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ORIGINAL ARTICLE

Randomised trial of three treatments for amblyopia: Vision therapy and patching, perceptual learning and patching alone

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Abstract

Background: Active vision therapy for amblyopia shows good results, but there is no standard vision therapy protocol. This study compared the results of three treatments, two combining patching with active therapy and one with patching alone, in a sample of children with amblyopia.

Methods: Two protocols have been developed: (a) perceptual learning with a computer game designed to favour the medium-to-high spatial frequency-tuned achromatic mechanisms of parvocellular origin and (b) vision therapy with a specific protocol and 2-h patching. The third treatment group used patching only. Fifty-two amblyopic children (aged 4–12 years), were randomly assigned to three monocular treatment groups: 2-h patching ($n=18$), monocular perceptual learning ($n=17$) and 2-h patching plus vision therapy ($n=17$). Visual outcomes were analysed after 3 months and compared with a control group ($n=36$) of subjects with normal vision.

Results: Visual acuity (VA) and stereoacuity (STA) improved significantly after treatment for the three groups with the best results for patching plus vision therapy, followed by monocular perceptual learning, with patching only least effective. Change in the interocular difference in VA was significant for monocular perceptual learning, followed by patching. Differences in STA between groups were not significant. For VA and interocular differences, the final outcomes were influenced by the baseline VA and interocular difference, respectively, with greater improvements in subjects with poorer initial values.

Conclusions: Visual acuity and STA improved with the two most active treatments, that is, vision therapy followed by perceptual learning. Patching alone showed the worst outcome. These results suggest that vision therapy should include monocular accommodative exercises, ocular motility and central fixation exercises where the fovea is more active.

KEYWORDS
amblyopia, monocular perceptual learning, patching, stereoacuity, vision therapy, visual acuity

INTRODUCTION

Amblyopia is a neuro-developmental visual disorder, typically causing a unilateral reduction in visual acuity (VA),[1] as well as other visual deficits such as reduced stereopsis[2] and greater mean accommodative response errors in amblyopic eyes, compared with the fellow eye or non-amblyopic control subjects.[3]

Until recently, occlusion therapy or patching was the more frequent treatment for amblyopia, but its efficiency decreases with age[4] and treatment adherence is low.[5] Although patching has been shown to improve the VA of the amblyopic eye, it may also negatively affect the dominant eye,[6] reduce the child's self-esteem[7] and fail to improve binocular vision.[8,9] There is an important risk of amblyopia recurrence when the patient abandons or reduces occlusion therapy,[10,11] causing loss of up to 25% of the best VA achieved with treatment.[12]

It has been suggested that combining treatments, such as patching and monocular perceptual learning shortens the required treatment duration.[13] This combination therapy might also improve contrast sensitivity,[14,15] VA[16] and stereopsis,[17] as well as reduce the crowding effect.[18] In addition, the effects of perceptual learning appear to be permanent and reflect the plasticity of the visual cortex.[18]

Based on the work of Ciuffreda et al.,[19] orthoptic therapy improves accommodative function in amblyopic eyes. It has also been observed that accommodation improves as the VA improves.[20] Therefore, another possible strategy might be to complement patching with vision therapy involving significant accommodative demand. However, there are few randomised studies reporting the efficacy of this treatment, and therefore its usefulness remains unproven.[21] In some investigations of this treatment, the authors did not include a complete list of tasks[22] or simply required participants to perform near tasks involving eye-hand coordination[23] but left the choice of task to the participant.

The aim of the present study was to compare the effectiveness of three monocular treatments: 2-h patching, monocular perceptual learning and 2-h patching combined with vision therapy after a period of 3 months. In addition, each treatment group was compared with a control group of children with normal vision. The parameters selected to evaluate treatment efficiency were VA, stereoacuity (STA) and the interocular difference in visual acuity (IOD-VA).

Key points

- The study provides evidence for the importance of active treatments for amblyopia.
- A combination of amblyopia treatments is desirable to shorten patching time, as well as direct follow-up of each patient.
- Binocular recovery is promoted by active treatments such as perceptual learning and vision therapy, even when performed monocularly.

MATERIALS AND METHODS

Participants

Participants, aged 4–12 years, were examined at the Lluís Alcanyís Foundation Optometric Clinic. The study was approved by the Ethical Committee of the University of Valencia and complied with the tenets of the Declaration of Helsinki. Before beginning the treatment, at least one parent of the participants read and signed the informed consent form, as required by Spanish law.

Inclusion criteria for the amblyopic group were monocular amblyopia with spherical refraction up to ±9 D compensated with spectacles, IOD-VA ≥ 2 lines, strabismus up to 35Δ and no history of ocular surgery, other than for strabismus. Individuals who had previously undergone amblyopia treatment were not excluded, provided treatment had finished at least 4 months before recruitment for this study. Inclusion criteria for the control group were VA ≤ 0.10 logMAR in both eyes, interocular VA differences of no more than one logMAR line and normal stereopsis for their age group according Birch et al.[24] Participants taking medication that might affect visual or cognitive functions or with neurological and developmental disorders or ocular patholog were excluded.

The total sample included 88 children (47 girls and 41 boys—mean age, 7.11 ± 2.19 years). The amblyopic children (*n* = 52) were randomly assigned to one of the three treatment groups at the time they were enrolled in the study, following a sequence generated with MATLAB's randperm function (mathworks.com) which considered 20 participants per treatment group. The final distribution was patching (*n* = 18; 10 girls and 8 boys; mean age 5.78 ± 1.80 years); monocular perceptual learning (*n* = 17; 12 girls and 5 boys; 7.38 ± 2.05 years) and patching + vision therapy (*n* = 17; 8 girls and 9 boys; 7.32 ± 2.78 years). An age-matched control group (*n* = 36) was formed of non-amblyopic children (17 girls and 19 boys; 7.55 ± 1.93 years). Figure 1 displays the study flowchart. Participants were not informed of the existence of other treatment groups and visits to the clinic were scheduled to avoid mixing participants of different groups.

