM (2011) Recovery of stereopsis through perceptual learning in human adults with abnormal binocular vision. Proc Natl Acad Sci U S A 108:E733-741. https:// doi. org/ 10. 1073/ pnas.1105183108
21. Groenewoud JH, Tjiam AM, Lantau VK, Hoogeveen WC, de Faber JT, Juttmann RE, de Koning HJ, Simonsz HJ (2010) Rotterdam AMblyopia screening effectiveness study: detection and causes of amblyopia in a large birth cohort. Invest Ophthalmol Vis Sci 51:3476–3484. https://doi.org/10.1167/iovs.08-3352
22. Birch EE, Jost RM, De La Cruz A, Kelly KR, Beauchamp CL, Dao L, Stager D Jr, Leffler JN (2019) Binocular amblyopia treatment with contrast-rebalanced movies. J AAPOS 23:160. e161 160.e165. https://doi.org/10.1016/j.jaapos.2019.02.007

How do parents experience patching or dichoptic action video gaming as amblyopia treatment?

A qualitative study exploring treatment preferences and information needs to facilitate decision-making



Emily T.C. Tan, Aveen Kadhum, Marieke A.J. Telleman, Annemieke Treur, Janna Bruijning, Sjoukje E. Loudon

Ophthalmic and Physiological Optics. 2023 Jul;43(4):649-659

Abstract

Purpose: To explore parents' experiences, preferences and information needs when either patching treatment or dichoptic action video gaming is used as an amblyopia treatment for their child.

Methods: A qualitative study was carried out on parents whose newly diagnosed amblyopic children participated in a randomised controlled trial (RCT) comparing the effects of dichoptic action video gaming versus patching. A purposive hetero genic sample was selected for an additional interview after the study period. Semi-structured interviews were conducted with one or both parents and transcribed verbatim, and a thematic analysis was performed.

Results: Ten families agreed to participate: seven in the patching group and three in the gaming group. Two themes emerged from the data exploring experiences with treatment: (1) factors influencing compliance and (2) burden with treatment. Parents reported creating a routine which improved compliance with patching, as opposed to gaming where parents felt less need to conduct the treatment themselves as it was performed in the outpatient clinic. In both groups, parents experienced an information hiatus regarding the role of refractive error. In deciding the type of treatment to be used, parents preferred to deliberate the choice with the healthcare professional and discuss considerations resulting in shared decisions. The emerging themes were (1) effect and efficiency of treatment, (2) organisational aspects of treatments and (3) their child's traits.

Conclusion: This study provides insight into the experiences of parents whose children underwent different types of amblyopia therapy. Both treatments have their own advantages and disadvantages. For parents, the effectiveness and efficiency of treatment were the most important aspects when deciding the method of management. Parents wish to come to a well- informed, shared decision regarding the type of amblyopia treatment.

Key-points

- This study provides insight into experiences of parents whose children underwent different types of amblyopia treatment. Both patching treatment and dichoptic action video gaming have their own advantages and disadvantages.
- Parents reported that creating a routine with patching improved compliance. With regard to gaming treatment, parents felt less responsibility to conduct the treatment themselves, as it was carried out in the outpatient clinic.
- Parents wish to come to a well-informed, shared decision after discussing the expected effect as well as several organisational aspects of treatment and their child's traits.

Introduction

Amblyopia is a decrease of visual acuity in either one or both eyes, without any evidence of organic eye disease, that persists after the correction of refractive error. Amblyopia may be caused by strabismus, anisometropia, a combination of strabismus and anisometropia or form deprivation.[1] The prevalence of amblyopia varies from 1.6% to 3.5%, and it is the most common visual disorder in children.[2] The standard treatment for amblyopia is patching of the better eye for several hours per day during the sensitive period.[3] Patching treatment has proven to be successful, with 75% of children having stable visual acuity 15 years after cessation of treatment.[4] However, the success of patching is often hindered by poor compliance. Previous studies have shown that the average compliance with this treatment is about 50%.[3,5–7] Therefore, there is interest in alternative amblyopia therapies. Over the past decade, behavioural treatments such as perceptual learning, video gaming and dichoptic training have become increasingly popular.[8–11] These treatments have also proven to be successful, even beyond the sensitive period.[8,12–14] Nowadays, there is an increasing demand for evidence, not only regarding the treatment effectiveness but also about the patient experience with the therapy. Several quantitative studies have been conducted on the impact of amblyopia and its treatment on the health-related quality of life in children.[15–18] However, there is limited qualitative research available concerning experiences with amblyopia treatment. Dixon-Woods et al. explored reasons for non-compliance with patching treatment in their qualitative study.[19] To our knowledge, no previous study has investigated these experiences with behavioural management. If these kinds of treatment are a potential alternative to standard amblyopia therapy, then it is imperative to know about the child and parents' preferences and experiences with these behavioural treatments and whether they differ from patching. In this study, the parents of participating children were used as proxy for the child's experiences. In addition, the information needs of the parents and children are unknown, thereby hampering clinical decision- making. Accordingly, the aim of this qualitative study was to explore parents' experience and preferences with patching treatment or dichoptic action video gaming as amblyopia treatment. It was conducted as part of our randomised controlled trial (RCT) in which we compared the effect of dichoptic action video gaming with patching treatment in newly diagnosed amblyopic children. We also evaluated parental information needs for participation in amblyopia treatment and clinical decision-making.

Methods

Participants

For the RCT (NCT03767985), children were recruited from five clinics during the period from December 2017 to April 2020. Children with newly diagnosed amblyopia (i.e., not having received any prior amblyopia treatment) and between 4 and 12 years of age were eligible for participation. Amblyopia was defined as a difference in best corrected visual acuity of two or more LogMAR lines between the eyes, and associated with refractive error, strabismus or a combination of the two. Exclusion criteria were non-comitance, strabismus >30 Δ, a neurological disorder, nystagmus, other ocular disorders or reduced visual acuity due to medication, brain damage or trauma. After a 16-week refractive adaptation period, children were randomised to either patching (2 h per day, 7 days a week) or dichoptic action video gaming (1 h per week at the outpatient clinic under the direct supervision of the researcher) for 24 weeks.

The principles of the video game have been reported in detail elsewhere.[20] Briefly, it was a custom-made, dichoptic action video game performed using Oculus Rift virtual reality (VR) goggles (oculus.com), and based on the games previously reported by Vedamurthy et al.[21] The type of game and the images in the VR goggles were designed for children 4 years of age and older. The game included two levels with different lay-outs (a marketplace and an ice cave). During the game, snowmen appeared and the child was instructed to throw snowballs at them to gain points. To ensure the child remained engaged during the game, a red snowflake was presented every 30 s to the amblyopic eye only for extra points. In the gaming group, compliance was registered by the researcher who supervised the gaming session and used a stopwatch to determine the exact game duration. Gaming treatment was performed at the outpatient clinic in the HMC Hospital, The Hague.

Compliance with patching was monitored electronically with the occlusion dose monitor (ODM) for 1 week every 6 weeks,[6,22] that is a total of four measurements. Parents were instructed to attach the ODM to the front of the patch with double sided tape. Every 6 weeks, a standard orthoptic examination was performed on all subjects. After completing the study, the child was referred back to their treating orthoptist. For detailed information about the study design and the treatments, see Appendix S1.

Sample

A purposive sample of parents was selected for an additional interview after participation in the RCT. In the gaming group, parents were considered eligible when their child was able to perform the game settings and completed at least one gaming session. Thus, experience with the gaming treatment could be ensured. In the patching group, all parents were considered eligible for participation in the interviews. Parents were selected in such a manner to create a heterogenic sample based on the age of the child undergoing treatment, the child's visual acuity (VA), type of amblyopia, socio-economic status and electronically monitored compliance with patching. The Ethics Committee of Erasmus University, Rotterdam, and the Boards of the participating clinics approved the protocol and informed consent forms. Additional written informed consent was obtained from each participant for the interview. The research adhered to the tenets of the Declaration of Helsinki.

Data collection

In this generic qualitative research, semi-structured interviews were conducted with one or both parents using Microsoft Teams (Microsoft.com) or by telephone due to COVID-19 restrictions at the time. Interviews were con ducted by authors ET and AT, both native speakers of the Dutch language. ET is an orthoptist with both clinical and research experience. AT is an optometry student and was trained for the study. Field notes and memos were obtained during the interviews. All interviews were audio-recorded and transcribed verbatim by the authors (ET and AT).

Development of the interview guide

During the RCT, the Child Amblyopia Treatment Questionnaire[23–25] and additional questions were completed by the parents and/or the child both at the start of the study and after finishing treatment. The questionnaires were carried out to collect information about the patient's preferences and experiences, as well as the parents knowledge of amblyopia and their information needs for participation in clinical decision-making. Based on these questionnaires, an interview guide was developed to gain more in-depth analysis of the parents' experiences and preferences with amblyopia treatment (see Appendix S2). The interview guide was extensively discussed within the research team. Interviews were conducted until data saturation was observed. Each interview was analysed and based on the results, the interview guide for the next interview was adjusted.

Data analysis

Thematic analysis was carried out in accordance with the guideline described by Braun and Clarke.[26] It consisted of the following phases: (1) familiarising with the data by reading and re-reading the transcribed interviews line- by- line and searching for meaningful fragments, (2) generating initial codes from the data, (3) grouping the codes together and searching for themes and subthemes, followed by (4) reviewing the themes, (5) defining and naming the themes according to the key aspects of the research questions and (6) producing the report. Each interview was manually coded individually by ET, MT and AK. Any discrepancies with the coding were resolved through discussion between ET, MT and AK. The final categories and emergent (sub)themes were confirmed by all the authors.

Results

Parents of 23 children were eligible for participation: nine in the gaming group and 14 in the patching group.[27] In the gaming group, all nine parents were approached to participate in the qualitative study of whom three agreed. Reasons for refusal were the time investment (N = 3) or parents did not respond despite repeated attempts to contact them (N = 3). In the patching group, seven parents were approached to participate in the interviews, all of whom agreed.

Eight interviews were conducted with the mother of the child, one with the father and one interview with both parents together. Of the interviewed parents, fluency in Dutch was rated 'excellent' in eight families, one was rated as 'good' and one was rated as 'moderate'. The duration of the interviews ranged between 25 and 50 min.

The median visual acuity of the amblyopic eye at the start of treatment in the patching and gaming groups was 0.40 logMAR (IQR 0.40– 0.80) and 0.50 logMAR, respectively. The mean overall age was 5.8 ± 2.8 years. Patient characteristics at baseline are presented in Table 1.

Table 1. Patient characteristics at baseline.

Participant no.	Age of the child (years)	Sex	Randomisation	Type of amblyopia	Refractive error		Amblyopic eye	BCVA (logMAR)	
					Right eye	Left eye		AE	FE
1	12	F	Patching	Anisometropia	S-0.50	S+3.75 C-1.25 x 170	Left	0.80	0.00
2	4	F	Patching	Anisometropia	S+2.25 C-1.50 x 10	S+1.50 C-2.50 x 20	Left	0.40	0.20
3	6	F	Gaming	Anisometropia	S+4.25 C-3.50 x 180	S+3.50 C-1.75 x 180	Right	0.50	0.20
4	4	F	Gaming	Anisometropia	S+3.00 C-0.50 x 180	S+1.00 C-0.50 x 180	Right	0.50	0.20
5	5	F	Patching	Combined	S+2.75	S+1.25 C-0.25 x 0	Right	0.20	0.00
6	4	M	Patching	Combined	S+9.00	S+10.25 C -1.00 x 2	Left	1.10	0.60
7	4	M	Patching	Combined	S 0.00 C-2.00 x 90	S 0.00 C-0.50 x 90	Right	0.40	0.20
8	4	F	Patching	Anisometropia	S+6.00 C -0.50 x 115	S+1.00	Right	0.40	0.10
9	6	F	Patching	Anisometropia	S+3.25 C-0.50 x 115	S+0.50 C-0.50 x 165	Right	0.50	-0.10
10	6	M	Gaming	Anisometropia	S+2.00 C-4.00 x 15	S+0.50 C-0.75 x 180	Right	0.60	0.00

Abbreviations: AE, amblyopic eye; BCVA, best corrected distance visual acuity; F, female; FE, fellow eye; M, male.

PART I: Experiences with amblyopia treatment

Two themes emerged from the qualitative analysis on experiences with amblyopia treatment: (1) factors influencing compliance and (2) burden with treatment. Themes and their subthemes are described below. Quotations are noted with the corresponding participant number (see Table 1). The type of treatment is indicated by (G) for gaming and (P) for patching.

Theme 1: Factors influencing treatment compliance

In both groups, parents described several factors that influenced the compliance, either positively or negatively.

Creating a routine

The need to create a routine is an important factor to maintain good compliance with both patching and gaming treatment. With patching, parents described the need to integrate patching into their family's daily routine by selecting a specific time a day. For example, from breakfast until their fruit and veggie break in school. In the gaming group, this routine was established by reserving a particular day and time per week for the gaming sessions. Creating these well- structured routines resulted in better acceptance of the treatment by the child. If the routine was interrupted or if the duration of treatment sessions was adjusted, then parents found it harder to maintain compliance.

> At one point we had to patch for 30 minutes per day. That I found particularly difficult. (…) With this sort of duration, I wasn't able to create a practical moment during the day. Mornings were always the easiest, because our morning routine is always the same. Later in the day it's always harder as afternoon activities vary per day.
>
> Participant 6 (P)

> With gaming I was glad that I could say 'we are going to the hospital and we are going to do the game'. This creates a structure. I think that flexibility [with gaming] would not work out for me. I think you will become more neglectful. It is more easy to say 'okay, we will skip gaming today, we'll do it tomorrow'.
>
> Participant 4 (G)

Perceiving the amblyopic eye as a problem

Parents experienced difficulties with explaining the need for treatment to their children, especially at a younger age. They reported that the children did not perceive the amblyopic eye as a limitation during their daily activities, as the other eye was functioning normally. As a result, some children refused to adhere to the amblyopia treatment and/or wearing spectacles. In some cases, this led to arguments.

> Having a lazy eye did not bother her during her daily activities, as she used her better eye. (…) And that's the struggle, because she didn't experience the patching treatment as making it 'better'. With both eyes open there is no problem for her.
>
> Participant 9 (P)

Expressing compassion

Parents often expressed a feeling of compassion towards their children, commenting that the most distressing moment is the anticipation of commencing the treatment, for example, putting the patch on the eye or completing the full 1 h gaming session. At the same time, parents realised that treatment is necessary.

> I think I felt more sorry for her that she had to patch, than she felt sorry for herself.
>
> Participant 2 (P)

> I think I truly underestimated what gaming takes from a child of that age. An hour is quite long at that age. (…) Sometimes I really had to encourage her to keep on gaming. So she fulfilled that hour. (…) Sometimes I said to the girls supervising the game 'let's just stop to continue this gaming session today is of no use'. Looking back at these moments, I think I made the right decision for my child terminating these gaming sessions earlier.
>
> Participant 4 (G)

Feeling responsible as a parent to conduct the treatment

Parents felt a certain responsibility for carrying out the treatment. Parents understood the need for treatment and were concerned about the consequences for their child if they did not conduct the treatment.

> At one point I was about to stop the treatment completely, because it was exhausting sometimes to keep on motivating her. But at that point I thought 'this is necessary for her health and we're going to do this. We're almost there'.
>
> Participant 4 (G)

> It is for my child. If it improves his eyesight, then it [coming in for weekly gaming sessions] doesn't matter. It is part of being a parent.
>
> Participant 10 (G)

In the patching group, parents reported they felt responsible for patching their child, thereby creating a certain anxiety every day. It was considered an additional activity in the family's daily routine.

> Of course it is very unpleasant for the child to have a patch on her eye for such a long time. But as a parent it is also unpleasant to keep convincing her that it needs to be done. (...) As a parent, of course you want your child to patch.
>
> Participant 9 (P)

In the gaming group, parents experienced the opposite. Since gaming treatment was performed under the direct supervision of the researcher, parents felt less anxiety and responsibility to conduct the treatment themselves. They also reported that the weekly session of gaming treatment, compared with daily patching, was the biggest benefit of gaming treatment.

> No, I wouldn't want that patchy- thing. [As a parent] you'll forget to patch every other day. With gaming, it was more of a routine, coming in every Thursday for treatment and you are done. This way, you are sure that it's treated, every single time, during the whole year.
>
> Participant 3 (G)

> You go every Wednesday [for the gaming session] and after that you're done for the rest of the week. As a parent you don't need to think about the treatment for the rest of the week. And the fact that you don't have any 'homework'.
>
> Participant 4 (G)

Rewards and motivation

Rewards by parents in the form of treats, presents or activities were used to motivate children to comply with treatment, in both the gaming and patching group.

> Sometimes she didn't want to go to the appointment for the game session. But when I promised her 'when we are done, we will go to the restaurant in the hospital to get a treat', it was fine.
>
> Participant 3 (G)

Children in the patching group liked the different de signs and colourful patterns of the patches and parents reported this as a motivating factor. In addition, parents reported that putting on the patch was relatively easy and understandable. Therefore, children were able to put on the patch and remove it themselves when it was linked to a specific moment in their day. By giving their children the opportunity to choose from different designs of the patch as well as putting on and removing the patch themselves, this allowed them to have a form of control over their treatment and stimulate their self- dependence.

