



REVIEW

An updated review about perceptual learning as a treatment for amblyopia



Antonio Rodán*, Elena Candela Marroquín, Laura C. Jara García

Universidad CEU-San Pablo, CEU Universities, Spain

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Amblyopia;
Perceptual learning;
Dichoptic therapy;
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Abstract The purpose of our work is to do an update of recent investigations about amblyopia treatment based on perceptual learning, dichoptic training and videogames. Therefore, we conducted a search of the studies published about this subject in the last six years. The review shows that the investigations during that period have used several kinds of treatments regarding their design (e.g., type of stimulus and context used, duration of the training), and in a wider range of age that also include adults. Most of the studies have found an improvement in some mono and binocular visual functions, such as visual acuity, contrast sensitivity and stereopsis, which for now, it seems advisable that these processes could be used, as an alternative or a complement of the traditional passive therapy. Nevertheless, it would be plausible to conduct additional, controlled and random, clinical trials in order to discover in a more deeply way which perceptive learning method of treatment is more effective for the improvement of visual functions and for how long the effects of the treatment could persist.

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Introduction

Amblyopia (from the greek word amblyos- weak, opia-vision), was defined by Burian in 1956 as a diminution in unilateral or bilateral vision, without any physical cause, detected in the eye exam.¹ This type of dysfunction is the principal cause of preventable children blindness, with a

prevalence between 1 and 5% and it is still considered one of the most common causes of unilateral visual impairment that persists in the adulthood.² Amblyopia is considered as a neurodevelopmental disorder of the visual system due to an abnormal binocular vision experience in early childhood.³ Even though amblyopia causes a range of monocular deficit (e.g., visual acuity; VA from now on), it has been proved that one of amblyopia determining characteristics is the loss of binocularity.³ Nowadays, this has led to increased interest in the development of amblyopia treatments that directly address binocular dysfunction by promoting binoc-

* Corresponding author.

ular vision and reducing inhibitory interactions within the visual cortex.³ Perceptual learning (PL from now on) refers to any rather stable change in the perception of a subject as a result of the experience with one or more stimulus.⁴ The repetitive training of a visual task looks forward to develop the perceptive capacity through the knowledge and the control of the corporal sensations, and in that way, to stimulate the cortical area responsible of the trained function. PL, in some skills (Vernier acuity, position discrimination and contrast sensitivity) seems to transfer, at least partially, to visual acuity improvements and stereoacuity, although it has been suggested that the transfer effect depends on the spatial frequency choice during the training and that the age (at least up to 30 years old) it does not seem to be an important limitation in PL efficacy.⁵ Nowadays it is believed that the alterations in neuronal responses in the visual cortex at a young age are the main cause of the visual disfunction in amblyopia, and the possibility to promote the plasticity of the visual cortex by a non-invasive method, such as PL, has opened a very promising field in amblyopia treatment.⁶ With the development of interactive tools, the PL based in visual stimulation is the new center of attention as a new treatment for amblyopia.

One of the approaches most commonly used to induce PL in amblyopia treatment is Dichoptic Therapy (DT from now on). The treatment for binocular vision using antisuppression dichoptic training is produced by the reduction of the suppression in the visual cortex using stimulus presented simultaneously which are perceived in a separately and different manner in each eye.⁷ Some computerized programs and videogames (VG from now on) have been thoroughly used in the visual cognition field to improve the selective visual attention and some visuospatial skills.⁸⁻¹⁰ In the optometry and ophthalmology field, for more than a decade they have been applied videogames of different types (falling blocks, action and adventure) for amblyopia treatment. The use of VG in the treatment of amblyopia is based in the idea that these can strengthen visual functions such as, VA and stereo acuity.

The conventional treatment for amblyopia is based on the increase of the visual stimulation of the amblyopic eye by occlusion, atropine or the optical penalization of the dominant eye. All of them have been shown effective in the visual improvement, specially in the monocular function. Nevertheless, the management of amblyopia is still a challenge due particularly to problems of compliance and suboptimal results. Recent studies have shown some evidence of different types of amblyopia treatments based in PL (monocular training with grating contrast detection tasks, monocular viewing of action movies and videogames, antisuppression DT, stereopsis training, etc), specially with the restoration of the binocular functions, although these are still under investigation. The main purpose of this article was to study the most recent investigations about amblyopia treatment based in PL and to try to establish the role that they have in these new kinds of treatment. In addition, the results obtained in last investigations that have compared classical occlusion therapy with new kinds of perceptive treatment were analyzed, in order to envisage if PL approach in amblyopia is necessary.

Material and methods

A bibliographic search was conducted using the data base of PubMed, using the following strategies:

- Strategy 1: Amblyopia[Mesh] AND Perceptual Learning[All Fields].
- Strategy 2: Amblyopia[Mesh] AND Dichoptic Therapy OR Dichoptic Training.
- Strategy 3: Video Games OR "Virtual Reality" [Mesh] AND Amblyopia[Mesh].

First documentary search was conducted on January 2019. In order to recover the most recent investigations, the publication date was limited to the last 5 years (from January 2014 to January 2019). The results were also limited to publications referring to humans and in English or Spanish. Databases were reviewed again on June 2020 in order to recover investigations published from February 2019 to June 2020, including 6 more studies. Article selection was conducted in different steps. Titles and abstracts were reviewed for excluding duplicates and those which were not relevant for this study because they did not fit into our study question. Following that, we proceeded to download the complete texts in order to review them, selecting those that fitted into our investigation, evaluating and extraction results. Fig. 1 shows schematically how the search and the systematic selection of the articles for this review took place.

Additionally, the GRADE system (Grading of Recommendations Assessment, Development, and Evaluation) was used, which is used to define the quality of the evidence in systematic reviews and to qualify the strength of the recommendations in guidelines, based on a series of considerations.¹¹

Results

In Table 1 the main methodological characteristics of studies in which our review is based are shown. In Table 2 the results, conclusions and limitations from the same studies as before are detailed.

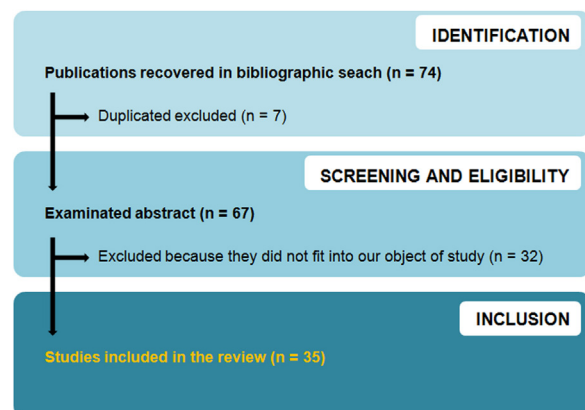


Fig. 1 Flow chart for article selection process.

Table 1 Methodological characteristics of studies included in the review.

Study	Sample type and size	Intervention	Characteristics of the PL group	Outcome measure
Hess et al., 2014 ¹²	<ul style="list-style-type: none"> • N = 14 • Age range: 13–50 years • Type of amblyopia: A(n = 7), S(n = 5), C(n = 2) 	<ul style="list-style-type: none"> • VG (<i>Tetris</i>) in a dichoptic format with lenticular screen (n = 5) or anaglyph (n = 9) presentation in IpadTouch at home • Duration of exposure (both): 10 h to 30 h • Home (both) 	<ul style="list-style-type: none"> • Antisuppression DT (lenticular screen / anaglyphic version) • PVG (<i>Tetris</i>) 	<ul style="list-style-type: none"> • VA • Stereo acuity
Mansouri et al., 2014 ¹³	<ul style="list-style-type: none"> • N = 22 • Age range: 5–73 • Mean age: 36.2 ± 20.3 years • Type of amblyopia: A(n = 7), S(n = 15) 	<ul style="list-style-type: none"> • Random dot kinematograms were presented dichoptically to identify the direction of motion of the targets • Duration of exposure: 2 h/session, 1000 trials/session, 18 sessions, 6 weeks (total: 36 h) • Laboratory / Clinic 	<ul style="list-style-type: none"> • Antisuppression DT (video stereo-google) • Motion identification task (initial contrast of the target and noise dots is 100% and 0% respectively) 	<ul style="list-style-type: none"> • VA
Xi et al., 2014 ¹⁴	<ul style="list-style-type: none"> • N = 11 • Mean age: 21.1 ± 5.1 years • Age range: 11–27 years • Type of amblyopia: A(n = 8), I(n = 3) 	<ul style="list-style-type: none"> • Different texture anaglyphs with different disparities with red/green glasses • Duration of exposure: 10–13 sessions • Laboratory / Clinic 	<ul style="list-style-type: none"> • Stereopsis (anaglyph textures) 	<ul style="list-style-type: none"> • Disparity threshold • Stereo acuity • VA
Zhang et al., 2014 ¹⁵	<ul style="list-style-type: none"> • N = 19 • Mean age: 22.5 years • Age range: 19–27 years • Type of amblyopia: A(n = 12), S(n = 2), C(n = 5) 	<ul style="list-style-type: none"> • Gabor stimulus. Configurations for contrast, orientation and Vernier discrimination at one orientation • 2 stages: low and high spatial frequency • Duration of exposure: 2 h/session, 30 sessions (total: 60 h) • Laboratory / Clinic 	<ul style="list-style-type: none"> • MT • Grating contrast detection (Gabor patch) 	<ul style="list-style-type: none"> • VA • Stereo acuity • CS (untrained orthogonal orientation)
Birch et al., 2015 ¹⁶	<ul style="list-style-type: none"> • N = 50 • Mean age: 5.6 ± 0.9 years • Type of amblyopia: A(n = 16), S(n = 11), C(n = 23) 	<ul style="list-style-type: none"> • Binocular iPad games + patching (n = 45) • Sham iPad games + patching (control) (n = 5) • Duration of exposure (both): iPad: 4 h/week, 4 weeks (total: 16 h); patching: 2 h/day at a different time of game • Laboratory / Clinic (both) 	<ul style="list-style-type: none"> • Antisuppression DT (anaglyphic version) • PVG (Game pieces: blocks, balloons, balls, paddles) 	<ul style="list-style-type: none"> • VA • Stereo acuity

Table 1 (Continued)

