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Effect of 7 and 20 Hz Flicker Glasses on Fixation and Saccadic Oculography, Accommodation, and Stereoacuity

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Abstract

Purpose: Recent studies have investigated Eyetronix Flicker Glasses (EFG) in treating refractive amblyopia. EFG provides rapid alternating occlusion of the two eyes at a particular rate. They have been shown to cause a significant improvement in visual acuity, contrast sensitivity, and stereoacuity in amblyopes. Amblyopia is a syndrome marked by a reduction in visual acuity as well as other monocular functions like fixations, saccadic eye movements, and accommodative lag. The purpose of this study was to investigate the intra-treatment effect of 7 and 20 Hz flicker on fixations, saccades, and the accommodative lag during reading, and on stereoacuity.

Methods: A Latin Square was used to balance the treatment order within subjects and order sets were randomized across subjects. 51 normal subjects (ages 22-34) were enrolled in the study. Fixations and saccades during reading were tested with infrared oculography (ReadAlyzer, Compevo AB, Stockholm, Sweden). The Grand Seiko WAM-5500 open-field autorefractor was used to measure accommodative lag. Distance Lea Stereo (M&S chart) was used to determine the stereoacuity. Each test was performed three times (no flicker glasses, 7 Hz flicker glasses, and 20 Hz flicker glasses). Outcome measures were: (1) number of fixations, (2) number of regressions, (3) fixation duration, (4) reading rate, (5) accommodative response, and (6) stereoacuity.

Results: Among the experimental conditions (no EFG, 7 Hz EFG, and 20 Hz EFG), the number of fixations, regressions, fixation duration, and accommodative lag did not differ significantly ($p = 0.98, 0.33, 0.12$, and 0.084, respectively). Reading rate ($p < 0.05$) and stereoacuity ($p < 0.001$) showed a significant difference, with 7 and 20 Hz negatively impacting reading rate and stereopsis. Reading rate dropped 18 words per minute with 7 Hz (7.4%), and 13 words per minute with 20 Hz (5.4%) compared with no flicker glasses. Stereoacuity was worse by 73 arc seconds with 7 Hz, and 17 arc seconds with 20 Hz.

Conclusion: While using EFG, most visual skills explored by this study are unaffected. However, while worn, the goggles at 7 Hz and 20 Hz reduced reading rate as well as stereopsis.

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EFFECT OF 7 AND 20 HZ FLICKER GLASSES ON FIXATION AND SACCADIC OCULOGRAPHY, ACCOMMODATION, AND STEREOACUITY

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Conclusion: While using EFG, most visual skills explored by this study are unaffected. However, while worn, the goggles at 7 Hz and 20 Hz reduced reading rate as well as stereopsis.

Keywords: flicker glasses, reading, eye movements/motility, stereoacuity, accommodation, amblyopia

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INTRODUCTION

Flicker Perception

Understanding the physiology of the human retina is important to understand the flicker perception. The existence of two types of retinal photoreceptors, rods and cones, is responsible for the duplicity theory developed by J. Von Kries (1929). Night vision or vision at low ambient light referred to as scotopic vision. Daylight vision is mediated by cone cells at higher light levels, vision is called photopic vision. Between scotopic and photopic, there is a range called mesopic vision where some rod and cone cells are simultaneously active. The duplicity theory states that rod cells are only effective at extremely low light levels. The duplicity theory explains the ability of the human visual system to operate over a remarkably broad range of light levels.[1]

One of the main difference between rod and cone system is the speed of processing. The scotopic, or rod, system is slow compared to photopic, or cones. Cones tend to be 10 times faster than rods due to temporal summation, which is the eye's ability to sum the effects of photons, or quanta, over a period of time. According to Bloch's law, with in the critical period, the nunber of quanta that are needed to reach the threshold is constant. The critical period for rods and cones are 100 ms and 10 ms, respectively. In 1929, Ives determined the critical flicker frequency (CFF), which is defined as the highest rate of the flicker that can be perceived as such. He found that CFF remained low under scotopic and low mesopic vision. As soon as the light intensity was enough to activate cones, the CFF started to increase. CFF was identified for scotopic and photoic systems by the Ferry-Porter law. It states that CFF of the human visual system under extremely dim light conditions (scotopic vision) is about 20 Hz where is about 70 Hz for high light conditions (photopic vision) (Figure 1).

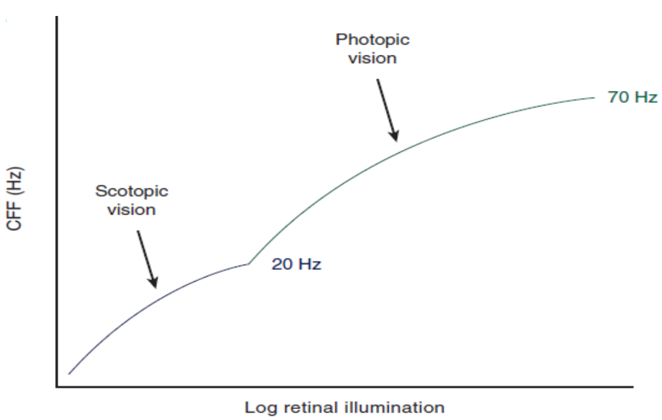


Figure 1: Graph represents Ferry-Porter law. It shows the increase of the CFF with the log of the retinal illumination. The CFF is about 20 Hz under scotopic conditions; it is 70 Hz under photopic conditions.[1]

As flicker perception varies under different light condtions, there is variation in CFF based on retinal location. According to Granit-Harper Law, CFF increases linearly with the log of retinal area stimulated.[1] Extrafoveal and peripheral retina is better in detecting flicker and motion than foveal cones. Retinal parasol ganglion cells in the retina ,which form the magnocellular system, have higher sensitivity to high temporal frequencies. Midget ganglion cells, forming the parvocellular system, are most concentrated in the fovea are able to detect low level of flicker, around 50 Hz, and motion.[1] The ability of parvocelluar system to detect slight flicker and motion is thought to be the mechanism behind the Eyetronix Flicker glasses (EFG) that are used in the current study to treat amblyopia.

Eyetronix Flicker Glasses (EFG)

Eyetronix Flicker Glasses (EFG) are spectacles with liquid crystal flicker lenses. This is a new technology that may be an alternative to treating amblyopia. These glasses provide rapid alternating occlusion of the two eyes at a particular rate. According the Eyetronix website, The company claims that the rapid alternation breaks suppression, “wakes up” the sensory pathway, and encourages the brain to accept visual sensory signals from both eyes. Flicker glasses showed significant improvement of vision in children in previous studies, including previously unsuccessfully treated children.[2]

Amblyopia and EFG

In Moore study, EFG was used on 20 amblyopic children with mild to moderate anisometropic amblyopia age from 6 to 17 years. The children were instructed to wear the EFG, programmed to 7 Hz flicker rate, daily for 1 to 2 hours during near vision activities. The participants were monitored for 3 months, and the change in visual acuity was the primary outcome. Secondary outcome measures included changes in stereopsis and fusion. The results showed improvement in the visual acuity of one line. Additionally, all but two subjects showed an improvement in stereopsis.[3] One of the most important advantages of liquid crystal glasses in treating amblyopic patients is overcoming the child’s poor compliance that some patents face with patching.[4]

Eye Movements in Reading

During reading, the eyes do not move smoothly across the printed page. Instead, the eyes make short and rapid movements, called saccades. The purpose of these movements is to bring the information into the center of fovea. Not including latency time, reading saccades take 20- 50 msec to complete. During saccades, 90% of vision is suppressed, so little information goes to the primary visual cortex (V1).[5] The amplitude of saccades varies. Some saccades only move the eyes a single character, whereas others are as large as 15–20 characters.[5]

Between saccades, the eyes stay stationary for short periods, called fixations. Fixations are required to identify and recognize the words. Only during fixations, the visual information is extracted from the printed pages. The average time required to identify the word during fixation (fixation duration) is approximately a quarter of a second (typically 200–250 msec). Similar to saccades, some fixation times may vary. Some are shorter than 100 msec and others are longer than 400 msec.[6] The fixation duration on a word is shorter if the reader has a valid preview of the word before, or if the word is easy to identify and understand.

