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Effectiveness of a Binocular Video Game vs Placebo Video Game for Improving Visual Functions in Older Children, Teenagers, and Adults With Amblyopia
A Randomized Clinical Trial

Tina Y. Gao, BOptom; Cindy X. Guo, PhD; Raiju J. Babu, PhD; Joanna M. Black, PhD; William R. Bobier, PhD; Arijit Chakraborty, PhD; Shuan Dai, MBBS, MSc, FRANZCO; Robert F. Hess, DSc; Michelle Jenkins; Yannan Jiang, PhD; Lisa S. Kearns, B Orth & Ophtha Sci; Lionel Kowal, MBBS, FRANZCO; Carly S. Y. Lam, PhD; Peter C. K. Pang, DHSc; Varsha Parag, MSc; Roberto Pieri, B Orth, MAOB; Rajkumar Nallour Raveendren, PhD; Jayshree South, BMedSc; Sandra Elfride Staffieri, BAppSc(Orth); Angela Wadham, BA; Natalie Walker, PhD; Benjamin Thompson, PhD; for the BRAVO Study Team

IMPORTANCE Binocular amblyopia treatment using contrast-rebalanced stimuli showed promise in laboratory studies and requires clinical trial investigation in a home-based setting.

OBJECTIVE To compare the effectiveness of a binocular video game with a placebo video game for improving visual functions in older children and adults.

DESIGN, SETTING, AND PARTICIPANTS The Binocular Treatment of Amblyopia Using Videogames clinical trial was a multicenter, double-masked, randomized clinical trial. Between March 2014 and June 2016, 115 participants 7 years and older with unilateral amblyopia (amblyopic eye visual acuity, 0.30-1.00 logMAR; Snellen equivalent, 20/40-20/200) due to anisometropia, strabismus, or both were recruited. Eligible participants were allocated with equal chance to receive either the active or the placebo video game, with minimization stratified by age group (child, age 7 to 12 years; teenager, age 13 to 17 years; and adult, 18 years and older).

INTERVENTIONS Falling-blocks video games played at home on an iPod Touch for 1 hour per day for 6 weeks. The active video game had game elements split between eyes with a dichoptic contrast offset (mean [SD] initial fellow eye contrast, 0.23 [0.14]). The placebo video game presented identical images to both eyes.

MAIN OUTCOMES AND MEASURES Change in amblyopic eye visual acuity at 6 weeks. Secondary outcomes included compliance, stereoacuity, and interocular suppression. Participants and clinicians who measured outcomes were masked to treatment allocation.

RESULTS Of the 115 included participants, 65 (56.5%) were male and 83 (72.2%) were white, and the mean (SD) age at randomization was 21.5 (13.6) years. There were 89 participants (77.4%) who had prior occlusion. The mean (SD) amblyopic eye visual acuity improved 0.06 (0.12) logMAR from baseline in the active group (n = 56) and 0.07 (0.10) logMAR in the placebo group (n = 59). The mean treatment difference between groups, adjusted for baseline visual acuity and age group, was −0.02 logMAR (95% CI, −0.06 to 0.02; P = .25). Compliance with more than 25% of prescribed game play was achieved by 36 participants (64%) in the active group and by 49 (83%) in the placebo group. At 6 weeks, 36 participants (64%) in the active group achieved fellow eye contrast greater than 0.9 in the binocular video game. No group differences were observed for any secondary outcomes. Adverse effects included 3 reports of transient asthenopia.

CONCLUSIONS AND RELEVANCE The specific home-based binocular falling-blocks video game used in this clinical trial did not improve visual outcomes more than the placebo video game despite increases in fellow eye contrast during game play. More engaging video games with considerations for compliance may improve effectiveness.

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Invited Commentary
Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: The Binocular Treatment of Amblyopia Using Videogames (BRAVO) Study Team members are listed at the end of this article.

Corresponding Author: Benjamin Thompson, PhD, School of Optometry and Vision Science, University of Waterloo, 200 Columbia Ave W, Waterloo, ON N2L 3G1, Canada (ben.thompson@uwaterloo.ca).

Current standard treatment for unilateral amblyopia involves refractive correction followed by patching or atropine penalization of the fellow eye.[1,2] Since 2006, a number of novel binocular treatments for amblyopia have been developed,[3-8] a subset of which involve presenting high-contrast stimuli to the amblyopic eye and different, lower-contrast stimuli to the fellow eye (contrast balancing).[3,9] This treatment principle was implemented in a falling-blocks video game,[10] which showed promising results in children[11-13] and adults[14,15] with amblyopia. The Binocular Treatment of Amblyopia Using Videogames study was a randomized double-masked clinical trial to evaluate the effectiveness of a home-based version of a binocular video game against a placebo video game for improving visual functions in children 7 years and older and adults.

Key Points

Question Is a home-based binocular video game more effective than a placebo video game for improving amblyopic eye visual acuity in older children and adults with unilateral amblyopia?

Findings In this randomized clinical trial including 115 participants aged 7 to 55 years, no significant difference was detected between the binocular video game treatment group and the placebo video game treatment group in amblyopic eye visual acuity after 6 weeks.

Meaning The specific home-based binocular video game used in this clinical trial did not improve visual function and did not produce statistically significant differences compared with the placebo video game.

Methods

The full clinical trial protocol is available in a previous publication[16] and Supplement 1. This trial was approved by the University of Auckland Human Participants Ethics Committee, the University of Waterloo Research Ethics Committee, the McGill University Health Centre, the Human Research and Ethics Committee of the Royal Victorian Eye and Ear Hospital, and the Human Subjects Ethics Subcommittee of the Hong Kong Polytechnic University and adhered to the principles of the Declaration of Helsinki. Written informed consent was obtained for adult participants and parents/guardians of younger participants, and either written or verbal assent was obtained for younger participants depending on local ethics board requirements. Key methods are described below.