Study	Sample type and size	Intervention	Characteristics of the PL group	Outcome measure
Khan et al., 2015 ¹⁷	<ul style="list-style-type: none"> • N = 61 • Age range: 12–30 years • Mean age: 17 years • Type of amblyopia: A(n = 61) 	<ul style="list-style-type: none"> • Occlusion therapy of better eye with on near visual task (VG, computers, mobile phone gaming, colouring patterns) • Duration of exposure: 2–4 h/day, end-point of therapy was considered as stable VA maintained at least three months of occlusion • Home 	<ul style="list-style-type: none"> • MT • Near visual task (VG and others) 	<ul style="list-style-type: none"> • VA
Li SL et al., 2015 ¹⁸	<ul style="list-style-type: none"> • N = 8 • Mean age = 7.4 ± 2.0 years • Age range = 4–10 years • Type of amblyopia: A(n = 3), S(n = 1), C(n = 4) 	<ul style="list-style-type: none"> • Watching 3 dichoptic movies per week, 2 weeks on a passive 3D screen • Duration of exposure: 9.4 ± 0.9 h • Laboratory / Clinic 	<ul style="list-style-type: none"> • Antisuppression DT (polarized version) • Movie viewing 	<ul style="list-style-type: none"> • V • Stereo acuity • Interocular suppression
Li J et al., 2015 ¹⁹	<ul style="list-style-type: none"> • N = 30 • Mean age = 22.2 ± 3.5 years • Age range = 17–31 years • Type of amblyopia: A(n = 20), S(n = 9), C(n = 1) 	<ul style="list-style-type: none"> • Dichoptic VG presented on iPod touch equipped with a lenticular overlay screen combined with tDCS (n = 15) • Dichoptic VG viewed through video goggles combined with MT (n = 15) • Duration of exposure (both): 5 days/week, 2 weeks • Laboratory / Clinic (both) 	<ul style="list-style-type: none"> • MT + Antisuppression DT (video goggles) • tDCS + Antisuppression DT (lenticular screen) • PVG (falling blocks) 	<ul style="list-style-type: none"> • VA • Stereo acuity • CS
Verdamurthy et al., 2015a ²⁰	<ul style="list-style-type: none"> • N = 23 • Mean age = 39.57 ± 15.74 years • Age range = 19–62 years • Type of amblyopia: A(n = 10), S(n = 13) 	<ul style="list-style-type: none"> • Dichoptic action VG (<i>Unreal Tournament 2004</i>) viewed through a stereoscope. • Duration of exposure: 40 h • Laboratory / Clinic 	<ul style="list-style-type: none"> • Antisuppression DT (stereoscope) • PAVG (first-person shooter with Gabor patch). 	<ul style="list-style-type: none"> • VA • Stereo-sensitivity (1/arc seconds) • Gabor resolution acuity • Index for suppression (IOR): • 0 indicates complete suppression • 1 indicates no suppression

Table 1 (Continued)

Study	Sample type and size	Intervention	Characteristics of the PL group	Outcome measure
Verdamurthy et al., 2015b ²¹	<ul style="list-style-type: none"> • N = 38 • Mean age = 39.7 ± 15.4 years • Age range = 19–66 years • Type of amblyopia: A(n = 16), S(n = 22) 	<ul style="list-style-type: none"> • Dichoptic VG (n = 23) • Monocular movies with patching (n = 15) • Duration of exposure (both): 40 h, in sessions lasting 1.5–2 h, 2–5 times/week • Laboratory / Clinic (VG group/movie group) • Home (movie group) 	<ul style="list-style-type: none"> • Antisuppression DT (stereoscope) • PAVG (first-person shooter with Gabor patch) • Monocular viewing of action movies 	<ul style="list-style-type: none"> • VA • Stereo acuity • CS • Reading speed • Self-report of amblyopia state
Chen et al., 2016 ²²	<ul style="list-style-type: none"> • N = 13 (PL group) • Mean age = 18.07 ± 7.84 years • Type of amblyopia: A(n = 13) • N = 10 (Patching group, test-retest) • Mean age = 10.46 ± 3.08 years • Type of amblyopia: A(n = 10) 	<ul style="list-style-type: none"> • Psychophysical suprathreshold binocular summation tasks within one log-unit from their cut-off spatial frequencies. • Duration of exposure: 7–12 days, 10 session/day and 70–100 trials/session (total: 5000–10,000 trials, ≈ 8 h) • Laboratory / Clinic 	<ul style="list-style-type: none"> • MT • Grating contrast detection 	<ul style="list-style-type: none"> • CS • Binocular function • Binocular phase combination • Dichoptic global motion coherence
Dadeya & Dangda, 2016 ²³	<ul style="list-style-type: none"> • N = 40 • Mean age: 6.03 ± 1.14 years • Type of amblyopia: A(n = 40) 	<ul style="list-style-type: none"> • Group A (control): patching alone (n = 20) • Group B (study): play action VG along with patching (n = 20) • Duration of exposure (both): 30 min/week, 12 weeks (total: 6 h) • Laboratory / Clinic (PAVG group) 	<ul style="list-style-type: none"> • MT • Television PAVG (car racing, Battle City, Mario) with hand-eye coordination 	<ul style="list-style-type: none"> • VA • Stereo acuity
Herbison et al., 2016 ²⁴	<ul style="list-style-type: none"> • N = 75 • Age range: 4–8 years • Type of amblyopia: A(n = 5), S(n = 24), C(n = 46) 	<ul style="list-style-type: none"> • I-BiTgame • I-BiT DVD • Non-I-BiT game (control group) • Duration of exposure (all): 30 min/week, 6 weeks (total: 3 h) • Laboratory / Clinic 	<ul style="list-style-type: none"> • Antisuppression DT (interactive binocular game, I-BiT game) • PAVG (shooter game) • Antisuppression DT (interactive binocular DVD, I-BiT DVD) 	<ul style="list-style-type: none"> • VA • Stereo acuity

Table 1 (Continued)

Study	Sample type and size	Intervention	Characteristics of the PL group	Outcome measure
Holmes et al., 2016 ²⁵	<ul style="list-style-type: none"> • N = 385 • Mean age: 8.5 ± 1.9 years • Type of amblyopia: A(n = 199), S(n = 66), C(n = 120) 	<ul style="list-style-type: none"> • Binocular VG in iPad (n = 190) • Patching (n = 195) • Duration of exposure: VG: 1 h/day; patching: 2 h/day (both: 16 weeks) • Home 	<ul style="list-style-type: none"> • Antisuppression DT (anaglyphic version) • PVG (falling blocks) 	<ul style="list-style-type: none"> • VA • Stereo acuity
Kelly et al., 2016 ²⁶	<ul style="list-style-type: none"> • N = 28 • Mean age: 6.7 ± 1.4 years • Age range: 4.6–9.5 years • Type of amblyopia: A(n = 14), S(n = 9), C(n = 5) 	<ul style="list-style-type: none"> • Binocular adventure VG iPad (<i>Dig Rush</i>) (n = 14) • Patching group (n = 14) • Duration of exposure (both): 2 h/day, 7 days/ week, 2 weeks (total: 28 h) • Home (both) 	<ul style="list-style-type: none"> • Antisuppression DT (anaglyphic version) • PAVG (oriented adventure) 	<ul style="list-style-type: none"> • VA • Stereo acuity • Suppression scotoma
Verdamurthy et al., 2016 ²⁷	<ul style="list-style-type: none"> • N = 11 • Mean age = 34.7 years • Age range = 19–56 years • Type of amblyopia: A(n = 2), S(n = 4), C(n = 5) 	<ul style="list-style-type: none"> • Crush a dichoptic virtual insect in an area at an angle, hitting it with a manual physical cylinder • Duration of exposure: 360 trials/session, 35 sessions (8–11 weeks) • Laboratory / Clinic 	<ul style="list-style-type: none"> • Antisuppression DT with stereoscopic cues (VR) • PVG (natural visuomotor task: a 'bug squashing' game) 	<ul style="list-style-type: none"> • Interocular suppression • Stereo acuity • VA • Vergence control
Barollo et al., 2017 ²⁸	<ul style="list-style-type: none"> • N = 10 • Age range = 7–53 years • Type of amblyopia: A(n = 2), S(n = 5), C(n = 1), others (n = 2) • N = 10 (controls, non amblyopic) • Age range = 7.0–51 years 	<ul style="list-style-type: none"> • Training in contrast detection (Gabor patch) • Duration of exposure: 21–93 sessions (16–43 weeks) • Laboratory / Clinic + Home 	<ul style="list-style-type: none"> • MT • Grating contrast detection (Gabor patch) 	<ul style="list-style-type: none"> • CS • AV • Foveal crowding
Bossi et al., 2017 ²⁹	<ul style="list-style-type: none"> • N = 22 • Age range = 3–11 years • Mean age: 6.6 ± 2.9 years • Type of amblyopia: A(n = 7), S(n = 6), C(n = 9) 	<ul style="list-style-type: none"> • Viewing of dichoptic movies and gameplay wearing goggles • Group 1: A; Group 2: S + C • Duration of exposure: group 1: 8 weeks; group 2: 24 weeks (both: 1 h/day) • Home 	<ul style="list-style-type: none"> • Antisuppression DT (shutter glasses) • Viewing movies 	<ul style="list-style-type: none"> • VA • Stereo acuity • Interocular suppression

Table 1 (Continued)

Study	Sample type and size	Intervention	Characteristics of the PL group	Outcome measure
Singh et al., 2017 ³⁰	<ul style="list-style-type: none"> • N = 68 • Mean age: 10 ± 2 years • Type of amblyopia: A(n = 68) 	<ul style="list-style-type: none"> • VG + occlusion (n = 34) • Duration of exposure: VG: 1 h/day, 1 month (total: 30 h); occlusion: 6 h/day, 3 months (total: 540 h) • Home • Occlusion (n = 34) • Duration of exposure: 6 h/day, 3 months (total: 540 h) • Home 	<ul style="list-style-type: none"> • PAVG (Monocular viewing) 	<ul style="list-style-type: none"> • VA • Stereo acuity • CS
Žiak et al., 2017 ³¹	<ul style="list-style-type: none"> • N = 17 • Mean age = 31.2 years • Age range = 17–69 years • Type of amblyopia: A(n = 17) 	<ul style="list-style-type: none"> • 2 different DT games • Duration of exposure: 8 sessions, 20 min/game, 40 min/session (total ≈ 5.5 h) • Laboratory / Clinic 	<ul style="list-style-type: none"> • Antisuppression DT (VR) • PAVG (flying spaceship)+PVG (block breaker) 	<ul style="list-style-type: none"> • VA • Stereo acuity
Gambacorta et al., 2018 ³²	<ul style="list-style-type: none"> • N = 21 • Age range = 7–17 years • Mean age = 9.95 ± 3.14 years • Type of amblyopia: A(n = 12), S(n = 9) 	<ul style="list-style-type: none"> • Dichoptic VG (n = 10) • Monocular VG (n = 11) • Duration of exposure (both): 20 h • Laboratory / Clinic (both) 	<ul style="list-style-type: none"> • Antisuppression DT (stereoscope) • PAVG (game worlds) • MT • PAVG (game worlds) 	<ul style="list-style-type: none"> • VA • Stereo acuity
Gao et al., 2018 ³³	<ul style="list-style-type: none"> • N = 115 • Age range = 7–55 years • 7–12 years (n = 45) • 13–17 years (n = 17) • ≥18 years (n = 53) • Active group (n = 56): Mean age = 22.1 ± 13.9 years • Placebo (n = 59): Mean age = 21.0 ± 13.4 years Years • Type of amblyopia: A(n = 37), S (n = 12), C(n = 61) 	<ul style="list-style-type: none"> • Active group (n = 56) • Placebo (n = 59): same VG with full contrast (no dichoptic presentation) • Duration of exposure (both): 1 h/day, 6 weeks • Home (both) 	<ul style="list-style-type: none"> • Antisuppression DT (anaglyphic version) • PVG (falling blocks) on iPod Touch 	<ul style="list-style-type: none"> • VA • Stereo acuity • Interocular suppression • Quality of life questionnaire

Table 1 (Continued)