All participants had undergone an ophthalmological examination within the previous 6 months and had been wearing spectacles, so they had completed refractive adaptation. Both at the beginning and at the end of the study, participants completed a test battery, under similar illumination conditions. The tests were monocular and binocular VA, refraction, best-corrected logMAR VA with a Tumbling E chart at 5 m and STA with the Randot Preschool Test (stereooptical.com). Ocular alignment (cover-uncover and alternate cover tests) and binocularity (Worth 4-dot lights) were also tested, both at distance and near vision. Compliance was assessed using a slightly adapted version of the PEDIG criterion from the Amblyopia Treatment Study,[25] to take into account both the number of tasks assigned/completed and the time spent on treatment. Details of the procedure are given in each treatment group.

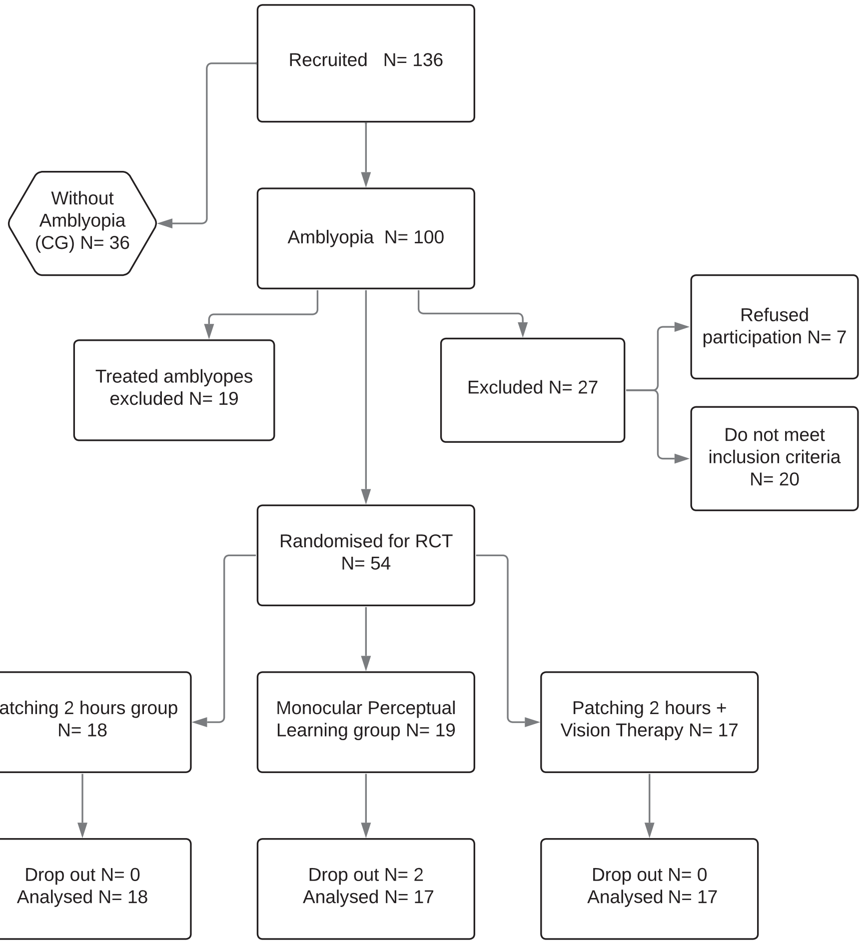

FIGURE 1 Flowchart of the study describing the randomisation process. CG, control group. RCT, randomised clinical trial.

Groups and treatments

Instructions were explained during the visits, but in addition, participants were issued a printed copy to improve knowledge of the rules, care and satisfaction of the patient.[26]

Patching

Participants were required to wear a patch on the fixating eye for 2 h a day after school, under adult supervision. Parents and tutors were asked to keep a written weekly register, using a standardised form, to be collected by the research team during the following visit.

Monocular perceptual learning

Participants played a computer game called 'Smiling Face'. Children wore a patch over the fixating eye only while playing the game. The treatment was home-based monocular perceptual learning. The program recorded the time spent by each participant in completing the task on a daily basis, as well as the results, including both successes and failures. Parents reported on the children's progress every 2 weeks by telephone message.

The game was a stand-alone Matlab application (mathworks.com) based on the COLORLAB library[27] and designed by the authors of this study. An achromatic schematic face (Figure 2), consisting of eyes, mouth and a circular face contour, deprived of any elements implying genre or race or introducing a gender bias, was superposed on a noisy achromatic background. At each trial, the face could appear either as smiling or sad, and the patient's task was to respond with a mouse-click to the smiling face. The face appeared for 300 ms and the maximum allowed response time was 1 s. The lack of a response during that interval was recorded as a failure. The success rate of the patient was computed as the percentage of hits during the game. Both responding to the smiling face and failing to respond to the sad face were counted as hits. Given the importance of positive reinforcement in perceptual learning[28,29] the programme showed a green square for a hit and a red one for a fail at the upper right corner of the scene, away from the fovea, and the children obtained prizes, in the form of stars, for the hits scored.