Participants

Participants 7 years and older were recruited through university-based and hospital-based sites in Auckland, New Zealand; Melbourne, Australia; Hong Kong, China; Waterloo, Ontario, Canada; and Montreal, Quebec, Canada. Eligible participants had unilateral amblyopia due to anisometropia, strabismus, or both (mixed mechanism) and were not undergoing any amblyopia therapy apart from wearing refractive correction. The visual acuity (VA) of the amblyopic eye was 0.30 to 1.00 logMAR (Snellen equivalent, 20/40-20/200) inclusive, and the VA of the fellow eye was 0.10 logMAR (Snellen equivalent, 20/25) or better, measured using the electronic Early Treatment Diabetic Retinopathy Study protocol[17,18] through optimal refractive correction. Participants who had not worn corrective lenses meeting the study prescribing criteria full time for 4 or more months before study entry underwent optical treatment, and VAs were reviewed every 4 weeks for a maximum of 16 weeks. Participants were required to demonstrate stable VAs (5 or less letters change over 4 weeks) within the inclusion range before randomization. Detailed results from this phase have been accepted for publication.[19] Participants received reimbursement for travel and were provided with spectacles and/or contact lenses if needed. Reimbursements and ages of consent/assent conformed to local ethics board requirements.

Video Game Treatment

Both the active and placebo treatments were falling-blocks video games on iPod Touch (Apple) devices, viewed through red-green anaglyphic glasses worn over appropriate refractive correction (eFigure 1 in Supplement 2). The active video game[10,14] presented different game elements to each eye. The amblyopic eye saw a subset of game elements at 100% contrast. The fellow eye saw remaining game elements at a lower contrast set individually using a dichoptic global motion measure of interocular suppression.[20-22] Where participants could not reliably perform this test, fellow eye contrast was manually set to allow simultaneous perception of all game elements during binocular viewing. Binocular combination was required to successfully play the active video game. Fellow eye contrast increased proportionally by 15% each day if the game was played for at least 15 minutes and a high score of at least 1000 points was achieved in the previous day. The placebo game presented all game elements to both eyes at full contrast (no dichoptic presentation), simulating a normal video game.

Participants were randomized to the active or placebo group by unmasked study staff within 3 days of becoming eligible. Randomization was conducted through a secure website in a 1:1 ratio using minimization method stratified by age group (child, age 7 to 12 years; teenager, age 13 to 17 years; and adult, 18 years and older). An unmasked staff member at each site allocated treatment, set up initial fellow eye contrast and game difficulty, and confirmed ability to play. Participants and parents/guardians were not informed about their treatment allocation or about video game designs. All participants were prescribed a minimum of 1 hour per day of home-based video game play for 6 weeks and could split game play over multiple daily sessions. Six weeks was selected because longer treatment periods may lead to boredom and falling compliance. Follow-up visits were conducted by clinicians masked to treatment allocation at week (required follow-up window in weeks) 3 (1), 6 (1), 12 (3), and 24 (4).

Outcome Measurements

The primary outcome was change from baseline in amblyopic eye distance VA at 6 weeks. Distance VAs were measured

at every visit using the electronic Early Treatment Diabetic Retinopathy Study protocol[17,18] on the Electronic Visual Acuity Tester (Jaeb Center for Health Research). Secondary visual outcomes were assessed at all visits and included near VAs at 40 cm (Sloan Letter Near Vision Card; Good-Lite Company), stereopsis (Randot Preschool Stereoacuity Test; Stereo Optical Company; and Fly Stereo Acuity Test with LEA Symbols; Vision Assessment Corporation),[23,24] ocular alignment (cover test), angle of strabismus (prism alternate cover test), binocular sensory status (Worth 4 dot test), and interocular suppression (iPod-based version of the Dichoptic Global Motion Test[20-22]). A modified version of the Amblyopia Treatment Index questionnaire[25-27] was used to assess treatment acceptability at 3 and 6 weeks. Quality of life for adult participants was assessed using the World Health Organization Quality of Life–Brief Version questionnaire[28] at baseline and 24 weeks. These outcomes were all assessed by masked clinicians.

Treatment compliance and fellow eye contrast were recorded by iPod video game software and were extracted at 3 and 6 weeks by unmasked staff. A written diary was also completed by participants.

Statistical Analyses

Our primary hypothesis was that the active video game would improve amblyopic eye VA more than the placebo video game when considering all participants. We also powered each age group separately to test for age-specific effects. Our original sample size was 108,[16] where 36 participants (18 in each arm) in each age group would provide 90% power at a 2-sided $P = .05$ to detect a group difference of 0.20 logMAR (2 lines) in the primary outcome, assuming a SD of 0.17 logMAR[10] and 10% loss to follow-up.

The primary hypothesis was tested using analysis of covariance, with adjustments for baseline VA and age group. Each age group was also separately analyzed where sufficient numbers were recruited. An intention-to-treat approach was used, and missing data were replaced using last value carried forward. Preplanned sensitivity analyses for the primary outcome included replacing missing values with multiple imputation, complete case analysis, and per-protocol analysis. An exploratory analysis was performed with additional adjustments for prior occlusion treatment and presence of strabismus to assess the effect of baseline differences between treatment groups. Dose response was examined by adjusting the regression model by cumulative game play time. Tests for heterogeneity were used to assess consistency of effects for prespecified subgroups based on age group, presence of random dot stereopsis before treatment, prior patching/atropine treatments, amblyopia severity, and amblyopia type. For amblyopia type, participants with strabismic or mixed mechanism amblyopia were combined into a "with strabismus" subgroup for comparison with participants with anisometropic amblyopia.