Study	Sample type and size	Intervention	Characteristics of the PL group	Outcome measure
Jia et al., 2018 ³⁴	<ul style="list-style-type: none"> • N = 19 • Mean age = 18.5 ± 1.26 years • Type of amblyopia: A(n = 19) 	<ul style="list-style-type: none"> • MT close to its cut off spatial frequency • Duration of exposure: 630 trials/day, 6–10 days • Laboratory / Clinic 	<ul style="list-style-type: none"> • MT • Grating contrast detection 	<ul style="list-style-type: none"> • VA • CS • Stereo acuity • Supression
Kelly et al., 2018 ³⁵	<ul style="list-style-type: none"> • N = 41 • Mean age = 7.0 ± 1.8 years • Age range = 4.4–10.7 years • Type of amblyopia: A(n = 21), S(n = 6), C(n = 14) 	<ul style="list-style-type: none"> • Game group: binocular adventure VG iPad (<i>Dig Rush</i>) (n = 20) • Duration of exposure: 1 h/day, 5 days/week, 2 weeks (total: 10 h) • Home • Movie group: watch binocular movie (n = 21) • Duration of exposure: 6 sessions, 2 weeks (total: 9 h) • Laboratory 	<ul style="list-style-type: none"> • Antisuppression DT (anaglyphic version) • PAVG (oriented adventure) • Antisuppression DT (polarized version) • Movie viewing 	<ul style="list-style-type: none"> • VA • Stereo acuity • Extent of suppression • Depth of suppression
Liu & Zhang, 2018 ³⁶	<ul style="list-style-type: none"> • N = 13 (who completed previous study, Zhang et al., 2014) • Mean age = 24 years • Age range = 21–29 years • Type of amblyopia: A(n = 9), S(n = 1), C(n = 3) 	<ul style="list-style-type: none"> • Gabor stimulus. Configurations for contrast, orientation and Vernier discrimination • DT (after MT in previous study) • Duration of exposure: 2 h/session, 9 sessions (total: 18 h) • Laboratory / Clinic 	<ul style="list-style-type: none"> • Antisuppression de-masking DT (stereoscope with Gabor patch) 	<ul style="list-style-type: none"> • VA • Stereo acuity • CS
Manh et al., 2018 ³⁷	<ul style="list-style-type: none"> • N = 100 • Mean age: 14.3 ± 1.1 years • Type of amblyopia: A(n = 100) 	<ul style="list-style-type: none"> • Binocular VG iPad group (n = 40) • Duration of exposure: 1 h/day (16 weeks) • Home • Patching group (n = 60) • Duration of exposure: 2 h/day (16 weeks) • Home 	<ul style="list-style-type: none"> • Antisuppression DT (anaglyphic version) • PVG (falling blocks) 	<ul style="list-style-type: none"> • VA

Table 1 (Continued)

Study	Sample type and size	Intervention	Characteristics of the PL group	Outcome measure
Mezad-Koursh et al., 2018 ³⁸	<ul style="list-style-type: none"> • N = 27 • Age range = 4–8 years • Mean age: 5 years • Type of amblyopia (treatment group): A(n = 7), S(n = 13), C(n = 7) 	<ul style="list-style-type: none"> • BinoVision (training group) (n = 19) • Duration of exposure: 60 min/day, 6 days/week, 8–12 weeks (total: 48–72 h) • Sham iPad games, equal stimuli for both eyes (control) (n = 8) • Duration of exposure: 60 min/day, 6 days/week, 4 weeks (total: 24 h) • Home 	<ul style="list-style-type: none"> • Antisuppression DT (BinoVision high-tech goggles) • Viewing movies or TV programs 	<ul style="list-style-type: none"> • VA • Stereo
Moret et al., 2018 ³⁹	<ul style="list-style-type: none"> • N = 20 • Age range = 27–58 years • Type of amblyopia: A(n = 20) 	<ul style="list-style-type: none"> • Contrast-detection behavioural training using the lateral masking paradigm + • + hf-tRNS (n = 10) • + Sham stimulation (control) (n = 10) • Duration of exposure (behavioural training): 8 sessions, 45 min/session, 2 weeks (total: 6 h/3840 trials) • Duration of exposure (stimulation): 25 min (both groups) • Laboratory / Clinic 	<ul style="list-style-type: none"> • MT • Grating contrast detection (Gabor patch) 	<ul style="list-style-type: none"> • VA • CS
Portela et al., 2018 ⁴⁰	<ul style="list-style-type: none"> • N = 32 • Age range = 7–14 years • Type of amblyopia: Ani and/or strab • A(n = 2), S(n = 18), C(n = 10) 	<ul style="list-style-type: none"> • Experimental group (n = 16): initial stimulation interval depended on the value of the stereopsis at baseline. • Comparison group (n = 16): stimulation interval was constant from 840 to 750". • Duration of exposure (both): 5 sessions/week, 12 weeks or less, 4800 responses, 60 sessions (total: 8 h) • Home (both) 	<ul style="list-style-type: none"> • Stereopsis (Random Dot Stimuli) • PVG 	<ul style="list-style-type: none"> • Stereo acuity

Table 1 (Continued)

Study	Sample type and size	Intervention	Characteristics of the PL group	Outcome measure
Holmes et al., 2019 ⁴¹	<ul style="list-style-type: none"> • N = 138 • Mean age = 9.6 years • Age range = 7–12 years • Type of amblyopia: A(n = 66), S(n = 26), C(n = 46) 	<ul style="list-style-type: none"> • Binocular adventure VG iPad (<i>Dig Rush</i>)+spectacle correction (n = 69) • Spectacle correction alone (control) (n = 69) • Duration of exposure (both): 1 h/day, 5 days/week, 8 weeks (total: 40 h) • Home (both) 	<ul style="list-style-type: none"> • Antisuppression DT (anaglyphic version) • PAVG (oriented adventure) 	<ul style="list-style-type: none"> • VA • Stereo acuity • Cover test
Law & Backus 2019 ⁴²	<ul style="list-style-type: none"> • N = 19 • Mean age = 27.9 years • Age range = 16–50 years • Type of amblyopia: A(n = 17), C(n = 2) 	<ul style="list-style-type: none"> • Mixed-contrast (n = 9): higher contrast to the amblyopic eye. • Fixed-contrast (n = 10): contrast was the same in both eyes. • Duration of exposure (both): 10 weeks, 45'/session, 10 sessions, 160 trials/session (total: 1600 trials, 7.5 h) • Laboratory / Clinic (both) 	<ul style="list-style-type: none"> • Antisuppression DT with stereoscopic cues (stereoscope) 	<ul style="list-style-type: none"> • Composite stereodepth (CSD) score: mapped stereoacuity thresholds and percent correct on highdisparity trials onto a single range of 0–20. Scores from 0 to 13.3 are given over to stereoacuity values, and scores from 13.3–20 are given over to percent correct.
Liu & Zhang, 2019 ⁴³	<ul style="list-style-type: none"> • N = 11 • Mean age = 23 years • Age range = 19–28 years • Type of amblyopia: A (n = 8), C(n = 3) 	<ul style="list-style-type: none"> • Gabor stimulus. Configurations for contrast and orientation discrimination • Group 1 (n = 6): contrast training and then orientation exposure; Group 2 (n = 5): orientation exposure and then contrast training • A subset of participants (n = 6) then performed orientation MT (9 sessions). • Duration of exposure (DT): 2 h/session; 800 1000 trials/session (5 sessions; total: 10 h) • Duration of exposure (MT): 2 h/session; 800 1000 trials/session (9 sessions; total: 18 h) • Laboratory / Clinic (both) 	<ul style="list-style-type: none"> • Antisuppression de-masking[‡] DT (stereoscope with Gabor patch) • Antisuppression DT (stereoscope with Gabor patch) + MT • [‡] discounting the masking effect from a noise masker presented to the fellow-eye 	<ul style="list-style-type: none"> • VA • Stereo acuity • CS

Table 1 (Continued)

Study	Sample type and size	Intervention	Characteristics of the PL group	Outcome measure
Sauvan et al., 2019 ⁴⁴	<ul style="list-style-type: none"> • N = 17 • Mean age = 34 years • Age range = 9–67 years • Type of amblyopia: A (n = 11), S (n = 2), C (n = 4) 	<ul style="list-style-type: none"> • DT or nonpatched group (n = 10) • Patched group (n = 7) (patching over AE two hours prior to each DT) • Duration of exposure (both): 6 sessions, 1.5 h/sesión (total: 9 h) • Laboratory / Clinic (both) 	<ul style="list-style-type: none"> • Antisuppression DT (polarized version) • Movie viewing 	<ul style="list-style-type: none"> • VA • Stereo acuity • Interocular suppression
Birch et al., 2020 ⁴⁵	<ul style="list-style-type: none"> • N = 48 • Mean age = 6.8 ± 1.8 years • Age range = 4.3–10.8 years • Type of amblyopia: A (n = 27), S + C (n = 21) 	<ul style="list-style-type: none"> • Game group: binocular adventure VG iPad (<i>Dig Rush</i>) (n = 24) • Duration of exposure: 1 h/day, 5 days/week, 2 weeks (total: 10 h) • Home • Patching group (n = 24) • Duration of exposure: 2 h/day, 7 days/week, 2 weeks (total: 28 h) • Home 	<ul style="list-style-type: none"> • Antisuppression DT (anaglyphic version) • PAVG (oriented adventure) 	<ul style="list-style-type: none"> • VA • Stereo acuity • Extent of suppression
Gu et al., 2020 ⁴⁶	<ul style="list-style-type: none"> • N = 46 • Mean age = 15.9 ± 4.0 years • Age range = 12–25 years • Type of amblyopia: A (n = 46) • N = 12 • Mean age = 24.4 ± 3.2 years • Age range = 21–30 years • Normal vision 	<ul style="list-style-type: none"> • MT + patching (n = 27) • Duration of exposure: MT: 10 sessions/day, 70–100 trials/sessions, 7–14 days (total: 5,000–10,000 trials, 8 h); patching: 2 h/days, 7–14 days. • Laboratory / Clinic • Patching group (n = 5) • Duration of exposure: patching: 2 h/day, 10–13 days • Home 	<ul style="list-style-type: none"> • MT • Grating contrast detection (Gabor patch) 	<ul style="list-style-type: none"> • VA • CSF • Stereo acuity • Interocular balance • SSVEPs

Note: A: anisometric amblyopia; AE: amblyopic eye; BiT: binocular treatment; C: combined mechanism amblyopia (i.e., strabismic and anisometric); cpd: cycles per degree; CS: contrast sensitivity; DT: dichoptic therapy; h: hour/ hours; hf-tRNS: high-frequency transcranial random noise stimulation; I: isometric; IOR: interocular ratio; min: minutes; MT: monocular training; PL: perceptual learning; S: strabismic amblyopia; SSVEPs: Steady-state visually evoked potentials; tDCS: transcranial direct current stimulation; VA: visual acuity; VG: video game; VR: virtual reality. Both refers applied equally to both groups.