The Michaelson contrast of the achromatic noise was always unity. During the first game, the initial contrast (C_i)

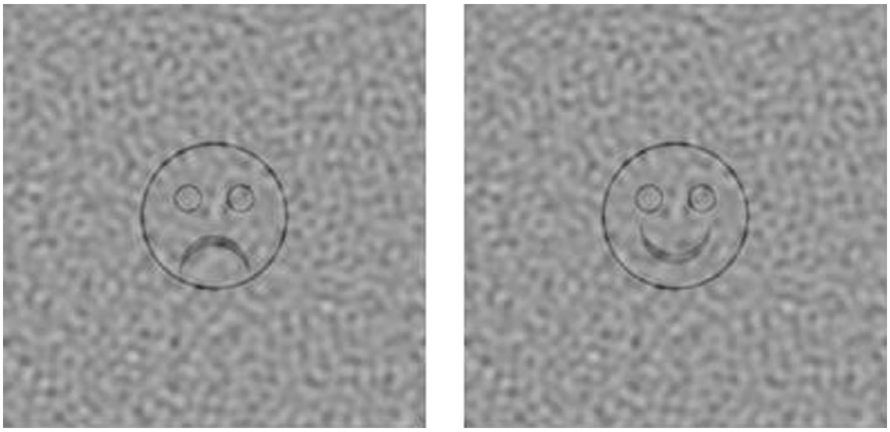

FIGURE 2 Example of achromatic schematic sad (left) and smiling (right) face and noisy background for the Monocular Perceptual Learning task. The smiling or sad faces appeared randomly.

of the face was chosen as a function of the patient's initial VA (C_i = 0.40 if VA was worse than 0.60 logMAR; C_i = 0.20 for VA between 0.30 and 0.60 logMAR and C_i = 0.10 for VA better than 0.30 logMAR). Contrast was progressively reduced when the patient scored 70% hits; otherwise, it was increased up to 0.8.

A game session was organised into blocks of 65 constant contrast trials, with a short pause (5 s) between blocks and a longer pause (30 s) after three blocks were completed. When the stipulated duration of the game was reached, the program announced the end of the session. After 3 months, children between 4 and 6 years of age should have played 24 h, while older children completed 36 h.

The characteristics of the stimuli and the task were chosen to favour responses of medium-to-high spatial frequency sensitive achromatic mechanisms of parvocellular origin. The background noise occupied a 15° by 15° square. During the initial sessions, the target face appeared in the centre of the screen but during the last stage of the training, once the subject reached high levels of success, the target appeared at random positions around the centre of the scene. The whole scene was surrounded by a grey stimulus with the same average luminance (50 cd/m^2) as the background. The background, equal-energy noise in the [0.5, 2] cycles per degree spatial frequency band, was introduced to desensitise low-spatial frequency-sensitive mechanisms of parvo-cellular origin, expected to mediate recognition of achromatic stimuli.[30]

Patching + vision therapy

Participants wore a patch over the fixating eye for 2 h a day, preferably during school time. The treatment was patching + home-based vision therapy and was carried out after school, under the supervision of an adult. Each child was given the necessary material and a weekly exercise plan. Exercises had to be carried out 3 days a week for either 20 min (subjects aged 4–6 years) or 30 min (subjects 6 years of age and older). Participants came to the clinic every 2 weeks. The supervising adult was given written instructions and a form to record the exercises the child performed each week and the hours of patching, to be handed in at the following visit.

The assigned exercises were conducted monocularly and developed in three categories: (1) accommodation exercises, consisting of Hart Chart, accommodation at three distances (near, middle and far) and Bull's Eye target; (2) eye-hand coordination exercises consisting of going-through-mazes[31] and filling-in letters of decreasing size, both composed of an intense colour, connecting the dots using cards with an increasing numbers of points and clicking on letters of decreasing size; (3) ocular motility with the Marsden ball, following the movements of a pointer or a torch and space fixator for saccadic eye movements. These procedures are described in detail elsewhere.[32–34]

Control group

This group was formed of subjects with normal vision. They were tested at the beginning of the study and 3 months later.

Data analysis and statistics

Changes in VA were evaluated by comparing results from the amblyopic eye of the amblyopic subjects and a randomly chosen eye for the control participants. The modulus of the interocular difference in logMAR VA was computed for each participant, and the STA in seconds of arc was transformed into STA in decibels (dB), to obtain a uniform scale, as follows:

$$\text{STA (dB)} = K \log_{10}\left(\text{STA}_{\min}(arcsec) \,/\, \text{STA}_{s}(arcsec)\right) \quad (1)$$

where $K=1$, STA_s(arcsec) is the STA of the subject measured with the Randot Preschool Test and STA_{min}(arcsec) represents the STA arbitrarily assigned to a subject that could not detect the least sensitive stimulus in the Randot Preschool Test. A value of 1600″ was selected for STA_{min}(arcsec), in agreement with the logarithmic scale used in this test. Subjects who did not detect the largest stimulus (800″) were thus assigned a ST=1600″, to yield STA=0.

For statistical analysis, the patient's refraction was expressed using the power vector components M (spherical equivalent), J_{0} and J_{45} (cross-cylinders at 0° and 45°, respectively).[35]

LogMAR VA, STA (dB) and IOD-VA from the normal and amblyopic groups did not follow a normal distribution; thus the results were analysed using nonparametric statistics. A general linear model was used to determine the variables that might influence the improvement of VA, STA and IOD-VA. Data were analysed using SPSS v.28.0 (ibm.com).

To assess the effect of treatment, baseline and end-of-treatment data were compared using the Wilcoxon test, with Holm–Bonferroni correction for multiple comparisons. Differences between groups were assessed with the Kruskal–Wallis test, also adjusted by the Bonferroni correction, with a Kolmogorov Smirnov post-hoc test. Passing-Blablok regression was used to visualise the effect of the treatment. Spearman's correlation was computed for VA, STA and IOD-VA between the baseline and post treatment values. The data supporting this study are published on the RODERIC platform of the University of Valencia, February 23, 2024 (https://hdl.handle.net/10550/95992).