Results from the Randot Preschool Test and Worth 4 dot test were combined into a binocular function score[29] for analysis. This score was either the log-transformed Randot Preschool Test stereoacuity, a value of 4.00 for nil stereopsis with fusion or diplopia on the Worth 4 dot, or a value of 5.00 for nil stereopsis and suppression on the Worth 4 dot (eMethods 1 in Supplement 2). Sensitivity analyses were conducted using fixed values to replace nil stereopsis (eMethods 2 in Supplement 2).

Treatment compliance was examined using an intention-to-treat approach, with missing outcomes assumed to be noncompliant. For all other secondary outcomes, missing values were excluded from analysis. Changes in quality of life for adults were analyzed using analysis of covariance, with adjustment for baseline scores. Changes from baseline for repeated secondary outcomes (fellow eye distance VA, binocular distance VA, near VA, stereoacuity, and interocular suppression) were analyzed using random-effects mixed models with a compound symmetry covariance structure, with adjustments for baseline values and age group. Analyses were performed using SAS version 9.4 (SAS Institute). All P values were 2-tailed, and significance was set at $P < .05$.

Results

Baseline Characteristics

Recruitment proceeded from March 13, 2014, to June 1, 2016. We were unable to recruit 36 participants aged 13 to 17 years, so recruitment for participants aged 7 to 12 years and 18 years and older was expanded to reach at least 108 participants. In total, 115 participants were randomized (**Figure 1**) (eTable 1 in Supplement 2). Fifty-one participants (44.3%) were randomized at study entry and 64 (55.7%) after optical treatment. Fifty-six participants (48.7%) were randomized to the active group and 59 (51.3%) to the placebo group. Baseline characteristics of randomized participants are summarized in **Table 1** and eTable 2 in Supplement 2.

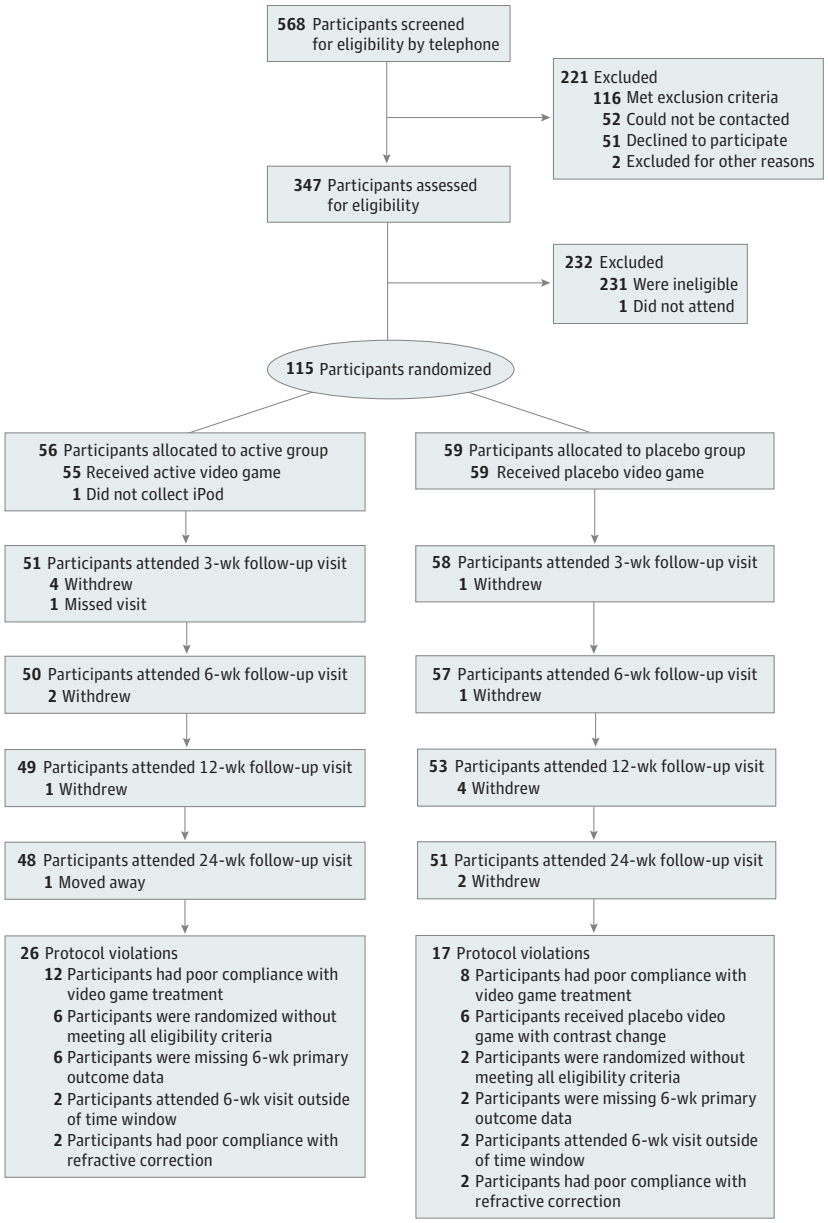
Visit Completion and Compliance

The 6-week primary outcome visit was completed by 50 participants (89%) in the active group and 57 (97%) in the placebo group (Figure 1). Double masking was successfully maintained at all follow-ups. Of the 8 participants who withdrew before 6 weeks, 2 children in the active group cited disliking the video game, 1 adult in the active group was unable to play for at least 1 hour per day, and the other 5 cited reasons unrelated to video game treatment or did not give a reason.