Types of training based on PL for amblyopia

Over the last years several investigations have been conducted, in which the effect that different approaches have in amblyopia treatment through PL has been analyzed.^{12–46} One of the approaches is monocular training (MT), which consists in making tasks while the dominant eye is occluded, the aim is that the amblyopic eye is stimulated. In some studies, MT has been conducted using grating contrast detection (Gabor patch)^{15,22,28,30,34,39,46} while other studies have used monocular videogames viewing in order to stimulate the amblyopic eye.^{17,23,30} It has been seen that both types of treatment improve VA,^{15,17,22,13,28,30,34,39,46} while contrast sensitivity (CS, from now on) improves when grating patterns are used, more specifically those frequencies near the cutoff frequency.^{15,34,46} The studies which have analyzed the grade of improvement in stereoacuity with monocular training have positive results,^{15,22,23,34,46} although it has not been like that when the treatment is used for children and using a similar time of treatment or, even higher, compared with those which have improved stereoscopic function.⁴⁰

The other treatment approach for amblyopia through PL is the so called DT, which has been used over the last years in several investigations in order to reduce suppression and to improve binocular function using the presentation of different information to each eye.^{12,13,16,18–21,24–27,29,31–33,35–38,41–45} The basis used in DT are different though different studies using anaglyphs,^{12,16,25,26,33,35,37,41,45} stereoscopes,^{20,21,32,36,42–44} lenticular screen,^{12,19} virtual reality,^{27,28} polarized lens,¹⁸ and other types of mechanisms used to improve binocular vision (e.g., video stereo-goggles, liquid crystal shutter glasses).^{13,19,24,29,38} In general, an improvement in VA has been noticed using this type of dichoptic procedures,^{12,13,16,18,20,21,24–26,29,31,32,35,38,43–45} though some studies conducted in children⁴¹ and in adult patients^{27,33,36} have failed to show that evidence.

Regarding the improvement in stereopsis, the results are unlike, so some investigations^{12,20,21,27,29,31,35,36,42,43} have shown an improvement of the binocular function, even though the intervention has been conducted in adult population,^{12,20,21,27,31,36,42,43} while other investigations have not proved this improvements even though the treatment has been conducted in children.^{16,18,24,25,26,44} In order to use suppression, which has not always been analyzed, different findings have been obtained, while some authors have obtained a reduction of suppression in children³⁵ and in adults,^{20,27} other authors have not obtained these improvements.^{16,18,25,26,44} CS is another function which can be improved using dichoptic therapy.^{19,20,21,43}

In other investigations they have explored if the two types of treatments mentioned (monocular and dichoptic) can have different effects over the improvement of the evaluated visual functions in amblyopic patients. For example, in one of the investigations²¹ it has been seen through an action video game in DT format, the improvements in VA are significantly better than monocular viewing of action movies, although both treatments are equally effective in the improvement of CS, stereoacuity and reading speed. In a similar way, in a different investigation³² it has been seen

that antisuppression DT produces better increments in VA, although not in stereopsis compared to MT. In other investigation, with a crossover design,¹⁹ because improvements were small in the monocular group, this group was crossed over to DT for 10 days longer once the monocular training was completed in order to assess whether additional improvements would occur. Authors found out that DT was more effective at improving CS than monocular training, suggesting that this kind of DT modifies the sensitivity of the neural systems that underpin monocular CS. In other studies, they have compared the effects of occlusion classical therapy with the ones produced by the use of VG with iPad in a DT format,^{25,26,37,45} with the viewing of VG in monocular conditions,^{23,30} or with grating contrast detection tasks.^{22,46} While some authors have seen that DT produce higher improvements in VA than occlusion therapy,^{26,45} other authors have not seen those differences.^{25,37} Studies which have compared the effectivity obtained in VG viewing in monocular condition compared to the improvements obtained with patching therapy have demonstrated that PL in monocular conditions is more effective.^{23,30} Meanwhile Chen et al.²² have not concluded if there are differences between both techniques (monocular task of detecting contrast patterns vs. patching) in terms of visual improvements. The gain produced using DT has also been compared to the gain obtained with a simple refractive grating with glasses, finding that increments in VA after 4 weeks of treatment is similar between patients that only wear glasses and those who besides wearing glasses conduct dichoptic therapy using VG.⁵¹ Other investigations have been centered in analyze different effects in the improvements produced in VA, CS, stereopsis and suppression when DT is applied by itself or when combined with MT⁴³ or with patching,⁴⁴ in other studies it has been seen that MT combined with a high-frequency transcranial random noise stimulation is more effective for VA improvement than MT by itself.³⁹

As previously mentioned, there exists some divergence in the results obtained about the improvement that can be achieved in stereopsis in a training based in DT antisuppression. This fact has motivated, at least partially, that some authors have used the paradigm of directly training stereoscopic vision through PL in order to restore depth vision. And it has been suggested that training using stereograms can stimulate neurons that respond to disparity.⁴⁷ For example, Xi et al.¹⁴ using different texture anaglyphs with different disparities found an improvement in disparity threshold, stereoacuity and VA. In a similar way, in another study²⁷ that used DT with stereoscopic cues in a virtual reality environment, that also found a significant reduction of the suppression and an improvement in stereoacuity, even though it is a trend to an improvement in VA. Portela et al.⁴⁰ using VG in Random Dot stimuli format, and have found a significant improvement of stereoacuity in two levels on Wirt Circles and stereoacuity 140 s of arc or less, besides *stereopsis* remained stable after 6 months when it was measured with the Randot Preschool Stereoacuity Test.

Use of VG as a resource of PL in amblyopia

The investigation about the use of VG has increased over the last years, in an effort to improve the level of

Table 2 Most relevant results, conclusions and limitations of studies included in the review.

Study	Results	Limitations / recommendations exposed by the authors	Compliance
Hess et al., 2014 ¹²	<ul style="list-style-type: none"> • Binocular perception improved in 13 of 14 cases • VA: 1.1 lines^{***} • Stereo: 0.61 log units^{***} • The anaglyph and lenticular platforms were equally effective 	<ul style="list-style-type: none"> • Unspecified 	<ul style="list-style-type: none"> • Considerable variability, 9 of 14 (85.7%) achieving close to the expected levels or above expected levels
Mansouri et al., 2014 ¹³	<ul style="list-style-type: none"> • VA: 3.4 lines^{**} • Follow-up (6 months): Improvement VA is maintained^{**} • Increased significantly as a function of the number of sessions completed ($r^2 = 0.27^*$) 	<ul style="list-style-type: none"> • It would be necessary to determine the number sessions to maximize the result and the minimum number of sessions needed to treatment 	<ul style="list-style-type: none"> • Although no compliance data is provided, pre-post results of the 22 participants are presented, so it is understood that all of them completed the training. Mean 146 sessions over a period of 4–6 weeks
Xi et al., 2014 ¹⁴	<ul style="list-style-type: none"> • VA: 0.9 lines[*] • Stereo: 200.3" to 81.6" ^{**} • Disparity threshold: 776.7" to 490.4" ^{**} • 2 of the 3 subjects reevaluated maintained the effects in VA and stereo at 5 months reevaluation 	<ul style="list-style-type: none"> • Unspecified 	<ul style="list-style-type: none"> • Although no compliance data is provided, pre-post results of the 11 participants are presented, so it is understood that all of them completed the training
Zhang et al., 2014 ¹⁵	<ul style="list-style-type: none"> • VA: 1.55 lines^{***} • Stereo: 53%^{***} • CS: specially on high spatial frequencies near the cutoff frequency^{**} 	<ul style="list-style-type: none"> • Unspecified 	<ul style="list-style-type: none"> • All participants completed the first stage. Only a subset of them (63.15%) completed the second stage. 58.33% completed training at an oblique orientation
Birch et al., 2015 ¹⁶	<ul style="list-style-type: none"> • VA: 0.2 lines^{ns} (Sham iPad); 0.9 lines^{***} (Binocular iPad) • Stereo acuity: (ns) 	<ul style="list-style-type: none"> • Not a randomized clinical trial, cohort study • Patching at a different time was allowed, which can be a confusion factor 	<ul style="list-style-type: none"> • Binocular iPad game play time of 16 h was reported to be $\geq 50\%$ by 62% of the participants
Khan et al., 2015 ¹⁷	<ul style="list-style-type: none"> • VA: 6 lines^{***} 	<ul style="list-style-type: none"> • Small sample size • Short follow-up time 	<ul style="list-style-type: none"> • Although no compliance data is provided, pre-post results of the 61 participants are presented, so it is understood that all of them completed the training

Table 2 (Continued)

Study	Results	Limitations / recommendations exposed by the authors	Compliance
Li SL et al., 2015 ¹⁸	<ul style="list-style-type: none"> • VA: 2.0 lines** • Suppression^{ns} • Stereo^{ns} 	<ul style="list-style-type: none"> • Small sample size • Anecdotal nature of the data, it is not possible to draw firm conclusions 	<ul style="list-style-type: none"> • All children completed the study
Li J et al., 2015 ¹⁹	<ul style="list-style-type: none"> • CS: improved across all spatial frequencies tested for both groups • No significant correlation between the change in CS and changes in VA or suppression in neither group 	<ul style="list-style-type: none"> • Data were combined from two different studies that used different experimental designs • Both groups of participants were not directly matched in terms of age and amblyopic eye VA • CS measured at a relatively high mean luminance 	<ul style="list-style-type: none"> • Although no compliance data is provided, pre-post results of the 30 participants are presented, so it is understood that all of them completed the training
Verdamurthy et al., 2015a ²⁰	<ul style="list-style-type: none"> • VA: 1.4 lines** • Stereo (1/arcsec): 0.007* • CS: 3.07 cpd** • IOR increased by a factor of ≈ 1.6, indicating a reduction in suppression* • The reduction in suppression was not significantly correlated with the improvement in the visual function • Stereopsis improved in 9 subjects (39%), of 200 in 20 arcseg (a 10 factor) 	<ul style="list-style-type: none"> • The participants were "A" and "S" amblyopic patients, it would be necessary to conduct a randomized clinical trial in a large population of amblyopia to determine the most effective method according to the type of amblyopia 	<ul style="list-style-type: none"> • Compliance data unespecificied
Verdamurthy et al., 2015b ²¹	<ul style="list-style-type: none"> • VA: 1.4 lines*** (game group); 0.7 lines*** (movie group) • VA (difference between groups): 0.7 lines* • Stereo acuity: Overall significant change**, but no difference between groups^{ns} • CS: Overall significant change*, but no difference between groups^{ns} • No effect for timeXgroup in reading speed^{ns} • Most improvements were largely retained following a 2-month no-contact period 	<ul style="list-style-type: none"> • Dichoptic VG intervention required that subjects receive extensive training (40 h) in the laboratory, which resulted in a large drop-out rate (38%) 	<ul style="list-style-type: none"> • Drop-out rate 38% vs 28% in VG group and movie group, respectively

Table 2 (Continued)

