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Authors
Gambacorta, Christina
Nahum, Mor
Vedamurthy, Indu
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An action video game for the treatment of amblyopia in children: A feasibility study

Christina Gambacorta[a,1], Mor Nahum[a,b,1], Indu Vedamurthy[c], Jessica Bayliss[d], Josh Jordan[f], Daphne Bavelier[c,e], Dennis M. Levi[a,*]

[a] School of Optometry, Graduate Group in Vision Science and Helen Wills Neuroscience Institute, University of California, Berkeley, Berkeley, CA 94720-2020, USA
[b] School of Occupational Therapy, Faculty of Medicine, Hebrew University, Jerusalem, Israel
[c] Department of Brain & Cognitive Sciences, University of Rochester, Rochester, NY 14627-0268, USA
[d] School of Interactive Games and Media, Rochester Institute of Technology, Rochester, NY 14623, USA
[e] Faculty of Psychology and Education Sciences, University of Geneva, Switzerland
[f] California School of Professional Psychology at Alliant International University, USA

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ABSTRACT

The gold-standard treatment for childhood amblyopia remains patching or penalizing the fellow eye, resulting in an average of about a one line (0.1 logMAR) improvement in visual acuity following ≈120 h of patching in children 3–8 years old. However, compliance with patching and other treatment options is often poor. In contrast, fast-paced action video games can be highly engaging, and have been shown to yield broad-based improvements in vision and attention in adult amblyopia. Here, we pilot-tested a custom-made action video game to treat children with amblyopia. Twenty-one (n = 21) children (mean age 9.95 ± 3.14 [se]) with unilateral amblyopia (n = 12 anisometropic and n = 9 strabismic) completed 20 h of game play either monocularly, with the fellow eye patched (n = 11), or dichoptically, with reduced contrast to the fellow eye (n = 10). Participants were assessed for visual acuity (VA), stereo acuity and reading speed at baseline, and following 10 and 20 h of play. Additional exploratory analyses examined improvements after 6–10 weeks of completion of training (follow-up). Following 20 h of training, VA improved, on average, by 0.14 logMAR (≈38%) for the dichoptic group and by 0.06 logMAR (≈15%) for the monocular group. Similarly, stereoacuity improved by 0.07 log arcsec (≈17%) following dichoptic training, and by 0.06 log arcsec (≈15%) following monocular training. Across both treatment groups, 7 of the 12 individuals with anisometropic amblyopia showed improvement in stereoacuity, whereas only 1 of the 9 strabismic individuals improved. Most improvements were largely retained at follow-up. Our feasibility study therefore suggests that the action video game approach may be used as an effective adjunct treatment for amblyopia in children, achieving results similar to those of the gold-standard treatment in shorter duration.

1. Introduction

While the consequences of abnormal visual development have been known for several centuries, millions of children go undiagnosed and therefore untreated every year. Current reports put the prevalence of amblyopia at about 2.4% of the population, affecting approximately 15 million children worldwide (Wu & Hunter, 2006). As a result, these patients face the possibility of permanent monocular vision loss and a greater likelihood of complete impairment if vision to the good eye is disturbed through injury or disease (Williams & Harrad, 2006). Amblyopia can also negatively impact one's quality of life, resulting in reduced reading and fine motor skills, and may even negatively affect an individual's self-image (Choong, Lukman, Martin, & Laws, 2004; Chua & Mitchell, 2004; Horwood, Waylen, Herrick, Williams, & Wolke, 2005; O'Connor et al., 2010; O'Connor et al., 2009; Packwood, Cruz, Rychwalski, & Keech, 1999; Rahi, Cumberland, & Peckham, 2006; Webber, Wood, Gole, & Brown, 2008a, 2008b).

Amblyopia is accompanied by widespread processing deficits in a range of visual functions that cannot be solely explained by abnormalities in primary visual cortex (see Kiorpes, 2006; Levi 2006; Levi 2013 for reviews). Despite this, the standard treatment for amblyopia, refractive correction and occlusion ('patching') or penalization of the

* Corresponding author.
E-mail address: dlevi@berkeley.edu (D.M. Levi).
[1] Co-first authors.