At 6 weeks, iPod compliance data were extracted for 48 participants (86%) in the active group and 57 (97%) in the placebo group. The remaining participants either did not attend follow-up sessions or refused to play and were assumed to have played 0 hours. Mean (SD) cumulative game play time at 6 weeks was 22.8 (17.3) hours in the active group and 27.2 (16.0) hours in the placebo group. Thirty-six participants (64%) in the active group and 49 (83%) in the placebo group met the study definition of compliance (playing at least 25% of minimum prescribed dose or at least 10.5 hours at 6 weeks, based on data suggesting that 10 hours of playing a dichoptic video game could produce treatment effects[14,15]). A detailed breakdown of treatment compliance by age group at 3 and 6 weeks can be found in eTable 3 in Supplement 2.

Progression of fellow eye contrast in the active video game is shown in eFigure 2 in Supplement 2. After 6 weeks of video

Figure 1. CONSORT Flowchart



The total number of protocol violations is less than the sum of all categories because some participants had more than 1 protocol violation. Detailed descriptions of protocol violations can be found in the eAppendix in Supplement 2.

game training, 36 participants (64%) in the active group reached fellow eye contrasts greater than 0.9, indicating they could tolerate near-equal contrast to the 2 eyes while playing the active video game.

Primary Outcome: Amblyopic Eye Distance VA at 6 Weeks

Mean (SD) improvement in amblyopic eye distance VA from baseline was 0.06 (0.12) logMAR (3 letters) in the active group and 0.07 (0.10) logMAR (3.5 letters) in the placebo group at 6 weeks. There were no statistically or clinically significant differences between groups for any of the primary outcome analyses (**Table 2**). Separate analyses for the child and adult age groups also did not reveal significant differences between the active and placebo video games (eTable 4 in Supplement 2). No cumulative dose-response effects were found for change in amblyopic eye VA at 6 weeks (**Figure 2**).

We found no significant effects of age group, type of amblyopia, stereopsis at baseline, or prior occlusion treatment on treatment group differences in the primary outcome (eFigure 3 in Supplement 2). Prespecified subgroup comparison based on amblyopia severity could not be conducted because only 17 participants had severe amblyopia (amblyopic eye VA worse than 0.70 logMAR) at randomization.

Secondary Outcomes

No significant differences were found between the active and placebo groups for change from baseline in any secondary outcomes (**Table 3**) (eTables 5, 6, and 7 in Supplement 2).

Table 1. Baseline Characteristics of Participants at Randomization[a]

Characteristic	No. (%)	
	Active (n = 56)	Placebo (n = 59)
Female	22 (39)	28 (47)
Race/ethnicity[b]		
White	42 (75)	41 (69)
Asian	11 (20)	17 (29)
Other	6 (11)	3 (5)
Age at randomization, y		
Mean (SD)	22.1 (13.9)	21.0 (13.4)
Range	7-52	7-55
Age groups, y		
Child, 7-12	22 (39)	23 (39)
Teenager, 13-17	8 (14)	9 (15)
Adult, ≥18	26 (46)	27 (46)
Prior amblyopia treatment		
Optical[c]	49 (88)	55 (93)
Patching	41 (73)	48 (81)
Atropine[d]	14 (25)	10 (17)
Type of amblyopia		
Anisometropia only	17 (30)	25 (42)
Strabismus only	9 (16)	3 (5)
Mixed mechanism	30 (54)	31 (53)
Spherical equivalent of cycloplegic refraction, mean (SD)		
Amblyopic eye, diopters	3.49 (2.82)	3.72 (2.44)
Fellow eye, diopters	1.16 (2.23)	0.85 (1.74)
Distance VA (e-ETDRS test at 3 m), mean (SD), logMAR		
Amblyopic eye VA	0.53 (0.16)	0.51 (0.18)
Snellen equivalent of mean	20/63 −2	20/63 −1
Range	0.28-0.94	0.24-0.98
Fellow eye VA	−0.11 (0.09)	−0.11 (0.08)
Snellen equivalent of mean	20/16 +1	20/16 +1
Range	−0.26 to 0.10	−0.24 to 0.08
Near VA at 40 cm, mean (SD), logMAR		
Amblyopic eye VA	0.63 (0.18)	0.56 (0.20)
Snellen equivalent of mean	20/80 −2	20/80 +2
Range	0.34-1.00	0.22-1.02
Fellow eye VA	−0.02 (0.11)	−0.03 (0.09)
Snellen equivalent of mean	20/20 +1	20/20 +1
Range	−0.24 to 0.38	−0.20 to 0.22
Baseline stereoacuity (Randot Preschool Test)		
Binocular function score, mean (SD), log(seconds of arc)	3.76 (1.08)	3.67 (1.09)
Median binocular function score, median (IQR), log(seconds of arc)	4.00 (2.60-5.00)	4.00 (2.60-5.00)
Nil stereoacuity	33 (59)	35 (59)
Interocular suppression (Dichoptic Global Motion Test)		
Able to complete test	46 (82)	52 (88)
Dichoptic contrast ratio (amblyopic eye/fellow eye), mean (SD)	0.46 (0.33)	0.45 (0.32)
Initial fellow eye contrast in video game[e]		
Game data available	51 (91)	59 (100)
Initial contrast	0.23 (0.14)	0.29 (0.16)

(continued)

Stereoacuity

At 6 weeks, mean (SD) binocular function score improved by 0.23 (0.76) log(seconds of arc) in the active group and 0.25 (0.95) log(seconds of arc) in the placebo group. Differences between groups in changes from baseline were not statistically significant (Table 3) (eTable 5 in Supplement 2). Changes in binocular function score at 6 weeks were not related to video game compliance (Figure 2).