For people with normal vision and normal oculomotor control, their eyes exhibit a series of involuntary movements even when they attempt to maintain steady fixation on a visual target. These movements involve microsaccades, tremors, and slow drifts. Microsaccades are fast small conjugate movements that occur 1-3 times per second. They tend to be less than 30 arc min in amplitude, but can be up to 1 degree or more.[7] Tremors are disconjugate high-frequency, and low oscillatory motion of the eye with 90 Hz in frequency. Tremors are generally considered to provide no functional purpose, but may represent electrical and mechanical “noise” in the system. Drift refers to the slow eye movements that occur between the microsaccades during attempted fixation. They are usually slower and smaller than microsaccades (typically < 0.5 degree per second in speed, < 10 arc min in amplitude).[8] Several studies found that microsaccades and drifts play a main role on correcting fixation position [9] and fixation disparity.[10]

Reading and Amblyopia

A reduction in visual acuity, contrast sensitivity, and stereopsis are all associated with amblyopia. In addition, fixations and saccadic eye movements are routinely found affected in amblyopic patients. Several studies have shown impaired oculomotor function and fixation stability are associated with amblyopia. As shown in previous studies, amblyopic children and adults are slower readers compared with normal controls.

In Kelly et al study, the number of forward saccades, regressions and reading rate were measured using ReadAlyzer in 29 amblyopic children, and compared to 23 strabismic children without amblyopia and 21 normal controls. The findings of the study proved that amblyopic children read significantly more slowly than the other two groups. Also, the number of forward saccades were significantly higher in amblyopic than in strabismic children without amblyopia ($P < 0.001$) and normal controls ($P < 0.001$). Comparing the strabismic children without amblyopia with the normal controls did not reveal any significant difference in reading rate and number of saccades.[11]

Individuals with amblyopia had higher speed and larger amplitude of slow drifts in the amblyopic eye compared to the non-amblyopic eye.[12] Similar to tremors, microsaccades increase in frequency and amplitude when the amblyopic eye monocularly fixates on a visual target. Chung et al investigated the amplitude and speed of the eye movements during fixation in amblyopes. They found that the amplitude of microsaccades in the amblyopic eyes was significantly greater from the nonamblyopic eyes and the control group. The microsaccadic amplitude in the amblyopic eyes was between 5-50 arc mins, compared to 2-20 arc mins in the nonamblyopic eyes.[13]

Additionally, saccadic reaction time in amblyopes is longer on average: 40 to 80 msec longer in the amblyopic eye than in the nonamblyopic eyes. Anisometropic amblyopes tend to have shorter saccadic latency compared to strabismic amblyopes.[12]

Accommodation and Amblyopia

The accommodative response is generally less than the accommodative demand during viewing near stimuli. The difference between the accommodative response and the accommodative demand called accommodative lag. The reason is thought that a minimum level of accommodative effort is used to bring the image of an object within the depth of focus of the visual system. Generally, accommodative lag increases with increasing the accommodative demand.[14] Accommodative lag is less in optically corrected myopia relative to emmetropia and hyperopia.[15] Children have been shown to demonstrate an average accommodative lag of 0.41 D during binocular viewing of near targets (25–50 cm).[16]

Several studies have demonstrated poor accommodative response in the amblyopic eye in unilateral amblyopic adults. It is believed the impaired accommodation is due to early, prolonged presence of suppression, defocus, and abnormal contrast sensitivity. Individuals with amblyopia show clinically-significant accommodative lag in the amblyopic eye during monocular viewing. Thus, individuals with unilateral amblyopia may experience defocus while patching the non-amblyopic eye, particularly when they perform a near visual activities. The accommodative lag tends to decrease after patching treatment in amblyopic patients. In a recent study, the accommodative lag in 17 amblyopic children went down from 1.82 D to 1.48 D in the amblyopic eye after an average of 5 months of patching treatment, though this was not clinically significant.[17]

Stereoacuity and Amblyopia

In addition to the purposeful error in ocular alignment called fixation disparity, our visual system creates the perception of depth based on the small horizontal differences between the images projected onto each eye. Generally, the period of stereopsis development starts at approximately three months and lasts until at least three years of age[18,] while improving very rapidly the first 10 months of that period.[19] According to a 1980 study by Birch et al, stereopsis can be measured using Forced Preferential Looking and a pair of line displays. It increases from around 5000 arc seconds to less than 60 arc seconds in a few weeks.[20]

Persons with amblyopia tend to have underdeveloped stereoscopic depth perception for several reasons, all rooted in the significantly different percepts between the two eyes. Strabismus severely impacts stereoscopic development. It is logical, then, that more strabismic amblyopes have severely reduced stereoscopic perception compared to refractive amblyopes. More than half of refractive amblyopes passed the Randot circles test, compared to 10% of strabismic amblyopes.[21]Holopigian et al found that anisometropic amblyopes have better stereopsis at low, but not high, spatial frequencies.[22]

A 1989 study investigated the effect of several temporal frequencies (no flicker, 1, 5, 10, and 20 Hz), and spatial frequencies (0.6, 1, 2, 4, and 8 cycles per degree) on stereo-acuity. Stereoacuity was better when tested with high spatial-frequency and low temporal frequency.[23]

Adaptation to flicker

Flicker adaptation is the time required for flicker to disappear after prolonged exposure to flickering lights. Since EFG has been used in treating amblyopia in several studies, it is important to know the effect of various flicker rates on CFF and adaptation. Most of the studies investigated the adaptation to flicker in the periphery. A 1971 study showed the sensitivity of peripheral retina to flicker decreases progressively every 500 msec with a 20 Hz flicker target presented in the peripheral field, sometimes dropping to more than ten times their initial values.[24] Schieting and Spillman showed that a small flickering target presented in the peripheral retina rapidly appears to lose contrast and stop flickering within 35 seconds, before fading completely.[25] The time required for flicker adaptation tends to decrease with decreasing stimulus diameter, increasing retinal eccentricity, and increasing flicker frequency. This observation may be related to Troxler Fading Phenomenon which is the disappearance of low temporal frequency stimuli.[1]

EFG is a new alternative treatment method for amblyopia. In the literature, effects while flicker glasses are worn; the direct effects during the use of EFGs on visual skills has not been studied. The main purpose of our study is to investigate the impact of two different flicker rates (7 and 20 Hz) on fixations, saccades, and accommodation response during reading and stereoacuity.

Methods

Subjects

The research protocol was approved by the Institutional Review Board of Pacific University. Students of Pacific University were recruited through an advertisement email for this study. A total of fifty-one of non-amblyopic individuals (12 male and 39 female, mean age 25.08 years) and three amblyopic subjects (1 male and 2 female, mean age 24 years) were enrolled with no preference given to gender or ethnicity. Participants had to be over the age of 18. Pregnant women were excluded. Each subject was contacted via email and asked to sign up for a two-hour visit. Each subject had to sign a consent form prior starting taking measurements. All subjects had a best-corrected visual acuity (BCVA) 20/30 or better at distance, normal range of eye movement and no significant ocular pathology. Three individuals with amblyopia had a BCVA between 20/30 and 20/200 in their amblyopic eyes, and at least better than 20/30 for the non-amblyopic eye. All the amblyopic subjects were anisometropic amplyopes.

Procedure

In this study, we chose to investigate the effect while flicker glasses are worn on some visual skills. In the Previous EFG studies, 7 Hz was the default flicker rate based on the findings of Schor et al study. In Schor et al study, visual acuity of three amblyopic subjects was measured under binocular viewing conditions by adjusting the temporal relationship between inputs of the normal and amblyopic eye. Optimal visual acuity was obtained with flicker rate around 7 Hz.[26] In addition to continuing the use of 7 Hz in this study, twenty Hz was chosen in this study to get away from the brightness enhancement phenomenon which is around 10 Hz. With EFG, 20 Hz is the maximum flicker rate that can be adjusted to. Another reason to select 20 Hz is to approach the frame rate for motion picture in movies, which is 24 frame per second.