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fellow (non-amblyopic) eye, focuses on improving visual acuity. While it is now clear that occlusion therapy can be effective, it also has some significant limitations. For one thing, patching is slow. For example, Stewart, Stephens, Fielder, Moseley, and Cooperative (2007) report that it takes approximately 170 h of patching for two lines of improvement in VA for a 4-year-old, and 236 h for a similar effect in a 6-year-old. This jumps to over 400 h for children older than 7 years of age (Fronius, Cirina, Ackermann, Kohnen, & Diehl, 2014). Moreover, covering one eye is conspicuous, and requires the child to accept reduced visual perception while the fellow eye is covered. For these reasons, compliance can be very challenging. Further, the visual function of many children often does not improve to normal levels. In fact, a substantial proportion of amblyopic children fail to achieve normal acuity even after extended periods of treatment (Birch & Stager, 2006; Birch, Stager, Berry, & Leffler, 2004; Repka et al., 2003; Repka et al., 2004; Repka et al., 2005; Rutstein et al., 2010; Stewart, Moseley, Stephens, & Fielder, 2004; Wallace et al., 2006; Woodruff, Hiscox, Thompson, & Smith, 1994). Even when vision is fully normalized, as many as 25% of patients experience a recurrence within the first year of treatment (PEDIG, 2004).

For these reasons, over the last two decades, there have been a number of attempts to develop more efficient treatments for childhood amblyopia, using perceptual learning and video game techniques (see Birch, 2013; Hess & Thompson, 2015; Levi, 2012; Levi, Knill, & Bavelier, 2015; Levi & Li, 2009 for reviews), either monocularly (with the amblyopic eye; AE) or dichoptically (with different information presented to the two eyes in order to reduce suppression and/or enhance fusion). A summary of the main studies testing such treatments in children is provided in Table 1.

An important limitation on clinical adoption of these methods for treating amblyopia in children is compliance. Laboratory-based perceptual learning is generally repetitive and tedious. As a result, several groups have recently moved toward either gamified versions of perceptual learning tasks or full-fledged video games that exploit the appeal of games developed for entertainment. However, gamified perceptual learning tasks may not have the same level of appeal and engagement as commercial action video games. Unlike lab-based gamified perceptual learning, the video game industry is a multi-billion-dollar segment of the entertainment media, and designers face intense competition to create rich, immersive and engaging environments. The result is a more compelling experience that is more enjoyable and overcomes much of the tediousness experienced in perceptual learning regimes. Importantly, it is now well established that in normal adults, action video games enhance various aspects of visual perception, above and beyond other video game genres such as social simulation games or Tetris (see for example, Green, Li, & Bavelier, 2010).

While action video games were initially defined as first- and third-person shooter video games by the video game industry, we (and others) now consider action video games as those that combine a number of features or game mechanics that facilitate brain plasticity and learning. Among these mechanics, are the need to execute actions under time constraints, a high load on divided attention, the appropriate switch between focused and divided attention as task demands change, the requirement to plan at many different time scales, from milliseconds to hours, and the use of variable value and time reward schedules, to cite a few (Green et al., 2010). Thus, video games do not have to have violent content in order to be considered as action games.

Commercial action video games are compelling and highly engaging. These games often include targets and enemies that move into and across the visual field. To succeed, players must be able to both distribute their attention widely and focus to the most relevant areas of the screen, and make spatial decisions under time pressure by aligning a cross hair or viewing scope to the target of interest. Once a decision has been made, the player receives immediate feedback in the form of points or negative consequences. Like perceptual learning, the level of game difficulty also increases as the players improve.

Action video games also trigger arousal and provide nuanced feedback on performance, which may be critical for efficient learning (Bavelier, Green, Pouget, & Schrater, 2012). Most importantly, however, action video games have a variety of salient content over the entire screen, leading to behavioral enhancements that are broader than the retinotopic and task-specific changes that are often observed in PL (but see Xiao et al., 2008; Zhang, Cong, Klein, Levi, & Yu, 2014). Playing action video games results in significant improvements in a broad range of visual functions, from low-level to high level in normal adults (Green & Bavelier, 2007; Li, Polat, Makous, & Bavelier, 2009; Li, Polat, Scalzo, & Bavelier, 2010).