> It was an easy treatment, What usually took the longest was her deciding the patch she wanted to wear that day. She would have 10 different designs to choose from. That is what took the most time: choosing the patch. Putting on the patch was only 10 seconds of work. [...] Exactly, it is easy. Everybody is able to patch. When she was around 5 years old she could do it herself. That's also a positive point of the patching treatment, it gave her a kind of responsibility.
>
> Participant 2 (P)

Parents indicated that they would prefer more clear feedback from the healthcare professional on the progression in the visual acuity of the amblyopic eye, as this would be an additional rewarding and motivating factor for both the child and themselves.

> We really wanted more feedback on how her eyesight improved. During the study the eye sight was measured every six weeks. If we asked 'did it improve?' the answer was 'yes'. You really need to ask questions to get some numbers. (...) It would be nice for parents and even the child to understand 'this is why I patch every day, for this amount of improvement in my eye sight...' If you see positive results, you know that this is why you are doing the treatment.
>
> Participant 2 (P)

> If nobody says, 'you have to do it' and without the check-ups and nobody tells you the progression, especially for the child, she wouldn't have the structure [with patching] anymore.
>
> Participant 1 (P)

Theme 2: Burden with treatment

Discomfort during treatment

Children in the patching group experienced several forms of discomfort with the patch, such as irritation of the skin around the eye, difficulty with blinking or wearing the patch on humid summer days. To cope with these problems, parents tried different types of patches or other ways to cover the non-amblyopic eye.

> She had difficulties with blinking. As a parent you try to come up with a solution, so we started patching the lens of the spectacles. But the orthoptist noted that this could influence the effect of the treatment (…) We tried a bigger patch, but that did not solve the problem. (…) We also tried to find a sort of pirate-eyepatch, but that didn't work out either.
>
> Participant 9 (P)

Some children experienced difficulties with reading when wearing the patch and needed adjustments to minimise visual problems while wearing the patch during the school day. In one child the ocular alignment deteriorated with patching, resulting in a constant esotropia and the need for strabismus surgery.

> When she was sitting in the back of the class, she wasn't able to read the schoolboard properly. I can imagine that if you have to look with just one eye that gives you an extra disability. (…) In the end we patched every other day and alternated between patching during school hours and patching at home.
>
> Participant 9 (P)

Interestingly, most of the parents in the patching group reported the patching treatment as having a low impact on the daily life of their children. The majority did not report any limitations on their child's activities when wearing the patch. Families in the gaming group expected their children to play and enjoy the game. However, they indicated that they underestimated the impact of the lengthy gaming sessions. During each session, the child gamed for 1 h with an extra half hour due to multiple breaks. Children became more and more reluctant to play the game as the study continued. In addition, with time, the game became less challenging for some of the children.

> You start the treatment with the impression: nice, just playing a video game! But every game session, she was required to game one hour. I underestimated what it takes of a child of that age, in terms of concentration and keeping a regularity with it. (…) In the beginning she liked the game. But at a certain point it turned into 'you have to'.
>
> Participant 4 (G)

Cooperation and understanding of how to perform the game by the child

Parents of children participating in the gaming group estimated that their child would not be able to complete the game sessions at a younger age as their concentration span was limited. Parents did assume that gaming would be easier if their child was older.

> An hour is quite long for a child that age [4 years]. I think, if you let her play the game for 45 minutes per session, it would be easier for children of her age. (…) Also because if things take longer than 45 minutes, the concentration span is lost.
>
> Participant 4 (G)

PART II: Parental information needs for participation in amblyopia treatment and clinical decision-making

Information hiatus regarding the role of refractive error in amblyopia treatment
In both groups, parents experienced an information hiatus regarding the role of refractive error as part of amblyopia treatment. Parents assumed that as a result of the amblyopia treatment, VA improved and therefore the refractive error would also resolve. Additionally, they reported being unaware that their child must continue to wear glasses after the patching or gaming treatment ended to maintain optimal VA.

> I thought she needed the glasses temporarily. (...) I did not realise she needed to wear the glasses for the rest of her life. I thought that it [the refractive error] would resolve by training her eye and then you're done with the glasses. (...) I never thought she still needs glasses after the patching stopped. (...) I didn't realise she had to wear the glasses to remain a good eye sight.
>
> Participant 8 (P)

> I knew what a lazy eye was. But when it was diagnosed I searched on the internet what it was, to find out what is really going on? What exactly does his glasses correct for him? And with the prescription you know, he also had astigmatism, what does that mean? For you [the healthcare professional] that's all pretty straightforward. But for me, I have really have no idea what it means.
>
> Participant 6 (P)

The advisory role of the healthcare professional and shared decision- making
In deciding the type of treatment, some of the parents preferred to deliberate the choice with the healthcare professional (i.e., orthoptist, optometrist or ophthalmologist). Parents would like to be informed and discuss several considerations that apply to their specific situation to arrive at a shared decision.

> I think that the advice of the healthcare professional is the most important factor in deciding the type of treatment. (...) But I do think it is very important for the physician to clearly explain and discuss with us [parents] 'why are we doing this, why do we think it is the best option for us as a family?'
>
> Participant 4 (G)

Considerations that parents take into account when deciding the type of treatment are (1) effect and efficiency of treatment, (2) organisational aspects of treatments and (3) their child's traits.

Effect and efficiency of treatment
Parents in both the patching and the gaming groups reported that the effect and efficiency of treatment were the most important consideration when deciding on the type of treatment.

> The effect is certainly number one. What is the most effective but also time efficient.
>
> Participant 2 (P)

Parents reported that they would be more likely to choose for most effective form of treatment, even if this meant more logistical challenges for the parents.

> You choose what [type of treatment] is most successful, whatsoever. Even if it requires more effort. (...) And we [as parents] will do whatever it takes.
>
> Participant 6 (P)

Organisational aspects of treatments
If it is assumed that the effect and efficiency of the two treatments were comparable, then parents would choose based on several organisational aspects of the treatments.

Patching group
Parents reported that flexibility and ease of implementing treatment were important aspects when choosing the type of treatment. With patching, parents were able to adapt the treatment to their daily life. In addition, since the patching therapy was easy to understand and perform, they felt secure that other caretakers such as teachers, grandparents or day- care workers would also be able to perform the treatment. As such, parents felt in control of managing the therapy. This was also a reason not to prefer the gaming treatment in the outpatient clinic.

> For example, when she had a birthday party, you don't want to hinder her. So in these cases we put the patch on while driving to the location and when we got back we put the patch on again. This way you still complied to the treatment hours.
>
> Participant 9 (P)

> You can do the patching everywhere. If we go out for weekend trips or if she has a sleepover at Grandma's. Everyone can patch and you can do it in all sorts of places. The flexibility of this treatment is a big plus for me.
>
> Participant 2 (P)

Parents in the patching group reported they would be more willing to choose the gaming treatment if it could be performed at home. They assumed that gaming in the outpatient clinic would be logistically more challenging and less flexible because of the weekly appointments. On the other hand, parents realised that if performing the game at home, they would be responsible to conduct this more complex treatment in the correct manner.

> First I was disappointed we were not randomised to the gaming group, but looking back I'm happy I wasn't. Otherwise I had to come in every week [for the gaming sessions]. That would be very difficult for us as a family. So if you ask me, the easiness of the treatment is an important aspect in deciding the type of treatment. If you have to go somewhere every week to be treated, it's not easy anymore.
>
> Participant 2 (P)

Parents reported that in their normal daily life, they were trying to restrict screen time on electronic devices, such as smartphones or tablets. To choose gaming as amblyopia treatment would not match their parenting decisions.

> We have a kind of "no screens policy" at home: no television and all that kind of stuff, so yeah… An hour of gaming doesn't quite fit in with that.
>
> Participant 6 (P)

Gaming group

Parents who participated in the gaming group reported they would be more likely to choose the more structured treatment. The weekly scheduled gaming with appointments on a fixed time and day for the game sessions was a reason for them to maintain compliance with treatment.

Since gaming treatment was conducted in the outpatient clinic, parents in the gaming group felt that the healthcare professional was responsible for conducting the treatment rather than themselves. This was also the reason why parents in the gaming group were unwilling to perform the game at home, if this became possible in the future.

> They asked me 'would you like to perform the game at home if it would be possible?' No, I wouldn't want that. […] In the outpatient clinic it is more serious than at home. I think you will be more tempted to say 'we will do it later' and then it doesn't happen.
>
> Participant 3 (G)

The child's traits

Parents reported that if properly informed about all considerations of each treatment, they would be able to decide what would suit their child best based on their individual traits.

> … Sometimes you hear stories about a treatment of which you think: that [treatment] does not suit my child at all. It depends on the total package, I will say. If you think: this [treatment] is not feasible for my child or this is too intense, you are less likely to choose that treatment.
>
> Participant 8 (P)

Discussion

This study reported on the experiences and preferences of parents whose children underwent either dichoptic action video gaming or patching as amblyopia treatment. Additionally, we evaluated the information needs of the parents to support participation in amblyopia treatment and clinical decision-making. For both of the treatments evaluated here, two themes emerged from the experiences reported by the parents. The theme factors influencing treatment compliance was derived from the following subthemes, creating a routine, perceiving the amblyopic eye as a problem, expressing compassion, feeling responsible as a parent to conduct the treatment and rewards and motivation. The theme burden of treatment was derived from the following subthemes, discom fort during treatment and cooperation and understanding how to perform the game treatment by the child. Parents reported the effect and efficiency of the treatment as the most important considerations when deciding on the type of amblyopia management for their children. In addition, if parents were able to decide on the type of amblyopia treatment, they would make their choice based on organisational aspects and their child's traits. Overall, they wish to come to a shared decision with their healthcare professional.

Both treatments had their own advantages and dis advantages. A conspicuous difference was the feeling of being responsible as a parent for conducting the patching treatment. In contrast, parents in the gaming group felt less anxiety and responsibility with this method of treatment. In the present study, the game sessions were con ducted and performed under the direct supervision of the researcher, which might have intensified this feeling. Parents reported that the stringent weekly scheduling of the gaming treatment helped with the compliance. This was also stated as the reason why parents in the gaming group were unwilling to perform the therapy at home, if this were to become possible in the future. From previous studies on behavioural treatment for amblyopia, we know that compliance with these therapies is low when they are performed at home.[10,11,28] A recent study on objectively recorded adherence with a binocular treatment for amblyopia using video games at home showed an average adherence of 65% (SD 37%) of the minimum hours prescribed. Furthermore, game training was generally performed in short sessions with frequent pauses (median every 4.1 min, IQR 6.1) which was significant in younger children ($p < 0.0001$).[29]

Presenting the child with an assortment of engaging action video games, preferably one that is popular at the time, could influence compliance. This issue was addressed by Gambacorta et al. who wrote that gamified behavioural treatments may not be as

appealing and engaging as commercial action video games. Unlike these laboratory-based gamified behavioural treatments, the video game industry is a multi- billion dollar segment of the entertainment media. Designers are addressed to create rich, immersive and engaging gaming environments, resulting in a compelling experience that is more enjoyable for children and/ or adults.[30] To keep up with this rapidly evolving commercial gaming industry would be financially demanding, especially since these games need to be adjusted for treatment purposes.

Amblyopia treatment using video games is often assumed to be more appealing and motivating for children.[20] Nevertheless, the parents in this study reported that their children (both boys and girls) became more reluctant to play the game as the study continued. Research highlighted the importance of paying attention to gender-dependent differences and person–environment transactional processes when studying gaming- related behaviours.[31] The dichoptic action video game used in the present study was designed to be gender-neutral. This could have influenced the children's experiences with the game. It would be interesting to investigate whether this pattern would also be found in a larger cohort, and if additive- and moderation effects of gender and personality occur with these video games, or whether providing a choice of video games would influence these experiences.

The recruiting orthoptists as well as the research team emphasised the importance of wearing the spectacles full- time and explicitly explained that by correcting the refractive error, amblyopia could be remedied. Parents assumed that the amblyopia treatment would improve VA and, therefore, the refractive error would resolve. They were unaware of the necessity for the glasses after completing patching or gaming treatment. Therefore, it is of great importance for the practitioner to ensure that parents understand amblyopia treatment regimens and provide additional information, as needed, to optimise compliance.[32]

This study had several limitations. First, a limited number of parents in the gaming group were eligible to participate in the interviews. As reported in a previous publication,[20] the RCT providing eligible parents for this qualitative study had a high drop-out rate in the gaming group; only nine children were able to perform the game settings and undergo this therapy. The main reason for this high drop- out rate in the gaming group was that children <5.5 years of age were unable to perform the game. The parents of these children had no lived experiences with this treatment and were not included in this qualitative study. Furthermore, none of the children or their parents experienced both treatments, since this qualitative research was part of a larger RCT study where children were randomised to either gaming or patching.

Second, experiences with behavioural training explored here only apply to our dichoptic action video game per formed using VR goggles in an outpatient clinic for 1 h, once a week. Therefore, experiences with this form of therapy could change as video games are changing rapidly. Additionally, other forms of behavioural treatment might provide different outcomes. Therefore, future advances may alter the findings of this study.

Third, visual acuity at the start of the treatment was relatively good, that is 0.4 LogMAR in the patching group and 0.5 LogMAR in the gaming group. From previous studies we know that initial low visual acuity is an important reason for non- compliance with patching, as acceptance of the patch is reduced with poor VA in the amblyopic eye.[6] Therefore, the relatively good VA at the start of treatment could have influenced experiences with both treatments, which were largely positive. Moreover, parents who dropped out of the RCT were not willing to participate in the interviews. This could have influenced the overall positive experiences.

This study provided more insight into the experiences of parents whose children underwent two different types of amblyopia treatment. Several important themes emerged for both gaming and patching treatment. The main difference was the responsibility for conducting treatment was reduced for parents in the gaming group when compared with the patching group. If a home-based gaming treatment was offered to overcome logistical challenges, this would burden parents with the responsibility to conduct the game therapy themselves. When selecting the type of treatment, parents reported that effectiveness and time efficiency were the most important aspects. Parents would like to arrive at a well-informed, shared decision regarding the type of amblyopia treatment, wherein the healthcare professional discusses organisational aspects of treatment and their child's traits. Future research should focus on the experiences of families with a wider variety of behavioural treatments in a larger population.

Acknowledgements

We would like to thank the children and their parents who participated in this study. We would also like to thank Dr Maurits Joosse and the orthoptists for recruiting the children. Particularly, we extend our thanks to Gerdien Holtslag for her contribution to conceptualising the study

References

1. Attebo K, Mitchell P, Cumming R, Smith W, Jolly N, Sparkes R. Prevalence and causes of amblyopia in an adult population. Ophthalmology. 1998;105:154–9.
2. Reeves BC. Taxonomy and epidemiology of amblyopia. In: Moseley M, Fielder A, editors. Amblyopia: a multidisciplinary approach. London: Butterworth- Heinemann; 2002. p. 68– 80.
3. Stewart CE, Moseley MJ, Stephens DA, Fielder AR. Treatment dose-response in amblyopia therapy: the Monitored Occlusion Treatment of Amblyopia Study (MOTAS). Invest Ophthalmol Vis Sci. 2004;45:3048–54.
4. Kadhum A, Simonsz- Tóth B, Rosmalen J, Pijnenburg SJM, Janszen BM, Simonsz HJ, et al. Long- term follow- up of an amblyopia treatment study: change in visual acuity 15 years after occlusion therapy. Acta Ophthalmol. 2021;99:e36–42.
5. Loudon SE, Polling JR, Simonsz HJ. Electronically measured compliance with occlusion therapy for amblyopia is related to visual acuity increase. Graefes Arch Clin Exp Ophthalmol. 2003;241:176–80.
6. Loudon SE, Fronius M, Looman CWN, Awan M, Simonsz B, Van Der Maas PJ, et al. Predictors and a remedy for noncompliance with amblyopia therapy in children measured with the occlusion dose monitor. Invest Ophthalmol Vis Sci. 2006;47:4393–400.
7. Stewart CE, Fielder AR, Stephens DA, Moseley MJ. Design of the Monitored Occlusion Treatment of Amblyopia Study (MOTAS). Br J Ophthalmol. 2002;86:915–9.
8. Tsirlin I, Colpa L, Goltz HC, Wong AM. Behavioral training as new treatment for adult amblyopia: a meta- analysis and systematic re view. Invest Ophthalmol Vis Sci. 2015;56:4061–75.
9. Holmes JM, Manh VM, Lazar EL, Beck RW, Birch EE, Kraker RT, et al. Effect of a binocular iPad game vs part- time patching in children aged 5 to 12 years with amblyopia: a randomized clinical trial. JAMA Ophthalmol. 2016;134:1391–400.
10. Manh VM, Holmes JM, Lazar EL, Kraker RT, Wallace DK, Kulp MT, et al. A randomized trial of a binocular iPad game versus part- time patching in children aged 13 to 16 years with amblyopia. Am J Ophthalmol. 2018;186:104–15.
11. Pediatric Eye Disease Investigator Group, Holmes JM, Manny RE, Lazar EL, Birch EE, Kelly KR, et al. A randomized trial of binocular dig rush game treatment for amblyopia in children aged 7 to 12 years. Ophthalmology. 2019;126:456–66.
12. Fronius M, Cirina L, Ackermann H, Kohnen T, Diehl CM. Efficiency of electronically monitored amblyopia treatment between 5 and 16years of age: new insight into declining susceptibility of the visual system. Vision Res. 2014;103:11–9.
13. Stewart CE, Stephens DA, Fielder AR, Moseley MJ. Objectively monitored patching regimens for treatment of amblyopia: randomised trial. Br Med J. 2007;335:707–11.
14. Pineles SL, Aakalu VK, Hutchinson AK, Galvin JA, Heidary G, Binenbaum G, et al. Binocular treatment of amblyopia: a report by the American Academy of Ophthalmology. Ophthalmology. 2020;127:261–72.
15. Carlton J, Kaltenthaler E. Amblyopia and quality of life: a systematic review. Eye. 2011;25:403–13.