All examinations were made by the same examiner using the same procedure. A Latin Square was used to balance the treatment order within subjects and order sets were randomized across subjects. Four pairs of Eyetronix flicker glasses adjusted at flicker rate of 7 Hz and 20 Hz were used for this study. ReadAlyzer (Compevo AB, Stockholm, Sweden) was used to assess fixations and saccadic eye movements during reading. ReadAlyzer uses infrared tracking system to follow eye movements. Subjects were asked to wear the ReadAlyzer goggles over their habitual correction (spectacle or contact lenses). The flicker glasses were attached over the ReadAlyzer goggles. Each subject sat at a comfortable, reading distance (50 cm), and the pupillary distance was adjusted for near. The tests were repeated three times with three different conditions (no flicker glasses, flicker glasses at 7 Hz, and flicker glasses at 20 Hz) for each subject.

Eyetronix Flicker Glasses [54]

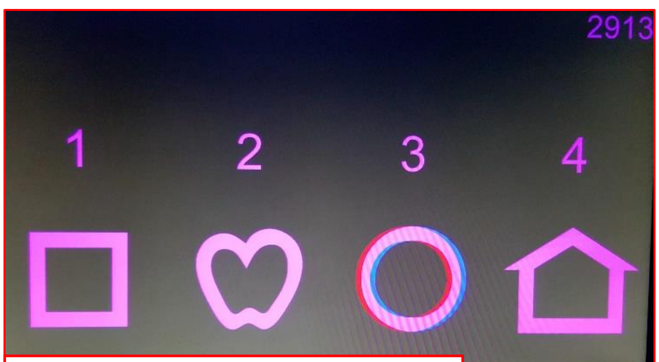
The subjects were instructed to read silently three different two-page long stories from the Readalyzer booklet. The booklet contains 10 levels of text difficulty, and each level has three different stories. Each passage averaged 26 lines and 239 words. After reading each story, the subjects were asked to answer 20 yes-or-no comprehension questions on the computer using a keyboard. For this experiment, we chose to use the level seven passages since it would not be a language challenge for most participates. Also, it will limit the language processing variable and reveal differences in eye movements. Recordings were included from the statistical analyses if comprehension was ≥70% and tracking reliability was ≥70%. The outcome measures obtained from the recordings were number of fixation (per 100 words), number of regressive saccades (per 100 words), reading rate (words per minute), fixation duration (milliseconds), and grade level equivalent.

ReadAlyzer and Reading materials [55]

Accommodative response was measured using an open field auto-refractor (Grand Seiko WAM-5500). Online streaming videos with subtitles were used as a target, which was presented on a screen monitor in a small window (10 cm wide and 7 cm high). The screen was placed at 50 cm in front of subjects' eyes. The accommodation was measured for three minutes with each condition (no flicker glasses, flicker glasses at 7 Hz, and flicker glasses at 20 Hz) under binocular viewing conditions. Subjects were instructed to read the subtitles silently. Spherical equivalent was determined with the same instrument over the subject's habitual correction and was used to calculate the actual accommodative response. For amblyopic subjects, the accommodation of each eye was measured separately under binocular viewing conditions.

Grand Seiko open field autorefractor [56]

We chose distance Lea Stereo M&S chart to quantify stereoacuity. Lea Stereo test uses anaglyphic glasses (red/green filters) and measures stereoacuity with a range from 285 arc seconds to 18 arc seconds at far. The test was performed under the three different conditions (no flicker glasses, flicker glasses at 7 Hz, and flicker glasses at 20 Hz) with the subjects' habitual correction. Subjects who had stereoacuity worse than 285 arc seconds were recorded as 300 arc seconds.



Lea Stereo test M&S digital chart

Data Analysis

SPSS software (Version 22, IBM Inc.) was used for data analysis. Repeated measures ANOVA was chosen to compute the statistical significance of differences among conditions (no flicker glasses, flicker glasses at 7 Hz, and flicker glasses at 20 Hz) in number of fixation, number of regressions, reading rate, fixation duration, and accommodative response. Fixation Duration was skewed. A log-log transformation was used to bring the variable into conformance with ANOVA assumptions. Post hoc comparisons were made using Fisher's Least Significant Difference Tests. The effect of device was tested with a Friedman non-parametric tests and individual paired comparisons were made using the Wilcoxon matched pairs test.

Results

Each of the 54 subjects performed all three tests (ReadAlyzer, Grad Seiko, and Lea Stereo). A total of 42 subjects met the comprehension and tracking reliability criteria (mean age with standard deviation [SD], 24.9 ± 2.46 years; age range, 22-34 years).

Repeated measures ANOVA was performed to determine the difference among the three experimental conditions (no EFG, EFG at 7 Hz, and EFG at 20 Hz). A repeated measure within-subject analysis showed that number of fixations per 100 words, regressions per 100 words, and fixation duration (msec) did not differ significantly across conditions (p value = 0.98, 0.33, and 0.12, respectively, Table 1).

The data of non-amblyopic subjects revealed a nonsignificant difference in accommodative lag between the three conditions (p value = 0.084). Similarly, accommodative lag with and without EFG in the three amblyopic subjects was not statistically significant (p value = 0.71). Even though EFG had an apparent small negative impact on fixation duration regardless the flicker rate, fixation duration did not differ significantly across the three conditions; Figure 1.

Reading rate (words per minute) (p value < 0.05) and stereoacuity (p value < 0.001) showed a significant difference, with 7 and 20 Hz negatively impacting reading rate and stereopsis. Reading rate dropped 18 words per minute with 7 Hz and 13 words per minute with 20 Hz a 7.4% and 5.4% reduction, respectively compared with no flicker glasses. Stereoacuity was worse by 73 arc seconds with 7 Hz and 17 arc seconds with 20 Hz. EFG has an impact on fixation duration regardless the flicker rate; Figure 4,5. Five ESL subjects were included in this study, ESL subjects were substantially poorer performers in reading rate compared to native speakers; Figure 5.

Information provided in Table 2 shows the effect sizes of the all variables. Reading rate and stereoacuity had a large effect size across the three conditions. Fixation duration had a medium effect size between control and 7 Hz of 0.44.

The ReadAlyzer and stereoacuity data of the three amblyopic subjects were excluded. Only two subjects out of three met the inclusion criteria of the ReadAlyzer, and two of them were stereoblind. The number of amblyopic subjects who met criteria of the study was not sufficient to run statistical tests.

ANOVA test shows that number of fixations, regressions and fixation duration are not affected by device. However, EFG does effect reading rate by itself in an ANOVA. Based on the regression equation (Table 3), number of fixations, regressions and fixation duration are significant with reading rate which means they all contribute independent variance to reading rate. We have found that the individual eye movements are not affected by EFG, but it also showed eye movements do affect reading rate.

As the data of stereoacuity were not normally distributed. The most appropriate test is Wilcoxon singed-ranked test. The Wilcoxon test, which evaluated difference between medians of stereoacuity across the three conditions, was significant, $p = <0.01$ for all conditions. The results indicate significant differential difference on stereoacuity caused by EFG, medians and quartiles are shown in Table 4.

Tables

Table 1: mean ± standard deviation of number of fixations, regression, fixation duration, reading rate, accommodative response, and stereoacuity among the three conditions (no EFG, EFG at 7 Hz, and EFG at 20 Hz**)**

Variable	Control Mean ± SD	7 Hz Mean ± SD	20Hz Mean ± SD	p value
Fixations per 100 words	86.161 ± 32.03	86.675 ± 30.95	86.498 ± 31.63	0.980
Regressions per 100 words	12.61 ± 8.7	12.21 ±9.25	13.58 ± 11.17	0.328
Fixation duration (msec)	317.156 ± 62.11	333.19 ± 42.9	327.92 ± 30.83	0.115
Reading rate (WPM)	245.71 ± 77.67	227.47 ± 67.58	232.51 ± 71.58	0.003
Accommodative response (diopters)	1.373 ± 0.71	1.318 ± 0.67	1.305 ± 0.67	0.084
Stereoacuity (arc seconds)	87.68 ± 78.1	162.1 ± 100.26	105.04 ± 79.1	<0.001
Log(log(fixation duration)	312.3	329.4	325.0	0.048

Table 2: effect size of number of fixations, regression, fixation duration, reading rate, accommodative response, and stereoacuity

Variable	**Control to 7Hz**	**Control to 20Hz**	**7 Hz to 20 Hz**
Fixations per 100 words	0.043	0.028	0.015
Regressions per 100 words	0.090	0.22	0.31
Fixation duration	0.44	0.30	0.15
Reading rate	0.73	0.53	0.20
Accommodative response	0.34	0.42	0.08
Stereoacuity	1.62	0.38	1.24