In contrast to neurotypical adults, adults with amblyopia show improvements in vision after playing commercial video games – either action (Medal of Honor) or non-action (Sim City) video games (Li, Ngo, & Levi, 2015; Li, Ngo, Nguyen, & Levi, 2011) monocularly, with the fellow eye patched. For example, Li et al. (2011, 2015) showed that playing video games monocularly with the AE resulted in a broad range of improvements (visual acuity, stereoacuity, positional acuity, and spatial and temporal attention) in adults with amblyopia. However, an important principle of learning is that task difficulty should be adapted to the learner's capacity. From this point of view, commercially available action video games designed by the industry for experienced gamers with normal vision may not be ideal, but should be modified to include easier levels adapted to the specific challenge of playing with degraded vision. Scaffolding the learning experience for the patient is a key design principle that should not be overlooked.

A number of recent studies have used dichoptic games, aimed at improving stereovision by reducing suppression and/or enhancing fusion for both adults (Hess & Thompson, 2015; Vedamurthy et al., 2015) and children (Kelly et al., 2016). For example, in a recent study, Kelly et al. (2016) had children play DigRush - a game in which children manipulate miners and their surroundings to dig for gold, while avoiding obstacles. However, to date there have not been studies using action video games (either monocular or dichoptic) with amblyopic children.

The aim of the current study was to test the feasibility and initial efficacy of using a customized action video game with a population of amblyopic children (age 7–17). While several groups have recently conducted studies with similar goals using both non-action games and movie viewing (see Table 1), they all cite motivation and compliance as challenging factors that may be limiting their results. Importantly, we compared the dichoptic video game to an identical video game played monocularly, with the fellow eye patched. Unlike the "sham" treatment where the content to the two eyes is reversed (i.e., high contrast to the fellow eye and low contrast to the weak eye, ensuring that the AE will be suppressed during play – e.g. Birch et al., 2015; Li et al., 2014), this control condition incorporates the traditional gold standard treatment. Our 'patching-while-playing' control should help provide further insight into whether dichoptic action video game play yields greater improvement than monocular action video game play. Previous studies in children have been equivocal, with some reporting greater improvement with dichoptic training (e.g. Kelly et al., 2016) and others reporting little or no advantage to the effects of dichoptic training (Tetris) over patching (e.g. Holmes et al., 2016).

2. Methods

2.1. Study participants and ethics statement

The study took place in research laboratories, at University of

Table 1
Previous studies.

Approach	Study	N	Age (years)	Task	Duration (hours)	LogMAR gain	Stereo gain	Suppression change	setting	compliance	comments
Monocular PL & VG											
	Li et al. (2007)	2	9 &12	Position discrimination in noise	≈100	0.3	2/2		lab	100%	
	Polat, Ma-Naim, and Spierer (2009)	5	7–8	Gabor detection	≈40	0.21	1/5	Yes	lab		(patching failed/non-compliant)
	Liu et al. (2011)		8–17	Grating acuity	40–60						
	patched	10				0.07	3/9		lab		
	not patched	13				0.11	9/11		lab		additional training resulted in further improvement
	Kelly et al. (2016)	14	4.6–9.5	patching	28	0.07	NS	Yes	home	?	
	Holmes et al. (2016)	195	5–12.9	patching	224	0.14	NS			?	
	Current study	11	7–17	VGP + Gabor	20	0.06	5/11		lab	75%	
					Mean	0.14					
					95% CI	0.07					
Dichoptic PL & VG											
Anti-suppression	Knox, Simmers, Gray, and Cleary (2012)	14	5–14	Motion coherence	5	0.09	7/14	NS	lab	100%	
Anti-suppression	Li et al. (2014)		4–12	tetris; Balloon; Pong & Labyrinth					home	76%	
**	binocular group	45		AE high contrast; FE low	16–32	0.08	NS	NS			25 also patched the FE
	sham group	24		AE low contrast; FE high	16	NS	NS	NS			13 also patched the FE
Anti-suppression	Birch et al. (2015)		3–6.9							62% ≥ 8 h	
**	binocular group	45		AE high contrast; FE low	at least 16	0.09	NS	NS	home		some also patched the FE
	sham group	5		AE low contrast; FE high	at least 16	0.02	NS	NS	home		some also patched the FE
Anti-suppression	Kelly et al. (2016)	14	4.6–9.5	binocular iPad adventure game	10	0.15	NS	Yes	home	85% ≥ 7.5 h	
Anti-suppression	Holmes et al. (2016)	190	5–12.9	binocular iPad Tetris game	112	0.11	NS			22% ≥ 84 h	
Anti-suppression	Li et al. (2015)	8	4–10	dichoptic movies	9.4	0.2	NS	NS	lab	–	
Anti-suppression	Webber, Wood, and Thompson (2016)	18	7–12	Dichoptic iPod	11.7	0.09	9/16	Yes	home		Improved fine motor skills
iBIT	Cleary, Moody, Buchanan, Stewart, and Dutton (2009)	12	6–11	Video AE; Frame NAE	3.5	0.18		Transient	hospital		
iBIT	Waddingham et al. (2006)	6	5.4–7.8	Video AE; Frame NAE	4.4	0.27	–		hospital		
iBIT	Herbison et al. (2013)		4–8	Video AE; Frame NAE					hospital		
iBIT	Herbison et al. (2016)		4–8		3					> 90%	RCT
	Arm 1	24		Video AE; BG OU		0.1	NS		hospital		No significant difference between the 3 arms
	Arm 2	26		Action VG AE; BG OU		0.06	NS		hospital		
	Arm 3	25		BG and FG OU		0.03	NS		hospital		
BBV	Bossi et al. (2017)	22	3–11	movie viewing	75	0.27	9/22	NS and NC	home	90%	No prior Tx aside from optical Rx
BBV + AE GP	Current study	10	7–17	dichoptic action VGP + Gabor	20	0.14	3/10	Yes but NC	lab	65%	
Total		680			Mean	0.14					
					95% CI	0.04					