16. van der Sterre GW, van de Graaf ES, van der Meulen- Schot HM, Abma- Bustraan E, Kelderman H, Simonsz HJ. Quality of life during occlusion therapy for amblyopia from the perspective of the chil dren and from that of their parents, as proxy. BMC Ophthalmol. 2022;22:135. https://doi.org/10.1186/s12886-022-02342-w
17. Hatt SR, Leske DA, Castaneda YS, Wernimont SM, Liebermann L, Cheng- Patel CS, et al. Understanding the impact of residual amblyopia on functional vision and eye- related quality of life using the PedEyeQ. Am J Ophthalmol. 2020;218:173–81.
18. Wang Y, Wang H. Adverse influences of nonstrabismic amblyopia on quality of life of teenagers in China. Comput Math Methods Med. 2022;2022:2621991. https://doi.org/10.1155/2022/2621991 19. Dixon-Woods M, Awan M, Gottlob I. Why is compliance with occlusion therapy for amblyopia so hard? A qualitative study. Arch Dis Child. 2006;91:491–4.
20. Kadhum A, Tan ETC, Levi DM, Colpa L, Fronius M, Simonsz HJ, et al. Barriers to successful dichoptic treatment for amblyopia in young children. Graefes Arch Clin Exp Ophthalmol. 2021;259: 3149–57.
21. Vedamurthy I, Nahum M, Huang SJ, Zheng F, Bayliss J, Bavelier D, et al. A dichoptic custom- made action video game as a treatment for adult amblyopia. Vision Res. 2015;114:173–87.
22. Simonsz HJ, Polling JR, Voorn R, van Leeuwen J, Meester H, Romijn C, et al. Electronic monitoring of treatment compliance in patching for amblyopia. Strabismus. 1999;7:113–23.
23. Carlton J. Comparison of the CAT- QoL and PedsQL(TM) instruments in measuring quality of life in amblyopia treatment: preliminary results. Strabismus. 2019;27:165–71.
24. Carlton J. Developing the draft descriptive system for the Child Amblyopia Treatment Questionnaire (CAT- Qol): a mixed methods study. Health Qual Life Outcomes. 2013;11:174. https://doi. org/10.1186/1477-7525-11-174
25. Carlton J. Refinement of the Child Amblyopia Treatment Questionnaire (CAT- QoL) using Rasch analysis. Strabismus. 2019;27:66–77.
26. Braun V, Clarke V. Using thematic analysis in psychology. Qual Res Psychol. 2006;3:77–101.
27. Kadhum A. Dose-response relationship and treatment efficiency for patching vs gaming therapy for amblyopia. Invest Ophthalmol Vis Sci. 2022;63:ARVO E- Abstract 2286.
28. Manny RE, Holmes JM, Kraker RT, Li ZK, Waters AL, Kelly KR, et al. A randomized trial of binocular dig rush game treatment for amblyopia in children aged 4 to 6 years. Optom Vis Sci. 2022;99:213-27.
29. Gao TY, Black JM, Babu RJ, Bobier WR, Chakraborty A, Dai S, et al. Adherence to home-based videogame treatment for amblyopia in children and adults. Clin Exp Optom. 2021;104:773–9.
30. Gambacorta C, Nahum M, Vedamurthy I, Bayliss J, Jordan J, Bavelier D, et al. An action video game for the treatment of amblyopia in children: a feasibility study. Vision Res. 2018;148:1–14.

31. Lopez-Fernandez FJ, Mezquita L, Griffiths MD, Ortet G, Ibanez MI. The role of personality on disordered gaming and game genre preferences in adolescence: Gender differences and person- environment transactions. El papel de la personalidad en el juego problematico y en las preferencias de generos de videojuegos en adolescentes. Adicciones. 2021;33:263–72.
32. Newsham D. Parental non- concordance with occlusion therapy. Br J Ophthalmol. 2000;84:957–62.

Appendix S1:
Study protocol randomised controlled trial

Participants

The study was conducted at five clinics in the Netherlands, from December 2017 until June 2020. Treating orthoptists referred all newly diagnosed amblyopic children aged four tot twelve to the research center. Amblyopia was defined as a best corrected visual acuity of 2 or more LogMAR lines difference between both eyes and was associated with a refractive error, strabismus or a combination of the two. Exclusion criteria were non-comitant or large angle strabismus >30 prism diopters, a neurological disorder, nystagmus, other eye disorders and diminished visual acuity due to medication, brain damage or trauma. At the start of the study a baseline standard orthoptic examination was performed by the research orthoptist. This included the best corrected visual acuity (BCVA) using the crowded tumbling E-chart, stereo acuity using the Randot Circles Sterotest at 40cm, contrast sensitivity using the Pelli-Robson chart in older subjects and CSV-1000 in the younger children, ocular motility and ocular alignment using the (alternated) prism-covertest at 30cm and 5m.

After a 16-week refractive adaptation period, included children were randomised to either patching treatment (2 hours per day, 7 days a week) or gaming (1 hour per week at the out-patient clinic under direct supervision of the researcher) for a period of 24 weeks. The randomize R package version 1.3 was used for generating the randomisation list using a permuted block design with R version 3.3.2.

Every six weeks until the end of the study, the BCVA, stereo acuity and contrast sensitivity was assessed by the research orthoptist. After completing the study, the child was referred back to their treating orthoptist, see figure S1.

Written informed consent was obtained from each subject parents or guardian. The Ethics Committee of the ErasmusMC University Medical Center Rotterdam and the Boards of the participating clinics approved the protocol and informed consent forms. The study adhered to the tenets of the Declaration of Helsinki. The study is listed on www.clinicaltrials.gov under identifier NCT03767985.

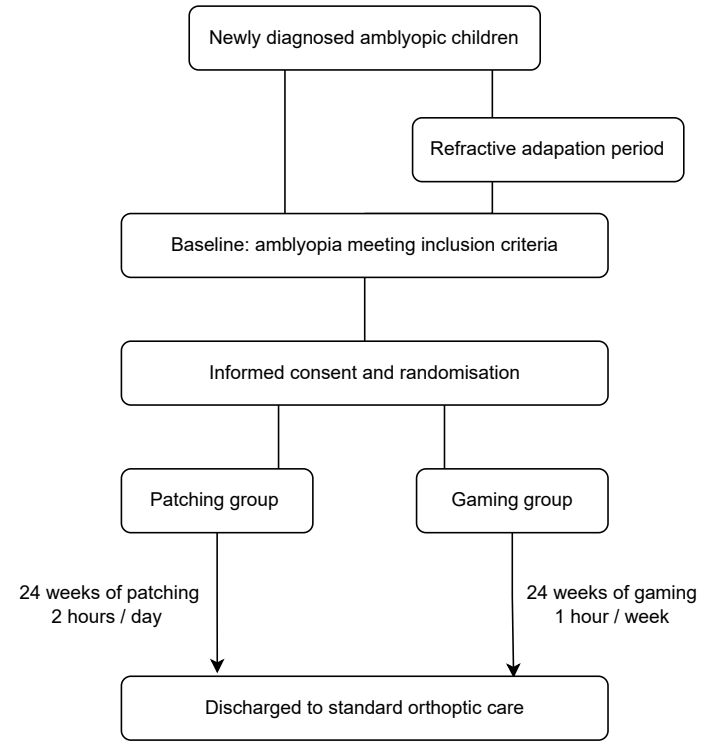


Figure S1. Study design

Gaming treatment

The gaming treatment was a dichoptic action video game using VR goggles, custom-made and based on the principles of the dichoptic game developed by Levi et al. as described by Vedamurthy et al.[1,2] The game is played under dichoptic viewing conditions in order to reduce suppression and promote fusion, while challenging the amblyopic eye.

The devices used to perform the dichoptic game were the Oculus Rift and the laptop Asus ROG Strix SCAR Edition GL503VS-EI012T. This was a fixed set-up located at the outpatient-clinic. The game was modified by Alting (Dfab) to fit the Oculus Rift VR goggles. The images in the VR-goggles were adjusted to make it suitable for children from age four. It is an active and engaging game for children, with settings for adequately attenuating the perceptual balance of the images and the ability to correct for alignment at the start of each game session. The game included two levels with different lay-outs (a market place and an ice cave) with difficulty increasing during game play. The child wearing the VR goggles and holding the controllers, was standing in the market place or in the

cave. See figure 2a and 2b. Snowmen appeared and the child was instructed to throw snowballs at the approaching snowmen. Points were awarded for hitting the snowmen. A suppression check was incorporated in the form of a snowflake, which was presented every 30 seconds for ten seconds solely to the amblyopic eye. To gain extra points, the child was instructed to catch the snowflake before it disappeared. Catching the snowflake also confirmed that the amblyopic eye was still engaged.

Figure S2 a. An eight year old boy playing the game

At the start of each gaming session, a perceptual balance and alignment task was performed. First, for the perceptual balance task, two images were presented dichoptically and the contrast/luminance presented to the fellow eye was modulated in order to match the appearance of the high-contrast image perceived by the amblyopic eye. Based on the feedback of the child, the contrast/luminance was adjusted by the researcher. This was repeated for four times and

the mean of these four attempts was applied as the contrast/luminance level during the gaming session. Balancing the perceptual input to the two eyes is purported in the literature to reduce suppression and is believed to be a key factor in dichoptic therapy effects on visual acuity and stereoacuity.[1,3] The primary goal of the perceptual balance task was to reduce suppression and facilitate fusion. We chose to base the level of contrast/luminance subjectively on the patient's feedback as opposed to randomly assigning a contrast level to ensure genuine conditions.

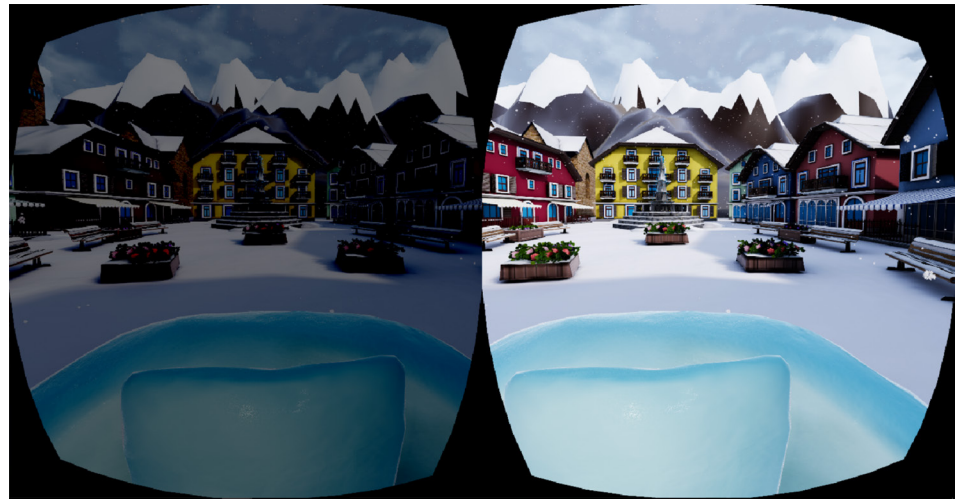


Figure S2 b. Dichoptic presentation in the VR goggles with attenuated contrast/luminance for the fellow eye (left eye) in order to match the image perceived by the amblyopic eye (right eye).

Second, the alignment task was performed according to the principles of Levi et al.[1,2,4] This included the presentation of two nonius lines dichoptically, see figure 3. These two images had to be aligned properly until a full cross was perceived. Both the perceptual balance and alignment tasks were based on the patient's subjective responses.[5] In the gaming group compliance was registered by the researcher, who supervised the gaming session and used a stop-watch to determine the exact game duration. The gaming treatment was performed at the out-patient clinic at the HMC Hospital, The Hague.

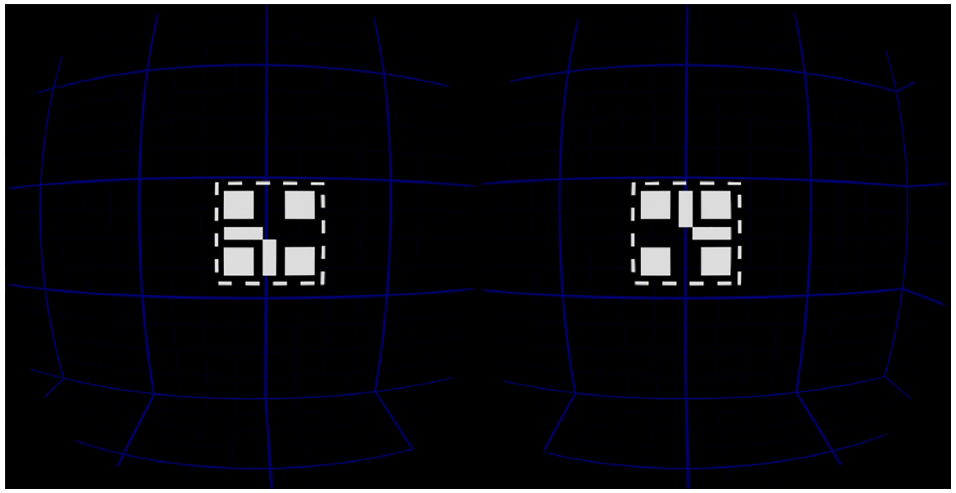


Figure S3 Alignment task presenting two nonius lines to fuse into one full cross.

Patching treatment

The non-amblyopic eye was patched using a regular eyepatch for two hours, seven days a week for 24 weeks until equal VA was reached. Compliance with patching was electronically monitored with the Occlusion Dose Monitor (ODM) for one 1 week every 6 weeks,[6,7] i.e. 4 measurements. The ODM measured the temperature difference between the front and the back of the patch every three minutes, enabling to determine exactly when and how long the patch with the ODM was worn. Parents were instructed to attach the ODM to the front of the patch with double sided scotch tape.

References

1. Vedamurthy I, Nahum M, Huang SJ, Zheng F, Bayliss J, Bavelier D, et al. A dichoptic custom-made action video game as a treatment for adult amblyopia. Vision Research. 2015;114:173-87.
2. Gambacorta C, Nahum M, Vedamurthy I, Bayliss J, Jordan J, Bavelier D, et al. An action video game for the treatment of amblyopia in children: A feasibility study. Vis Res. 2018;148:1-14.
3. Hess RF, Thompson B. Amblyopia and the binocular approach to its therapy. Vis Res. 2015;114:4-16.
4. Ding J, Levi DM. Recovery of stereopsis through perceptual learning in human adults with abnormal binocular vision. Proceedings of the National Academy of Sciences of the United States of America. 2011;108(37):E733-41.
5. Kadhum A, Tan ETC, Levi DM, Colpa L, Fronius M, Simonsz HJ, et al. Barriers to successful dichoptic treatment for amblyopia in young children. Graefe's Arch Clin Exp Ophthalmol. 2021;259(10):3149-57.
6. Simonsz HJ, Polling JR, Voorn R, van Leeuwen J, Meester H, Romijn C, et al. Electronic monitoring of treatment compliance in patching for amblyopia. Strabismus. 1999;7(2):113-23. Epub 1999/07/27.
7. Loudon SE, Fronius M, Looman CWN, Awan M, Simonsz B, Van Der Maas PJ, et al. Predictors and a remedy for noncompliance with amblyopia therapy in children measured with the occlusion dose monitor. Invest Ophthalmol Vis Sci. 2006;47(10):4393-400.

Appendix S2: Interview guide

- The questions are noted with a dot. Interviewer directions are in [brackets].
- Pointers:
  - Try to follow natural leads in the discussion. If needed, circle back to particular areas that were mentioned earlier but not yet elaborated on by parent.
  - Encourage the parents to talk about anything they want to.
  - Re-cap for parent what they just said in natural gaps of the discussion.
  - Ensure all domains are covered but try to keep the interview conversational.
- Probes are examples and will be discussed when the parents response requires a deeper understanding

Possible/standard prompts:
"Tell me more about that."
"Help me understand [insert what the parent just said] better."
"How do you feel about that?"

- Interviews were conducted in Dutch. For publication purposes the questions were translated to English.

Ice breaker and introduction:
"Your child has participated in our study on comparing the effect of patching treatment with gaming treatment to treat [his/her] lazy eye. During our study your child participated in the [patching group/gaming group]. After the study, you were referred back to your own treating orthoptist. So we were wondering, how is [name of the child] doing?

"Good to hear that! And how are [his/her] eyes doing?"

"After completing our study, we became interested in how the parents experienced both treatments, especially since experiences with these different treatments of the lazy eye is still little known."

- **Parents of children who participated in the patching group:**
  "During the study, [name of the child] participated in the patching group. The patching treatment is currently the standard treatment for the lazy eye. In this interview we would like discuss your experiences with this treatment to better understand these experiences and preferences with this kind of treatment of the lazy eye."

- **Parents of children who participated in the gaming group:**
  "The game treatment that [name of the child] has undergone is a potentially new treatment for the lazy eye. The effect of this treatment is still under research. So you and your child were among the first to experience this treatment. In this interview we would like discuss your experiences to better understand these experiences and preferences with this kind of treatment of the lazy eye."