RESULTS

Baseline characteristics

Baseline characteristics of the sample are summarised in Table 1. The mean age of the patching group was smaller than the control group ($H=3.18$; $p=0.009$ adjusted by Bonferroni correction). The averages of the M, J_0 and J_{45} components of the vectorial refraction and their absolute values, $|M|$, $|J_0|$ and $|J_{45}|$ (Table 1), reflect the low rate of myopic participants.

Improvements in VA, STA and IOD-VA

The comparison between baseline and post-treatment was performed using the Wilcoxon signed rank test with the Holm–Bonferroni correction for multiple comparisons ($p=p_{uncorrected}\times(n-\text{rank}+1)$) (Table 2). Statistically significant changes were observed between the three variables for all groups of treatment (Table 2), with medium ($0.3\le r<0.5$) to large ($r\ge0.5$) effect sizes. The effect sizes appeared smaller for STA than for VA and IOD-VA, except for the patching + vision therapy group. The patching group showed the smallest effects in VA and STA.

In spite of an improvement after the treatment period, amblyopic subjects showed significantly worse VA, IOD-VA and STA than non-amblyopic subjects. Differences in STA between treatment groups were not significant, but participants in the patching group showed significantly poorer VA than those undergoing monocular perceptual learning or patching + vision therapy. These two groups did not differ significantly in VA, STA and IOD-VA (Table 3). This analysis was carried out with the Kruskal–Wallis test, using the Kolmogorov–Smirnov test as a post-hoc test.

Improvements in VA, STA and IOD-VA after the treatment period for each group were checked using Passing–Bablok linear regression diagrams. The results for the control group are shown in the upper part of Figure 2 while the results for the three treatment groups (i.e., patching, monocular perceptual learning and patching + vision therapy) are shown in the lower part of Figure 3.

Factors that could influence the changes in VA, STA and final IOD-VA

Baseline values of VA, STA, IOD-VA and age were used as independent variables and treatment group as a factor in a general linear model (Table 4). For VA and IOD-VA, the improvements were significantly influenced by the initial value of VA and IOD-VA, respectively, with greater improvements in subjects with poorer initial values. In addition, the general linear model suggests that, with all other factors being equal, the patching + vision therapy group would undergo the largest improvement in VA, followed by the monocular perceptual learning group and finally the patching only group. The monocular perceptual learning group would obtain greater improvements in STA, followed by the patching + vision therapy group and finally the patching group (Table 2). The patching group presented the greatest change of IOD-VA, followed by monocular perceptual learning and finally patching + vision therapy. In the model, it was observed that age only had a significant effect on the improvement in STA, with smaller improvement in STA for younger children (Table 4).

Considerations on sample size and power

Once the size of the changes between the pre- and post-outcome variables and the differences between the treatment groups were determined, the required sample size was computed for $\alpha=0.05$, power $=0.95$ and the power of the test with the actual sample, using GPower 3.1.9.7 (psychologie.hhu.de/arbeitsgruppen/allgemeine-psychologie-und-arbeitspsychologie/gpower).[36] For the treatment effect on each group, the required sample size for a Wilcoxon test of paired samples was used. For the differences between groups, the sample size was computed for an ANOVA test with the groups.

To determine an improvement in VA in each group, the required sample size varies from five for the

TABLE 1 Baseline characteristics of the normal subjects and randomised subjects with amblyopia.

Characteristic	Control group; *n* = 36	Patching; *n* = 18	Monocular perceptual learning; *n* = 17	Patching + Vision therapy; *n* = 17	Kruskal–Wallis; *p*- value
Gender					
Female	17	10	12	8	
Male	19	8	5	9	
Race	Caucasian	Caucasian	Caucasian	Caucasian	
Age (years) Mean ± SD	7.55 ± 1.93	5.78 ± 1.80	7.38 ± 2.05	7.32 ± 2.78	$H = 10.553$ $p = 0.01$*
Refraction[c] (vector notation) (D) AE					
M	–	2.28 ± 2.61	3.13 ± 1.71	2.74 ± 2.55	
J_0	–	0.32 ± 0.67	0.10 ± 0.29	0.39 ± 0.67	
J_{45}	–	0.07 ± 0.41	0.06 ± 0.12	0.14 ± 0.45	
Refraction (D) (absolute value) AE					
M	–	2.81 ± 2.47	4.82 ± 2.33	2.73 ± 2.21	
J_0	–	0.42 ± 0.52	0.33 ± 0.32	0.47 ± 0.59	
J_{45}	–	0.22 ± 0.26	0.15 ± 0.24	0.31 ± 0.33	
Refraction (D) (vector notation) NAE					
M	0.51 ± 1.37	2.42 ± 2.41	3.54 ± 1.98	1.37 ± 1.96	
J_0	0.27 ± 0.96	0.21 ± 0.36	0.19 ± 0.31	0.20 ± 0.62	
J_{45}	−0.07 ± 0.19	0.01 ± 0.09	0.00 ± 0.13	0.01 ± 0.01	
Refraction (D) (absolute value) NAE					
M	–	2.46 ± 2.37	3.54 ± 1.98	1.53 ± 1.83	
J_0	–	0.25 ± 0.34	0.24 ± 0.27	0.33 ± 0.56	
J_{45}	–	0.04 ± 0.09	0.06 ± 0.11	0.07 ± 0.11	
VA AE (logMAR)					$H = 64.678 < 0.001$*
Median	–	0.28 ± 0.12	0.39 ± 0.19	0.34 ± 0.14	
CI	–	0.20 to 0.30	0.24 to 0.50	0.26 to 0.50	
25th/75th percentile	–	0.20/0.30	0.23/0.51	0.23/0.50	
VA NAE (logMAR)					$H = 15.439 < 0.001$*
Mean	−0.03 ± 0.08	0.09 ± 0.12	0.03 ± 0.13	0.12 ± 0.23	
CI	−0.12 to 0.14	0.00 to 0.14	−0.10 to 0.10	−0.05 to 0.20	
25th/75th percentile	−0.10/0.00	0.00/0.20	−0.10/0.11	−0.10/0.25	
Stereoacuity (dB)					$H = 65.408 < 0.001$*
Mean	1.52 ± 0.12	0.61 ± 0.42	0.30 ± 0.48	0.34 ± 0.370	
CI	1.20 to 1.60	0.30 to 0.75	0.00 to 0.60	0.00 to 0.60	
25th/75th percentile	1.43/1.60	0.30/0.98	0.00/0.60	0.00/0.60	
Interocular difference in VA					$H = 50.284 < 0.001$*
Mean	0.03 ± 0.05	0.19 ± 0.17	0.36 ± 0.25	0.23 ± 0.15	
CI	0.00 to 0.20	0.12 to 0.20	0.20 to 0.54	0.16 to 0.30	
25th/75th percentile	0.00/0.05	0.10/0.20	0.20/0.57	0.13/0.30	
Types of amblyopia					
Anisometropic (*n*)	–	8	6	9	
Strabismic (*n*)	–	2	4	3	