**These appear to be the same study.
NS = Not significant NC = not correlated.

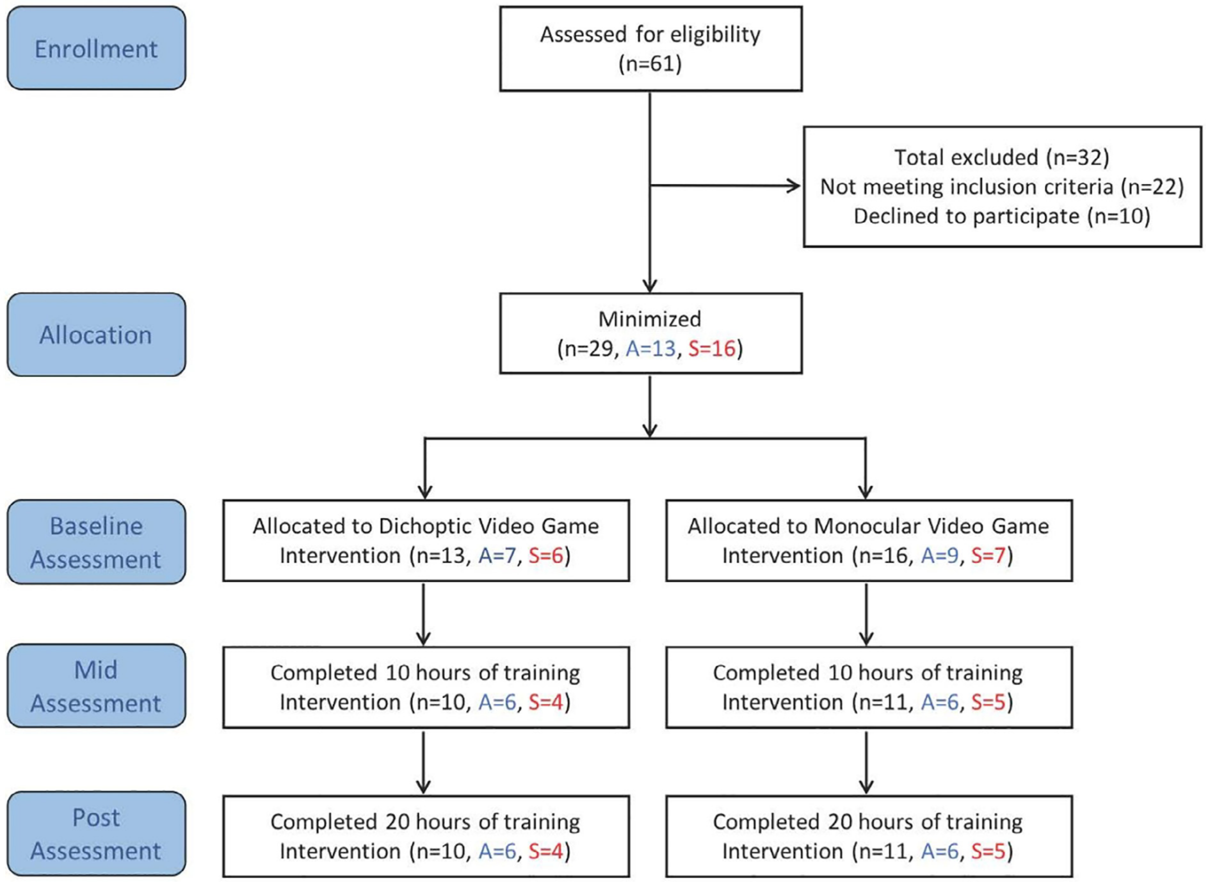

Fig. 1. Study design. Total number of participants included in each portion of the study (n), further divided into anisometropic amblyopes (A) and strabismic amblyopes (S).

Rochester, NY and University of California, Berkeley, CA. The Institutional Human Subjects Review Boards at both institutions approved the study protocol. The study was conducted according to the tenets of the Declaration of Helsinki and informed consent was obtained from each participant and their parent/guardian. Twenty-one (N = 21) children[2] (mean age: 9.95 ± 3.14 [se], range 7–17 years) with unilateral amblyopia completed 20 h of video game training and their data were analyzed. Participants were recruited through the eye clinic at both sites as well as through print advertisements at both locations. All participants were provided complete eye exams prior to enrolling. Fig. 1 shows the study design with numbers of participants screened, qualified and dropped out.

The inclusion criteria were: (1) age 7–17 years old; (2) anisometropic amblyopia, strabismic amblyopia, or mixed (i.e., anisometropic and strabismic); (3) interocular visual acuity (VA) difference of at least 0.2 LogMAR; and (4) no history of eye surgery except those to correct strabismus. Exclusion criteria included: (1) non-concomitant or large angle constant strabismus (> 30 prism diopters); and (2) any ocular pathological conditions (e.g., macular abnormalities) or nystagmus. All of our participants had normal or near normal VA in the fellow eye (FE – $20/12^{-1}$ – 20/25). The retinal health of all participants was assessed as normal, and they all had clear ocular media as assessed by ophthalmoscopy. Cover tests were used to assess ocular alignment at both distance and near.