Table 3: regression model of reading rate

Parameter	Estimate	Std. Error	t value	p value
Intercept	1137.59	100.55	11.31	0.00
20 Hz EFG	-7.89	3.35	-2.36	0.02
7 Hz EFG	-8.56	3.37	-2.54	0.01
Number of fixations per 100 words	-2.50	0.18	-13.78	0.00
Number of regressions per 100 words	1.63	0.48	3.38	0.00
Log(log(fixation duration))	-1753.86	237.05	-7.40	0.00

Table 4: Wilcoxon test, medians and quartiles of stereoacuity

	Control vs. 7 Hz	**Control vs. 20 Hz**	**7 Hz vs 20 Hz**
Z value	-5.72	-3.21	-4.71
p value	<0.001	0.001	<0.001
	Control	7 Hz	20 Hz
Median	53	107	89
Percentiles			
25th	36	71	53
50th	53	107	89
75th	111.50	285	125

Figures

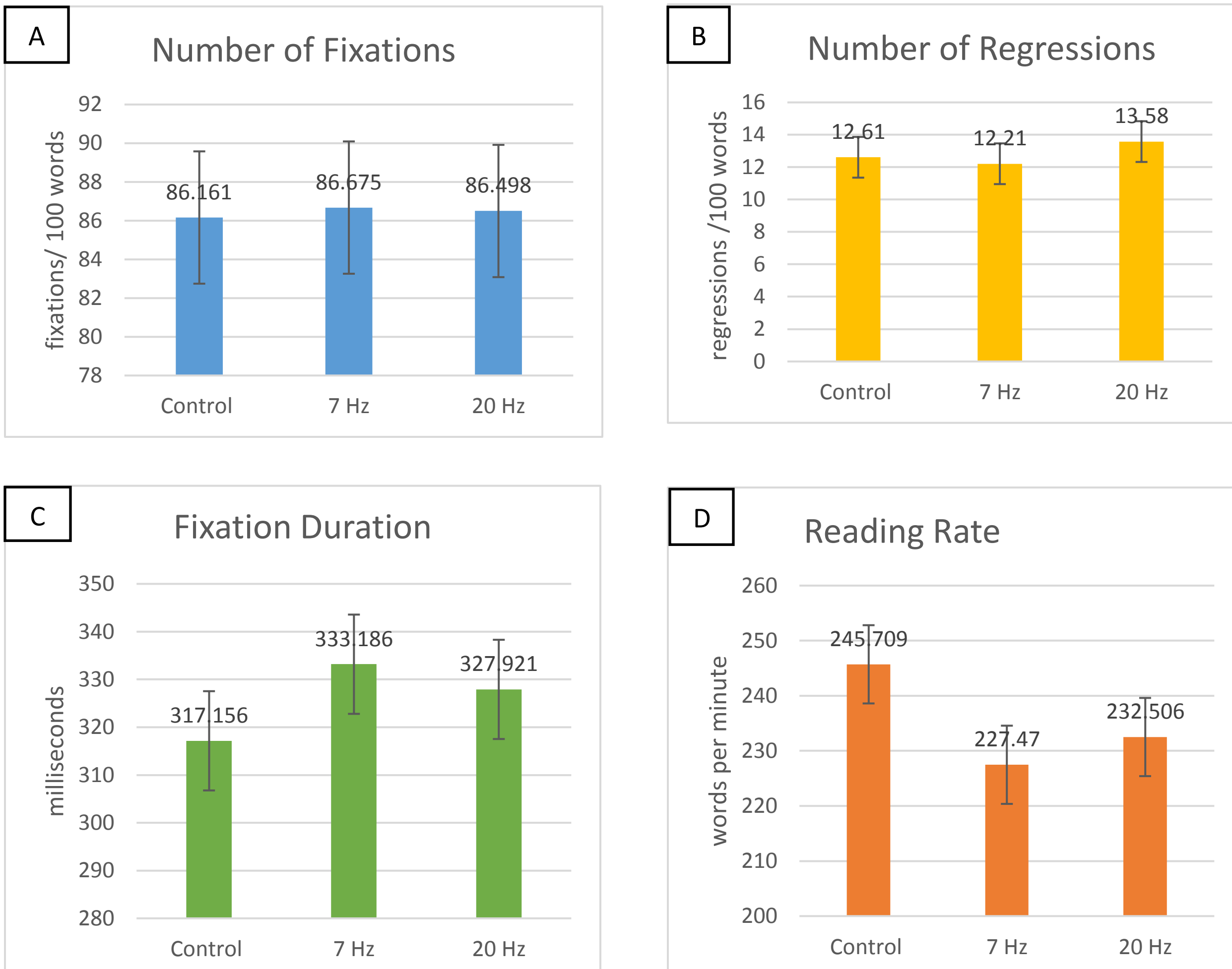


Figure 2: bar graphs depicting condition means and standard error for (A) number of fixations, (B) number of regressions, fixation durations (C), and reading rate (D) for 51 non-amblyopic subjects.

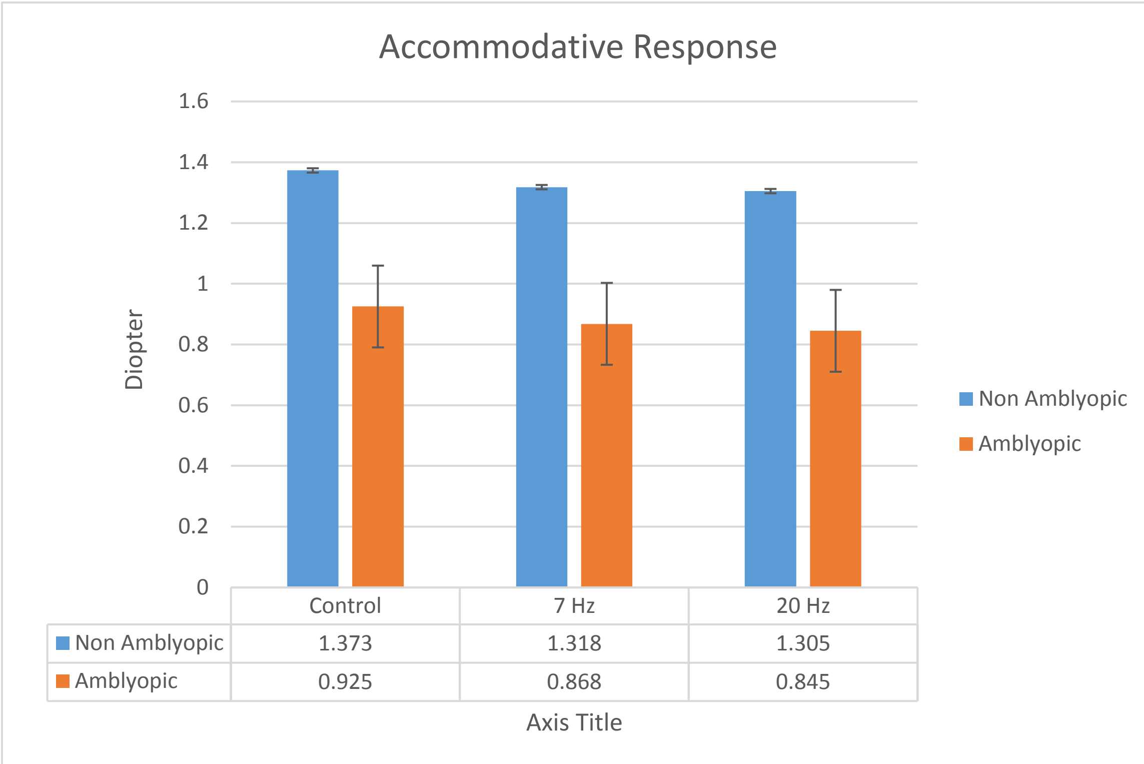


Figure 3: bar graph shows the means and standard error of accommodative response of 51 non-amblyopic subjects versus three amblyopic subjects