Table 1. Baseline Characteristics of Participants at Randomization (continued)[a]

Characteristic	No. (%) Active (n = 56)	Placebo (n = 59)
Near Worth 4 dot test		
Suppression (2 or 3 dots)	5 (9)	7 (12)
Fusion (4 dots)	45 (80)	44 (75)
Diplopia (5 dots)	6 (11)	8 (14)
Distance Worth 4 dot test		
Suppression (2 or 3 dots)	29 (52)	25 (42)
Fusion (4 dots)	26 (46)	24 (41)
Diplopia (5 dots)	1 (2)	9 (15)
Unable to perform	0 (0)	1 (2)
Near maximum angle of strabismus[f]		
Orthotropic	25 (45)	38 (64)
1-9Δ	26 (46)	15 (25)
≥10Δ	5 (9)	6 (10)
Distance maximum angle of strabismus[f]		
Orthotropic	26 (46)	33 (56)
1-9Δ	28 (50)	17 (29)
≥10Δ	2 (4)	9 (15)

Abbreviations: e-ETDRS, electronic Early Treatment Diabetic Retinopathy Study; IQR, interquartile range; VA, visual acuity; Δ, prism diopter.

[a] Baseline vision-related measurements were taken at the study entry visit for participants who did not require optical treatment and at the last optical treatment follow-up before randomization for participants who underwent the optical treatment phase.

[b] Percentages in this subsection may add to more than 100% because some participants identified with more than 1 ethnicity.

[c] Refers to optical treatment before enrolling in this clinical trial. Six additional participants (3 in active group and 3 in placebo group) underwent optical treatment for the first time during the prerandomization phase of this clinical trial.

[d] All participants in this trial who had atropine therapy also had patching prior to or concurrently with atropine eyedrops. None had atropine as the sole first-line treatment.

[e] Both active and placebo video games had an initial fellow eye contrast setting based on participants' baseline interocular suppression, which was used in a nonius cross task displayed at the start of each game session. The active game used this contrast setting for the game elements displayed to the fellow eye. The placebo game did not use this contrast setting (eFigure 1 in Supplement 2).

[f] Measured using prism alternate cover test through optimal refractive correction.

Table 2. Change in Visual Acuity (VA) of the Amblyopic Eye at 6 Weeks[a]

Analysis Method	Active No.	Active Adjusted Mean (SE)[b]	Placebo No.	Placebo Adjusted Mean (SE)[b]	Adjusted Treatment Group Mean Difference (95% CI)[c]	*P* Value
ITT analysis with LVCF	56	0.05 (0.02)	59	0.07 (0.01)	−0.02 (−0.06 to 0.02)	.25
ITT analysis with multiple imputations	56		59		−0.01 (−0.06 to 0.03)	.48
Complete case analysis, excluding missing 6-wk visits	50	0.06 (0.02)	57	0.07 (0.01)	−0.02 (−0.06 to 0.03)	.45
Per protocol analysis, excluding protocol violations and missing 6-wk visits[d]	30	0.04 (0.02	42	0.08 (0.02)	−0.03 (−0.09 to 0.02)	.22
ITT analysis with LVCF, adjusting for baseline VA, age groups, prior occlusion, and presence of strabismus	56	0.05 (0.02)	59	0.08 (0.02)	−0.02 (−0.06 to 0.02)	.24

Abbreviations: ITT, intention-to-treat; LVCF, last value carried forward method to replace missing data.

[a] All VA changes are reported in logMAR.

[b] Means were adjusted for baseline amblyopic eye VA and age groups.

[c] Positive treatment group differences indicate that the active group improved more than the placebo group.

[d] Details of protocol violations can be found in the eAppendix in Supplement 2.