Subject Classification. Study participants were categorized as either anisometropic ('aniso') or strabismic ('strab') amblyopes. Anisometropia was defined as ≥0.50D difference in spherical equivalent refraction or ≥1.5D difference in astigmatism in any meridian, between the two eyes (Wallace et al., 2011). Amblyopic subjects with anisometropia and an absence of manifest ocular deviation were classified as anisometropic amblyopes. Those with an ocular deviation (strabismus), as indicated by the cover test, were classified as strabismic amblyopes, irrespective of their refractive state, meaning that participants with both strabismus and anisometropia were defined as 'strabismic'. Clinical details of study participants who completed the study are provided in Table S1. Several of the subjects had been recently treated (as indicated by the $^{+}$ in Table S1), and discussed in Section 3.4.3.

Correction of Refractive Error. Participants were instructed to wear their most recent optical prescription at all times, but were given trial frames with their refractive correction for training in the lab if they arrived without spectacles or contact lenses. Two children required an updated prescription. They were provided with full optical correction and were monitored for 6–8 weeks. They then returned to the lab for a new baseline assessment before starting the study.

2.2. Study design overview

The complete experimental design is detailed in Fig. 1. Following consent and screening, eligible participants were assigned to one of two intervention groups: (1) dichoptic game group (n = 13): playing the custom-made dichoptic video game using a mirror stereoscope and balanced input (see description below); (2) monocular game group (n = 16): playing the same game with the FE view turned off and that eye occluded with a black eye patch. Groups were assigned via a minimization procedure (Taves, 1974; see Green, Strobach, & Schubert, 2014 for a discussion), i.e. the first several participants were randomly

[2] Both the NIH and our IRBs define children as individuals under 18 years of age.