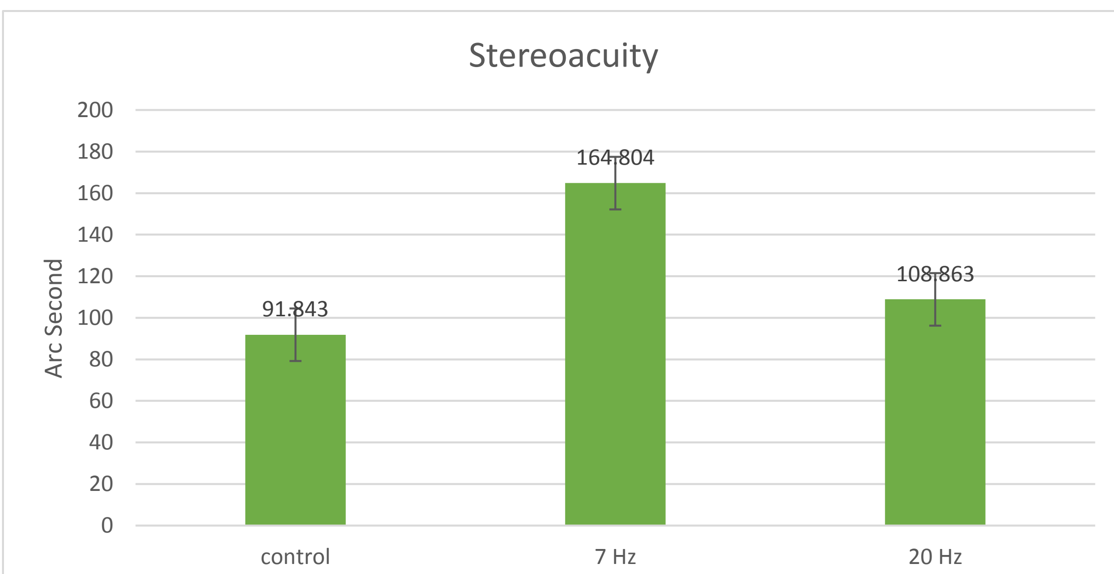


Figure 4: a bar graph illustrates the means and standard error for stereoacuity of 51 non-amblyopic subjects

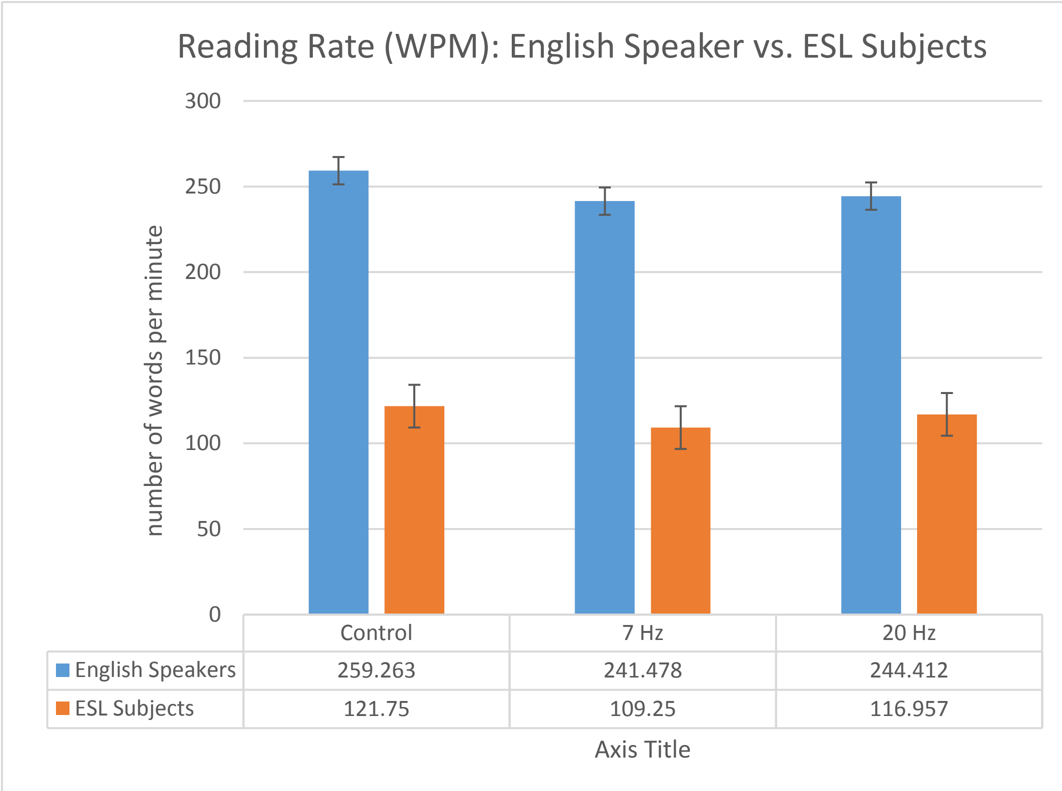


Figure 5: bar graph shows the means and standard error for reading rate of native English speaker subjects versus three English as second language subjects

Discussion

In the current study, we examined the effect on several measures of visual control during reading with two different flicker rates. Previous research studies using EFG in treating amblyopia showed positive results in improving visual acuity, contrast sensitivity, and stereopsis. However, the effect of wearing EFG on reading rate has not been investigated. Amblyopes are slow readers compared to normal controls under binocular conditions [11]. It has been suggested that near activities such as reading may be beneficial and provide better results in amblyopic patients undergoing treatment. When EFG are being worn, our results showed that normal individuals read slower with 7 and 20 Hz compared to no flicker. It is important to note that our finding of a slower reading rate with 7 and 20 Hz flicker glasses is unlikely to be due to comprehension difficulties. Only data from subjects who scored 70% or higher on the comprehension questions were included in the analyses. We were not able to recruit a sufficient number of amblyopes for comparison, so the effect of EFG on reading rate while the EFG is being worn remains to be investigated among amblyopic individuals. Should the same negative intra-treatment effect of EFG be present in amblyopic subjects, this would make amblyopes slower readers than they already are as long as EFGs are in use.

Reading rate is usually calculated based on saccadic latency, speed, and duration. The average time required to identify and recognize each word during reading is about 240 msec. With EFG at 7 Hz, one cycle of alternating occlusion of the two eyes takes approximately 143 msec, which allows each eye to view the text for 71.5 msec without disturbance. Whereas, for 20 Hz flicker, there is only 25 msec of time for one eye to see the text between flicker. One speculation could be that since fixation is being interrupted multiple times in one fixation, the time needed to identify the word would increase. However, our data in this study did not show a significant difference in fixation duration (p value = 0.115, Table 1).

Note that EFG did not influence the number of fixations, regressions, and fixation duration which indicates these factors are not responsible for the reduction of reading rate. To clarify interpretation, results in Table 3 show that the number of fixations and fixation duration independently contribute to reading speed, and the number of regressions also contribute, but to a lesser degree. We speculate fixation duration is the biggest factor of the three. ANOVA test of log-log transformation of fixation duration, that was used to control the skewness, gave a p value of 0.048. Other factors such as saccadic amplitude, latency, and speed might contribute to a slower reading rate with EFG use; a further carefully controlled study is needed to investigate the effect of EFG on these factors.

Five subjects out of 49 were not native English speakers. Figure 5 shows the difference in reading rate among the three experimental conditions of native English-speaking subjects and non-native speakers. Reading rate seems to be significantly lower in non-native speakers compared with native English-speaking subjects. However, it was significantly different with and without EFG as mentioned earlier.

Our finding was that the accommodative response exhibited more accommodative lag in the amblyopic eyes among the three amblyopic subjects compared to the 51 nonamblyopic subjects. Increasing accommodative lag is routinely found in amblyopic patients. Among the three conditions in this study, the average difference in the mean of accommodation lag between amblyopes and non-amblyopes was 0.45 diopters. It is important to point out that there were not enough amblyopic subjects in this study to analyze variability of the response, however.

Friedman non-parametric and Wilcoxon matched pairs tests showed that EFG caused a significant difference. This was statistically and clinically significant ($p < 0.001$). Stereoacuity results in this study were reduced in both experimental conditions, especially while wearing the seven Hz flicker glasses. Stereoacuity had a large effect size between control and 7 Hz (>0.80).