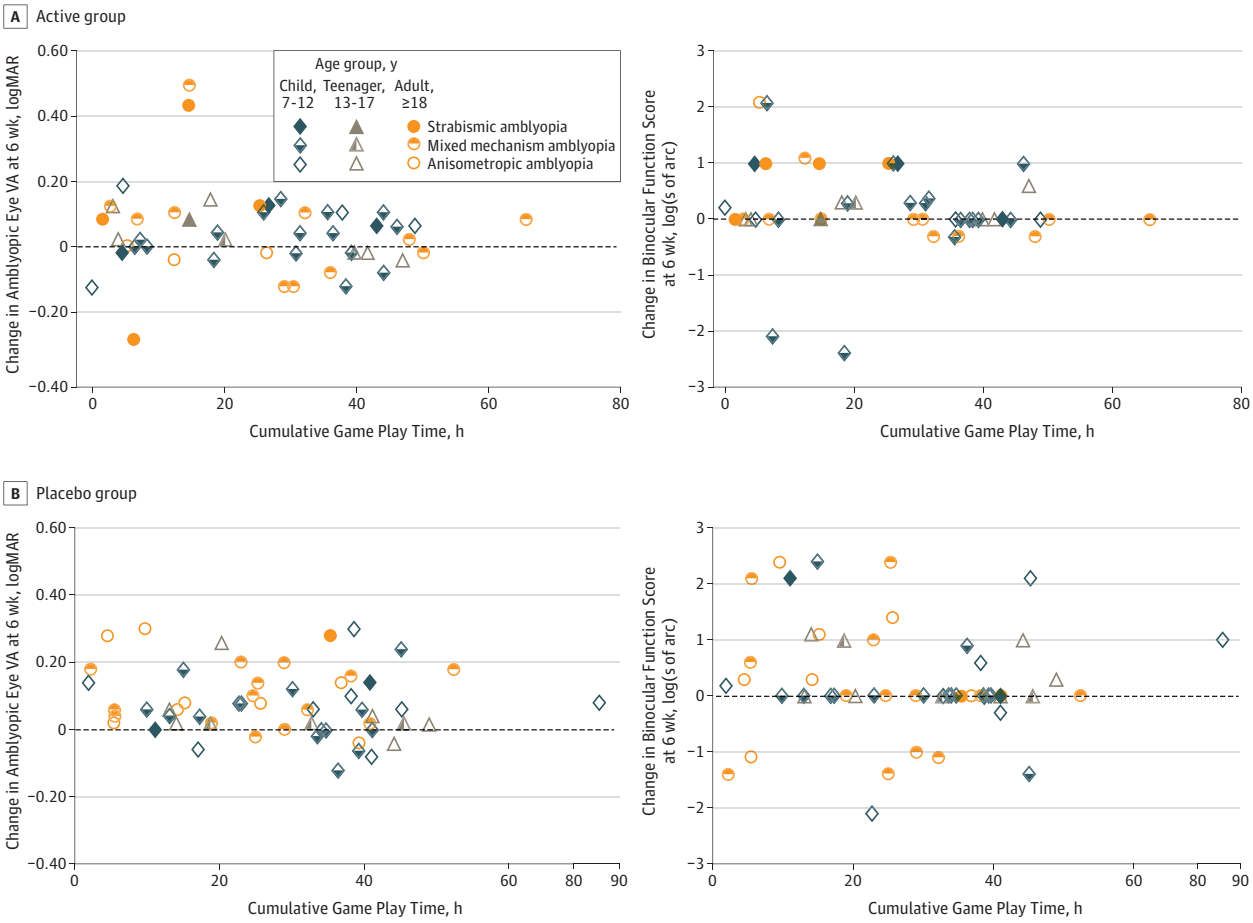
Interocular Suppression

The iPod-based Dichoptic Global Motion Test was successfully completed at both the baseline and 6-week visits by 43 participants (77%) in the active group and 51 (86%) in the placebo group. Small decreases in mean suppression were found in both groups, but there was no statistically significant difference between groups (Table 3).

Angle of Strabismus

At 6 weeks, 1 participant (2%) in the placebo group showed an increase in strabismus angle of 6 prism diopters (Δ) or greater from baseline, and 4 participants (2 [4%] in the active group and 2 [3%] in the placebo group) showed reductions in strabismus angle of 6Δ or greater. Mean changes in strabismus angles in both treatment groups were

Figure 2. Scatterplots of Changes in Visual Functions vs Cumulative Game Play Duration at 6 Weeks



A, There were 18 participants aged 7 to 12 years, 8 aged 13 to 17 years, and 24 aged 18 years or older. B, There were 23 participants aged 7 to 12 years, 9 aged 13 to 17 years, and 25 aged 18 years or older. For all y-axes, positive change values indicate improvement from baseline. Each data point represents 1 participant. Participants were prescribed a total minimum dose of 42 hours of video game treatment over 6 weeks.

less than 1Δ and not clinically significant, so further analysis was not performed.

Fellow Eye Distance VA

At 6 weeks, distance VA in fellow eyes improved by less than 1 letter in both the active and placebo groups (mean [SD] changes of 0.019 [0.06] and 0.018 [0.05] logMAR, respectively) (Table 3).

Adverse Events

No participants reported diplopia. Two participants (4%) in the active group and 1 (2%) in the placebo group described transient asthenopia when playing the video games. Non-video game-related adverse events are detailed in eTable 8 in Supplement 2.

Discussion

This clinical trial applied a laboratory-developed binocular treatment in a home-based setting and included only participants 7 years and older. A total of 89 of 115 participants (77.4%) had previous occlusion or penalization therapy but still had residual amblyopia, representing the patients most difficult to treat. Both the active and placebo groups showed small VA and stereoacuity improvements, but the 2 groups did not significantly differ on any visual outcome, and no significant subgroup treatment effects were found. There were also no significant dose-response relationships for either video game (Figure 2). Therefore, the small improvements in our 2 treatment groups were unlikely to be video game–related and may instead have been caused by regression to the mean,[30] optical treatment, and/or placebo effects. Our negative result indicates that the specific home-based binocular video game we tested was not effective in this older, previously treated population.

Previous laboratory-based studies of contrast-balancing treatments found mean amblyopic eye VA improvements of 0.15 to 0.35 logMAR (1.5 to 3.5 lines).[4,11,15,31] Participants in these studies completed treatment under supervision, ensuring full attention to the task at all times. Studies of home-based contrast-balancing video games reported mean improvements of 0.08 to 0.11 logMAR (0.8 to 1.1 lines) in amblyopic eye VA.[12-14,29]

Table 3. Secondary Visual Outcomes

Change From Baseline[a]	Active (n = 56) No.	Active (n = 56) Adjusted Mean (SE)[b]	Placebo (n = 59) No.	Placebo (n = 59) Adjusted Mean (SE)[b]	Adjusted Treatment Group Mean Difference (95% CI)	*P* Value
Distance VA (e-ETDRS test at 3 m), logMAR						
Fellow eye	52	0.01 (0.01)	58	0.02 (0.01)	−0.002 (−0.02 to 0.01)	.75
Binocular	52	0.01 (0.005)	58	0.01 (0.005)	0.001 (−0.01 to 0.01)	.90
Near VA at 40 cm, logMAR						
Amblyopic eye	52	0.04 (0.01)	58	0.04 (0.01)	0.01 (−0.03 to 0.04)	.72
Fellow eye	52	0.02 (0.01)	58	0.02 (0.01)	−0.004 (−0.02 to 0.02)	.69
Binocular	52	0.02 (0.01)	58	0.02 (0.01)	0.003 (−0.02 to 0.02)	.73
Binocular function score, log(seconds of arc)	52	0.16 (0.09)	58	0.15 (0.08)	0.01 (−0.21 to 0.23)	.92
Interocular suppression, dichoptic contrast ratio	43	−0.065 (0.030)	51	−0.118 (0.027)	0.053 (−0.022 to 0.128)	.17

Abbreviations: e-ETDRS, electronic Early Treatment Diabetic Retinopathy Study; VA, visual acuity.