TABLE 1 (Continued)

Characteristic	Control group; $n=36$	Patching; $n=18$	Monocular perceptual learning; $n=17$	Patching + Vision therapy; $n=17$	Kruskal–Wallis; *p*- value
Mixed (*n*)	–	8	7	5	
Use of spectacles	5	18	14	16	
Contact lenses (*n*)			2		

Note: Data are mean ± standard deviation and confidence interval (CI). Visual acuity (VA) shown for the non-amblyopic eye (NAE) of amblyopic subjects. In the control group, one eye was chosen at random to calculate the mean refraction values, labelled NAE. The Kruskal–Wallis test was used to compare the groups.

Abbreviations: AE, amblyopic eye; dB, decibels.

*Statistically significant differences $p<0.05$, adjusted by Bonferroni correction for multiple comparisons. Refraction values in dioptres (D).

TABLE 2 Comparison of baseline and post-treatment results, post-minus pre-treatment differences are shown as mean ± standard deviation (SD).

	VA (logMAR)		STA (dB)		IOD-VA (logMAR)	
Parameter	Post-pre change mean ± SD	Wilcoxon (test statistic, corrected *p*-value, effect size)	Post-pre change mean ± SD	Wilcoxon (test statistic, corrected *p*-value, effect size)	Post-pre change mean ± SD	Wilcoxon (test statistic, corrected *p*-value, effect size)
Control group	−0.01 ± 0.05	$Z=-1.41$ $p=0.32$ $r=0.17$	0.06 ± 0.12	$Z=-2.92$ $p=0.04$* $r=0.34$	−0.00 ± 0.03	$Z=-0.63$ $p=0.53$ $r=0.07$
Patching	−0.12 ± 0.17	$Z=-3.19$ $p=0.01$* $r=0.53$	0.15 ± 0.18	$Z=-2.58$ $p=0.04$* $r=0.43$	−0.08 ± 0.07	$Z=-3.31$ $p=0.009$* $r=0.55$
Monocular perceptual learning	−0.22 ± 0.10	$Z=-3.63$ $p=0.01$* $r=0.62$	0.27 ± 0.36	$Z=-2.53$ $p=0.04$* $r=0.46$	−0.18 ± 0.20	$Z=-3.24$ $p=0.008$* $r=0.56$
Patching + vision therapy	−0.25 ± 0.08	$Z=-3.65$ $p=0.01$* $r=0.63$	0.27 ± 0.21	$Z=-3.35$ $p=0.007$* $r=0.58$	−0.08 ± 0.16	$Z=-2.23$ $p=0.08$ $r=0.38$

Note: *p*-Values of the Wilcoxon test have been corrected for multiple comparisons with the Holm–Bonferroni criterion ($p=p_{uncorrected}\times(n-\text{rank}+1)$).

Abbreviations: dB, Decibels; IOD-VA, intraocular difference in visual acuity; STA, stereoscopic acuity; VA, visual acuity.

*Statistically significant differences, $p<0.05$. Effect size is computed as $r=|Z|/\sqrt{2n}$, where n is group size.

TABLE 3 Comparison between groups using the Kolmogorov–Smirnov test for differences in visual acuity, stereoacuity and interocular difference in visual acuity.

Parameter	Control group versus patching	Control group versus monocular perceptual learning	Control group versus patching + vision therapy	Patching versus monocular perceptual learning	Patching versus patching + vision therapy	Monocular perceptual learning versus patching + vision therapy
Visual acuity	$Z=1.93$ $p=0.001$*	$Z=2.30$ $p<0.001$*	$Z=3.40$ $p<0.001$*	$Z=1.62$ $p=0.01$*	$Z=2.29$ $p<0.001$*	$Z=0.86$ $p=0.45$
Stereo acuity	$Z=1.25$ $p=0.09$	$Z=1.52$ $p=0.02$*	$Z=2.33$ $p<0.001$*	$Z=0.53$ $p=0.94$	$Z=0.95$ $p=0.33$	$Z=0.86$ $p=0.45$
Interocular difference in visual acuity	$Z=2.21$ $p<0.001$*	$Z=2.52$ $p<0.001$*	$Z=1.74$ $p=0.005$*	$Z=1.06$ $p=0.21$	$Z=0.57$ $p=0.90$	$Z=0.86$ $p=0.45$

*Statistically significant differences $p<0.05$.

patching + vision therapy and monocular perceptual learning groups, which show large effect sizes, to 22 for the patching only group. For STA, the sample sizes should be greater (19, 22 and 9 for patching, monocular perceptual learning and patching + vision therapy, respectively).