"Before we start the interview, do you have any questions?"

Knowledge about amblyopia
- "Can you tell me how you found out that [name of the child] had a lazy eye?"
- "Did you notice in any way that [he/she] had a lazy eye?"
  - [*Interviewer*: If "No" → proceed to the next question]
  - [*Interviewer*: If "Yes" → "In what ways did you notice this?"]
- "When [he/she] first visited the orthoptist and the lazy eye was diagnosed, did you know what a lazy eye was?"
  - [*Interviewer*: If "Yes" → "How did you know what a lazy eye was?"]
- "I'm wondering, did you look up any additional information about what a lazy eye is?"
  - [*Interviewer*: if "yes",
  - "At what point did you look this up? Was this before you went to the orthoptist or afterwards?"
  - "What information did you look up about the lazy eye?"
  - "Where did you look up this information?"
  - "Did looking up this information help you understand what a lazy eye is? Were you able to find everything you were looking for?"]

[*Interviewer:* If answer shows that parent was already familiar with lazy eye: "What experience did you had before the lazy eye of [name of the child] was diagnosed?"]

Knowledge about amblyopia treatment
"I would like to discuss what you knew about the treatment of the lazy eye, before it was diagnosed in [name of the child]."
- "Did you know how the lazy eye is usually treated?"
  - [*Interviewer*: If "Yes" → "Can you tell how did you know this?"]
- "Before you began the patching treatment, what were your expectations with the treatment?"

- [*Interviewer*: if unclear, follow up with examples as 'burden on you/your child', 'number of times you have to come to the hospital for check-ups', 'difficulty of treatment of you or your child', 'effect of treatment'.]
- "Looking back on the treatment of the lazy eye of [name of the child], what information would you have liked to have before starting treatment?"
  - [*Interviewer*: "What aspects of treatment would you liked to have known before starting the treatment?"]

Experiences with treatment

- **Parents whose children participated in the patching group:**
  "During the study, [name of the child] participated in the patching group. So you had to patch [his/her] better eye for 2 hours every day of the week. How did you feel about patching his/her eye every day?"
  - [*Interviewer*: follow-up with: "And how do you think your child feel about this?"]
- **Parents whose children participated in the gaming group:**
  "During the study, [name of the child] participated in the gaming group. Therefore you had to come in to the out-patient clinic of [name hospital] every week for the gaming sessions. How did you experience coming to these sessions every week?
  - [*Interviewer*: follow-up with: "And how do you think your child feel or experienced this these appointments/sessions?"]
- **Parents whose children participated in the patching group:**
  "At what times was it difficult to patch? And what caused this difficulty?"
  - [*Interviewer*: follow-up with: "Can you maybe explain that?"/ "Why was it difficult to patch because of [reason]?"]
- **Parents whose children participated in the gaming group:**
  "At what times was it difficult to come to the out-patient clinic for the gaming sessions? Would you like to tell me for what reasons it was not possible to come to the gaming sessions?"
  - [*Interviewer*: follow-up with: "Can you maybe explain that?"]
- "Were there certain things, activities or chores you or your child could not do because of the treatment of [his/her] lazy eye?
  - [*Interviewer*: follow-up if needed with: "Can you tell me a little more about that?" or "what do you mean by that?"]
- "Looking back now on the treatment with [patching/gaming], how stressful did you find the treatment for [name of the child]?"
  - [*Interviewer*: What caused this strain?]
  - [*Interviewer*: In what way did [reason] influence the treatment?]

- "Did your expectations with the treatment match with what you expected beforehand?"
  - [*Interviewer*: If "Yes" → "Could you tell me which aspect(s) matched your expectations?"]
  - [*Interviewer*: If "No" → "Could you tell me which aspect(s) did not match your expectations or where different than you expected beforehand?" → "How did they differ?"
- "When [name of the child] participated in the study [he/she] was [x] years old. In what way do you think your child's age at the time played a role in how the treatment went?"
  - [*Interviewer*: if example is needed: Would it made any difference if [he/she] was [older or younger]?
- "What advice or suggestions would you have to improve the experience with the treatment?"
  - [*Interviewer*: "And what would have improved the experience for [name of the child]?"]

Choice of treatment

- "During the study, you were not able to choose the type of treatment for the lazy eye of [name of the child]. Prior to your participation in the study, did you prefer or hope to be enrolled in either the gaming or the patching group? Or did you had no preference at all?"
- "When looking back on the treatment, where you satisfied with the treatment you were assigned to?"
  - [*Interview*: if needed, ask for clarification: "can you explain further?"]
- "If you were allowed to make your own choice of treatment for the lazy eye with either patching or gaming. What would you base this choice on?"
- "Now that you have experienced the [patching/gaming] treatment, would you choose differently if you had the chance to decide the type of treatment for [name of the child]?"
  - [*Interviewer*: "For what reason would you choose this treatment?"]
- "If you had to make your own choice regarding treatment, what information would be relevant/necessary for you to make this choice?"
  - [*Interviewer*: If unclear answer, ask for clarification: "can you explain further?"]
- "With whom would you like to discuss the choice of treatment? Or by whom would you like to be advised regarding the choice of treatment?"
  - [*Interviewer*: If unclear or little answer, give examples: partner, child, family, school, orthoptist, family doctor, experience expert]

- If you faced a family member or friend to make this choice of treatment, what would you advise them to do?
  - [*Interviewer*: if reason not directly stated: "Why would you recommend this treatment?"]
- "During the study, [name of the child] have participated in the [patching/gaming] treatment. What advantages do you see of the this treatment?"
  - [*Interviewer*: if clarification is needed, follow-up with: "Can you maybe explain that?"]
- What disadvantages do you see of this treatment?
  - [*Interviewer*: if clarification is needed, follow-up with: "Can you maybe explain that?"]

Parents whose children participated in the patching group:

"The children that participated in the other treatment group underwent the gaming therapy as treatment for the lazy eye. The child and their parent(s) had to come in to the out-patient clinic of [name hospital] every week for 1-hour of gaming.

If the effect of both treatments would be the same. What advantages do you see of the gaming treatment?"

- [*Interviewer*: If unclear or little answer, give examples: possible burden on you/your child, number of visits to the hospital, how long the sessions would last, whether it would be difficult for your child]

Parents whose children participated in the gaming group:

"The children that participated in the other treatment group underwent patching therapy as treatment for the lazy eye. The parents had to patch their child's better eye for 2 hours every day of the week.

If the effect of both treatments would be the same. What advantages do you see of the patching treatment?"

- [*Interviewer*: If unclear or little answer, give examples: possible burden on you/your child, number of visits to the hospital, whether it would be difficult for your child]

Closure

"We are now at the end of this interview. I have no further questions for you to ask, but I want to make sure I'm not missing anything."

"Is there a particular topic that was not covered or that you would still like to discuss?"

"Is there a particular question that I have not asked, or that you would like to answer?"

"Do you have any further questions for us?"

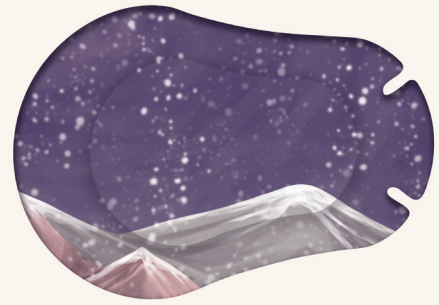
"To check that we have correctly understood your main points regarding your experience and perception of the treatment of the lazy eye of [name of the child], we would like to send a summary to you to check if you agree with it. Are you okay with that?"

- [*Interviewer*: check e-mail address]

"On behalf of the research team, we would like to thank you very much for sharing your experiences and thoughts about the treatment!"

8

General discussion and future prospects



General discussion and future prospects

Introduction

Amblyopia, a lazy eye, is the leading cause of visual acuity loss in children with a prevalence of 2-4% in the population.[1-3] It is a neurodevelopmental visual disorder in which early visual development is disrupted, most commonly due to refractive error, strabismus, or a combination of the two.[4] Timely treatment is required during the so-called 'sensitive period' in early childhood.

For centuries, the standard treatment has consisted of optical treatment, i.e. spectacles, followed by occlusion of the fellow eye for several hours per day.[5-7] The purpose is to achieve equal visual acuity in both eyes and to prevent any future disability. Persistent amblyopia imposes a significant burden on society due to a reduced quality of life as well as financial issues.[8] It almost doubles the time an individual spends with bilateral visual impairment in case of vision loss in the fellow eye later in life.[9]

Over the past decade, there has been a renewed interest in alternative, non-occlusion treatments, summarised under the term 'behavioural training'.[10] This treatment method is often delivered in the form of video games, in which the brain is stimulated and trained by repetitively offering a certain set of tasks. While these treatments are gaining popularity, there is a lack of objective comparison with the standard treatment.

Whereas occlusion treatment is a monocular treatment considering it a monocular disease, dichoptic action video gaming is a binocular treatment considering amblyopia a binocular problem and therefore engaging both eyes during therapy.[11]

In this thesis we objectively compared the effectiveness of a novel dichoptic action video game using virtual reality (VR) goggles with occlusion therapy in children, and examined parental preferences and experiences with both treatments.

We also analysed the role of optical treatment (i.e. refractive adaptation) in amblyopia treatment and evaluated the long-term effectiveness of occlusion therapy.

The main findings of our research will be discussed and the clinical and practical implications for the health care provider will be considered.

Optical treatment

When a child is diagnosed with amblyopia caused by a refractive error, the initial step in treatment is correction of the refractive error using spectacles. We evaluated visual acuity changes over 16 weeks of optical treatment in children newly diagnosed with amblyopia (Chapter 4). They were asked to wear the spectacles during all waking hours. Electronically monitored compliance with spectacle wear was relatively good, with spectacles worn for approximately 10 hours per day (mean compliance 73%) (Figure 1).

Figure 1. Compliance with spectacle wear was monitored electronically using the Occlusion Dose Monitor (ODM), which measures the temperature difference between the front and the back every 3 minutes. It was attached to the temple of the spectacles using an eye patch.

Spectacles alone proved highly effective: we found that visual acuity improved in more than a third of the children in such a way that they no longer met the criteria for amblyopia, thereby avoiding the need for occlusion treatment. The overall improvement in visual acuity with spectacles alone was 0.20 logMAR in the amblyopic eye. Even if occlusion treatment would still be necessary after optical treatment, the baseline visual acuity in the amblyopic eye would be better, which in turn would lead to improved compliance and shorter treatment duration.[5,7] Interestingly, children with strabismus and very mild hypermetropia showed visual acuity improvement with optical treatment alone. Our study emphasises the importance of optical treatment, also known as refractive adaptation, as an essential first step in amblyopia treatment before commencing occlusion therapy, even in children with strabismus amblyopia.[12-14]

A recent manuscript by Proudlock et al. has questioned this treatment approach and suggested that in most children with amblyopia, spectacles and occlusion treatment should commence almost simultaneously.[15] The arguments proposed were that (1) a longer optical treatment period could result in reduced motivation and lower compliance with both occlusion treatment and spectacle wear; and (2) since generally, the response to treatment is higher in younger children compared to older children, delaying occlusion treatment may lead to less overall visual

acuity improvement. The visual acuity in the amblyopic eye at start of treatment in their cohorts was very poor: on average 0.67 logMAR with two-third of the group having severe amblyopia. When taking a closer look at the visual acuity distribution in a cohort of 344 children with amblyopia, as demonstrated by Sloot et al.[16] (Figure 3), children with severe amblyopia are a minority. Most children have mild or moderate amblyopia. Proudlock et al. also found that wearing the spectacles for 18 weeks improved visual acuity with 0.26 logMAR lines, which, in cases of mild amblyopia would be sufficient treatment.

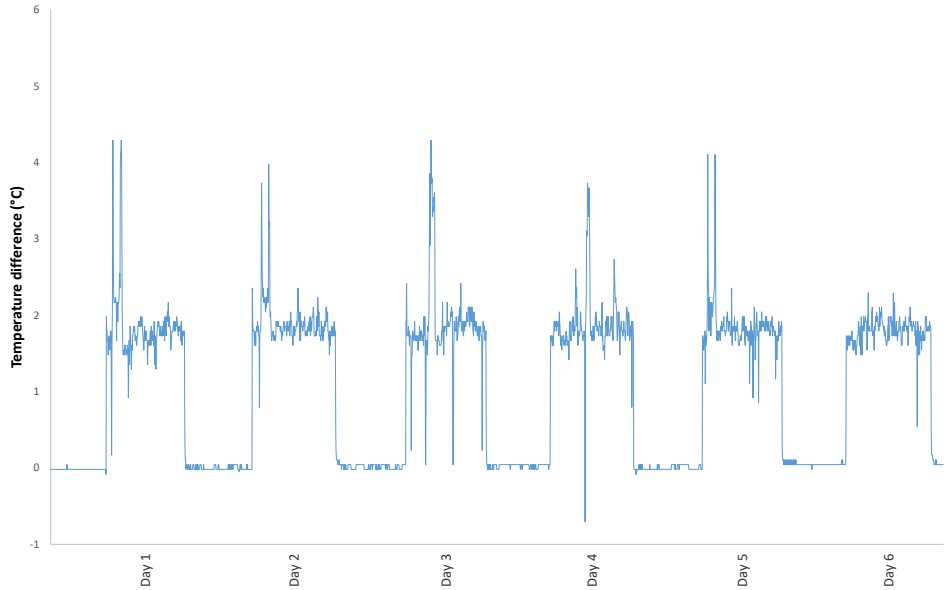


Figure 2. Example of a 1-week recording of spectacle wear with the occlusion dose monitor (ODM). The x- and y-axis show the day of the recording and the temperature difference between the front and the back of the ODM in °C, respectively. The temperature difference when the spectacles were not worn was approximately 0 °C. *From: Effectiveness of optical treatment in amblyopia and validation of measuring spectacle compliance with the ODM. Ophthalmic and physiological optics, 2024.*

We understand that the urge to commence occlusion treatment as soon as possible is strong amongst orthoptists, especially in older children. However, in countries with population-based screening programmes, where most amblyopia cases are detected before the age of 4-5 years, most of the children present with mild to moderate amblyopia that typically improves by at least 2 lines in visual acuity with spectacles alone. Visual acuity improvement is not only found in anisometropic amblyopia, but also in strabismus and combined-cause of amblyopia.

- Based on the work of this thesis, we highly recommend to implement a 16-weeks optical treatment period in all children with newly diagnosed amblyopia irrespective of the cause of amblyopia. In children older than 6 years of age and very poor visual acuity in the amblyopic eye caused by strabismus with eccentric fixation the orthoptist may consider commencing with spectacles and occlusion treatment simultaneously as they have a poorer prognosis (Chapter 3). These children would also benefit from a longer and more tapered approach of treatment. In addition, approximately half of the children had discontinued spectacle wear upon entering secondary school. It would be valuable to investigate the influence of wearing spectacles on any change in degree of anisohypermetropia and visual acuity in these subjects.

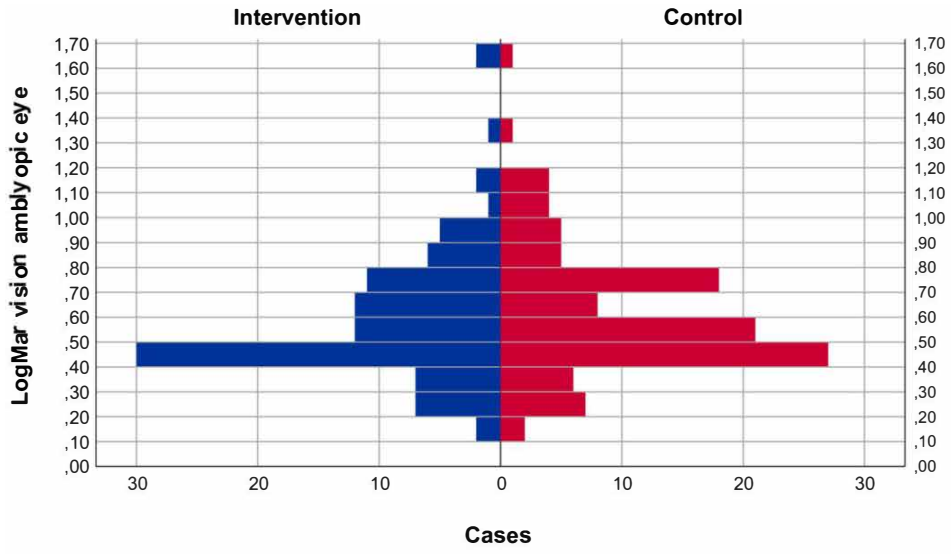


Figure 3. Frequencies and distribution of the visual acuity (logMAR) of the amblyopic eye for the intervention and control group. *Figure from: Effectiveness of routine population-wide orthoptic preschool vision screening tests at age 6–24 months in the Netherlands. Sloot F, Telleman MAJ, Benjamins J, et al. © 2021 The Authors. Acta Ophthalmologica published by John Wiley & Sons Ltd on behalf of Acta Ophthalmologica Scandinavica Foundation.*

Dichoptic video gaming compared with occlusion treatment

Visual acuity

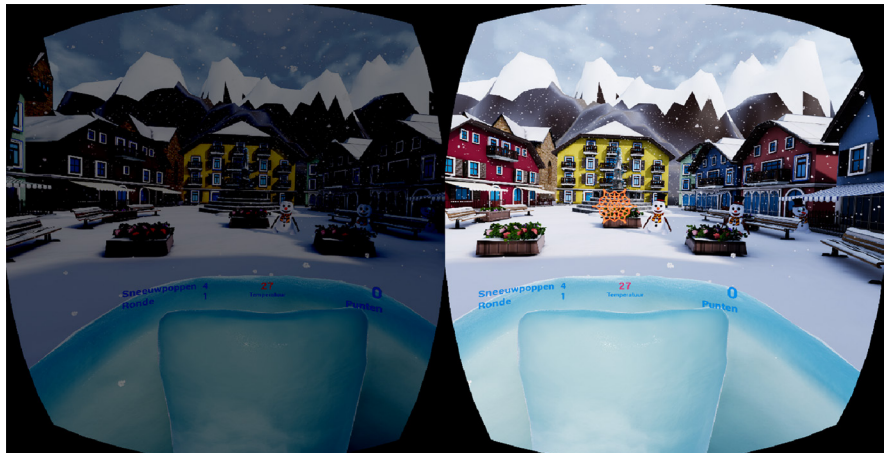
If, after optical treatment amblyopia still exists, occlusion treatment usually commences. Occlusion treatment is the standard treatment for amblyopia and involves exclusion of the fellow eye from visual activity, thereby stimulating the use of the amblyopic eye (Figure 4).