Fig. 2. Screenshots from the custom-made child-friendly action video game. Top Left: Children in the dichoptic game play group aligned the game with a mirror stereoscope. Top right: Dichoptic display showing the image sent to the AE on the left and that sent to the NAE on the right, in the Magical Garden game world; during set-up, children adjusted the mirrors and contrast level of the NAE image, such that both images of the stereoscope were equally visible. Bottom Panels: The lower two screenshots show the two other game worlds, Amblyopia World (top) and Chinatown (bottom); Various games were included in order to keep the children engaged for as many as 20 h.

assigned to a treatment and later participants were assigned to reduce the imbalance between the groups. This was particularly important to approximately balance the amblyopic subtypes (anisometropic and strabismic) for each training method.

Before starting the 20-h intervention, participants completed a test battery (described in 2.4) to assess vision and related functions ('baseline assessments'). Participants repeated the battery after the completion of 10 h ('mid-assessment'), and 20 h ('post-assessment'). Additionally, 12 of the participants who completed the study returned for one last assessment following a no-contact period of at least six-week ('follow-up assessment'). Although this follow-up assessment was initially planned in our design, it became rapidly clear it would lead to a too great attrition rate and thus participants were kept in the study even if they made it clear they could not comply with a follow-up visit. This led to a self-selected subgroup at follow-up; for this reason, their data will be discussed separately from the main study.

2.3. Study interventions

Participants from both groups were required to complete a total of 20 h of experimental treatment, in sessions lasting approximately 1 h, 1–3 times/week. Participants played a child-friendly action video game developed using the Unreal Tournament engine (see Fig. 2 and Gambacorta et al., 2014). The general gaming principles were similar to those used in our adult video game version (Bayliss, Vedamurthy, Bavelier, Nahum, & Levi, 2012; Bayliss, Vedamurthy, Nahum, Levi, & Bavelier, 2013; Vedamurthy et al., 2015; Vedamurthy, Nahum, Bavelier et al., 2015). However, in the child-friendly version of the action game, we removed the violent elements of the original Unreal Tournament action game while maintaining the motivating nature of a commercial game, as well as the heavy attentional load and relatively fast pacing of action video games.

Easier training levels were included so that young children with little gaming experience could master the skills required to play the game. The initial training levels included basic environmental cues and boundaries to keep the children focused while learning to move, pick up objects, and orient their pointer tools. Children were instructed to move throughout the scene, collect health points and tag one or more robot opponents. To tag the opponents, the fixation scope was aligned onto the center of the robot and the mouse was clicked to activate the pointer tool. This was operationally similar to a first-person-shooter game, but instead of guns, the pointer tools included a juice machine, bubble wand, and flower button.

Once basic proficiency with the game was achieved, the children played the tag game in one of three main worlds, each with a variety of objects and scenes, meaning players were exposed to many colors and spatial frequencies. Each world had a different theme, including the Magical Garden with imaginative plants, Amblyopia World with bridges and elevators to access the multiple stories, and Chinatown, with hidden alleys and takeout food boxes (see example scenes in Fig. 2). To maintain engagement over the course of the entire study, additional robot opponents were added, and the difficulty level of the game was modulated based on the child's individual progress, causing the robots to vary not only in number but also in speed, moving faster across the screen as the child progressed in the game.

A perceptual learning task was seamlessly integrated within the game, with an oriented Gabor patch that randomly appeared every few seconds in the view of the AE only (Vedamurthy, Nahum, Huang et al., 2015 and Vedamurthy, Nahum, Bavelier et al., 2015). Participants were required to respond to one orientation by tagging the target, and to the other orientation by either ignoring the patch or pressing the letter 'E'. An incorrect response transformed the Gabor patch into a particularly powerful game enemy. The spatial frequency of the Gabor patch was adapted to maintain participant's performance at 79% correct (Levitt, 1971). The Gabor patch task enabled us to monitor the AE's resolution limit, while simultaneously serving as a suppression check (particularly important under dichoptic mode, see below), ensuring that the AE was actively engaged during game play.