To determine differences in VA between groups of treatment, the total sample size should be 87, that is, 29 subjects per group. With the sample used in the present study, the power of the test was 0.8. In the present study, no significant differences between treatment groups were found,

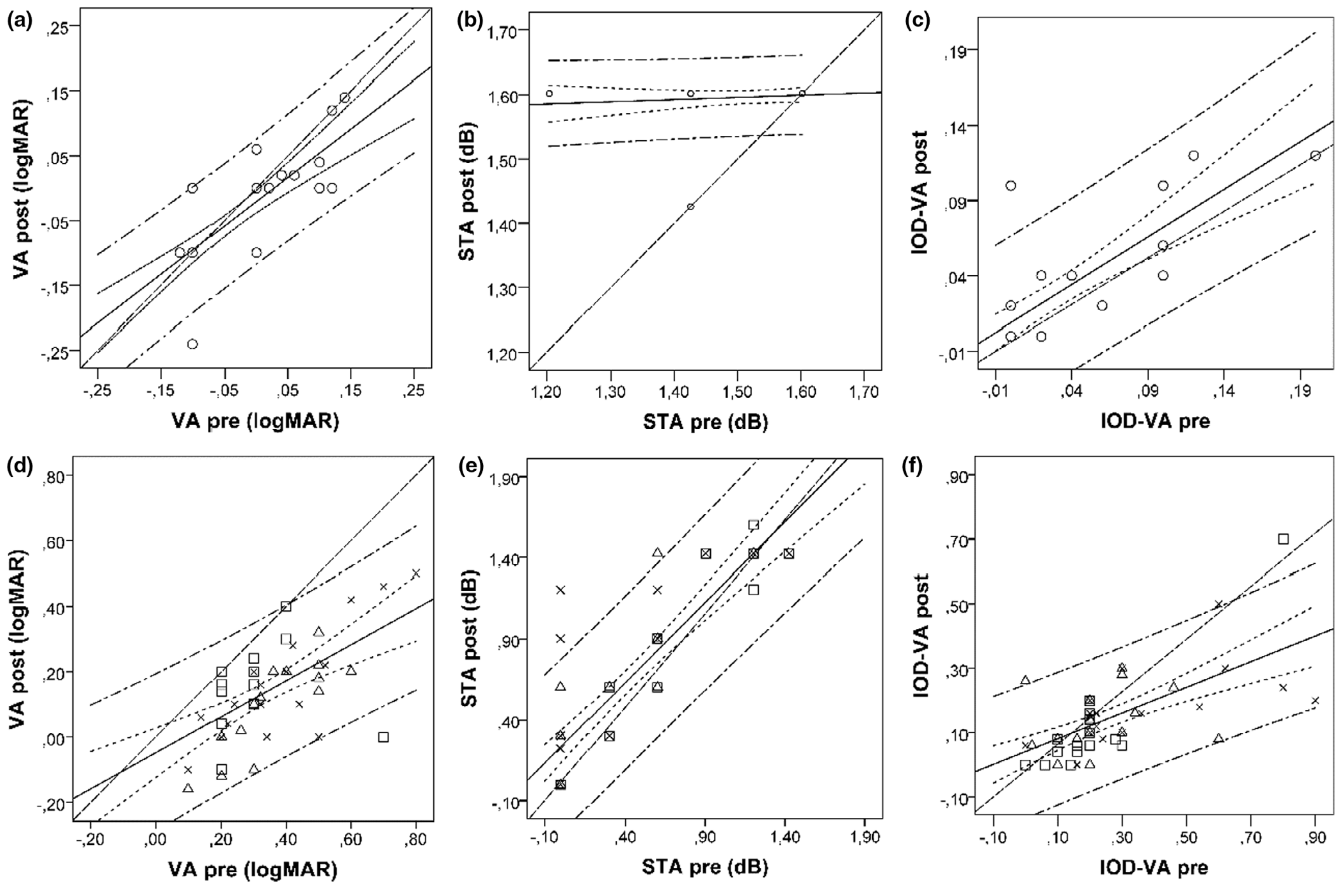

FIGURE 3 Passing–Bablok scatter diagrams for baseline (pre) and post-treatment values of visual acuity (VA), stereoacuity (STA) and interocular difference in VA (IOD-VA). Also indicated are the regression line (solid line), the confidence interval for the regression line (dotted line, short strokes) and the identity line ($x=y$, dashed line, long strokes). Panels (a–c) show data for the control group (open circles). Spearman's correlations were strong for VA (ρ = 0.84; $p<0.001$) and IOD-VA (ρ = 0.75; $p<0.001$) but weak for STA (ρ = 0.28; $p=0.07$). Panels (d–f) show the effects for the three treatment groups (*x*, patching group; □ monocular perceptual learning group; Δ patching + vision therapy group). Spearman's correlations were moderate for VA (ρ = 0.57; $p<0.001$) and strong for STA (ρ = 0.89, $p<0.001$) and IOD-VA (ρ = 0.72, $p<0.001$).

TABLE 4 Statistical data of the general linear model for increment of visual acuity (VA), increment of stereoacuity (STA) and final interocular difference in VA (IOD-VA), for patching, monocular perceptual learning and patching + vision therapy groups.

Parameter	Increment VA		Increment STA		Final IOD-VA	
	B	*p*-Value	*B*	*p*-Value	*B*	*p*-Value
Intercept	−0.01	0.83	0.13	0.43	0.02	0.75
VA pre	−0.34	0.01*	−0.46	0.14	0.01	0.92
STA pre	−0.03	0.34	−0.03	0.76	0.04	0.25
IOD-VA pre	−0.04	0.76	−0.007	0.98	−0.62	<0.001*
Age	−0.01	0.08	0.04	0.03*	0.003	0.71
Patching	0.10	0.02*	−0.01	0.39	−0.03	0.41
Monocular perceptual learning	0.05	0.21	0.01	0.90	−0.02	0.62
Patching + vision therapy	0	–	0	–	0	–

Note: *B* is the coefficient for each variable in each model.