Figure 4. A five-year-old girl wearing an occlusion patch.

It has been proven to be a successful treatment; however its success is restricted by non-compliance (i.e. the eye is not occluded in accordance with the orthoptists' prescription).[5-7]

From North-America, behavioural training, i.e. dichoptic training, perceptual learning and video gaming, has been increasingly popular over the past 15-20 years.[10] Although presented as new treatment modalities, these approaches show a striking resemblance to previous treatment methods, such as fusion exercises (Chapter 2). In summary, the rationale behind dichoptic training is to use dichoptic stimulation, whereby the patient is required to use both eyes simultaneously: the contrast of the stimuli presented to the fellow eye is reduced to match the appearance of the stimuli shown to the amblyopic eye (Figure 5).[17]

A



B

Figure 5. a. The image on the left shows attenuated contrast for the left eye (fellow eye) in order to match the image seen by the right (amblyopic) eye. These images are shown to both eyes simultaneously using Virtual Reality goggles. Snowmen appeared and the child was instructed to throw snowballs at them to gain points. A red snowflake was intermittently presented to the amblyopic eye only for extra points. B. Setup at the outpatient clinic. The child is wearing the headset and using controllers enabling the child to move freely in the room. *From: Barriers to successful dichoptic treatment for amblyopia in young children*. Graefe's Archive for Clinical and Experimental Ophthalmology, *2021*.

The goal is to attain optimal binocular viewing conditions, so that, with training, suppression of the amblyopic eye can be alleviated and may possibly lead to better results in terms of visual acuity as well as stereo acuity. In our study we objectively compared supervised dichoptic action video gaming with electronically monitored occlusion treatment in newly diagnosed children with amblyopia. We found that both gaming and occlusion treatment resulted in a significant increase in visual acuity and stereo acuity with no significant difference between the two treatment groups (Chapter 5).

Although there are abundant publications about the positive effect of gaming, it proved difficult to compare our results with the current literature. Some studies only investigated the effectiveness of gaming, whereas others assessed combinations of treatments, making it difficult to identify the sole contribution of spectacles, occlusion treatment or gaming. Furthermore, many of these studies included children who were previously occluded, in whom treatment was either incomplete or ineffective. Our study is the first to measure *and* compare the efficacy and efficiency of supervised outpatient dichoptic action video gaming using VR goggles with objectively monitored occlusion therapy in 4–12-year-old children with newly diagnosed amblyopia. Table 1 in the appendix shows an up-to-date overview of publications in which binocular treatment for children with amblyopia was investigated.

It proved difficult to include children for our study, comparable to the numbers published in the literature. This is a short-coming of our study; in addition the large number of dropouts in the gaming group. Studies that used home-based game treatments, such as gaming using an Ipad, generally included larger number of participants. However, they also had compliance issues due to its home-based setting.

We did however, find a large difference in treatment efficiency between gaming and occlusion treatment: visual acuity improvement with gaming was 0.30 logMAR with 1h of gaming per week over 24 weeks. Visual acuity improved 0.20 logMAR with occlusion treatment 2h per day, prescribed over the same time period. Treatment efficiency with gaming was 15 times higher than with occlusion treatment.

How is this difference in efficiency explained? The more rapid visual acuity improvement seen with gaming may reflect greater plasticity in the visual cortex. A possible theory could be that there may be various pathways in the brain

involved in improving visual acuity, which are addressed differently by occlusion treatment or gaming treatment. The pathway involved in gaming treatment may result in greater plasticity in the visual cortex. *Reward* and *attentional systems* are significant drivers for learning.[18] Both concepts are present in dichoptic action video gaming. The theory is that by using these concepts, it surpasses the specific characteristics of the gaming environment and transfers to a more general skill of 'learning new tasks'.[19]

In the context of our treatment, by including the task of catching a snowflake presented intermittently to the amblyopic eye for extra points during each gaming session, this *attention task* may have increased cortical plasticity and 'speed up the treatment of amblyopia'. Compared to children in the occlusion group, no specific task was given during daily occlusion.

In addition, these pathways may also influence cortical plasticity differently at different ages. This would also explain the difference in efficiency between both treatments as well as the apparent plasticity in the brain beyond the sensitive period.[20]

The exact pathways remain unravelled making amblyopia an interesting subject not only for orthoptists and ophthalmologists but also for neuroscientists in understanding the brain and its plasticity.

- Amblyopia can be successfully treated with dichoptic action video gaming as well as occlusion treatment. Treatment efficiency was higher in the gaming group. We found good long-term results following occlusion treatment (Chapter 3). For future research a similar study needs to be conducted following gaming treatment to investigate whether the acquired visual acuity is maintained into adulthood; a phase 4 study. As long-term results with gaming treatment are still unknown clinical implementation remains precarious. In a separate study we will address the effect of dichoptic video gaming in adults with amblyopia who will also undergo MRI scans determining any possible changes in the visual cortex after treatment. The size of the population receptive field before and after gaming will also be investigated.

Stereo acuity

Occlusion therapy is a monocular treatment in contrast to the binocular gaming treatment. The initial theory was that by creating binocular training conditions suppression could be alleviated resulting in better stereo acuity

outcome. However, in practice this does not appear to be the case. Most studies show a significant improvement in stereo acuity with gaming, but often fail to demonstrate superiority over occlusion therapy.[21] In our study, we found a significant improvement in stereo acuity in the gaming group as well as the occlusion group with no significant difference between them.

Patients' preference for either treatment

Many publications have reported on the impact of amblyopia and occlusion treatment on health-related quality of life in children.[22-25] As behavioural training has become increasingly popular as amblyopia treatment, it is imperative to understand the preferences and experiences of families with these treatments to facilitate clinical decision making in the future. We also evaluated the information needs of parents to support participation in clinical decision making (Chapter 7).

Creating a routine was found to be hugely important in maintaining compliance, in both the occlusion and gaming group. This has been previously described.[25] For example, parents with children in the occlusion group indicated that they occluded at set times. Parents with children in the gaming group reported that attending the outpatient clinic on a set day and time each week, made it easier to maintain compliance, as it provided structure and clarity.

A major difference between the two treatments was that parents in the gaming group appreciated not being responsible for carrying out the treatment themselves, since this was done by the researcher. When asked if they would then have preferred to do the gaming treatment at home because of the logistical problems, they did not want to, for this very reason.

Parents also reported on the 'burden of treatment'. With occlusion treatment, parents found the visual impairment caused by the occlusion at school particularly troublesome. Parents of children in the gaming group indicated that they started the treatment full of enthusiasm. However, they soon realised that when children had to play the game regularly, they became less enthusiastic.

- In choosing the type of amblyopia treatment all parents emphasised that the effectiveness and efficiency of the treatment were the most important considerations. Parents were strict in allowing screen time on electronic devices, so choosing gaming as treatment felt like creating a sedentary lifestyle. In addition, the logistics of the treatment were an important issue. Finally, parents primarily relied the advice of the treatment provider.

Clinical and practical implications for the health care provider

We recruited almost 100 children for our study, but only a third reached the randomisation phase. Twenty-nine families declined participation, mainly caused by the burden of the weekly game sessions at the clinic, and because they felt that gaming did not fit with their parenting ethos. Also, half of the children assigned to the gaming group dropped out. The large number of drop-outs was unexpected, since we thought children and parents would be more willing to play a video game than to occlude an eye. We also found hardly any literature to corroborate our findings. We therefore recorded factors that influenced the applicability of dichoptic video gaming with VR goggles in young children (Chapter 6). These factors ranged from the recruitment of eligible patients to the successful completion of dichoptic treatment.

Age of the child

Age proved to be a key factor in determining eligibility and the success of dichoptic game treatment in practice. Children younger than 5.5 years of age, with limited language skills and cognitive ability, had too much difficulty comprehending the game and also in giving feedback regarding its settings. In countries with an extensive vision screening program, such as the Netherlands, children with strabismic amblyopia are detected at 2.5 years and those with refractive amblyopia at 4.5 years.[26] This raises the question of whether this type of treatment would be feasible. Amblyopia treatment should commence as soon as it is discovered. Children with strabismic amblyopia would mostly be ineligible for treatment, due to a young age at detection and a strabismus angle too large for conducting the game.

Another important finding was that 1 hour of active gameplay was too tedious for young children. Also, younger children with a shorter concentration span were more easily distracted during the game. Older children were more successful in understanding and playing the game; unfortunately they and their parents were often unwilling to comply with the weekly game schedule. Losing interest in the game was apparent at all ages. Keeping the child engaged is an essential quality of the game used for treatment. It is important to note that we had only one game with different levels available for the treatment; this may have been a limiting factor for success. Ideally there would be several games available depending on age group. Young children need a gaming environment with minimal stimuli and simplistic objects, whereas older children need a more complex and varied gaming environment with more stimuli to keep them engaged.

Dichoptic movie watching might be considered an alternative, especially for younger children.[27] However, it remains unclear if this *passive* form of binocular therapy is as effective as the *active* action video game especially considering the importance of reward and attentional mechanism as mentioned earlier.

- Age is a key factor in determining eligibility and success of dichoptic treatment. Games should target their age-appropriate audience. Children younger than 5.5 years were unable to understand and play the game; for them, a passive form of treatment may be more suitable. The effectiveness of passive dichoptic treatment compared with active action game treatment should be objectively investigated.
- Dichoptic treatment in children is most feasible for small-angle strabismic, anisometropic or combined amblyopes at an older age. This treatment may hold potential in countries lacking an effective screening programme, where amblyopia is discovered at a later age.

Financial issues

The major expense for our study was the required hardware to perform the game including the laptop and virtual reality headset. Secondly, the software: the development and modifications of an engaging child-friendly dichoptic video game with two different game environments, including settings for perceptual balance, alignment and a suppression check. Important to note is that the video game industry is a whole separate branch developing rapidly with large teams set up specifically to develop games. Games developed by research groups cannot match the quality of industry-produced games, due to their expertise and experience. Ideally, researchers should collaborate with the game industry to produce compelling video games.

The VR goggles used in our game treatment were not primarily designed for young children. Despite an abundance of Velcro, it was still difficult to keep the goggles firmly attached. New inexpensive consumer VR headsets such as the Oculus Go, which can be operated via a smartphone, may help to offset some of these issues. Offering dichoptic treatment for amblyopia in other forms, such as using an iPad with red-green anaglyphic glasses, may be more suitable for younger children.[28-30]

In our study, the game was played under direct supervision of the researcher. This design was chosen to ensure the game treatment was conducted correctly and to monitor compliance. However, this set-up revealed its own costs. Due to a fixed game set-up at the outpatient clinic, parents had to incorporate this into their daily routine and maybe even take time off work—the costs of which needs to be considered. There were also travel expenses and parking fees.

If the gaming treatment using VR goggles were to be applied to in orthoptic practice the question remains: who should supervise the treatment? The orthoptist? The parent? If possible, a home-based alternative might be offered; however, Holmes et al. have reported very poor compliance with iPad games at home.[28,30] In addition, moving to a home-based setting would require more parental responsibility and supervision to ensure the sessions are performed correctly and, with VR specifically, to avoid injury if children move around while wearing the goggles.

- Overall, even if the gaming treatment is 15 times more efficient, the costs of conducting dichoptic treatment with VR goggles remain considerable, mainly due to the required hardware and software. Ideally, there should be a variety of different highly engaging games tailored to different age categories.

Who should pay for these costs: the national or private health insurance; out of pocket of the families; the hospital or department itself? In comparison: the cost of an occlusion patch is approximately €1.50. Even when correcting for the duration of treatment, which is on average 22 months for occlusion therapy, it still remains the cheapest option.[7]

Compliance

Both treatment options had compliance and logistical challenges. This has been well documented for occlusion treatment,[5-7] but is under-reported for gaming treatment. Patient and parental motivation with the game treatment is essential. Unlike adults with amblyopia, who are generally intrinsically motivated to improve their vision and therefore comply with treatment, children must be actively kept engaged.

- Even when offered a broad range of games suitable for different age categories, we cannot overlook the psychological factor that assigning a child to play a video game as treatment is not the same as when a child voluntarily chooses to play one. Therefore, compliance rates should not be overestimated.

Key findings

1. Occlusion therapy for amblyopia is a successful treatment, even in the long term. Children with poor visual acuity at the start of treatment, microstrabismus and eccentric fixation are at greater risk of poor visual outcome and may benefit from a longer and more tapered approach.

2. Optical treatment is an important first step in amblyopia treatment: it effectively treated one third of newly diagnosed amblyopic children.
3. Both occlusion treatment and dichoptic action video gaming improved visual acuity in the amblyopic eye. Dichoptic video gaming demonstrated a higher treatment efficiency and can be considered a viable alternative to occlusion treatment. However, the applicability of this treatment is severely hampered by practical and financial concerns. Dichoptic video gaming appears better suited for *older (>5.5 years) children with refractive amblyopia after spectacle adaptation,* as they are more able to understand the game and its settings. In countries with an extensive vision screening programme, whereby amblyopia is discovered and treated early, the applicability of gaming is limited.
4. Both occlusion treatment and dichoptic action video gaming have their own advantages and disadvantages. Parents reported that creating a routine with occlusion treatment improved compliance. With regard to dichoptic video gaming, parents felt less responsibility for the treatment, as it was carried out at the outpatient clinic. When selecting the type of treatment, parents wished to reach a well-informed, shared decision after discussing the expected effect, as well as several organisational aspects of treatment and their child's traits.

Concluding remarks

The research described in this thesis focused on obtaining a valid comparison between the effect of occlusion treatment and dichoptic action video gaming in the treatment of amblyopia in children. Both treatments are effective and showed their own benefits and disadvantages. As awareness of these new therapies rises, we aimed to explore all aspects of both treatments as thoroughly as possible, thereby providing guidelines for health care providers to properly inform parents and the children about the treatment methods available. Our future research will focus on refining which treatment is most suited for each child, taking into account the various aspects of treatment and the child's traits. Further investigations are also needed to determine which pathways in the brain are involved during both types of amblyopia treatment, and whether the effect of gaming treatment persists into adulthood. Lastly, the effect of dichoptic gaming in adults needs to be investigated, including possible changes in the visual cortex after treatment using MRI scans. Population receptive field size before and after treatment is also an interesting parameter for further research.

References

1. Attebo K, Mitchell P, Cumming R, et al. Prevalence and causes of amblyopia in an adult population. Ophthalmology 1998;105(1):154-9.
2. Brown SA, Weih LM, Fu CL, et al. Prevalence of amblyopia and associated refractive errors in an adult population in Victoria, Australia. Ophthalmic Epidemiol 2000;7(4):249-58.
3. Friedman DS, Repka MX, Katz J, et al. Prevalence of amblyopia and strabismus in white and African American children aged 6 through 71 months the Baltimore Pediatric Eye Disease Study. Ophthalmology 2009;116(11):2128-34 e1-2.
4. Miller NP, Aldred B, Schmitt MA, Rokers B. Impact of Amblyopia on the Central Nervous System. J Binocul Vis Ocul Motil 2020;70(4):182-92.
5. Stewart CE, Moseley MJ, Stephens DA, Fielder AR. Treatment dose-response in amblyopia therapy: the Monitored Occlusion Treatment of Amblyopia Study (MOTAS). Invest Ophthalmol Vis Sci 2004;45(9):3048-54.
6. Stewart CE, Stephens DA, Fielder AR, et al. Objectively monitored patching regimens for treatment of amblyopia: randomised trial. BMJ 2007;335(7622):707.
7. Loudon SE, Fronius M, Looman CW, et al. Predictors and a remedy for noncompliance with amblyopia therapy in children measured with the occlusion dose monitor. Invest Ophthalmol Vis Sci 2006;47(10):4393-400.
8. van de Graaf ES, van der Sterre GW, van Kempen-du Saar H, et al. Amblyopia and Strabismus Questionnaire (A&SQ): clinical validation in a historic cohort. Graefes Arch Clin Exp Ophthalmol 2007;245(11):1589-95.
9. van Leeuwen R, Eijkemans MJ, Vingerling JR, et al. Risk of bilateral visual impairment in individuals with amblyopia: the Rotterdam study. Br J Ophthalmol 2007;91(11):1450-1.
10. Tsirlin I, Colpa L, Goltz HC, Wong AM. Behavioral Training as New Treatment for Adult Amblyopia: A Meta-Analysis and Systematic Review. Invest Ophthalmol Vis Sci 2015;56(6):4061-75.
11. Sengpiel F. Plasticity of the visual cortex and treatment of amblyopia. Curr Biol 2014;24(18):R936-R40.
12. Stewart CE, Moseley MJ, Fielder AR, et al. Refractive adaptation in amblyopia: quantification of effect and implications for practice. Br J Ophthalmol 2004;88(12):1552-6.
13. Cotter SA, Pediatric Eye Disease Investigator G, Edwards AR, et al. Treatment of anisometropic amblyopia in children with refractive correction. Ophthalmology 2006;113(6):895-903.
14. Writing Committee for the Pediatric Eye Disease Investigator G, Cotter SA, Foster NC, et al. Optical treatment of strabismic and combined strabismic-anisometropic amblyopia. Ophthalmology 2012;119(1):150-8.
15. Proudlock FA, Hisaund M, Maconachie G, et al. Extended optical treatment versus early patching with an intensive patching regimen in children with amblyopia in Europe (EuPatch): a multicentre, randomised controlled trial. Lancet 2024;403(10438):1766-78.
16. Sloot F, Telleman MAJ, Benjamins J, et al. Effectiveness of routine population-wide orthoptic preschool vision screening tests at age 6-24 months in the Netherlands. Acta Ophthalmol 2022;100(1):e100-e14.