[a] Change (baseline to follow-up) was analyzed using mixed models with a compound symmetry covariance structure and adjusting for baseline values and age groups. In these models, the treatment by visit interaction effect was not significant; therefore, only the overall results collapsed across all follow-up visits (3, 6, 12, and 24 weeks) are reported. Missing values were excluded from analysis.

[b] All models are adjusted for baseline value and age groups. Missing data were excluded from analysis. For all variables except for interocular suppression, positive change values indicate an improvement in visual function. For interocular suppression, a negative value indicates decrease in suppression.

The supervised environment in laboratory studies may have played an important role, as constant viewing of dichoptic stimuli without distractions may be required for treatment effects. In addition, participants may play home-based video games in several short sessions to fit around other activities. Shorter sessions may also help to alleviate video game-related asthenopia (eTable 8 in Supplement 2). In contrast, participants attending typical laboratory or in-office training generally performed treatment in dedicated 1-hour to 2-hour blocks. Multiple short sessions and 1 long daily session can both produce similar cumulative game play times, but it is currently unknown if continuous binocular stimulation is important for the effectiveness of binocular treatments.

Our results are similar to a previous randomized clinical trial,[32] which evaluated in-office I-BiT treatment (dichoptic presentation without contrast-balancing[7]) in 75 children aged 4 to 8 years where no significant differences were found between binocular and nonbinocular treatments. Another clinical trial[33] conducted by the Pediatric Eye Disease Investigator Group compared an iPad version of the current home-based contrast-balancing falling-blocks video game with 2 hours per day of patching in 385 children aged 5 to 12 years old. This trial also found a lack of dose response for this binocular video game, although the primary noninferiority analysis was indeterminate and compliance was poorer than the current clinical trial because of a much longer treatment period of 16 weeks. However, the Pediatric Eye Disease Investigator Group trial[33] did find substantial improvements in children aged 5 to 6 years with no prior treatment (mean VA gain of 2.5 logMAR lines in the binocular video game group vs 2.8 lines in the patching group), suggesting that binocular video games could be effective for this subgroup of patients.

Mean compliance in our active group appeared worse than the placebo group partly because of a greater number of withdrawals during the 6-week treatment period. Treatment acceptability appeared similar between the 2 groups (eTable 6 in Supplement 2), so we do not know if these compliance and attendance differences were related to the active game possibly being more difficult or if they simply occurred by chance.

Compliance fell in weeks 4 to 6 compared with weeks 1 to 3 of treatment (eTable 3 in Supplement 2), and some participants mentioned declining interest in the falling-blocks video game during follow-up. More engaging content, along with greater game play variety, will help to maintain compliance and attentional engagement over longer treatment periods. Dig Rush is a recently developed video game that uses the same contrast-balancing principle as the falling-blocks game in this trial but contains more interesting tasks to stimulate attentional engagement and video game rewards to motivate continued play. In a previous crossover randomized clinical trial in 28 children aged 4 to 9 years,[34] Dig Rush produced significantly more amblyopic eye VA improvement than 2 hours per day of patching after 2 weeks (mean improvement, 1.5 and 0.7 logMAR lines, respectively), and mean compliance with at-home video game treatment was 82% to 100% of the prescribed dose. A randomized clinical trial comparing Dig Rush plus spectacle correction with spectacle correction alone in children aged 4 to 12 years began recruitment in February 2017 (NCT02983552). The results of this trial will indicate the degree to which video game features designed to increase patient engagement may affect treatment outcomes.

The active binocular video game treatment used in this trial was developed based on the hypothesis that interocular suppression underlies visual deficits in amblyopia.[3] However, our active game did not change interocular suppression more than placebo (Table 3) despite progression of fellow eye contrast evident in game data (eFigure 2 in Supplement 2). This may be because of factors such as compliance with anaglyphic glasses, potential dose-continuity effects, or a failure of the active game stimulus in strengthening binocular vision. However, the iPod-based Dichoptic Global Motion Test used in this trial was found to be somewhat unreliable, as the portable display was prone to image misalignment and the task was difficult for younger children. Thus, from the results of this trial alone, we are un-

able to adequately evaluate the hypothesis of suppression playing a causal role in visual deficits associated with amblyopia.

Strengths and Limitations

Outcomes in this study were measured using a stringent double-masked protocol. Our refractive criteria ensured that participants who had not worn appropriate correction full-time for at least 4 months underwent optical treatment and had stable distance VA (0.10 logMAR change or less over 4 or more weeks) before starting video game treatment.

Our study had limitations. Although we had reliable iPod-extracted data for most participants to objectively assess game play compliance, we were unable to monitor participants' attention to the video game at home or whether they wore anaglyphic glasses correctly. These factors may reduce or nullify treatment effects of the active game.

Conclusions

The results of the current randomized clinical trial indicate that the specific binocular falling-blocks video game tested did not produce greater clinical visual improvements than placebo in older, mostly treated patients with amblyopia. Further development of more engaging video games, more sophisticated means of monitoring compliance and attention, and proven effectiveness in randomized clinical trials are required before binocular treatments are ready for clinical use.