*Statistically significant differences $p<0.05$.

and in fact, the effect size was small for STA, requiring a sample size of 303 subjects or 101 per group to detect a significant difference. The power with the actual sample size used here was 0.3.

DISCUSSION

The aim of this study was to compare the effectiveness of three monocular treatments: patching, monocular perceptual learning and patching + vision therapy after a treatment period of 3 months. VA, STA and interocular difference in VA were assessed both before and after treatment because they are important to determine whether the visual performance of subjects with amblyopia has actually improved.[2] In addition, all participants had clear guidelines during treatment, included in a detailed set of written instructions to improve compliance. Participants in the three treatment groups performed the assigned tasks at home.

The improvement in VA and STA after 3 months of treatment was greatest in the patching + vision therapy group followed by the monocular perceptual learning group and finally the patching group. The PEDIG study[37] showed that near vision activities improved VA, as does the present investigation. However, there were some differences between the strategies followed in this paper for the patching + vision therapy group and similar approaches in the literature. First, instead of just suggesting generical near vision tasks such as homework, reading, computer work[37] etc., a specific and fixed vision therapy routine was assigned for participants in the patching + vision therapy group, including accommodation exercises. Secondly, these activities were performed 3 days a week, while other authors have suggested either twice a week or even daily tasks.[38] In addition, good compliance was observed in the patching + vision therapy group, following an adapted PEDIG criterion.[25] These aspects could be the reason for the greater improvement in VA and STA with this combined treatment compared with patching alone. In Figure 3d it appears that there is minimal improvement in VA, but this could be due to the fact that the three treatment groups are shown together. On average, this improvement is -0.12 ± 0.17 for patching and -0.25 ± 0.08 for patching + vision therapy. This is also related to the moderate Spearman correlation between pre- and post-treatment values for VA versus a strong association for STA and IOD-VA.

The monocular perceptual learning group also exhibited significant improvements in VA, STA and IOD-VA. A neuronal model[39] suggests that perceptual learning strengthened direct feeding connectivity between the lateral geniculate nucleus and V1. If this happens, it may be possible that learning occurred before the binocular signals were combined in a way that was specific to the trained eye and contributed to binocular combination. Therefore, increasing the use of monocular perceptual learning tasks in a clinical setting may be beneficial before moving on to binocular tasks or even performing them at the same time. Thus, this option may be more practical than prolonged occlusion, where the amblyopic eye is more passive.[40] Several studies[41,42] have shown the benefits of combining treatments such as patching, vision therapy, perceptual learning or dichoptic treatments. Specifically, we suggest both monocular perceptual learning and patching + vision therapy as a treatment paradigm in severe amblyopia to shorten the duration of occlusion prior to binocular treatment. This would avoid, at least in part, the negative effects of patching on the visual system and on the child's psychosocial well-being and self-esteem.[7,43]

One potentially significant difference between the routines of the patching, monocular perceptual learning and patching + vision therapy groups was that the patching + vision therapy group attended the Optometric Clinic every 2 weeks to be prescribed a change in exercises. It is known that contact with the clinician favours adherence to treatment[44] and that direct communication between the clinician and the child improves compliance and leads to better results.[45] To ensure regular contact with the patching only and monocular perceptual learning groups, the research team sent a cell-phone text message every 2 weeks to the child's tutor. However, the monocular perceptual learning group also showed significantly better results than the patching group after 3 months. This result suggests that the improvement in monocular perceptual learning may not be due just to the monitoring by the clinicians via text message, but also to the tasks being performed by the participants. It should also be noted that the patching only group had a lower mean age than the other two groups. The review by Leat et al.[46] showed that VA reaches a fully mature state between 5 and 15–16 years of age, and all of the participants in the present study were within this age range.

The change in STA points to improvements in the groups with more active treatments, with monocular perceptual learning achieving the highest mean value, followed by patching + vision therapy and finally the patching only group (Table 4). There are contradictory results in the literature regarding stereopsis, with some results supporting an improvement in STA with binocular training[47,48] while others show a lack of significant improvement despite binocular treatment because only 22% of the children achieved >75% adherence, suggesting that adherence should be reviewed more frequently.[49] In a recent retrospective study[41] where only six subjects had previous stereopsis values, all of them improved in STA with active vision therapy. The Monitored Occlusion Treatment for Amblyopia Study (MOTAS),[50] using optical treatment and occlusion, reported unmeasurable STA in 43% of the sample at the study exit. In general, binocular treatments favour the improvement of STA more than monocular treatments. However, different authors have suggested that compliance should be checked more frequently and that games should be made more attractive, especially for children.[41,49,51] The present control group also showed a significant improvement in STA, probably because it continues to mature into the school-age years at least for small disparities[52] and also to the learning effect of the STA test. Ciner et al.[53] observed that although the median STA was the same for all three age groups investigated, the percentage attaining the best levels of STA (60 or 120 s of arc) increased with age (81.6% in 3-year olds, 89.2% in 4-year olds and 91.6% in 5-year olds, $p < 0.001$), indicating that STA either may not be fully developed or some children's ability to complete all disparity levels is still improving as they enter the preschool years. Amblyopic subjects showed significantly worse VA, IOD-VA and STA than non-amblyopic subjects, despite an improvement after the treatment period.

Regarding the decrease in IOD-VA after treatment, the patching group showed the highest improvement, followed by monocular perceptual learning and finally patching + vision therapy. This could be a consequence of the superior baseline values in the patching group, although the differences between the three groups were not statistically significant (Table 1). The monocular perceptual learning group started with a higher IOD-VA value, and therefore might experience greater improvement than the patching group.