Study	Results	Limitations / recommendations exposed by the authors	Compliance
Chen et al., 2016 ²²	<ul style="list-style-type: none"> • VA (PL group): 1.64 lines^{***} • CS (PL group): Significantly improved^{***}and it varies with frequency^{***} • Stereo (PL group): Increases significantly* 	<ul style="list-style-type: none"> • Test-retest reliability was assessed in a patching group instead of a non-intervention group because of the regulation of clinical practice • There were not well matched in terms of age and interventional periods between both groups • Patching could be considered as a confounding factor (too short-term monocular deprivation) 	<ul style="list-style-type: none"> • Compliance data unespecifed
Dadeya & Dangda, 2016 ²³	<ul style="list-style-type: none"> • VA: 2.9 lines^{***} (group A); 4.2 lines^{***} (group B) • VA (difference between groups): 1.3 lines^{**} • Stereo acuity: (Group A): 5 subjects had 200 arcseg; (group B): 7 subjects had 100 arcseg 	<ul style="list-style-type: none"> • Small sample size • Short duration of exposure • Initial dropouts have been excluded from analysis • Lack of objectively recorded compliance at home for both groups 	<ul style="list-style-type: none"> • Compliance to the VG was fully ensured as the examiner was present throughout the session and monitored each child
Herbison et al., 2016 ²⁴	<ul style="list-style-type: none"> • VA: \approx 0.7 lines in all three groups at 6 and 10 weeks^{***} • VA (difference between groups): No difference between I-BiT DVD (1 line) and non-I-BiT games (0.3 lines) compared with I-BiT games (0.6 lines) in terms of gain in vision^{ns} • Stereo: No significant changes in any of the three groups^{ns} 	<ul style="list-style-type: none"> • Short duration of treatment, and duration and frequency of the sessions • High proportion of patients with strabismic (93%) and residual amblyopia (89%) 	<ul style="list-style-type: none"> • With each of the treatments was excellent (>90%) with the majority of participants playing the game/watching the DVD for 30 min at each session
Holmes et al., 2016 ²⁵	<ul style="list-style-type: none"> • VA: 1.05 lines (binocular); 1.35 lines (patching) • VA (difference between groups): 0.3 lines^{ns} • VA (5 to <7 years without prior amblyopia treatment): 2.5 lines (binocular) and 2.8 lines (patching) • Stereo: did not differ significantly between treatment groups for the overall cohort or for participants with no history of strabismus at baseline 	<ul style="list-style-type: none"> • Compliance data were monitored by the parent's report for the patching group and for the time connected to the game for the game group. In both cases there could be errors in compliance monitoring • Compliance with the use of the red-green glasses required to play the game was not monitored 	<ul style="list-style-type: none"> • 22% achieved greater than 75% compliance. See 'limitations'

Table 2 (Continued)

Study	Results	Limitations / recommendations exposed by the authors	Compliance
Kelly et al., 2016 ²⁶	<ul style="list-style-type: none"> • VA: 1.5 lines^{***} (binocular); 0.7 lines^{**} (patching) • VA (difference between groups): 0.8 lines[*] • No differences between the binocular game vs patching treatments for change in stereo^{ns}, extent of suppression^{ns} and depth of suppression^{ns} 	<ul style="list-style-type: none"> • Small sample size. • Short duration of treatment, it is necessary to analyze the effects of treatment in the longer-term • Unassessed baseline factors (ie, BCVA, age) that may be important modifiers of treatment effect 	<ul style="list-style-type: none"> • 85% (23 of 27) of children played at least 75% of prescribed treatment
Verdamurthy et al., 2016 ²⁷	<ul style="list-style-type: none"> • VA: just a trend for improved (p = .06) • Stereo: Significant change[*] • Suppression: Significantly reduced^{***}. These effects were retained at follow-up^{**} • For the stereo-deficient group, no significant differences in noise vergence measured pre-training, post-training and at follow-up (p = .36). • Follow-up 2 month post-training: 5 out of 6 subjects maintained improvements in stereo[*] 	<ul style="list-style-type: none"> • Vergence measure is a subjective measure, and not be sufficiently sensitive to detect very small changes in oculomotor control. • Training was carried out in a virtual reality environment, trying to recreate a natural environment. 	<ul style="list-style-type: none"> • Compliance data unespecificied
Barollo et al., 2017 ²⁸	<ul style="list-style-type: none"> • VA: 1.8 lines^{**} (after PL) and 0.9 lines[*] (follow up 5–7 months post-training) • Vernier acuity: just a trend for improved (p = .06) • Reduction of crowding[*] • CS: Significant change at intermediate spatial frequencies (7 cpd) after PL[*] and follow-up[*] 	<ul style="list-style-type: none"> • A direct comparison can not be made with previous results 	<ul style="list-style-type: none"> • Compliance data unespecificied
Bossi et al., 2017 ²⁹	<ul style="list-style-type: none"> • VA (overall): 2.7 lines^{***} • VA (group 1): 2.6 lines • VA (group 2): 2.7 lines • VA (difference between groups)^{ns} • Stereo (group 1): Improvement was 165 ± 182''[*] • Suppression: no reduction^{ns} 	<ul style="list-style-type: none"> • Treatment duration varied across children • Small sample size 	<ul style="list-style-type: none"> • Compliance (calculated as the percentage of days when treatment was received) was 68.0 ± 12.2%. On average, 89.4 ± 24.2% of daily dose (54' /day; total: 75 h)

Table 2 (Continued)

Study	Results	Limitations / recommendations exposed by the authors	Compliance
Singh et al., 2017 ³⁰	<ul style="list-style-type: none"> • VA: 1 line^{***} (VG + occlusion); 0.5 lines^{***} (occlusion) at 1 month • VA: 2.1 line^{***} (VG + occlusion); 1.7 lines^{***} (occlusion) at 3 months • VA (difference between groups): 0.5 lines^{**} (1 month); 0.4 lines[*] (3 months) 	<ul style="list-style-type: none"> • Long-term studies with weaning of occlusion therapy may be required to assess for the recovery of stereo 	<ul style="list-style-type: none"> • Patients who failed to follow-up at 1 month or follow the prescribed therapy or who had poor compliance were excluded. No further data specified
Žiak et al., 2017 ³¹	<ul style="list-style-type: none"> • VA: 1.5 lines^{**} • Stereo: 263.3 ± 135.1–176.7 ± 152.4 arcseg^{**} 	<ul style="list-style-type: none"> • Small sample size • Short follow-up • Absence of a control group • Stereo test used measures values of 400" as max. 	<ul style="list-style-type: none"> • Although no compliance data is provided, pre-post results of the 17 participants are presented, so it is understood that all of them completed the training
Gambacorta et al., 2018 ³²	<ul style="list-style-type: none"> • VA: 1.4 lines (≈38%) (DT group); 0.6 lines (≈15%) (MT group) • VA (difference between groups): 0.8 lines (3.14)^a • VA: 1.1 lines (A) and 0.7 (S) (Cohen's $d = 1.33$)[*] • Stereo: improved ≈17% (DT) and ≈15% (MT) (0.1)^a • Follow-up 6–10 weeks pos-training: VA and stereo improvements were maintained in 57% of the participants at follow-up^{***}, and improvements did not differ between both groups^{ns} 	<ul style="list-style-type: none"> • General dropout rate of 28% perhaps due to visits to the laboratory (2–3 times per week). • Small sample size 	<ul style="list-style-type: none"> • 21 of 29 subjects (72%) completed 20 h of training under supervision with number of weeks to completion varying widely between participants (from 3 to 20 weeks) • Drop-out rate was about 31% for the MT group and 23% for DT group
Gao et al., 2018 ³³	<ul style="list-style-type: none"> • VA: 0.6 lines^{ns} (active group); 0.7 lines^{ns} (placebo group). • VA (difference between groups)^{ns} • No difference for changes of any secondary outcomes were found between both groups^{ns} 	<ul style="list-style-type: none"> • Unable to monitor participants' attention to the video game at home or whether they wore anaglyphic glasses correctly. 	<ul style="list-style-type: none"> • Compliance with more than 25% (≥10.5 h) was achieved in 64% (active group) and 83% (placebo group) of participants

Table 2 (Continued)

Study	Results	Limitations / recommendations exposed by the authors	Compliance
Jia et al., 2018 ³⁴	<ul style="list-style-type: none"> • VA: 1.7 lines** • CS: an improvement of 278.4% at the trained spatial frequency** • Stereo: 929.11" to 80.42" * • Suppression^{ns} • Dominance duration ratio (amblyopic eye): 9%–15%* 	<ul style="list-style-type: none"> • Training time too short 	<ul style="list-style-type: none"> • Compliance data unespecificed
Kelly et al., 2018 ³⁵	<ul style="list-style-type: none"> • VA: 1.4 lines*** (VG group) • Stereo: Significant change* (VG group) • Suppression: Extent/depth of suppression were reduced** (VG group) • Depth of suppression was reduced more in children aged <8 years than in those aged ≥8 years** 	<ul style="list-style-type: none"> • Pooled data from two ongoing studies of binocular treatment and was limited in that there was no control group 	<ul style="list-style-type: none"> • Game group: 87% prescribed treatment time • Movie group: 100% prescribed treatment time
Liu & Zhang, 2018 ³⁶	<ul style="list-style-type: none"> • VA^{ns} • Stereo: 146.9" to 103.1" ** • Maximal tolerable noise contrast*** • Improvements persist for 10 months after DT in 54% cases 	<ul style="list-style-type: none"> • Results based on 70% of cases with type A amblyopia • Results may be specific to the training used • Small sample size, and not run a control group 	<ul style="list-style-type: none"> • Although no compliance data is provided, pre-post results of the 13 participants are presented, so it is understood that all of them completed the training
Manh et al., 2018 ³⁷	<ul style="list-style-type: none"> • VA: 0.74 lines (binocular group); 1.26 lines (patching group) • VA (difference between groups): 0.52 lines^{ns} 	<ul style="list-style-type: none"> • Poor treatment adherence 	<ul style="list-style-type: none"> • Binocular group (data from the iPad device for 97% of participants): 13% of participants completed >75% of the prescribed treatment
Mezad-Koursh et al., 2018 ³⁸	<ul style="list-style-type: none"> • VA (training group, 12 weeks): 2.6 lines** • VA (control group, 4 weeks)^{ns} • VA (difference between groups)** • VA (training group, follow-up 24 weeks): remained stable** • Improvement is greater the longer the treatment time 	<ul style="list-style-type: none"> • Nonrandomized study • Small sample size • Most subjects were previously treated and had residual amblyopia • No compare the effectiveness on different types of amblyopia 	<ul style="list-style-type: none"> • All 19 patients in the treatment group completed 8 weeks of treatment; 16 (84%) completed 12 weeks of treatment.