Exploring potential reasons for 7Hz reducing stereopsis as measured in this study, phenomena relating to 7Hz should be considered. According to Brücke–Bartley effect, the flickering light at 10 Hz appears brighter than a steady light of the same luminance. Also, any stimulus with a duration of 50 to 100 msec is perceived as brighter than stimulus with a temporal frequency less or greater than that range [1]. Seven and 20 Hz EFG have flash durations of 71.5 msec and 25 msec, respectively. Seven Hz EFG tends to be closer to the peak of maximum enhancement of brightness than 20 Hz. Thus, strobe effect is more noticeable. See figure 5. Our results in figure 4 clearly illustrates that 7 Hz has a greater impact on stereopsis.

As mentioned earlier that 20 Hz was chosen because it was the maximum frequency available with the EFG. It also happens to be close to the frame rate for motion pictures watched in theaters, and additionally, avoids the brightness enhancement peak at which flicker is most visible. The difference between control and 20 Hz in stereoacuity is about 17 arc seconds. Based on the results in this study, we can extrapolate that 24 Hz flicker glasses should yield a stereoacuity similar to what we found in the control condition. Additionally, note that mesopic (low-light) conditions are predicted to have a critical flicker fusion (CFF) frequency between 20 Hz (the scotopic CFF) and 70 Hz (the photopic CFF). This might also be contributory for the worse stereoacuity with 7 Hz flicker compared to 20 Hz flicker.

Another possible explanation of why 7 Hz had worse stereoacuity than 20 Hz EFG may relate perceptual task of stereopsis. Stereoscopic perception comes from cortical comparisons of each eye's image. When differences in monocular image quality exist (either from the input or perception), stereoptic perception is predictably reduced. Logically, this could also occur due to temporal differences. With constant occlusion of one eye, no stereoscopic perception exists; with no occlusion, maximal stereoscopic perception is possible for the conditions at hand. EFG provides alternating imagery, preventing simultaneous cortical comparison of each eye's image. With slow alternating occlusion, the penalty to simultaneous image comparison is greater; with faster alternating occlusion, the penalty less so. The results of this study cleanly show this trend with statistically different stereopsis in each condition, accordingly.

We chose distance Lea stereo test in this study to measure stereopsis. With other stereo test such as Randot 3, the three-dimensional effect tends to disappear when the flicker glasses have the polarized glasses behind them. It may be possible placing polarized filters in front of the EFG may resolve the cancellation problem. Because the Lea stereo test uses anaglyphic filters which make it possible to appreciate the 3D effect with the filters behind the flicker glasses, this was an accessible choice for this study.

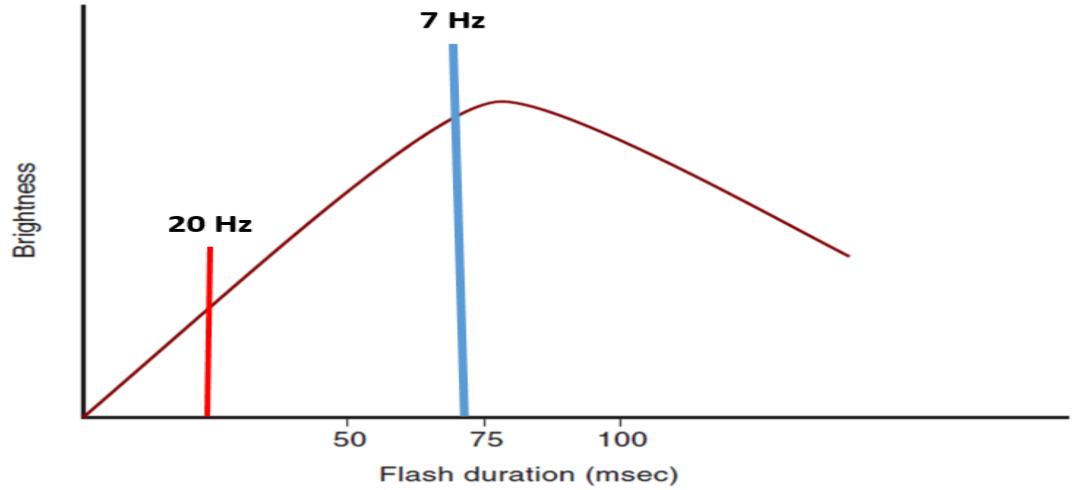


Figure 6: a graph shows the Broca–Sulzer effect. The stimuli with 50 – 100 msec flash duration tend to appear brighter.

Although there are limitations to this study due to small sample size of amblyopic subjects, the present study showed a significant effect of 7 and 20 Hz EFG on reading rate and stereoacuity among non-amblyopic subjects. EFG is a new approach that uses temporally-separated signals creating by alternating on-off flicker on treating amblyopia. Carefully controlled clinical studies are necessary to further evaluate the effect of EFG on amblyopic patients. It is important to mention some visual difference among the three conditions (no EFG, EFG at 7 Hz, and EFG at 20 Hz) have not been analyzed in this study such as illumination, glare from all refractive surfaces, pupil size, and the average illuminance of the retina with control, 7 Hz and 20 Hz conditions. These analyses may offer insight into the variables that are more significant during and after treatment with EFG. Future studies with control of these variables are recommended.

Conclusion

With this study we proved that while wearing Eyetronix Flicker Glasses (EFG), most of skills during reading, such as number of fixations, regressions, fixation duration, and accommodation were not affected. However, seven Hz and 20 Hz settings reduced reading rate in visually-normal, young adults by 7.4% and 5.4% respectively. When using EFG for therapeutic purposes, the clinician should be aware of the reduced stereopsis and reduced reading rates while wearing EFG. In turn, their use should be discouraged during tasks where these reductions are not desirable, such as time-limited reading tasks.

Amblyopia is also associated with impairment of contrast sensitivity and pursuit eye movements, as well as other visual skills. Further studies are needed to investigate the impact of EFG on contrast sensitivity and pursuit eye movements.

References

1. Schwartz S. *Visual perception: A clinical orientation: A clinical orientation.* McGraw Hill Professional; 2009.

2. Advancing binocular approaches using flicker. http://eyetronix.com/July 11, 2015.

3. Moore BD, Vera-Diaz FA, Srinivasan G, et al. Improved compliance with a novel EFG therapy for the treatment of amblyopia. *Invest Ophthalmol Vis Sci*. 2014;55(13):802-802.

4. BenEzra O, Herzog R, Cohen E, Karshai I, BenEzra D. Liquid crystal glasses: Feasibility and safety of a new modality for treating amblyopia. *Arch Ophthalmol*. 2007;125(4):580-581.

5. Ishida T, Ikeda M. Temporal properties of information extraction in reading studied by a text-mask replacement technique. *JOSA A*. 1989;6(10):1624-1632.

6. Rayner K. Eye movements in reading and information processing: 20 years of research. *Psychol Bull*. 1998;124(3):372.

7. Cherici C, Kuang X, Poletti M, Rucci M. Precision of sustained fixation in trained and untrained observers. *Journal of vision*. 2012;12(6):31-31.

8. Rolfs M. Microsaccades: Small steps on a long way. *Vision Res*. 2009;49(20):2415-2441.

9. Steinman RM, Cunitz RJ, Timberlake GT, Herman M. Voluntary control of microsaccades during maintained monocular fixation. *Science*. 1967;155(3769):1577-1579.

10. Cyr GJS, Fender DH. The interplay of drifts and flicks in binocular fixation. *Vision Res*. 1969;9(2):245-265.

11. Kelly KR, Jost RM, De La Cruz A, Birch EE. Amblyopic children read more slowly than controls under natural, binocular reading conditions. *Journal of American Association for Pediatric Ophthalmology and Strabismus*. 2015;19(6):515-520.

12. Schor C, Hallmark W. Slow control of eye position in strabismic amblyopia. *Invest Ophthalmol Vis Sci*. 1978;17(6):577-581.

13. Chung ST, Kumar G, Li RW, Levi DM. Characteristics of fixational eye movements in amblyopia: Limitations on fixation stability and acuity? *Vision Res*. 2015;114:87-99.

14. Leat SJ, Gargon JL. Accommodative response in children and young adults using dynamic retinoscopy. *Ophthalmic and Physiological Optics*. 1996;16(5):375-384.