The general linear model showed that participants with the lowest baseline VA exhibited the greatest improvements in VA. This was also suggested by Tsirlin et al.[54] in a meta-analysis. This trend was also found for the final IOD-VA, that is, if the initial IOD-VA was high, then it will likely be lower in the final outcome. However, the general linear model indicated that neither the VA nor the stereopsis at baseline influenced the change in STA. This result seemed surprising, and therefore was reanalysed with another linear model that included the final STA value as the dependent variable instead of the change in STA. It was observed that the initial STA was significant (coefficient $B = 0.80$; $p < 0.001$), so that a low initial STA is likely to result in poorer final STA. This finding is partially consistent with the results of Stewart et al.,[50] where poor STA at baseline was associated with poor VA and a large angle strabismus at baseline and follow-up. However, in the present study, baseline VA did not influence the final STA outcome significantly (coefficient $B = -0.30$; $p = 0.20$). This discrepancy may be explained by several factors. For example, in the present study the mean age was 7.1 ± 2.1 years, the treatment lasted 12 weeks and the Randot Preschool Test was used, whereas in Stewart et al. the mean age was 5.1 ± 1.5 years, the treatment lasted 18 weeks and the Frisby STA test was used.

The results suggest that for successful treatment, with improvements in both VA and stereopsis, patching alone is not sufficient. Treatments that were combined and developed through computer games received a more enthusiastic response from the children. This approach is in line with Levi and co-workers,[2] who stressed the need for more active treatments to restore stereo vision. Other sources also support the use of vision therapy for the treatment of amblyopia.[38,55,56]

Furthermore, Tsirlin et al.,[54] suggested that if the amblyopic eye is given the opportunity to work effectively, either alone or together with the fellow eye, then improvement will occur. In this line, Levi and Li[57] proposed making perceptual learning more attractive to young children, along the lines of "Psychophysical Rocketship".[58] In this way, in addition to speeding up treatment, the negative emotional effects of patching could be reduced.[59]

We expected that improved VA and reduced IOD-VA might contribute to improved stereopsis at least for low fixation disparity. The fact that the different treatment groups included anisometropic, strabismic and mixed amblyopia patients might obscure the result, which should be more apparent in anisometropic amblyopia, regardless of treatment group. To explore this idea further, the effect of amblyopia type was analysed. However, anisometropics did not show a significant correlation between post-treatment STA and VA values ($\rho = -0.31$, $p = 0.15$), although for the other groups this correlation was even lower. The number of participants per treatment group and amblyopia type who showed improved STA was computed. In the patching only group, 50% of the anisometropic and mixed amblyopes demonstrated measurable improvement in stereopsis, but the only two strabismic participants in this group did not show any improvement. In the monocular perceptual learning and patching + vision therapy groups, the percentage of anisometropic subjects who improved their stereopsis was larger than for the other amblyopes (67% and 89% of the anisometropic participants, respectively, in comparison with 50% and 66% of strabismic and 29% and 60% of mixed amblyopes, respectively), a χ^2 test did not reveal a significant effect of amblyopia type and treatment group in the STA improvement ratio ($\chi^2 = 11.31$, $p = 0.50$). If the change in STA is compared between the three amblyopic groups (anisometropic, strabismic and mixed), regardless of treatment, the anisometropic and mixed participants showed significant improvement while the strabismic participants did not, regardless of the value assigned to participants with findings worse than 800″. Only in this limited sense could one conclude that the binocular benefits of the monocular treatment might be greater for the anisometropic participants.

This study has some limitations. Participants did not find the 'smiling faces' game attractive, making adherence to treatment difficult. Confirming patching and compliance with the exercises relied on the information that the parents recorded in writing. This register was kept by the parents and is therefore subjective and not fully reliable, although some of the exercises, such as following the mazes, filling in letters and joining dots were brought to the next follow-up visit, allowing the clinician to check progress and task completion. In particular, it was ascertained that subjects had handed all the required exercises. Another limitation was linked to the inability of the Randot Preschool test to measure greater disparities accurately, that is, poorer STA or small changes due to the reduced number of STA steps. The choice of a particular finding for participants with STA worse than the coarsest measurable level did not affect the conclusions regarding significant differences between pre- and post-treatment stereopsis, but it influenced the remainder of the computations. Finally, the examiner received the participants, gave instructions for each treatment, received periodic feedback and carried out the necessary measurements. This could have introduced a bias into the results, although the examiner had no preconceived notion about the final results.

In conclusion, improvement in VA and STA was greater in the two groups with more active treatments, that is, monocular perceptual learning and vision therapy + patching. The findings suggest that vision therapy including accommodation exercises and monocular perceptual learning should be considered as treatments for amblyopia in conjunction with patching, in order to shorten the duration of the occlusion. In addition, both monocular treatments were able to transfer their results to improvements in binocular function.

AUTHOR CONTRIBUTIONS

Rosa Hernández-Andrés: Conceptualization (equal); data curation (lead); formal analysis (supporting); investigation (equal); methodology (equal); writing – original draft (lead). **Miguel Ángel Serrano:** Conceptualization (equal); data curation (supporting); formal analysis (supporting); investigation (equal); methodology (equal); supervision (lead); writing – review and editing (equal). **Adrián Alacreu-Crespo:** Conceptualization (supporting); data curation (supporting); formal analysis (supporting); investigation (supporting); methodology (supporting); writing – review and editing (supporting). **María José Luque:** Conceptualization (equal); data curation (supporting); formal analysis (lead); investigation (equal); methodology (equal); supervision (lead); writing – review and editing (lead).

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CONFLICT OF INTEREST STATEMENT

None of the co-authors have any conflict of interest.

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