Training took place in the lab, under supervision of research assistants. While logistically more challenging to the patients and their families, this design offers several key advantages. First, we can ensure that all patients receive the same training dosage with the proper optical correction. Second, we can have participants use a mirror-stereoscope to view the game content dichoptically, which is important for proper binocular alignment in some of the patients. For example, several of the strabismic amblyopes in the current study initially experienced difficulty fusing the dichoptic content. By starting with a very low contrast image in the fellow eye and adjusting the mirrors of the stereoscope until bifoveal alignment was achieved, patients learned to fuse the two images with practice. These patients became more proficient with maintaining fusion as the training progressed. While several previous studies used dichoptic content, it was presented with anaglyph or shutter glasses, which do not allow the same control over binocular alignment.

For all participants, the video game was displayed on a gamma corrected monitor (Mitsubishi Diamond Pro 2070 SB), with resolution 1024 × 768 pixels and refresh rate of 60 Hz.

2.3.1. Dichoptic game mode

In the dichoptic game mode, the game was presented via a split screen view, allowing independent control of the images presented to the left and right eyes, and in particular their respective luminance and contrast. The split images of the game were viewed with a custom designed stereoscope (Fig. 2, top left panel) at a distance of 68 cm. These dichoptic viewing conditions were designed to reduce suppression and promote fusion, while challenging the AE with an embedded psychophysical resolution task. Alpha blending (see Vedamurthy, Nahum, Huang et al. (2015) and Vedamurthy, Nahum, Bavelier et al. (2015) for details) was used to balance the perceived image strength of the NAE with that of the AE eye at the start of each play session, in an effort to reduce suppression and facilitate fusion.

Each session began with both horizontal and vertical alignment of the dichoptic nonius lines by adjusting the mirrors of the stereoscope (Fig. 3). The image to one eye was the bottom and left side of the cross, while the image to the other eye was the top and right side of the cross. With proper alignment, the image was a cross with a square cutout of the center, surrounded by four additional squares and a high contrast border that was visible in both eyes. Older children performed the alignment themselves. When necessary (for young children), the experimenter adjusted the mirrors. Children were shown key cards on how the cross should appear for each eye and both eyes together, and they were asked to draw the image as observed via the stereoscope. Confirmation of alignment was obtained after this iterative approach to ensure the nonius lines were aligned. After launching the game, the experimenter checked in again with the child to ensure that both parts of the fixation scope were visible. The experimenter also monitored the performance of the perceptual learning task to confirm that the child was not suppressing the AE.

We note that there are important differences between our method of dichoptic presentation and those used by others. Our action video game presented the same image to each eye (except for Gabor patches and part of the fixation scope) with reduced luminance/contrast in the NAE, in an attempt to promote binocular fusion. Other dichoptic video game studies have presented different game elements to each eye so that binocular combination is required to play the game (see Hess & Thompson, 2015 for a review). Both approaches have been reported to reduce binocular suppression as well as to improve VA and stereopsis (Hess & Thompson, 2015; Vedamurthy et al., 2015).

2.3.2. Monocular game mode

Participants in the monocular game group played the custom video game described above, but with the NAE display turned off, and a patch over this eye. Other features of the game, such as the perceptual learning task presented to the AE, were identical to the dichoptic group. Training parameters, such as game difficulty and duration of sessions were also kept the same in both groups.

2.4. Visual function assessments

Participants were required to wear their best optical correction (if any) for all visual assessments. Assessments included three main measures: visual acuity (VA), stereoacuity, and reading speed. Assessments were administered at baseline and following 10 and 20 h of training. Follow-up assessments were conducted in 12 of the participants 6–10 weeks post training.

2.4.1. Main visual function assessments

Visual Acuity (VA). Clinical VA at distance was measured using either Bailey-Lovie logMAR letter charts (UCB site), or using the high-contrast ETDRS format chart with Sloan optotypes (catalog No. 2104; Precision Vision, La Salle, Illinois; U of R site). Monocular acuities for both the AE and NAE, as well as binocular acuity were all measured with the same conditions.

Stereoacuity. Stereopsis was measured using the Randot Stereotest (Stereo Optical Co., Inc.; See description in Simons, 1981). Analyses were performed on the logarithm (base 10) of the stereoacuity values. Participants who 'failed' the stereo test were assigned a value of 800 arcsec (similar to Vedamurthy et al., 2015 and Wallace et al., 2011). Additional analyses were performed only for patients who had measurable stereoacuity initially, with similar results, i.e. there were no patients that went from no measureable stereoacuity to some consistently measurable stereoacuity.