15. Gwiazda J, Thorn F, Bauer J, Held R. Myopic children show insufficient accommodative response to blur. *Invest Ophthalmol Vis Sci*. 1993;34(3):690-694.

16. ROUSE MW, HUTTER RF, SHIFTLETT R. A normative study of the accommodative lag in elementary school children. *Optometry & Vision Science*. 1984;61(11):693-697.

17. Chen AM, Wong V, Cotter SA, Tarczy-Hornoch K, Candy TR. Changes in accommodative accuracy with patching therapy for amblyopia. *Invest Ophthalmol Vis Sci*. 2012;53(14):3890-3890.

18. Birch E, Hale L. Operant assessment of stereoacuity. *Clinical Vision Sciences*. 1989;4(4):295-300.

19. Birch EE, Salomao S. Infant random dot stereoacuity cards. *J Pediatr Ophthalmol Strabismus*. 1998;35(2):86-90.

20. Birch EE, Gwiazda J, Held R. Stereoacuity development for crossed and uncrossed disparities in human infants. *Vision Res*. 1982;22(5):507-513.

21. McKee SP, Levi DM, Movshon JA. The pattern of visual deficits in amblyopia. *Journal of Vision*. 2003;3(5):5-5.

22. Holopigian K, Blake R, Greenwald MJ. Selective losses in binocular vision in anisometropic amblyopes. *Vision Res*. 1986;26(4):621-630.

23. PATTERSON R. Spatiotemporal properties of stereoacuity. *Optometry & Vision Science*. 1990;67(2):123-128.

24. Pantle A. Flicker adaptation—I. effect on visual sensitivity to temporal fluctuations of light intensity. *Vision Res*. 1971;11(9):943-952.

25. Schieting S, Spillmann L. Flicker adaptation in the peripheral retina. *Vision Res*. 1987;27(2):277-284.

26. Schor C, Terrell M, Peterson D. Contour interaction and temporal masking in strabismus and amblyopia*. *Optometry & Vision Science*. 1976;53(5):217-223.

27. Dobson V. Visual acuity testing in infants: From laboratory to clinic. *Early visual development, normal and abnormal*. 1993:318-334.

28. Ciuffreda KJ, Levi DM, Selenow A. *Amblyopia: Basic and clinical aspects.* Butterworth-Heinemann; 1991.

29. Reeves B. Taxonomy and epidemiology of amblyopia. *Amblyopia: a multidisciplinary approach.Oxford: Butterworth-Heinemann*. 2002;68:80.

30. Hess RF. Amblyopia: Site unseen. *Clinical and Experimental Optometry*. 2001;84(6):321-336.

31. Sherman SM, Stone J. Physiological normality of the retina in visually deprived cats. *Brain Res*. 1973;60(1):224-230.

32. Baro J, Lehmkuhle S, Kratz K. Electroretinograms and visual evoked potentials in long-term monocularly deprived cats. *Invest Ophthalmol Vis Sci*. 1990;31(7):1405-1409.

33. Choi MY, Lee KM, Hwang JM, et al. Comparison between anisometropic and strabismic amblyopia using functional magnetic resonance imaging. *Br J Ophthalmol*. 2001;85(9):1052-1056.

34. von Noorden GK, Crawford ML, Levacy RA. The lateral geniculate nucleus in human anisometropic amblyopia. *Invest Ophthalmol Vis Sci*. 1983;24(6):788-790.

35. Yoon SW, Park WH, Baek SH, Kong SM. Thicknesses of macular retinal layer and peripapillary retinal nerve fiber layer in patients with hyperopic anisometropic amblyopia. *Korean J Ophthalmol*. 2005;19(1):62-67.

36. Daw NW. Critical periods and amblyopia. *Arch Ophthalmol*. 1998;116(4):502-505.

37. Daw NW, Daw NW. *Visual development.* Vol 9. Springer; 2006.

38. Sireteanu R, Best J. Squint-induced modification of visual receptive field in the lateral suprasylvian cortex of the cat: Binocul interaction, vertical effect and anomalous correspondence. *Eur J Neurosci*. 1992;4(3):235-242.

39. Mayer DL, Beiser AS, Warner AF, Pratt EM, Raye KN, Lang JM. Monocular acuity norms for the teller acuity cards between ages one month and four years. *Invest Ophthalmol Vis Sci*. 1995;36(3):671-685.

40. Yuodelis C, Hendrickson A. A qualitative and quantitative analysis of the human fovea during development. *Vision Res*. 1986;26(6):847-855.

41. Adams RJ, Courage ML. Using a single test to measure human contrast sensitivity from early childhood to maturity. *Vision Res*. 2002;42(9):1205-1210.

42. Barrett BT, Bradley A, Candy TR. The relationship between anisometropia and amblyopia. *Prog Retin Eye Res*. 2013;36:120-158.

43. Attebo K, Mitchell P, Cumming R, Smith W, Jolly N, Sparkes R. Prevalence and causes of amblyopia in an adult population. *Ophthalmology*. 1998;105(1):154-159.

44. 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):603-611. doi: 10.1001/archopht.121.5.603 [doi].

45. Pediatric Eye Disease Investigator Group. A randomized trial of atropine vs. patching for treatment of moderate amblyopia in children. *Arch Ophthalmol*. 2002;120(3):268-278. doi: ecs10241 [pii].

46. 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.

47. Bhola R, Keech RV, Kutschke P, Pfeifer W, Scott WE. Recurrence of amblyopia after occlusion therapy. *Ophthalmology*. 2006;113(11):2097-2100.

48. Scheiman MM, Hertle RW, Kraker RT, et al. Patching vs atropine to treat amblyopia in children aged 7 to 12 years: A randomized trial. *Arch Ophthalmol*. 2008;126(12):1634-1642. doi: 10.1001/archophthalmol.2008.107 [doi].

49. Agervi P, Kugelberg U, Kugelberg M, Simonsson G, Fornander M, Zetterström C. Treatment of anisometropic amblyopia with spectacles or in combination with translucent bangerter filters. *Ophthalmology*. 2009;116(8):1475-1480.

50. Cotter SA, Foster NC, Holmes JM, et al. Optical treatment of strabismic and combined strabismic–anisometropic amblyopia. *Ophthalmology*. 2012;119(1):150-158.

51. Kupfer C. Treatment of amblyopia ex anopsia in adults: A preliminary report of seven cases. *Am J Ophthalmol*. 1957;43(6):918-922.

52. Vereecken EP, Brabant P. Prognosis for vision in amblyopia after the loss of the good eye. *Arch Ophthalmol*. 1984;102(2):220-224.

53. Khan T. Is there a critical period for amblyopia therapy? results of a study on older anisometropic amblyopes. *Journal of clinical and diagnostic research: JCDR*. 2015;9(8):NC01.

54. Image source: Http://Www.allaboutvision.com/conditions/amblyopia.htm/. .

55. Image source: http://Www.bernell.com/product/2462/1268/. .

56. Image source: http://Www.rehab.research.va.gov/jour/10/473/green.html/. .

Appendix

Amblyopia Pathogenesis: New and Old Discoveries

Our visual system, including the eyes and brain, is not fully developed at birth. It takes up to 5 years of age to reach normal visual acuity [27]. An optical deficit during the period of vision development can cause a neurological disorder called amblyopia. Amblyopia comes from a Greek word meaning “dull sight.” It causes a reduction of the best-corrected visual acuity in the absence of any structural or pathological abnormalities within the eye[28]. Aside from refractive error, amblyopia is the most common childhood vision disorder with an estimated prevalence of 1.6% to 3.6% worldwide [29].

Current treatments of amblyopia depend on adequate retinal image quality, which helps in improving the cortical synaptic function. Although the primary cause of amblyopia is an optical deficit in one eye compared to the other, the defect happens at the cortical level. The retina was previously thought to be the primary site of amblyopia [30], however, many studies have confirmed that the retina exhibits normal physiology in amblyopic subjects [31,32]. Additionally, a significant reduction in visual evoked potentials (VEPs) amplitudes are found in amblyopic patients, whereas electroretinograms (ERGs) are normal [1]. Choi et al investigated the blood flow and metabolism to detect focal brain activation (calcarine fissure activation) with functional magnetic resonance imaging (fMRI) on 14 amblyopes. It clearly showed reduced calcarine activation compared to the non-amblyopic eye [33]. In a 1983 study, dissection of an anisometropic amblyopic patient’s brain showed decreased cell size in the four parvocellular layers at the LGN that were innervated by the amblyopic eye compared to the ones innervated by the non-amblyopic eye [34].