Table 2 (Continued)

Study	Results	Limitations / recommendations exposed by the authors	Compliance
Moret et al., 2018 ³⁹	<ul style="list-style-type: none"> • VA (training group): 1.9 lines^{***} • VA (control group)^{ns} • VA (difference between groups) • VA (training group, follow-up 6 months): remained stable^{**} • CS: significantly improved in both groups^{***} • CS (difference between groups)^{ns} 	<ul style="list-style-type: none"> • unespecified 	<ul style="list-style-type: none"> • Although no compliance data is provided, pre-post results of the 20 participants are presented, so it is understood that all of them completed the training.
Portela et al., 2018 ⁴⁰	<ul style="list-style-type: none"> • Stereo: Improvement with RPST was 50% (RPST) and 46.42% (Wirt Circles) and it was statistically different when success was considered a gain of two levels on Wirt Circles and stereoacuity 140" or less[*] • Stereo remained stable after 6 months when measured with RPST 	<ul style="list-style-type: none"> • Computer and software settings: stimulation category be set manually, but it should be automatic according to the patient's evolution <small>Martin et al., 2020</small> • Study design: Too small sample of subjects with type A amblyopia; age range was restricted to 7–14 years; the stereoacuity range was between 800"-200" <small>Martin et al., 2020</small> 	<ul style="list-style-type: none"> • 100% compliance was considered if patients finished the training in less than 12 weeks (5 sessions/week). Compliance was excellent, with a median percentage value of 88.36%
Holmes et al., 2019 ⁴¹	<ul style="list-style-type: none"> • VA (4 weeks): 0.26 lines (binocular group); 0.34 lines (control group) • VA (difference between groups): 0.08 lines^{ns} • No difference for changes of any secondary outcomes were found between both groups ^{ns} • Analyzing possible differential treatment effect by baseline characteristics, no factors were found to be statistically significant, including basal stereo acuity 	<ul style="list-style-type: none"> • Possible biases due to the lack of correct monitoring (not playing for the entire time that the handheld device recorded, not wear the red-green glasses) 	<ul style="list-style-type: none"> • Spectacle wear (across 8 weeks, >75% of time): 90% (binocular) 98% (control) • PAVG (across 8 weeks, >75% of time): parent report: 75%; log file data: 56% • Median total hours of game play was 31 h of the intended 40 h at 8 weeks
Law & Backus 2019 ⁴²	<ul style="list-style-type: none"> • 44% of participants (mixed-contrast group) showed improvement in stereodepth individually*, none (fixed-contrast group) showed improvement individually^{ns} • Stereodepth (difference between groups)[*] 	<ul style="list-style-type: none"> • Training relatively sparse and only 1–2 sessions per week for a total of 10 sessions. It is possible that learning would be greater with additional or more frequent training 	<ul style="list-style-type: none"> • Although no compliance data is provided, first four and last four sessions results of the 19 participants are presented, so it is understood that all of them completed the training

Table 2 (Continued)

Study	Results	Limitations / recommendations exposed by the authors	Compliance
Liu & Zhang, 2019 ⁴³	<ul style="list-style-type: none"> • VA: 1.2 lines** (clinical E-Chart and single-E computerized); 0.8 lines* • Stereo: 60.2 ± 4.9%*** • CS: mainly at higher spatial frequencies** • Additional MT did not produce further AV and stereoacuity gains 	<ul style="list-style-type: none"> • Results based on >70% of cases with type A amblyopia • Results may be specific to the training used • Small sample size • No follow-up 	<ul style="list-style-type: none"> • Although no compliance data is provided, pre-post results of the 11 participants are presented, so it is understood that all of them completed the training
Sauvan et al., 2019 ⁴⁴	<ul style="list-style-type: none"> • VA: 0.8 lines** (nonpatched group); 1.9 lines** (patched group) • VA (difference between groups): 1.1 lines^{ns} • VA (follow-up 1 month): Improvement VA is maintained only in the patched group** • CS, stereo, interocular suppression^{ns} 	<ul style="list-style-type: none"> • Non-homogeneous groups • Non-randomization • Short period of training • Better measure of stereopsis • More sensitive test of binocular balance • Extend the periods of occlusion to see if its benefits for DT can be enhanced 	<ul style="list-style-type: none"> • Although no compliance data is provided, pre-post results of the 17 participants are presented, so it is understood that all of them completed the training
Birch et al., 2020 ⁴⁵	<ul style="list-style-type: none"> • VA: 1.5 lines (game group); 0.7 lines (patching group) • VA (difference between groups): 0.8 lines** • 35% of children of binocular game had recovered normal VA. Only 8% of the children in the patching group recovered normal VA for age • Only in the game group, baseline VA and ocular alignment were associated with response to treatment ($p < .001$). Age, etiology, prior treatment and baseline stereo were not associated with response to treatment • Dose-response: Only in the game group, moderate linear relationship between hours of game with VA improvement. 5 h (50% adherence) improved 0.1 logMAR; 10 h (100%), 0.18 logMAR; 15 h (150%) 0.26 logMAR 	<ul style="list-style-type: none"> • Single-site, small-cohort randomized clinical trial • The inclusion/exclusion criteria may limit generalization to other groups of amblyopic children • VA testing was not masked • Results may be dependent on the criteria chosen to dichotomize each variable • The brief duration may limit improvement of VA • Possible biases due to the lack of correct monitoring (number of hours of patching objectively, not wear the red- green glasses) 	<ul style="list-style-type: none"> • Parents overestimated time spent playing the game by 13% • Game group completed 10.3 ± 3.0 h (103% prescribed treatment time) • Patching group completed 27.7 ± 2.6 h (99% prescribed treatment time)

Table 2 (Continued)

Study	Results	Limitations / recommendations exposed by the authors	Compliance
Gu et al., 2020 ⁴⁶	<ul style="list-style-type: none"> • VA^{***}, CS^{***}, stereopsis* and interocular difference^{**} improved through behavioral measurements and SSVEP in MT group • (Due to the length of the results, it is recommended to see the results section in the original article) 	<ul style="list-style-type: none"> • Control group had only five subjects • Training effects may be due to the influences of both training and patching • Effects of patching were not entirely ruled out in this study. Further investigations with more subject and only training (no patching) are necessary 	<ul style="list-style-type: none"> • Although no compliance data is provided, pre-post results of the 32 (out of 46) participants are presented, so it is understood that not everyone completed the training

Note: A: anisometropic amblyopia; BCVA: Best corrected visual acuity; BiT: binocular treatment; cpd: cycles per degree; CS: contrast sensitivity; DT: dichoptic therapy; h: hour/ hours; IOR: interocular ratio; min: minutes; MT: monocular training; ns: no significance; PL: perceptual learning; S: strabismic amblyopia; SSVEPs: Steady-state visually evoked potentials; VA: visual acuity; VG: video game.

^a Cohen's "d" effect size has been calculated when the p-value is not shown in the study, but means and SD are shown ($d \geq 0.80$ is considered a large effect size). "Both" refers applied equally to both groups. The average improvement in VA lines is always referred from the baseline.

* $p < 0.05$;

** $p < .01$;

*** $p < .001$.

compliance of the patient and so the therapy for amblyopia will be more effective. Of the 35 studies gathered in this review, 18 of them (51.4%) use PL through several videogames of different contents, such as pieces and falling blocks^{12,16,19,25,31,33,37} and VG based on action or adventure.^{20,21,23,24,26,30,31,32,35,41,45} It is rare that VG are used in a form of PL in a monocular way, but some authors have conducted this type of treatment in order to analyse the visual improvements produced.^{23,30} In these studies with anisometropic amblyopes have compared the interaction with action VG monocularly and occlusion classical therapy, finding in both studies that the first method is more effective in order to improve VA. Nevertheless, the effects produced over stereopsis are not that clear. Dadeya and Dangda²³ found stereopsis improvement in children from 4 to 7 years old, conducting a training with a duration of 6 h in clinic, so the children were supervised constantly and this ensured that the compliance rate was total. On the contrary, Singh et al.³⁰ did not find improvement in depth perception in their group of children from 6 to 14 years old, in a training method conducted partially at home, even more (30 h in total) than the study of Dadeya & Dangda.

In most of VG, DT has been applied and improvements in VA have been found, even when compared with a control group or with a different group conducting a different strategy (e.g., patching).^{12,16,20,21,24,25,26,32} Several clinical trials have not found home training with VG more effective than a placebo training,³³ occlusion therapy,³⁷ or optical correction,⁴¹ although it should be pointed out that the rate of compliance of patients in these studies was <65%,^{33,41} and even in the study of Manh and colleagues, compliance rate was really low (13%). On the contrary, other clinical trials have found VG at home as a useful tool used to improve VA^{35,45} when compliance rate has been nearly or higher than 90% of the duration of the treatment prescribed. Regarding the improvements in stereoacuity, some unlike results have been found using this type of treatment consisting in DT in a gamified context of PL, so some authors have found improvements in this binocular function,^{12,20} while others have not.^{16,21,32} DT in a virtual reality environment has also been applied in a VG context.^{27,31} In the investigation conducted by Verdamurthy et al.,²⁷ a 'bug squashing' videogame was used in a VR environment and binocular functions improvements had been found (reduction of the suppression and stereopsis improvement). For their part, Žiak et al.³¹ used two types of VG (flying spaceship and block breaker games) in a DT with VR format, finding some improvements in VA and in stereoacuity.

In some investigations,⁴⁰ as mentioned previously, specific VG have been used in order to improve stereoscopic vision, using tasks with random dot stimuli (RDS), finding satisfactory results in depth vision, even in strabismic amblyopes.

Inclusion of control group

The incorporation of control and/or placebo groups in investigations is an important aspect in order to know the real efficacy of a certain treatment, although this has not always been taken into account in different PL studies. While some investigations have only included an experimen-

tal group,^{13–15,17,18,20,27,29,31,34,36} other investigations have included two experimental groups which have subjected two different approaches of the treatment related to PL, but there were not a participants group without an intervention or with a different type of treatment which was not related to PL.^{12,19,21,32,35,43,44} In other investigations a controlled or comparison group has been included, so the participants in this group have conducted a classical occlusion therapy^{22,23,25,26,30,37,45,46} or used the optical prescription by itself.⁴¹ In other studies, the control or comparison group has consisted in an ineffective type of treatment through stimulation strategies using the dominant eye –instead of the amblyopic eye–^{16,33} or using both eyes equally^{24,38,42} when using DT, gross stimulation of stereopsis⁴⁰ or the inclusion of non amblyopic patients.²⁸

Durability and transfer of training

The durability of the effects produced by a treatment using PL has not always been a considered aspect. Just in 12 (34.2%) studies of this review a follow-up has been conducted in order to value if the improvements obtained after the training is completed are maintained through time. Nevertheless, this follow-up sessions are very variable through different studies which have analyzed this longitudinal aspect, varying from 6 weeks³² to 10 months.³⁶ In general, it has been seen that the improvements in VA,^{13,14,21,28,32,36,38,39,44} in CS,²⁸ in stereoacuity^{14,21,27,32,36,40} and in the reduction of the suppression²⁷ can be maintained over time. It is worth it to say that in one study, the follow-up has been analyzed, like the one conducted by Xi et al.¹⁴ that found that visual improvements were maintained in two of the three patients re-evaluated after 5 months. Other authors have conducted a follow-up at 3 months after the cessation of game play but they have not informed about the obtained results.¹⁶

In general, it has been seen that training in amblyopic patients using specific skills that imply PL, transfers to an improvement in clinical trials such as VA and stereopsis as mentioned previously. Some investigations have proved the transfer effects that a monocular treatment may produce in binocular functions.^{15,22,23,34,46} Additionally, it has been seen that the binocular training through DT,^{12,13,16,18–21,24–26,29,31,32,35,38,43,44,45} or the specific training of stereopsis¹⁴ leads improvements in monocular functions. Nevertheless, it is not rare that PL produced a higher improvement in the trained skilled rather than VA or stereopsis as suggested by Liu and Zhang.³⁶ Recently, Liu and Zhang⁴³ have suggested that 'transfer of learning with training plus exposure through an irrelevant task, is because an improvement in high-level brain processing, and that may strengthen top-down attention to fellow eyes to counter the impacts of attentional bias to fellow eye and/or physiological interocular suppression and improve stereoacuity'.