17. Kadhum A, Tan ETC, Fronius M, et al. Supervised dichoptic gaming versus monitored occlusion therapy for childhood amblyopia: Effectiveness and efficiency. Acta Ophthalmol 2023.
18. Bavelier D, Green CS. Enhancing Attentional Control: Lessons from Action Video Games. Neuron 2019;104(1):147-63.
19. Green CS, Bavelier D. Learning, attentional control, and action video games. Curr Biol 2012;22(6):R197-206.
20. Levi DM. Rethinking amblyopia 2020. Vision Res 2020;176:118-29.
21. Tsani Z, Ioannopoulos D, Androudi S, et al. Binocular treatment for amblyopia: a systematic review. Int Ophthalmol 2024;44(1):362.
22. Carlton J, Kaltenthaler E. Amblyopia and quality of life: a systematic review. Eye (Lond) 2011;25(4):403-13.
23. van der Sterre GW, van de Graaf ES, van der Meulen-Schot HM, et al. Quality of life during occlusion therapy for amblyopia from the perspective of the children and from that of their parents, as proxy. BMC Ophthalmol 2022;22(1):135.
24. Hatt SR, Leske DA, Castañeda YS, et al. Understanding the Impact of Residual Amblyopia on Functional Vision and Eye-related Quality of Life Using the PedEyeQ. Am J Ophthalmol 2020;218:173-81.
25. Dixon-Woods M, Awan M, Gottlob I. Why is compliance with occlusion therapy for amblyopia so hard? A qualitative study. Arch Dis Child 2006;91(6):491-4.
26. Groenewoud JH, Tjiam AM, Lantau VK, et al. Rotterdam AMblyopia screening effectiveness study: detection and causes of amblyopia in a large birth cohort. Invest Ophthalmol Vis Sci 2010;51(7):3476-84.
27. Jost RM, Hudgins LA, Dao LM, et al. Randomized clinical trial of streaming dichoptic movies versus patching for treatment of amblyopia in children aged 3 to 7 years. Sci Rep 2022;12(1):4157.
28. Holmes JM, Manh VM, Lazar EL, et al. Effect of a Binocular iPad Game vs Part-time Patching in Children Aged 5 to 12 Years With Amblyopia: A Randomized Clinical Trial. JAMA Ophthalmol 2016;134(12):1391-400.
29. Kelly KR, Jost RM, Dao L, et al. Binocular iPad Game vs Patching for Treatment of Amblyopia in Children: A Randomized Clinical Trial. JAMA Ophthalmol 2016;134(12):1402-8.
30. Manh VM, Holmes JM, Lazar EL, et al. A Randomized Trial of a Binocular iPad Game Versus Part-Time Patching in Children Aged 13 to 16 Years With Amblyopia. Am J Ophthalmol 2018;186:104-15.

Appendix

Table S1. Overview of publications investigating binocular treatment for children with amblyopia.

Study	Type of study & patients	Treatment group(s)	Intervention	Outcome
Li et al. 2015[1] Dichoptic movie viewing treats childhood amblyopia.	Prospective cohort study N = 8 • Mean age: 7.4 ± 2.0 years • Age range: 4-10 years • Type of amblyopia: Anisometropia (n=3); Strabismus (n=1); Combined (n=4) Spectacles needed to be worn for at least 3 months prior to inclusion. Prior amblyopia treatment • Discontinued >1 year (n=2) • Prior occlusion therapy (n=6)	Watching 3 dichoptic movies per week for 2 weeks on a passive 3D screen • Duration of exposure: 9.4 ± 0.9 h • Laboratory / Clinic	Passive movie viewing High-contrast to AE, low-contrast to FE. Complementary dichoptic deficits presented to both eyes. Compliance: all children completed the study.	Mean VA AE improvement: 2.0 logMAR lines Suppression: no significant change Stereo acuity: no significant change *Dichoptic movie watching, no gaming. No comparison with occlusion therapy.*

Table S1. Continued

Study	Type of study & patients	Treatment group(s)	Intervention	Outcome
Kelly et al. 2016[2]* Binocular iPad game vs patching for treatment of amblyopia in children: A randomized clinical trial.	Randomized, clinical trial with a cross-over design N=28 • Mean age: 6.7 ± 1.4 years • Age range: 4.6 - 9.5 years • Anisometropia (n=14); Strabismus (n=9); Combined (n=5). Prior amblyopia treatment • None (n=8) • Prior treatment (n=20) Spectacles needed to be worn for at least 8 weeks prior to inclusion or no improvement in BCVA with current spectacle correction during 2 consecutive visits with a minimum of 4-6 weeks apart.	• Game group: binocular iPad game 1 hr/day 5 days/week for 2 weeks; total 10 hours. (n = 14) • Occlusion therapy 2h/day 7 days/week; total 28 hours (n = 14) • Both treatments at home.	• Binocular Dig Rush game played on an iPad. Action-oriented adventure game using red-green anaglyphic glasses. • Contrast for AE 100%; contrast FE set at 20% initially and increased with game success. • iPad device recorded minutes played.	Mean BCVA change (SD) after 2 weeks (before cross-over): • Game group: 0.15 ± 0.08 logMAR (p<0.001). • Occlusion group: 0.07 ± 0.08) logMAR (p=0.006) • Mean difference: 0.07 logMAR (95% CI, 0.01-0.14 logMAR) Stereo acuity: no significant change in both groups. Extent of suppression scotoma (using Worth 4-dot test): no significant change in both groups. Depth of suppression at baseline vs 2 weeks *(using minimum contrast ratio at which amblyopic eye was not suppressed)* • * Game group: 4.82 ± 2.82 vs 3.24 ± 2.87 (p=0.03) • * Occlusion group: 4.77 ± 3.10 vs 2.57 ± 1.67 (p=0.005) • Compliance 100% first 2 weeks according to recorded log file on iPad. *Results after cross-over are not included.*

Table S1. Continued

Study	Type of study & patients	Treatment group(s)	Intervention	Outcome
Holmes et al. 2016[3] * Effect of a binocular iPad game vs part-time patching in children aged 5 to 12 years with amblyopia: A randomized clinical trial.	Multi-center randomized clinical trial N = 385 • Mean age: 7.4 ± 2.0 years • Age range: 5-12 years • Anisometropia (n = 199); Strabismus (n = 66); Combined (n = 120). Prior amblyopia treatment • None (n=85) • Prior treatment (n=300)	Randomized: • Binocular iPad game 1h/day (n=190) • Occlusion therapy 2h/day (n=195) • Both treatments at home for 16 weeks.	Binocular falling blocks iPad game with red-green anaglyphic glasses. • Contrast for AE 100%; contrast FE set at 20% and automatically increased/ decreased depending on performance and duration game play. • Parents recorded number of treatment hours for gaming or occlusion therapy in diaries. • IPad device automatically recorded duration of gameplay, contrast and performance.	Mean VA improvement at 16 weeks: • Binocular group: 1.05 lines (2-sided 95% CI, 0.85-1.24) • Occlusion group: 1.35 lines (2-sided 95% CI, 1.17-1.54 lines) • Difference between groups: 0.31 lines favoring occlusion (upper limit of the 1-sided 95% CI, 0.53 lines) Mean VA improvement in younger children (5 to <7 years without prior amblyopia treatment) • Binocular group: 2.5 (SD 1.5) lines • Occlusion group: 2.8 (SD 0.8) lines Recorded compliance with iPad device: 22% achieved greater than 75% compliance.
Herbison et al. 2016[4] Randomised controlled trial of video clips and interactive games to improve vision in children with amblyopia using the I-BiT system.	Randomised clinical trial N = 75 • Mean age: 6.0±1.3 (I-BiT game); 5.6±1.1 (non-I-BiT game); 5.9±1.2 years (I-BiT DVD) • Age range: 4-8 years • Anisometropia (n = 5); Strabismus (n = 24); Combined (n=46). Prior amblyopia treatment • None (n=18) • Prior treatment (n=57) Exclusion criterium: achieving normal vision after refractive adaptation. Not specified how long the spectacles needed to be worn prior to inclusion.	• I-BiT game group: interactive game (n=26). • Non-I-BiT game (control group) (n=25). • I-BiT DVD (n=24). • Duration of exposure (all groups): 30 min/week, 6 weeks (total: 3 h) • Laboratory / Clinic	I-BiT system hardware consists of a desktop PC with two monitors using shutter glasses. One for the clinician and one for the patient; used under supervision. • I-BiT game group: interactive game 'Nux': some game elements are shown to both eyes; other game elements are solely presented to the AE. • Non-I-BiT game (control group): both eyes receive identical stimulation. • I-BiT DVD: some elements of the video footage is presented to both eyes; other parts predominately to the AE.	Mean BCVA change at 6 weeks: • I-BiT game group: 0.1 (0.02) logMAR • Non-I-BiT game: 0.06 (0.02) logMAR • I-BiT DVD: 0.03 (0.02) logMAR Significant improvement between baseline vs week 6 (p<0.001); but no significant difference between the three groups. Stereo acuity: no significant change in all three groups. Compliance for each group:>90%.

Table S1. Continued

Study	Type of study & patients	Treatment group(s)	Intervention	Outcome
Bossi et al. 2017[5] Binocular therapy for childhood amblyopia improves vision without breaking interocular suppression.	Prospective clinical trial N = 22 • Mean age: 6.6±2.9 years • Age range: 3.5-11.3 years • Group 1: Anisometropia (n=7) • Group 2: Strabismus (n=6), Combined (n=9) Prior amblyopia treatment: none. Spectacles needed to be worn for at least 16 weeks prior to inclusion or no change in BCVA in AE with current spectacle correction during 2 consecutive visits with a minimum of 8 weeks apart.	Viewing of dichoptic movies and gameplay wearing goggles • Group 1 (n=7) for maximum of 8 weeks • Group 2 (n=15) for a maximum of 24 weeks • Treatment duration: 1h/day at home.	Computer system presenting 3D movies dichoptically, installed in the child´s home. Shutter glasses were used to control the image presented to the two eyes, mounted in customized children´s ski mask to ensure comfort. A keypad was provided to respond to suppression task. Image presented to FE was blurred. Every minute the movie was interrupted by an interactive game measuring suppression.	Mean BCVA improvement Group 1 (only anisometropic amblyopia) at 8 weeks: 0.26±0.28 logMAR Group 2 (strabismic and combined amblyopia): 0.27±0.19 logMAR No significant difference between the two groups. Stereo acuity significantly improved in 6/7 children with anisometropic amblyopia. Mean compliance (percentage of days treatment received): 68.0±12.2%. Mean daily dose: 54±14.5 minutes (range: 25-89 minutes)
Kelly et al. 2018[6] Improved binocular outcomes following binocular treatment for childhood amblyopia.	Data pooled from two ongoing studies of binocular treatment for childhood amblyopia. N = 41 • Mean age: 7.0±1.8 years • Age range: 4.4-10.7 years • Anisometropia (n=21), Strabismus (n=6), Combined (n=14) Prior amblyopia treatment • None (n=32) • Prior treatment (n=9) Spectacles needed to be worn for at least 8 weeks prior to inclusion or no change in BCVA in AE with current spectacle correction during 2 consecutive visits with a minimum of 4-6 weeks apart.	• Game group (n=20): 1 h/day, 5 days/week for 2 weeks (total: 10h) • Home. • Movie group: binocular movie watching (n=21) 6 visits during 2-week treatment (1 movie per visit; total 9h) • Laboratory	• Game group: binocular Dig Rush game played on an iPad. Action-oriented adventure game using red-green anaglyphic glasses. Contrast for AE 100%; contrast FE set at 20% initially and increased with game success or decreased if gaming was not successful. • Movie group: Presented on a passive 3D display using polarized glasses that separate images between the two eyes. Similar to the binocular game treatment, high-contrast elements were seen by the AE, reduced contrast elements seen by FE; some elements seen by both eyes. Initial FE contrast customized based on each child's dichoptic motion coherence threshold minus 10% contrast, increased by 10% for each subsequent movie.	Mean BCVA improvement at 2 weeks: • Overall: 0.14±0.09 logMAR (p<0.001) • No difference between the two groups (p=0.92). Stereo acuity improved significantly (p=0.045) at 2 weeks. Extent of suppression scotoma (Worth 4-Dot): significantly reduced at 2 weeks (p=0.005). Compliance • Game group: 87% (8.7±3.0h) • Movie group: 100% (9.1±0.8h)

Table S1. Continued

Study	Type of study & patients	Treatment group(s)	Intervention	Outcome
Manh et al. 2018[7] * A randomized trial of a binocular iPad game versus part-time patching in children aged 13 to 16 years with amblyopia.	Multi-center randomized clinical trial N = 100 • Mean age: 14.3 ± 1.1 years • Age range: 13 - <17 years • Anisometropia (n = 51); Strabismus (n=14), Combined (n=35) Prior amblyopia treatment • None (n=16) • Prior treatment (n=84)	Randomized: • Binocular Videogame iPad group (n = 40) for 1 h/day (16 weeks). • Patching group (n = 60) for 2 h/day (16 weeks) • Both treatments at home for 16 weeks.	Binocular falling blocks iPad game with red-green anaglyphic glasses. • Contrast for AE 100%; contrast FE set at 20% and automatically increased/decreased depending on performance and duration game play. • Parents recorded number of treatment hours for gaming or occlusion therapy in diaries. • IPad device automatically recorded duration of gameplay, contrast and performance.	Mean VA improvement at 16 weeks: • Binocular group: 3.7 letters or 0.74 lines (95% CI, 1.3 to 6.0 letters) • Occlusion group: 6.3 letters or 1.26 lines (95% CI, 4.4 to 8.6 letters) • Difference between groups: 2.7 letters or 0.52 lines (95% CI -5.7 to 0.3 letters, p=0.082) Stereo acuity: no significant change. Compliance data from the iPad Binocular group (available from 97% of participants): 13% of participants completed >75% of the prescribed treatment.
Gambacorta et al. 2018[8] An action video game for the treatment of amblyopia in children: A feasibility study.	Prospective clinical trial N = 21 • Mean age: 9.95±3.14 years • Age range: 7-17 years • Anisometropia (n=12), Strabismus (n = 9) Prior amblyopia treatment • No occlusion treatment in the last 6 months (n=15) • Prior occlusion treatment in the last 6 months (n=6) Participants were instructed to wear most recent optical correction at all times; if prescription required an update they were monitored for 6-8 weeks with new spectacles, after which baseline measurement took place	• Dichoptic gaming (n=10): 20h in total. • Monocular gaming (n=11): 20h in total. • Laboratory.	• Dichoptic game group: custom-made dichoptic video game using a mirror stereoscope and balanced input. The dichoptic game presented the same image to each eye (except for Gabor patches and part of the fixation scope) with reduced luminance/contrast in the FE in an attempt to promote binocular fusion. The game included a perceptual learning task as well as a suppression task with a Gabor patch appearing every few seconds to the AE only with an orientation task. • Monocular game group: playing the same game with the FE occluded including the perceptual learning task.	• Dichoptic game group: 0.1±0.02 (SE) logMAR units after 10h and 0.14±0.02 (SE) logMAR units after 20h (compared to baseline). • Monocular game group: 0.06±0.03 (SE) after 10h and 20h (compared to baseline). Stereo acuity: Dichoptic game group: 0.07 log arcsec (≈17%) Monocular game group: 0.06 log arcsec (≈15%) *No statistical test for significance.* Drop-out: Dichoptic game group: 23% Monocular game group: 31% Other participants finished the 20h of training at the laboratory.