In a study by Von et al, anisometropic amblyopia was induced in infant monkeys and kittens either by removing the crystalline lens or putting a high-minus lens in front of one eye. The induced anisometropic amblyopia caused a significant reduction in cell area sizes of LGN [34]. Yoon et al investigated the thickness of the macular retinal and peripheral retinal nerve fiber layer (RNFL) in 31 hyperopic anisometropic amblyopic patients. They compared the macular and peripheral retinal nerve fiber layer of the amblyopic eye with the non-amblyopic eye of the same patient. No significant difference was found in the macular thickness, whereas the peripheral retinal nerve fiber layer thickness showed a statistically significant difference [35]. Von et al suggested that amblyopia may involve the peripheral human visual acuity develops from less than 20/200 to 20/20 during the first 3 to 5 years of life, which is called the critical period of development of acuity [27,36]. During those years visual acuity can be disrupted by various forms of deprivation leading to amblyopia. The disrupted acuity can be improved by effective therapy in children as old as teenagers. In adults, acuity can be improved with maintenance therapy [37]. Sireteanu et al. suggest that occlusion therapy can improve visual function even after the critical treatment period [38].

Development of visual Functions

The human visual system is not fully developed at birth. All visual functions such as visual acuity, stereopsis, color vision, and contrast sensitivity need few years to be completely developed. Structural alternations in the human visual system can be used to explain the improvement of visual acuity and contrast sensitivity.

At birth, immaturity of the fovea limits the grating acuity. The average of human monocular visual acuity was measured during the first 4 years of some children by using Teller acuity cards. It was found that birth is approximately 20/1200 and reaches the normal limit (20/20) around 5 years of age [39]. During the few years of age, several changes occur in the retina that can explain a large part of the development of acuity [37]. The density of cone photoreceptors in the fovea, which is the region of highest acuity, in newborns is lower than in adults. The foveal cones increases from 18 cones/100 μm at 1 week postnatal to 42 cones/100 μm in the adult. Additionally, the photoreceptors decreases from more than 6 μm compared to 1.9 μm in the adults), which clarifies the reduced foveal cone density in newborns [40].

The morphological alternations in cones with age increase their ability of light catching and contrast sensitivity [37]. Contrast sensitivity function (CSF) develops gradually during the first 10 years of life. In Adam et al study, the CSF curve starts to form a band-pass form at age of two months. The peak of CSF, which is at adult 4 cycles/degree, is formed at four years of age. The overall function hits the adult level at age nine years [41]. Contrast sensitivity at high spatial frequencies improves rapidly, continuing until 4 years of age. Improvement at low spatial frequencies is slow, which takes until 9 years of age to be completely developed [44].

Causes and Types of Amblyopia

Amblyopia may arise from a turned eye (strabismus), unequal refractive error (anisometropia), or form deprivation (e.g., cataract), and is usually classified based on the cause. The main problem in all types of amblyopia is loss of binocular function [37]. Any disruption in visual input of one eye during the vision development period can cause a unilateral amblyopia.

In strabismic amblyopia, each eye receives different images due to a deficit in the muscular control of the eyes [37]. Most cases with strabicmic amblyopia show poor acuity and poor contrast sensitivity compared to anisometropic amplyopes. The reason behind that is strbismic eye creates a new point of fixation during the first few years of life. The acuity is limited at the new point of fixation by the density of cone cells and the size of receptive fields of ganglion cell, where the density of cone cells gets lower and the size of receptive fields gets larger [37].

Anisometropic (refractive) amblyopia occurs when the two eyes have a large or unequal refractive error. Around 50% to 75% of amblyopes have anisometropia either alone or in combination with strabismus [42]. Unequal refractive error results in one eye receiving a blurred retinal image at all distances while the other eye has a clear retinal image at some distances. Anisometropia can cause amblyopia if the difference occur during the first 3 years. This type of amblyopia is higher in hyperopic anisometropic population than in myopic anisometropia [42].

Stimulus deprivation amblyopia develops from congenital cataract, ptosis, corneal opacities, or other media opacities that obstruct the vision during the first 3 to 5 years of the child's life [43]. In untreated cases of unilateral congenital cataract, the effect is much worse than in strabismus or anisometropia. The best-corrected visual acuity of untreated congenital cataract is less than 20/200, which is classified as legally blind [36]. The therapy is to remove the cataract surgically and provide optical correction to compensate for the loss of the lens [36].

Amblyopia Treatment

Current amblyopia treatment involves occlusion therapy with patching the non-amblyopic eye for a few hours a day. Opinions vary on number of hours of patching that should be prescribed per day, but there is an increasing body of evidence that all-day patching is not more effective than 2 hours/day [44]. Compliance and skin irritation from bandage patching are the major concern. In the Pediatric Eye Disease Investigator Group study, 41% of 215 amblyopic patients experienced mild skin irritation from patching, and an additional 6% experienced moderate to severe irritation [45]. Moreover, patching may lead to a reduction in binocular vision and stereopsis [46]. It also has a high risk of amblyopia recurrence when the treatment is stopped. In 2006, Bhola et al study showed that 27% of 653 amblyopic patients had recurrence amblyopia after stopping the occlusion therapy [47].

Penalization is a less widely prescribed alternative to occlusion therapy for amblyopia. This method involves using a long acting topical cycloplegic agent such as 1% atropine sulfate in the non-amblyopic eye. Cycloplegia prevents accommodation which create blurred retinal image at near. Patching effects may be initially faster, but after a full treatment course, atropine displays nearly equivalent improvement in visual acuity by 7.6 letters versus 8.6 letters in patching treatment after 17 weeks [48]. Using strong cycloplegic agents in treating amblyopia is as effective as patching, however it has several adverse effects such as causing light sensitivity and lid or conjunctival irritation [45].

Refractive correction is an important component of most cases of amblyopia therapy. It has been found that visual acuity improvement is more rapid with refractive correction in children with anisometropic amblyopia [49]. Cotter et al suggested prescribing refractive correction as the initial treatment for children with strabismic or combined mechanism amblyopia [50]. This correction includes full anisometropic and astigmatic correction from cycloplegic retinoscopy. In one of Pediatric Eye Disease Investigator Group studies, optical correction was used alone to treat refractive amblyopia. The results showed optical correction improves visual acuity in many cases in resolution of amblyopia in at least 30% of three to less than seven year-old children with untreated refractive amblyopia [49].

Can amblyopia in adults be effectively treated?

Many cases of amblyopia persist into adulthood, estimated to be 3.2% among adults age 49 and over, as defined by 20/30 or worse acuity in the amblyopic eye [43]. The notion that there is a critical period for successful treatment of amblyopia is limited to certain age becoming increasingly more controversial. Over the past two decades, many experimental and clinical studies have shown evidence of neuroplasticity in adults. In 1957, a study involved 7 adult strabismic amblyopes. All subjects were hospitalized for a 4 week intensive patching treatment and fixation training. They demonstrated improvements as dramatic as hand movements to 20/25 [51].

Many adult amblyopic patients have experienced visual acuity improvement of the amblyopic eye due to vision loss in the fellow eye such as macular degeneration enucleation of the nonamblyopic eye [52]. Taskin Khan's study showed a remarkable visual acuity improvement in 61 adult refractive amblyopes with age range 12 to 30 years of age. The patients were instructed to patch the amblyopic eye for 2-4 hours a day. After 3 months of treatment, 95% of the patients have reached visual acuity of 20/40 or better, and more than 50% had a visual acuity of 20/20 [53].

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RELEVANT PROJECTS

- Abahussin, M., AlAnazi, M., Ogbuehi, K. C., & Osuagwu, U. L. (2014). Prevalence, use and sale of contact lenses in Saudi Arabia: Survey on university women and non-ophthalmic stores. *Contact Lens and Anterior Eye*, *37*(3), 185-190.

- Master's thesis: Effect of 7 and 20 Hz flicker glasses on fixation and saccadic oculography, accommodation, and stereopsis

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