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Author Affiliations: School of Optometry and Vision Science, The University of Auckland, Auckland, New Zealand (Gao, Guo, Black, South, Thompson); School of Optometry and Vision Science, University of Waterloo, Waterloo, Ontario, Canada (Babu, Bobier, Chakraborty, Raveendren, Thompson); Department of Ophthalmology, Starship Children's Hospital, Auckland, New Zealand (Dai); Department of Ophthalmology, McGill Vision Research, McGill University, Montreal, Quebec, Canada (Hess, Thompson); National Institute for Health Innovation, School of Population Health, The University of Auckland, Auckland, New Zealand (Jenkins, Jiang, Parag, Wadham, Walker); Centre for Eye Research Australia, Royal Victorian Eye and Ear Hospital, Melbourne, Victoria, Australia (Kearns, Kowal, Pieri, Staffieri); Ophthalmology, University of Melbourne Department of Surgery, Melbourne, Victoria, Australia (Kearns, Kowal, Pieri, Staffieri); School of Optometry, The Hong Kong Polytechnic University, Hong Kong, China (Lam, Pang).

Author Contributions: Dr Thompson had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Gao, Guo, Balck, Bobier, Dai, Hess, Kowal, Parag, South, Staffieri, Walker, Thompson.
Acquisition, analysis, or interpretation of data: Gao, Guo, Babu, Black, Chakraborty, Jenkins, Jiang, Kearns, Lam, Pang, Parag, Pieri, Raveendran, South, Staffieri, Thompson.
Drafting of the manuscript: Gao, Guo, Black, Walker, Thompson.
Critical revision of the manuscript for important intellectual content: Gao, Guo, Babu, Black, Bobier, Chakraborty, Dai, Hess, Jiang, Kowal, Lam, Pang, Parag, South, Staffieri, Wadham, Walker, Thompson.
Statistical analysis: Jiang, Parag.
Obtained funding: Lam, Thompson.
Administrative, technical, or material support: Jenkins, Pieri, Wadham.
Study supervision: Black, Bobier, Dai, Hess, Kowal, Lam, Walker, Thompson.

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Group Information: The Binocular Treatment of Amblyopia Using Videogames (BRAVO) Study Team included the following members: *BRAVO Steering Committee:* Benjamin Thompson, PhD (principal investigator; School of Optometry and Vision Science, University of Waterloo, Waterloo, Ontario, Canada); Joanna M. Black, PhD (School of Optometry and Vision Science, University of Auckland, Auckland, New Zealand); William R. Bobier, PhD (School of Optometry and Vision Science, University of Waterloo, Waterloo, Ontario, Canada); Shuan Dai, MBBS, MSc, FRANZCO (Starship Children's Hospital, Auckland, New Zealand); Robert F. Hess, DSc (McGill Vision Research, McGill University, Montreal, Quebec, Canada); Yannan Jiang, PhD (National Institute of Health Innovation, University of Auckland, Auckland, New Zealand); Lionel Kowal, MBBS, FRANZCO (Ophthalmology, University of Melbourne, Melbourne, Australia); Carly S. Y. Lam, PhD (School of Optometry, The Hong Kong Polytechnic University, Hong Kong, China); Varsha Parag, MSc (National Institute of Health Innovation, University of Auckland, Auckland, New Zealand); and Natalie Walker, PhD (National Institute of Health Innovation, University of Auckland, Auckland, New Zealand); *BRAVO Management Committee:* Joanna M. Black, PhD (chair; University of Auckland, Auckland, New Zealand); Cindy X. Guo, PhD (University of Auckland, Auckland, New Zealand); Raiju J. Babu, PhD (University of Waterloo, Waterloo, Ontario, Canada); Tina Y. Gao, BOptom (University of Auckland, Auckland, New Zealand); Michelle Jenkins (University of Auckland, Auckland, New Zealand); Jayshree South, BMedSc (University of Auckland, Auckland, New Zealand); and Angela Wadham, BA (University of Auckland, Auckland, New Zealand); *Clinical Assessors*: Cindy X. Guo, PhD; Joanna M. Black, PhD; Tina Y. Gao, BOptom; and Jayshree South, BMedSc (n = 42; School of Optometry and Vision Science, University of Auckland, Auckland, New Zealand); Raiju J. Babu, PhD; Rajkumar Nallour Raveendren, PhD; and Arijit Chakraborty, PhD (n = 46; School of Optometry and Vision Science, University of Waterloo, Waterloo, Ontario, Canada); Simon Clavagnier, PhD; and Daniel Spiegel, PhD (n = 4; McGill Vision Research, McGill University, Montreal, Quebec, Canada); Sandra Elfride Staffieri, BAppSc(Orth); Lisa S. Kearns, B Orth & Ophtha Sci; and Roberto Pieri, B Orth, MAOB (n = 9; Centre for Eye Research Australia, Royal Victorian Eye and Ear Hospital, Melbourne, Victoria, Australia); and Peter C. K. Pang, DHSc; Ka Ching Ko, MSc; Geoffrey Chu, PhD; Lily Chan, OD; Mabel Leung, MSc; and Yee Mui Kwok (n = 14; School of Optometry, Hong Kong Polytechnic University, Hong Kong, China); *technical support for iPod video games*: Rifeng Ding, MSc (McGill University, Montreal, Quebec, Canada); and *project managers and support staff at the National Institute of Health Innovation, University of Auckland, Auckland, New Zealand*: Colin Howe, PhD; Taina von Blaramberg, RCompN, DPH; Joanna Michie, MSc; Michelle Jenkins; John Faafetai Faatui, MSc; Colleen Ng, BE, GradDipInfoSci; Stuart L. Uren, BCompSci; and Stephen J. Boswell, MSc.

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