Table S1. Continued

Study	Type of study & patients	Treatment group(s)	Intervention	Outcome
Mezad-Koursh et al. 2018[9] Home use of binocular dichoptic video content device for treatment of amblyopia: A pilot study.	Prospective pilot study N = 27 • Mean age: 6.0±1.4 years • Age range = 7-17 years • Anisometropia (n=7), Strabismus (n=13), Combined (n=7) Prior amblyopia treatment Wash-out period 4 weeks in the treatment group Wash-out period 2 weeks in the Sham group. Participants wore spectacle correction if needed and had stable VA 3 months prior to inclusion.	• Treatment group (n=19): 60 min/day, 6 days/week, 8–12 weeks (total: 48–72 h) • Control group (n = 8): 60 min/day, 6days/week, 4 weeks (total: 24 h) • Home	• Treatment group: viewing animated programs and videos at home using the BinoVision device. During each treatment session: 60 cycles of 1 minute containing dichoptic alterations of audio and visual elements. Dichoptic alterations superimposed on commercially available, non-altered video content. Control group: present equal stimuli for both eyes at all times with no special stimuli.	Mean BCVA improvement: • Treatment group at 12 weeks: 0.26 logMAR lines (p<0.01) • Control group at 4 weeks: no change in BCVA (p=0.285) Stereo acuity: no significant change. Compliance using log records for the first 8 weeks: 88%±16%

Table S1. Continued

Study	Type of study & patients	Treatment group(s)	Intervention	Outcome
Holmes et al. 2019[10] A randomized trial of binocular dig rush game treatment for amblyopia in children aged 7 to 12 years.	Multicenter, randomized clinical trial N = 138 • Mean age: 9.6 ± 1.6 years • Age range: 7-12 years • Anisometropia (n=66), Strabismus (n=26), Combined (n=46) Prior amblyopia treatment • None (n=6) • Prior treatment (n=132) Spectacles needed to be worn for at least 16 weeks prior to inclusion or no BCVA improvement in AE (<0.1 logMAR) with current spectacle correction during 2 consecutive visits with a minimum of 8 weeks apart.	• Game group: binocular iPad game 1hr/day 5 days/week plus spectacle correction for all waking hours (n=69) • Control group: continued spectacle correction alone all waking hours (n=69). • Both treatments at home, for 8 weeks.	• Game treatment: Binocular Dig Rush game played on an iPad. Action-oriented adventure game using red-green anaglyphic glasses. • Contrast for AE 100%; contrast FE set at 20% initially and increased with game success or decreased if gaming was not successful.	Mean BCVA AE change after 4 weeks: • Game group: 1.3 letter score improvement (95% CI: 0.1 -2.6; equivalent to 0.026 logMAR) • Spectacles group: 1.7 letter score improvement (95% CI: 0.4 -3.0; equivalent to 0.034 logMAR) • Difference between game and control treatment letter scores was -0.3 (95% CI: -2.2 to 1.5, P = 0.71; equivalent to -0.006 logMAR). Mean BCVA AE change at 8 weeks • Game group: 2.3 letter score improvement (98.3% CI: 0.7-3.9) • Control group: 2.4 letter score (98.3% CI: 0.8-4.0) No difference in letter scores between the two groups. Stereo acuity: no significant change in both groups. Median compliance according to log file data iPad 80% (range 1%-133%).

Table S1. Continued

Study	Type of study & patients	Treatment group(s)	Intervention	Outcome
Yao et al. 2020[11] * Binocular game versus part-time patching for treatment of anisometropic amblyopia in Chinese children: a randomised clinical trial.	Randomized, clinical trial N = 103 • Mean age: 5.99 ± 2.33 years • Age range = 3-13 years • Only anisometropic amblyopia Prior amblyopia treatment • None (n=76) • Prior treatment (n=27) Stable BCVA with current spectacles over 4 weeks (five or less letters change) after appropriate spectacle correction within the inclusion range before randomization.	• Game group: binocular game played on a computer: 40 min per day, divided into two training sessions. Each session had two items and each item lasted for 10 min with 10 min interval. • Occlusion group: 2-6h/day depending on the severity of amblyopia. • Combined group: 40min per day binocular gaming and occlusion therapy 2-6h/day depending on severity of amblyopia • Treatments at home, for 12 weeks.	• Binocular game played on a computer with polarized anaglyphic glasses.	Mean BCVA AE change at 12 weeks: • Game group: 0.18 logMAR (95% CI 0.10–0.26) • Occlusion group: 0.28 (95% CI 0.19–0.36) After adjusting for baseline VA, the difference was statistically significant (F=6.29, p=0.003), favouring as follows: the combined group, the occlusion group and the gaming group. Stereo acuity: greater improvement in gaming and combined group compared to occlusion (but not statistically significant). Compliance with binocular game: only number of login was recorded, not the duration of game play.
Rajavi et al. 2019[12] * Comparison between patching and interactive binocular treatment in amblyopia: A randomized clinical trial.	Randomized clinical trial N=38 • Mean age: 7.08 ± 1.82 years • Age range = 3-10 years • Type of amblyopia not specified. Prior amblyopia treatment • None (n=8) • Prior treatment (n=30) Spectacles needed to be worn for at least 16 weeks prior to inclusion; one month was required if no new prescription was needed but previous occlusion therapy was prescribed.	• Game group: i-BiT games using red-green glasses (n=19) 20-30min/day 5 days/week. • Control group: 2h or 4h of occlusion therapy for mild and moderate amblyopia respectively, with placebo I-BiT games with no red-green glasses (n=21) 20-30min/day 5 days/week. • Both treatments at home, for 4 weeks.	• Game group: I-BiT games were played using red-green glasses. • Control group: placebo I-BiT games were played with no red-green glasses in addition to occlusion therapy.	Mean BCVA change after 4 weeks: • Game group: 0.08 (SD 0.09) logMAR (p=0.003) • Control group: 0.09 (SD 0.09) logMAR (p<0.001) No significant difference between the groups (p=0.52) Stereo acuity: improvement in both groups with no significant difference between them. Recorded compliance with gaming: • Game group: 87.5% • Control group: 76%

Table S1. Continued

Study	Type of study & patients	Treatment group(s)	Intervention	Outcome
Manny et al. 2022[13] A Randomized Trial of Binocular Dig Rush Game Treatment for Amblyopia in Children Aged 4 to 6 Years.	Randomized, clinical trial N = 182 • Mean age: 5.7 ± 0.7 years • Age range = 4-6 years • Anisometropia (n=115), Strabismus (n= 30), Combined (n=37) Prior amblyopia treatment • None (n=60) • Prior treatment (n=109) Spectacles needed to be worn for at least 16 weeks prior to inclusion or no BCVA improvement in AE (<0.1 logMAR) with current spectacle correction during 2 consecutive visits with a minimum of 8 weeks apart.	• Game group: binocular iPad game 1hr/day 5 days/week plus spectacle correction for all waking hours (n=92) • Control group: continued spectacle correction alone all waking hours (n=90). • Both treatments at home, for 8 weeks.	• Binocular Dig Rush game played on an iPad. Action-oriented adventure game using red-green anaglyphic glasses. • Contrast for AE 100%; contrast FE set at 20% initially and increased with game success or decreased if gaming was not successful.	Mean BCVA AE change after 4 weeks: • Game group: 1.1±1.4 logMAR lines • Spectacles group: 0.6±1.3 logMAR lines Difference: 0.5 logMAR lines (95.1% CI, +0.1 to +0.9 logMAR lines; p=0.03). Mean BCVA change after 8 weeks: • Game group: 1.3±1.4 logMAR lines • Spectacles group: 1.0±1.4 logMAR lines Difference: 0.3 lines (98.4% CI, -0.2 – 0.8 lines; p=0.60) Stereo acuity: no significant change in both groups. Median compliance according to log file data iPad 62% (range 2%-122%).

Jost/Birch et al. 2022[14]*
 	
Randomized clinical trial of streaming dichoptic movies versus patching for treatment of amblyopia in children aged 3 to 7 years.
	Randomized clinical trial
	N = 65
	• Mean age: 6.0±1.4 (binocular treatment); 6.1±1.5 (occlusion therapy)
	• Age range: 3-7 years
	• Anisometropia (n=7), Strabismus (n=13), Combined (n=7)
	
	Prior amblyopia treatment
	• None (n=13)
	• Prior treatment (n=47)
	
	Participants wore spectacles for ≥8 weeks prior to enrollment.
		• Binocular treatment group: 3 movies/week (4.5h/week)
		• Occlusion group: 2h/day (14hours/week.)
		• For 2 weeks
		• Home
			• Binocular treatment group: movie watching at home on the Nintendo 3DS XL with dichoptic viewing with different parts of the display presented to each eye. With FE contrast start at 20% and increase with each consecutive movie.	Mean BCVA improvement:
				• Binocular group
				  • at 2 weeks: 0.07±0.05 logMAR (p<0.0001)
				  • at 4 weeks: 0.13±0.11 logMAR
				  • at 6 weeks: 0.15±0.10 logMAR
				• Occlusion group at 2 weeks: 0.06±0.05 logMAR (p<0.0001)
				
				No significant difference between the two groups at 2 weeks (CI 95%: − 0.02 to 0.04; p = 0.48).
				
				Stereo acuity
				• Binocular group at 2 weeks: 0.12 log arcsec; CI95%: 0.02–0.22.
				• Occlusion group: no improvement.
				
				Compliance: no recording, but parental written logs.
				
				Results of occlusion group after cross-over to gaming not included.

Table S1. Continued

Study	Type of study & patients	Treatment group(s)	Intervention	Outcome
Xiao et al. 2022[15] Randomized Controlled Trial of a Dichoptic Digital Therapeutic for Amblyopia.	Randomized clinical trial N = 105 • Mean age: 6.2±1.0 (gaming group); 6.0±1.1 (control group) • Age range: 4-7 years • Anisometropia (n=59), Strabismus (n=17), Combined (n=28) Prior amblyopia treatment • None (n=22) • Prior treatment (n=82) Participants wore spectacles for ≥16 weeks prior to enrollment or with stable VA on two consecutive measurements with 8 weeks apart.	• Gaming group (n=51): 1h/day 6 days/week at home, combined with continued full time spectacle wear. • Control group (n=54): only continued spectacle wear.	Gaming group: watching television shows and movies with contrast for the FE reduced to 15% and complementary dichoptic masks superimposed on the images such that use of both eyes was required to see the full video content. Head-mounted display with smartphone and virtual reality headset at home.	Mean BCVA improvement at 12 weeks: • Gaming group: 0.18 logMAR (95% CI, 1.4-2.3) • Control group: 0.08 logMAR (95% CI, 0.4-1.3). Significant difference between the two groups: 0.10 logMAR; 96.14% CI, 0.33-1.63; p=0.0011. Stereo acuity: no significant change with no difference between the two groups. Median compliance using electronic monitoring: 88.2% (IQR 61.0-99.7%).

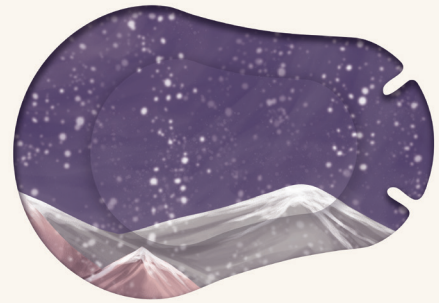
We included studies conducted with children under the age of 18 years with either newly diagnosed amblyopia or residual amblyopia treated with a binocular therapy. Studies that combined binocular therapy with occlusion therapy were omitted.

Only open access studies were included. Mean age with standard deviation is included per study. Studies that were comparable to our study and also compared gaming with occlusion therapy, are marked with an asterix*.

References

1. Li SL, Reynaud A, Hess RF, et al. Dichoptic movie viewing treats childhood amblyopia. J AAPOS 2015;19(5):401-5.
2. Kelly KR, Jost RM, Dao L, et al. Binocular iPad Game vs Patching for Treatment of Amblyopia in Children: A Randomized Clinical Trial. JAMA Ophthalmol 2016;134(12):1402-8.
3. Holmes JM, Manh VM, Lazar EL, et al. Effect of a Binocular iPad Game vs Part-time Patching in Children Aged 5 to 12 Years With Amblyopia: A Randomized Clinical Trial. JAMA Ophthalmol 2016;134(12):1391-400.
4. Herbison N, MacKeith D, Vivian A, et al. Randomised controlled trial of video clips and interactive games to improve vision in children with amblyopia using the I-BiT system. Br J Ophthalmol 2016;100(11):1511-6.
5. Bossi M, Tailor VK, Anderson EJ, et al. Binocular Therapy for Childhood Amblyopia Improves Vision Without Breaking Interocular Suppression. Invest Ophthalmol Vis Sci 2017;58(7):3031-43.
6. Kelly KR, Jost RM, Wang YZ, et al. Improved Binocular Outcomes Following Binocular Treatment for Childhood Amblyopia. Invest Ophthalmol Vis Sci 2018;59(3):1221-8.
7. Manh VM, Holmes JM, Lazar EL, et al. A Randomized Trial of a Binocular iPad Game Versus Part-Time Patching in Children Aged 13 to 16 Years With Amblyopia. Am J Ophthalmol 2018;186:104-15.
8. Gambacorta C, Nahum M, Vedamurthy I, et al. An action video game for the treatment of amblyopia in children: A feasibility study. Vision Res 2018;148:1-14.
9. Mezad-Koursh D, Rosenblatt A, Newman H, Stolovitch C. Home use of binocular dichoptic video content device for treatment of amblyopia: a pilot study. J AAPOS 2018;22(2):134-8 e4.
10. Pediatric Eye Disease Investigator G, Holmes JM, Manny RE, et al. A Randomized Trial of Binocular Dig Rush Game Treatment for Amblyopia in Children Aged 7 to 12 Years. Ophthalmology 2019;126(3):456-66.
11. Yao J, Moon HW, Qu X. Binocular game versus part-time patching for treatment of anisometropic amblyopia in Chinese children: a randomised clinical trial. Br J Ophthalmol 2020;104(3):369-75.
12. Rajavi Z, Sabbaghi H, Amini Sharifi E, et al. Comparison between patching and interactive binocular treatment in amblyopia: A randomized clinical trial. J Curr Ophthalmol 2019;31(4):426-31.
13. Manny RE, Holmes JM, Kraker RT, et al. A Randomized Trial of Binocular Dig Rush Game Treatment for Amblyopia in Children Aged 4 to 6 Years. Optom Vis Sci 2022;99(3):213-27.
14. Jost RM, Hudgins LA, Dao LM, et al. Randomized clinical trial of streaming dichoptic movies versus patching for treatment of amblyopia in children aged 3 to 7 years. Sci Rep 2022;12(1):4157.
15. Xiao S, Angjeli E, Wu HC, et al. Randomized Controlled Trial of a Dichoptic Digital Therapeutic for Amblyopia. Ophthalmology 2022;129(1):77-85.

Summary / Samenvatting



Summary

In this thesis we investigated the long-term visual acuity outcome of the current standard amblyopia treatment: occlusion therapy. In addition, we assessed the role of the optical treatment period and studied electronic monitoring of compliance with spectacle wear. We also conducted an objective comparison of dichoptic action video gaming with occlusion therapy in children newly diagnosed with amblyopia, who had not yet received treatment. Lastly, we explored parents' experiences, preferences and information needs regarding both therapies for their child. This summary presents the main findings of this thesis.

Chapter 1 commences with a general introduction to amblyopia and its definition. For understanding the pathophysiology of amblyopia the so-called 'sensitive period' is essential, as demonstrated by Hubel and Wiesel in their experiments in cats and monkeys introducing deprivation amblyopia by suturing an eyelid. The loss of vision could only be reversed by opening the eye within this time frame. The decrease in effectiveness of amblyopia treatment with age has been explained due to the decrease in plasticity in the brain over time. The first description of the current standard occlusion treatment dates back from the 9th -10th century.

Chapter 2 elaborates on amblyopia therapies across different historical periods. It starts with a historical overview of non-occlusion treatments proposed in the past up until more recent developments including gaming treatments. Historical therapies such as fusion exercises, different tools such as the stereoscope and amblyoscope, and pleoptics with Bangerter and Cüppers are all addressed. More recent therapies such as perceptual learning, dichoptic training and video gaming are also discussed. Striking are the similarities between more recent proposed non-occlusion therapies and historic non-occlusion therapies: both focus on amblyopia mainly as a binocular disorder needing a binocular approach; visual stimuli are used with sometimes specific visual tasks; treatment is according to a training schedule; they are often time consuming; a minimum age is often required to adequately perform the treatment; and children with larger strabismus angles are excluded.

Chapter 3 presents the long-term visual acuity results of standard occlusion treatment for amblyopia and assesses risk factors for deterioration over time. Children treated with occlusion therapy for their amblyopia in a previous randomised clinical trial were followed up 15 years later. On average, the interocular visual acuity difference (IOD) remained stable from end of occlusion treatment

to the follow-up period, demonstrating favourable long-term outcomes. Patients at risk for visual acuity deterioration after cessation of treatment had large initial interocular visual acuity, increasing anisometropia, eccentric fixation and non-compliance during treatment.

Chapter 4 investigates the role of optical treatment as a first step in the treatment of amblyopia. The impact of optical treatment on visual acuity proved significant not only in refractive amblyopia, but also in children with strabismus and combined cause. More than a third of the children improved to such an extent, that they no longer classified as having amblyopia. This emphasised the essential role of optical treatment. In addition, monitoring adherence to spectacle wear by attaching the occlusion dose monitor (ODM) to the temple of the glasses with a standard occlusion patch proved to be a reliable method. This offers opportunities for investigating compliance both in clinical practice and for research purposes.