An essential point of a treatment whatever the method of training chosen, is the impact that the improvements can have in real-life. For example, Vedamurthy et al.²⁷ found out that two of the eleven patients trained reported better distance judgement during driving, and one was able to appreciate depth from autostereograms for the first time. It would be plausible that the improvements produced in

Table 3 GRADE evidence profile.

Study	Design of study	Level of evidence†	A priori quality level	Detected criteria lowering and raising‡ ‘‘a priori quality level’’	Quality of the evidence
Hess et al., 2014 ¹²	Case-series study	IV	low	<ul style="list-style-type: none"> • Indirectness: wide age range • Imprecision: small sample size (per group / condition) 	very low
Mansouri et al., 2014 ¹³	Case-series study	IV	low	<ul style="list-style-type: none"> • Indirectness: wide age range • Imprecision: small sample size (per group / condition) 	very low
Xi et al., 2014 ¹⁴	Case-series study	IV	low	<ul style="list-style-type: none"> • Indirectness: wide age range • Imprecision: small sample size (per group / condition) 	very low
Zhang et al., 2014 ¹⁵	Case-series study	IV	low	<ul style="list-style-type: none"> • Indirectness: wide age range • Imprecision: small sample size (per group / condition) 	very low
Birch et al., 2015 ¹⁶	Cohort study	III-2	low	<ul style="list-style-type: none"> • Risk of bias: non randomized, non making • Indirectness: patching at a different time 	low
Khan et al., 2015 ¹⁷	Case-series study	IV	low	<ul style="list-style-type: none"> • Indirectness: wide age range 	very low
Li SL et al., 2015 ¹⁸	Case-series study	IV	low	<ul style="list-style-type: none"> • Indirectness: wide age range • Imprecision: small sample size (per group / condition) 	very low
Li J et al., 2015 ¹⁹	Cohort study (crossover design)	III-2	low	<ul style="list-style-type: none"> • Risk of bias: non randomized, non making • Indirectness: data were combined from two different studies that used different experimental designs; comparison group performs another type of PL—not a true control group– • Imprecision: small sample size (per group / condition) 	very low
Verdamurthy et al., 2015a ²⁰	Case-series study	IV	low	<ul style="list-style-type: none"> • Indirectness: wide age range 	very low

Table 3 (Continued)

Study	Design of study	Level of evidence†	A priori quality level	Detected criteria lowering and raising‡ ‘‘a priori quality level’’	Quality of the evidence
Verdamurthy et al., 2015b ²¹	Cohort study	III-2	low	<ul style="list-style-type: none"> • Risk of bias: non randomized, non making • Indirectness: wide age range; comparison group performs another type of PL—not a true control group– 	low
Chen et al., 2016 ²²	Cohort study	III-2	low	<ul style="list-style-type: none"> • Risk of bias: pseudo-randomized, non making • Indirectness: wide age range • Publication bias: Unreported intergroup results (control vs PL) 	very low
Dadeya & Dangda, 2016 ²³	Clinical trial (parallel, randomized, no masking)	II	high	<ul style="list-style-type: none"> • Risk of bias: non making • ‡ Dosis-response gradient 	high
Herbison et al., 2016 ²⁴	Clinical trial (parallel, randomized, simple-blind)	II	high	No highlights	high
Holmes et al., 2016 ²⁵	Clinical trial (parallel, randomized, simple-blind)	II	high	<ul style="list-style-type: none"> • Indirectness: duration of exposure in both groups is different 	high
Kelly et al., 2016 ²⁶	Clinical trial (cross-over, randomized, no masking)	II	high	<ul style="list-style-type: none"> • Risk of bias: non making • Imprecision: small sample size (per group / condition) • ‡ Dosis-response gradient 	high
Verdamurthy et al., 2016 ²⁷	Case-series study	IV	low	<ul style="list-style-type: none"> • Indirectness: wide age range • Imprecision: small sample size (per group / condition) 	very low
Barollo et al., 2017 ²⁸	Cohort study	III-2	low	<ul style="list-style-type: none"> • Indirectness: wide age range • Imprecision: small sample size (per group / condition) • ‡ Dosis-response gradient 	low

Table 3 (Continued)

Study	Design of study	Level of evidence†	A priori quality level	Detected criteria lowering and raising‡ ‘‘a priori quality level’’	Quality of the evidence
Bossi et al., 2017 ²⁹	Cohort study	III-2	low	<ul style="list-style-type: none"> • Risk of bias: non randomized, non making • Indirectness: wide age range; duration of exposure in both groups is different; both groups receive the same type of treatment—not a true control group– • Imprecision: small sample size (per group / condition) 	very low
Singh et al., 2017 ³⁰	Clinical trial (parallel, randomized, no masking)	II	high	<ul style="list-style-type: none"> • Risk of bias: non making • Indirectness: duration of exposure in both groups is different • ‡ Dosis-response gradient 	high
Žiak et al., 2017 ³¹	Case-series study	IV	low	<ul style="list-style-type: none"> • Indirectness: wide age range 	very low
Gambacorta et al., 2018 ³²	Clinical trial (parallel, randomized, no masking)	II	high	<ul style="list-style-type: none"> • Indirectness: wide age range; comparison group performs another type of PL—not a true control group– 	moderate
Gao et al., 2018 ³³	Clinical trial (parallel, randomized, double-blind)	II	high	No highlights	high
Jia et al., 2018 ³⁴	Case-series study	IV	low	No highlights	low
Kelly et al., 2018 ³⁵	Clinical trial (cross-over, randomized, no masking)	II	high	<ul style="list-style-type: none"> • Risk of bias: non making • Indirectness: data were pooled from two ongoing studies (clinical trials, NTC02365090) of binocular treatment for childhood amblyopia (Kelly et al., 2016; Li et al, 2015b);comparison group performs another type of PL—not a true control group– • Imprecision: small sample size (per group / condition) 	moderate
Liu & Zhang, 2018 ³⁶	Case-series study	IV	low	<ul style="list-style-type: none"> • Imprecision: small sample size (per group / condition) 	very low

Table 3 (Continued)

Study	Design of study	Level of evidence [†]	A priori quality level	Detected criteria lowering and raising [‡] “a priori quality level”	Quality of the evidence
Manh et al., 2018 ³⁷	Clinical trial (parallel, randomized, simple-blind)	II	high	<ul style="list-style-type: none"> ● Indirectness: duration of exposure in both groups is different 	high
Mezad-Koursh et al., 2018 ³⁸	Cohort study	III-2	low	<ul style="list-style-type: none"> ● Risk of bias: non randomized, non making ● Indirectness: duration of exposure in both groups is different ● Imprecision: small sample size (per group / condition) 	very low
Moret et al., 2018 ³⁹	Cohort study	III-2	low	<ul style="list-style-type: none"> ● Risk of bias: non making ● Indirectness: wide age range ● Imprecision: small sample size (per group / condition) ● ‡ Dosis-response gradient 	low
Portela et al., 2018 ⁴⁰	Clinical trial (parallel, randomized, double-blind)	II	high	<ul style="list-style-type: none"> ● Indirectness: wide age range ● Imprecision: small sample size (per group / condition) ● ‡ Dosis-response gradient 	high
Holmes et al., 2019 ⁴¹	Clinical trial (parallel, randomized, simple-blind)	II	high	No highlights	high
Law & Backus 2019 ⁴²	Cohort study	III-2	low	<ul style="list-style-type: none"> ● Risk of bias: non making ● Indirectness: wide age range; comparison group performs another type of PL—not a true control group—; Test, retest and training with the same type of task ● Imprecision: small sample size (per group / condition) 	very low

Table 3 (Continued)

Study	Design of study	Level of evidence†	A priori quality level	Detected criteria lowering and raising‡ ‘‘a priori quality level’’	Quality of the evidence
Liu & Zhang, 2019 ⁴³	Cohort study	III-2	low	<ul style="list-style-type: none"> • Risk of bias: non making • Indirectness: Comparison group performs another type of PL–not a true control group– • Imprecision: small sample size (per group / condition) 	very low
Sauvan et al., 2019 ⁴⁴	Cohort study	III-2	low	<ul style="list-style-type: none"> • Risk of bias: non randomized, non making • Indirectness: wide age range; duration of exposure in every participant is different; comparison group performs another type of PL–not a true control group– • Imprecision: small sample size (per group / condition) 	very low
Birch et al., 2020 ⁴⁵	Clinical trial (cross-over, randomized, no masking)	II	high	<ul style="list-style-type: none"> • Risk of bias: non making • Indirectness: enrolling two pre-planned cohorts (Kelly et al., 2016; clinical trial NTC02365090) and an additional 20 children to be combined with the primary cohort to allow for evaluation of factors that may affect treatment outcomes including baseline factors. • Imprecision: small sample size (per group / condition) • ‡ Dosis-response gradient 	moderate
Gu et al., 2020 ⁴⁶	Cohort study	III-2	low	<ul style="list-style-type: none"> • Risk of bias: non randomized, non making • Indirectness: wide age range; it is possible that the observed training effects were due to the influences of both training and patching • Imprecision: small sample size (per group / condition), specially in control group 	very low

Note: † National Health & Medical Research Council clinical evidence hierarchies.

some activities in real –life were evaluated through questionnaires or questions regarding the quality of life after the treatment.

Quality of evidence

In many investigations, the conclusions obtained are limited by the desing of the study (e.g. absence of a control group or the aplication of a method of masking [i.e., blind-ing] in order to reduce the risk of bias). The procedures used to organize the evidence hierarchically and to establish the recommendation are the basis for the development of the clinical practice guidelines. GRADE provides explicit criteria for rating the quality of evidence that include limitations in the study design (*risk of bias*), inconsistency of the results (*inconsistency*), uncertainty of the evidence being direct (*indirectness*), inaccuracy for wide confidence intervals (CI), small samples or small events (*imprecision*), bias of publication or notification (*publication bias*).¹¹ Table 3 shows the GRADE evidence profile of the different studies included in this review.

Of the 35 studies included, 23 of them (65.7%) are of the observational type, and eleven of those (31.4%) are case-series study and twelve (34.3%) are cohort study. The other twelve (34.3%) remaining investigations are experimental or clinical trial, that vary in their design (see column “Design of the study in Table 3). After making a series of decisions based on the criteria for rating the quality of evidence¹¹ (see “Discussion” section for a more thorough explanation), nine (25.7%) present “high” quality (a lot of confidence that the true effect is similar to the estimated effect), three (8.6%) in a “moderate” level (the true effect is probably close to the estimated effect), five (14.3%) in a “low” level (the true effect might be markedly different from the estimated effect) and 18 (51.4%) in a “very low” level (the true effect is probably markedly different from the estimated effect).