With the recently emerging alternative non-occlusion treatments for amblyopia the question arises as to how effective they are compared with standard occlusion treatment. **Chapter 5** compares a dichoptic action video game using virtual reality goggles with standard occlusion therapy in untreated, newly diagnosed children with amblyopia. To make an objective comparison, electronic monitoring and direct supervision were implemented to monitor compliance. This also enabled treatment efficiency calculations. Both treatments resulted in significant visual acuity improvement with no significant difference between them. However, treatment efficiency for gaming was fifteen times higher compared to occlusion therapy. Stereo acuity also improved significantly in both groups, again with no significant difference between the two groups. A striking finding was the large dropout rate in the gaming group: 9 of the 16 (56%) children in the gaming group dropped out.

Chapter 6 elaborates on this finding together with all other encountered barriers while applying dichoptic video gaming using virtual reality goggles in practice. These challenges could be divided into three main domains: 1) equipment and usage; 2) parental and child adherence and 3) costs. Age was a key factor determining eligibility and success of gaming treatment: younger children (i.e. <5.5 years) were unable to comprehend the game and its settings. The game design based on weekly sessions at the outpatient clinic with direct supervision, made it logistically challenging for parents. This led to difficulty incorporating the game session into their schedule contributing to the high number of dropouts.

Keeping the child engaged with the gaming therapy also proved challenging, leading to compliance issues and dropout. Ideally, there would be a variety of highly engaging games aimed at different age categories, though this would entail high costs.

Chapter 7 discusses the results of our qualitative study exploring parents' experiences, preferences and information needs regarding dichoptic action video gaming and occlusion therapy as amblyopia treatment for their child. From the data concerning experiences with the treatment two main themes became apparent: 1) factors influencing compliance and 2) burden with treatment. Creating a routine was reported to be a compliance-enhancing factor with occlusion treatment, unlike gaming, which was performed at the outpatient clinic by the researcher. Parents in both groups reported the assumption that improvements in visual acuity and the resolution of amblyopia would be accompanied by a corresponding resolution of the refractive error. They were unaware that continued spectacle wear was advised even after amblyopia treatment had ended to maintain optimal visual acuity. This exposed a critical information hiatus. When given a choice of which treatment their child should receive, parents preferred to reach a well-informed, shared decision after discussing the following aspects: 1) effect and efficiency of treatment; 2) organisational aspects of treatment; and 3) their child's traits.

Chapter 8 presents and discusses the key findings of this thesis and their interpretation. It further considers the clinical implications and outlines directions for future research.

Samenvatting

In deze thesis hebben we de lange-termijn visusuitkomsten onderzocht van de huidige standaard amblyopiebehandeling: occlusietherapie. Bovendien hebben we de rol van de briladaptatie fase onderzocht en elektronische monitoring van de therapietrouw met het bril dragen bestudeerd. Verder hebben we een objectieve vergelijking gemaakt tussen dichoptisch video gamen en occlusietherapie bij nog onbehandelde, nieuw gediagnosticeerde kinderen met amblyopie. Tenslotte hebben we ervaringen, voorkeuren en informatiebehoeften van ouders onderzocht voor beide behandelingen voor hun kind. Deze samenvatting bespreekt de belangrijkste uitkomsten van deze thesis.

Hoofdstuk 1 begint met een algemene introductie over amblyopie en de definitie ervan. Voor een goed begrip van de pathofysiologie van amblyopie is de zogeheten 'sensitieve periode' essentieel, die door Hubel en Wiesel werd onderzocht in hun experimenten bij katten en apen. Zij introduceerden deprivatie amblyopie door een ooglid dicht te maken. Het verlies in visus kon enkel hersteld worden door het oog weer binnen deze sensitieve periode te openen. Het verlies in effectiviteit van amblyopiebehandeling met toenemende leeftijd wordt verklaard door de afnemende plasticiteit van het brein. De vroegste beschrijvingen van de standaard occlusie therapie dateren uit de 9e-10e eeuw.

Hoofdstuk 2 bespreekt diverse non-occlusie therapieën voor amblyopie die door de eeuwen heen werden geïntroduceerd. Het begint met de vroegste behandelingen en eindigt met een overzicht van de meer recent geïntroduceerde therapieën. Historische therapieën zoals de fusie oefeningen, diverse apparaten zoals de stereoscoop en de amblyoscoop, en pleoptics met Bangerter en Cüppers worden allen besproken. Vervolgens worden recentere therapieën behandeld zoals perceptual learning, dichoptisch trainen en gamen. Opvallend zijn de overeenkomsten tussen deze historische en meer recente behandelingen: beide beschouwen amblyopie over het algemeen als een binoculair probleem dat een binoculaire aanpak vereist; vaak is er een trainingsschema; ze zijn vaak tijdsintensief; een minimumleeftijd is meestal vereist om de behandeling goed uit te kunnen voeren; en kinderen met grotere scheelzienshoeken worden geëxcludeerd.

Hoofdstuk 3 presenteert de resultaten van de lange-termijn visusuitkomsten van de standaard occlusiebehandeling voor amblyopie en risicofactoren voor visusverslechtering in de loop der tijd na afronding van de amblyopiebehandeling. Kinderen die in een eerdere gerandomiseerde gecontroleerde trial voor hun amblyopie behandeld zijn met occlusietherapie, zijn 15 jaar later opnieuw onderzocht. Over het algemeen waren de uitkomsten positief: het interoculair visusverschil bleef over het algemeen stabiel vanaf het einde van de amblyopiebehandeling tot aan het follow-up onderzoek. Patiënten die risico liepen op verslechtering na afronding van de behandeling hadden een groter initieel interoculair visusverschil, toenemende anisometropie, excentrische fixatie en non-compliance tijdens de behandeling.

Hoofdstuk 4 onderzoekt de rol van de briladaptatiefase als de eerste stap in de behandeling van amblyopie. De impact hiervan bleek significant, niet alleen in gevallen met refractieve amblyopie, maar ook bij kinderen met een strabismus of een gecombineerde oorzaak. Meer dan een derde van de kinderen verbeterde zodanig dat ze niet meer voldeden aan de definitie van amblyopie. Dit benadrukte de essentiële rol van een briladaptatiefase als eerste stap. Verder bleek het elektronisch monitoren van de therapietrouw van het dragen van de bril betrouwbaar te zijn door de occlusie dose monitor (ODM) met een occlusiepleister te bevestigen aan de poot van de bril. Dit biedt mogelijkheden om deze therapietrouw te monitoren in de kliniek en voor onderzoeksdoeleinden.

Hoofdstuk 5 vergelijkt een dichoptische video game gespeeld met een virtual reality headset met standaard occlusie behandeling in nog onbehandelde, nieuw gediagnosticeerde kinderen met amblyopie. Om een valide vergelijking te maken, werd gebruik gemaakt van elektronische monitoring van de therapietrouw of directe supervisie. Dit maakte het ook mogelijk om de behandelefficiëntie te berekenen. Beide behandelingen resulteerden in significante visusverbetering zonder statistisch significant verschil. Echter, de behandelefficiëntie van het gamen bleek vijftien keer hoger dan die van de occlusiebehandeling. Het stereozien verbeterde significant in beide groepen, opnieuw zonder verschil tussen de twee groepen. Een opvallende bevinding was het grote aantal uitvallers in de game groep: 9 van de 16 (56%) kinderen vielen uit.

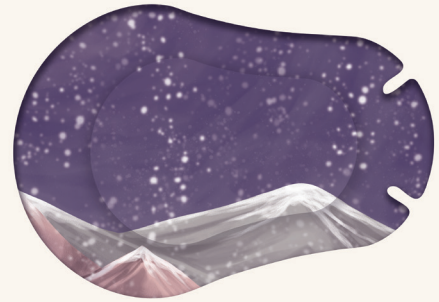
Hoofdstuk 6 gaat dieper in op deze bevinding samen met alle andere barrières, die werden ondervonden tijdens het toepassen van dichoptisch gamen met de virtual reality headset in de praktijk. Deze uitdagingen konden onderverdeeld worden in 3 hoofddomeinen: 1) apparaat en gebruik; 2) therapietrouw van ouders

en kind; en 3) kosten. Leeftijd bleek een sleutelrol te spelen bij het bepalen van geschiktheid en succeskans van de game behandeling. Voor jonge kinderen (<5.5 jaar) was het niet mogelijk om de game en de instellingen goed te begrijpen en uit te voeren. De wekelijkse gamesessies op de polikliniek met directe supervisie bleken in de praktijk logistiek uitdagend voor ouders. Zij hadden moeite om deze sessies in hun eigen schema te plannen, wat bijdroeg aan het hoge aantal drop-outs. Kinderen geboeid houden met de game behandeling bleek eveneens uitdagend en leidde tot problemen met de therapietrouw en uitval. Idealiter zou er een keuze zijn uit meerdere spellen gericht op verschillende leeftijdscategorieën, maar dit zou hoge kosten met zich meebrengen.

Hoofdstuk 7 bespreekt de resultaten van onze kwalitatieve studie waarin ervaringen, voorkeuren en informatiebehoeften van ouders werden onderzocht voor beide behandelingen (gamen en occlusie). Twee hoofdthema's kwamen naar voren: 1) factoren die de therapietrouw beïnvloeden; en 2) de 'lasten' van de behandeling. Het creëren van een routine bleek de therapietrouw te bevorderen in de occlusiegroep. Ouders uit beide groepen gaven aan in de veronderstelling te zijn dat verbetering van de amblyopie tevens de refractie zou oplossen. Zij waren zich er niet van bewust dat het dragen van de bril nog steeds noodzakelijk was, ook na afronding van de amblyopiebehandeling. Dit bracht een cruciaal gebrek aan informatie aan het licht. Indien ouders een keuze kregen voor het type behandeling, gaven zij de voorkeur aan een goed geïnformeerde, gezamenlijke beslissing na het bespreken van de volgende aspecten: 1) effect en efficiëntie van de behandeling; organisatorische aspecten van de behandeling; en 3) de karaktereigenschappen van hun kind.

Hoofdstuk 8 tenslotte bespreekt de belangrijkste bevindingen van dit proefschrift met de bijbehorende interpretatie. Tevens gaat dit hoofdstuk in op de klinische implicaties en toekomstperspectieven.

List of publications



List of publications

Kadhum A, Simonsz-Tóth B, van Rosmalen J, Pijnenburg SJM, Janszen BM, Simonsz HJ, Loudon SE. Long-term follow-up of an amblyopia treatment study: change in visual acuity 15 years after occlusion therapy. *Acta Ophthalmologica. 2021 Feb;99(1):e36-e42*

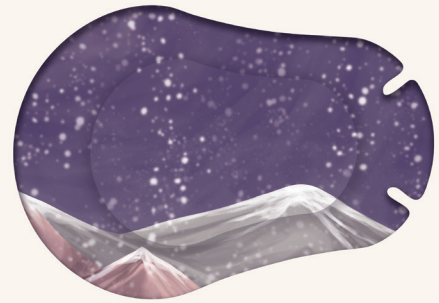
Kadhum A, Tan ETC, Wenner Y, Joosse MV, Loudon SE. Effectiveness of optical treatment in amblyopia and validation of measuring spectacle compliance with the ODM. Spectacles resolve a third of amblyopia cases. *Ophthalmic and Physiological Optics. 2024 Jul;44(5):945-953.*

Kadhum A, Tan ETC, Fronius M, Baart SJ, Levi DM, Joosse MV, Simonsz HJ, Loudon SE. Supervised dichoptic gaming versus monitored occlusion therapy for childhood amblyopia: effectiveness and efficiency. *Acta Ophthalmologica. 2024 Feb;102(1):38-48*

Kadhum A, Tan ETC, Levi DM, Colpa L, Fronius M, Simonsz HJ, Loudon SE. Barriers to successful dichoptic treatment for amblyopia in young children. *Graefe's Archive for Clinical and Experimental Ophthalmology. 2021 Oct;259(10):3149-3157*

Tan ETC, **Kadhum A**, Telleman MA, Treur A, Bruijning J, Loudon SE. How do parents experience patching or dichoptic action video gaming as amblyopia treatment? A qualitative study exploring treatment preferences and information needs to facilitate decision-making. *Ophthalmic and Physiological Optics. 2023 Jul;43(4):649-659*

PhD Portfolio



PhD Portfolio

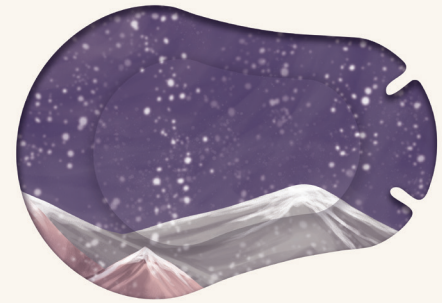
Name PhD student:	Aveen Kadhum
Department:	Ophthalmology, Erasmus MC, Rotterdam, The Netherlands
PhD period:	September 2016 - 2024
Promotor:	Prof. dr. J.R. Vingerling
Copromotor:	Dr. S.E. Loudon

	Year	ECTS
Courses		
Basic Introduction Course SPSS	2016	**1.0**
CPO course (Patient Oriented Research: design, conduct and analysis)	2017	**0.3**
Systematic Literature Retrieval in PubMed – 1 Endnote	2017	**0.3**
Systematic Literature Retrieval in PubMed – 2	2017	**0.3**
NIHES: Principles of research in medicine & epidemiology	2017	**0.7**
NIHES: Introduction to data-analysis	2017	**0.7**
NIHES: Regression analysis	2017	**1.4**
Basiscursus Regelgeving en Organisatie (BROK)	2017	**1.5**
Research Integrity	2018	**2.0**
Biomedical English Writing Course	2018	**2.0**
NIHES: Biostatistical Methods I: Basic Principles [CC02]	2018	**5.7**
(Inter)national conferences and presentations		
Orthoptie Congres (ORCA)	2017	**0.5**
Dutch Ophthalmology PhD Students congress, Nijmegen	2017	**0.5**
Nederlands Oogheelkundig Gezelschap (NOG), *presentation*.	2017	**0.5**
Association for Research in Vision and Ophthalmology (ARVO), Baltimore. *Poster presentation*.	2017	**0.5**
Child Vision Research Society (CVRS), Coleraine. *Poster presentation*.	2017	**0.5**

	Year	ECTS
Amblyopie symposium orthoptisten (HU). *Oral presentation.*	2017	**0.5**
Nederlands Oogheelkundig Gezelschap (NOG). *Oral presentation.*	2018	**0.5**
Association for Research in Vision and Ophthalmology (ARVO), Honolulu, Hawaii. *Poster presentation.*	2018	**1.0**
Rotterdam Amblyopia Meeting (RAM). *Organisation and oral presentation.*	2018	**2.0**
Geneve Amblyopia Meeting, Genève. *Oral presentation.*	2019	**0.5**
Association for Research in Vision and Ophthalmology (ARVO), Vancouver. *Poster presentation.*	2019	**0.5**
Nederlands Oogheelkundig Gezelschap (NOG). *Oral presentation.*	2019	**0.5**
Association for Research in Vision and Ophthalmology (ARVO). *Poster presentation (online).*	2020	**0.5**
Nederlands Oogheelkundig Gezelschap (NOG). *Oral presentation.*	2020	**0.5**
Nederlandse Vereniging voor Orthoptie (NVVO). *Oral presentation (online).*	2021	**0.5**
Nederlands Oogheelkundig Gezelschap (NOG). *Oral presentation.*	2021	**0.5**
Association for Research in Vision and Ophthalmology (ARVO). *Oral presentation (online).*	2021	**0.5**
Nederlands Oogheelkundig Gezelschap (NOG) *Oral presentation.*	2022	**0.5**
Association for Research in Vision and Ophthalmology (ARVO). *Poster presentation.*	2022	**0.5**
Nederlands Oogheelkundig Gezelschap (NOG), oral *presentation.*	2023	**0.5**
Nederlands Oogheelkundig Gezelschap (NOG). *Oral presentation.*	2024	**0.5**

	Year	ECTS
Teaching		
Supervision of Orthoptics students (Minor): Annabel Schermer and Esmeralda Visser	2017	**3.0**
Supervision of Orthoptics students (Minor): Annefleur Boers and Veron Verhorst	2018	**3.0**
Supervision of Orthoptics students (Minor): Merve Kocak and Marieke Mutsaers	2019	**3.0**
Supervision of Orthoptics students (Minor): Nihad Hammach and Marya Chakari	2019-2020	**3.0**
Supervision of Orthoptics students (Minor): Lyon van Dongen and Lonneke Kamperman	2020-2021	**3.0**
Prizes		
ARVO Travel Grant	2021	

About the author



About the author

Aveen Kadhum was born in Baghdad, Iraq, on March 5, 1992. She immigrated with her parents to the Netherlands at the age of 1.5 years. In 2010 she completed her secondary education (Gymnasium) at Penta College Blaise Pascal in Spijkenisse. She studied Medicine at the Vrije Universiteit Brussel in Belgium for 1 year. After completing this first year, she started her medical education at the Erasmus University in Rotterdam in 2011. As part of her medical training, she conducted a research project in 2016 on the long-term outcomes of occlusion therapy in adolescents, who had been treated for amblyopia during childhood. After finishing this project she started with her PhD training at the Ophthalmology department under supervision of dr. Loudon, comparing dichoptic action video game therapy with standard occlusion therapy in children with amblyopia. In 2020 she resumed her medical education and finished the last two years of clinical rotations. She graduated as a medical doctor in 2022. In 2023 she started with her Ophthalmology residency at Erasmus MC, Rotterdam. She is currently a 3rd year resident.