Discussion

Impact of PL in the visual improvement in amblyopes

As a result, the trials published in the last 6 years state some consistent aspects regarding the idea that amblyopia treatment might be aimed to restore visual functions (improvements in VA, CS or estereopsis and reduction in interocular suppression) using new active strategies such as perceptive learning taking advantage of technological resources that we now have, like videogames or virtual reality. Regarding the gain of one of the key visual functions, VA, different clinical trials^{23,26,30,32,35,45} have shown that a notorious increase can be achieved through an extent range of stimulus, tasks and duration of the training based in PL. The augmentation degree in VA varies from one study to another, but the increment found was from 1 and 2 lines in a logMAR chart. Even in a study conducted in 6 years old children it has been seen that the group who conducted a PL training for a small amount of time (6 h) gained an average of 4.2 lines.²³ Also in some cohort studies^{19,21,22,28,39,43,44,46} conducted in adults it has been seen that the gain produced in VA breaks the theory that was established that the visual deficiency

of amblyopic people, more concretely the VA, could just be recovered if the treatment was implemented before the end of the critical period. In some of these studies conducted in adult population, even the depth vision it is possible to restore.^{22,42,43,46} This opens an encouraging path for this kind of population or group of age, for those whose treatment was reduced to surgery or, directly, those who were relegated to not being able to do any treatment.

Regarding the time employed in order to achieve some improvements, the results seem to be encouraging, due to the improvements found in a relatively small period of time. In some of the clinical trials of this review, training with PL took place that have varied from 6 to 30 h of training, in order to improve VA or stereopsis. In general, it is estimated that therapy with patching requires 120 h of training in order to achieve a 1-line gain in amblyopic children that were previously treated with glasses.⁴⁸ In a recent investigation⁴⁵ it has been seen that in just 2 weeks (10 h) of PL with a binocular adventure VG are enough to produce a gain in VA of 1.5 lines, a result which is a remarkably result when compared to previous findings in which 16 weeks of occlusion were needed (224 h in total) in order to produce improvements in VA of more than one line,^{25,37} If the satisfactory results obtained in this controlled clinical trials are confirmed throughout other trials so the rate of gain of visual functions can be analyzed like stereopsis in adults with amblyopia, it could be confirmed that perceptual learning could be useful as a primary, complementary or maintenance treatment, obtaining improvement in a relatively brief period of time.

Empirical evidence of PL in amblyopia

Regarding the level and quality of evidence, it is important to point out that several investigations included in this review have a case-series study design, this fact makes a lower level of evidence. Even when cohort studies are conducted, where a control group inclusion is considered, it has been suggested that a randomized clinical trial is needed to evaluate the effectiveness of a potential amblyopia treatment in routine clinical practice^{16,18} and to compare its effectiveness with the current standard of care.¹⁶ It seems that over the last few years, the number of experimental studies have increased (clinical trials) in the context of perceptual learning as a treatment for amblyopia.^{23,24–26,30,32,33,35,37,40,41,45} This type of experimental investigations are characterized for the high level of evidence, because systematic mistakes or bias can be minimized considering the existence of a comparison or control group, that allows to prove if the intervention is better (or not) than the existing ones. Nevertheless, in the investigations there are presented some relative criteria for risk of bias (non making), imprecision (small sample size per group or per condition [i.e., stype of amblyopia]) and indirectness (wide age range, duration of exposure in both groups is different), and all of them lower the quality level of the study, and could affect negatively to their evidence rate. It is not usual in this kind of studies to inform about risk ratio (RR) or dose-response gradient, criteria that are used to improve the quality of the evidence. In fact, none of the studies provide RR, while the dose-response gradient was

informed in two of the studies,^{30,45} where it can be seen that the effects produced improve when the duration of the treatment is longer. In other cases,^{23,26,28,39,40} we have considered the dose-response gradient when significant gain has been obtained with a training that has implied a substantial training with a duration and intensity (number of trials) enough to produce that gain. In this case, in order to have the certainty that the training effects were not related to a learning effect, we just consider the dose-gradient response in those studied that had a control group who did not conduct a therapy related to PL. Furthermore, this criteria was only considered when both treatment and control groups had the same dosage (duration and intensity) of treatment.

Of all of the studies included in this review, just the 34.3% are clinical trials, and the 25.7% of those have a “high” evidence quality, and the 8.6% have a “moderate” clinical evidence. In spite of that, it is interesting to remark that the investigation about PL (and the use of VG) is promising. Currently there are 15 clinical trials in process about this types of treatment for amblyopia and that are registered in ClinicalTrials.gov (<http://www.clinicaltrials.gov>), a database maintained by the National Library of Medicine (NLM) at the National Institutes of Health (NIH) where there are privately and publicly funded clinical studies conducted around the world.

Guidelines for home training and compliance rate of the patient

Some authors⁴⁹ have proposed a protocol or a viable and detailed therapy guideline, based on the results of a clinical trial about PL using random-dot stimuli in a video game format to improve stereoacuity.⁴⁰ This type of protocol can help the clinician in the decision making and the optimal management of the amblyopic patient who is treated with this type of training based on perceptual learning. In the first face-to-face session in the consult it is essential to provide to the patient/parents some guidelines such as the suitable distance to the monitor where the stimulus is presented, the correct position of the monitor in order to avoid light reflections, the previous configuration of the game or the appropriate position of the dissociative filters so the amblyopic eye is stimulated correctly. Evidently, it is not less important the realization of frequent follow-ups that serve to analyze the development and value if this type of treatment is being effective.⁴⁰

Compliance or compromise rate that the patient has with the treatment will also determine the usefulness of the treatment. Most of the studies included in this review have been conducted in a laboratory or a clinic (see [Table 1](#)) using tasks that can be more or less tedious for the patient, but at the same time assures that the compliance rate of the patient increases because the clinician is keeping the patient under observation (in order to have a more detailed information about compliance rate, see [Table 2](#)). The use of serious VG, that have a series of qualities and mechanics of the game can help to benefit neuronal plasticity and a learning experience to the patient.³² Moreover, the VG used have to be attractive in order to increase compliance rate of the patient, although it has been seen that is not always that way when training has been conducted at home,^{25,37} In the

study conducted by Holmes et al.²⁵ compliance percentage was at first optimal according to the information provided by parents/patients (66.7%), but analyzing the database registered generated by iPad, the rate of compliance reported was significantly lower (22.2%). In a similar way, Manh et al.³⁷ also found a poor adherence to the treatment with a VG using the iPad at home, so only 13% of participants completed more than 75% of the prescribed treatment. The use of VG at home as a way of amblyopia treatment could be an interesting resource, specially for those patients that have serious difficulties to go regularly to the consult, but in order to achieve that the program or the VG should allow the clinician to do a follow-up in a remotely and reliable manner about the duration and frequency of use by the patient.

Altogether, previous guidelines, compliance rate evaluation and frequent follow-ups to the patient, could be three important foundations so the success rate and the effectiveness of the treatment can be increased when using the VG method from home.

Limitations and future research

The PL studies reviewed show some limitations that sometimes their authors have acknowledge in the studies (see [Table 2](#)). Doubtlessly, one of the more important limitation is the small amount of subjects, so when analyzing by group segmentation (e.g., treatment groups, kind of amblyopia, group of age), the results could be spurious and inconclusive. Furthermore, some factors such as age of the patient, previous treatments (e.g., patching) in residual amblyopia, the modification or adaptation of the refraction using lenses during the training period, or the baseline of VA and stereopsis could have influence in the effects produced by the training. That is why, it would be plausible that in future investigations this differential factors are taken into account, something that has not been considered, or when considered dissimilar results have been obtained in different studies. Other limitation that affects to the quality of an investigation, as we have seen previously, could be the absence of a control group an aspect that is determining if you pretend to evaluate the truly effects of the training. The evaluation of the compliance rate of the patient regarding the training, short-medium term follow-ups in order to analyze the duration of the effects or the dose-response gradient (which has been thoroughly analyzed in occlusion therapy)⁴⁸ are limitations that have been found in this review, and that are also key pieces in order to determine if therapy is effective or not.

Regarding the evident of PL using VG, some encouraging discoveries have been found, due to the fact that it seems to have obtained better and quicker results than with occlusion.^{26,45} When VG have been combined with occlusion, it has been seen more benefits than occlusion by itself, that is why nowadays it could be recommended to use both types of treatments in a combined manner.^{23,30} Some authors⁴⁰ have suggested that a home treatment based in PL could provide compliance rates higher than other treatments, like occlusion. However additional studies are needed, because some investigations where has not been found that the use of VG is more effective than optical correction⁴¹ or than occlusion therapy,^{25,37} a low compliance rate has been obtained.

In this case, it could be encouraging to determine how to transform binocular games in an amblyopia treatment that could be comfortable and enjoyable in order to achieve a better adhesion. In this regard, it would be plausible to implement attractive VG, that have goals and rewards, in order to maintain the attention for longer periods of treatments maintaining an optimal compliance rate. Regarding that, Holmes y colleagues⁵⁰ have proposed new studies with the goal of analyzing if the incorporation of longer periods of time with the game before increasing the contrast or carrying out shorter contrast steps in the fellow eye could generate better improvements in the visual functions. Regarding VG, nowadays some of the VG used in investigation, like *Dig Rush*, are in process of being authorized and commercialized, and other, like *Tetris*, are easily accessible in a simplified version for computer, smartphone and tablet. Another very useful PL tool (Gabor patches, DT and Random Dot stimuli for stereopsis) that is currently being commercialized is Visionary (<https://www.visionarytool.com/>). This tool has proven effective for working from home with amblyopic children.⁴¹

The limitations detailed until now are related to the ones found throughout the studies included in this review. But we also want to mention some limitations of the review itself. Although we think that the level of evidence showed in Table 3 could be precise, it needs to be said that we only have considered some criteria (risk of bias, indirectness, imprecision, publication bias) that low the "a priori quality level". Regarding the criteria that could increase the "a priori quality level" these are more limited, considering that just the existence of the dose-response gradient, from the small studies which reflected this aspect. In the investigations in which this gradient has not been provided, we have applied this criteria in those studies when significant gain has been obtained using a training that has implied -to our judgement- a substantial training duration or intensity. Nevertheless, this criteria application should be considered cautiously. Another limitation of this study is that it has not considered doing a statistical analysis for the evaluation of the size of the medium effect throughout different studies about the improvements of visual functions (e.g., VA). This could be considered in future meta-analysis about this subject.

Conclusions

This systematic review of recent studies has found evidence of the new kind of amblyopia treatment, that pretends to stimulate the binocular system by perceptive training, using the dichoptic treatment with or without the use of videogames. In general, the studies conducted until now expose that this kind of treatment is effective, improving some visual functions such as VA even in adults that have exceeded the critical period. This could be, partially at least, due to the format used in this type of active therapy, and is that some authors have suggested that gamification has been used to enhance patient motivation and compliance.⁴⁹ Nevertheless, it would be plausible to conduct additional controlled and random clinical trials in order to know more deeply in which visual functions they are more efficient and how long the effects that this kind of

treatment based in perceptual learning would persist over time. Based on the results obtained through different studies, for the moment, it seems reasonable to recommend this kind of active therapy as a complementary procedure to the different options of passive therapy like optic correction, occlusion or the penalization with atropine.

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Conflict of interest

The authors declare that they have no conflict of interest.

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