Reading Speed. Amblyopic adults read slowly with their amblyopic eye (Levi, Song, & Pelli, 2007), and children with amblyopia have reading impairments, even when using both eyes (Kelly, Jost, De La Cruz, & Birch, 2015). Therefore we evaluated reading speed for reading

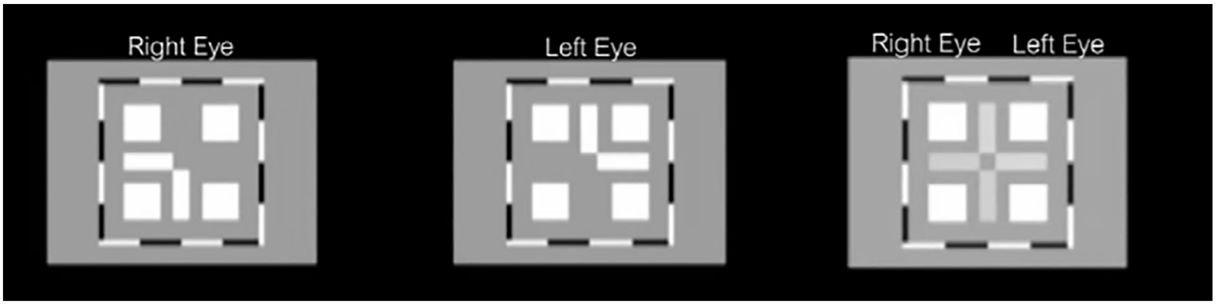

Fig. 3. Dichoptic alignment: Fusion was achieved by aligning dichoptic horizontal and vertical lines to make a cross. A high contrast border and additional squares presented to both eyes provided context to aid in this process.

out-loud using the standardized MNREAD Acuity Chart (Legge, Ross, Luebker, & LaMay, 1989). This chart includes 16 lines, with a full sentence on each line, and each successive line is reduced in letter size by 0.1 Log units. The words chosen for the sentences are ones that commonly occur in second or third grade reading material. All but one child in the study could comfortably read the sentences with supra-threshold print size. This child was removed from the reading analysis. The test was run for each eye separately and then binocularly. One of two charts, each with the same parameters, was chosen for each viewing condition.

The time it takes to read each line, and the number of errors on that line were used to assess reading metrics. Basic reading speed was calculated in words per minute (WPM) after accounting for reading errors. We then calculated a difference reading speed score for each participant. This was derived by first calculating the reading speed difference (post minus pre) for each print size value, and averaging across the number of print sizes read by that participant. This difference between WPM was used for data analysis.

Missing data: Out of the 21 participants, one strabismic patient in the dichoptic group (S7) had missing data for the MNREAD sessions at 10 and 20 h post-tests. One anisometrope patient did not have a 20 h time-point data for all 3 assessments. Another participant was missing stereo data for the 10 h time-point. Four other participants had missing MNREAD data at the 10 h time-point and 2 additional participants had missing MNREAD data at the 20 h time-point, due to data not being recorded correctly. We detail below at each step how missing data were treated.

2.4.2. Exploratory visual function measures

In-game Suppression (Inter Ocular Ratio – IOR). For subjects in the dichoptic group, each session began with careful alignment of the stereoscope and reducing the luminance and contrast level of the NAE's image (by adjusting the alpha value) relative to the AE's image to perceptually equalize the input to the two eyes. The Inter-Ocular Ratio (IOR – the ratio of fellow, NAE to AE luminance/contrast) provides a convenient index for suppression (Ding & Levi, 2014; Vedamurthy, Nahum, Bavelier, & Levi, 2015), with higher ratios indicating less suppression. IOR of 0 indicates complete suppression while IOR of 1 indicates no suppression. We averaged the IOR values in two-hour bins, and report the running average IOR.

2.5. Data analysis

We report here two complementary analyses. In all cases, in order to assess any differences in the effects of training between the two treatment groups (monocular and dichoptic) and the two subject populations (anisometropic or strabismic), our analyses focused on performance differences over time. Since the three tests (visual acuity, stereo test and MNREAD were on different scales, we first converted them to Z scores based on the values of each of the tests at baseline. Additionally, since for VA and stereo acuity lower values indicate better performance while for the MNREAD test higher values indicate better performance, we converted the z-scores for VA and stereo by multiplying them by −1.

Our first analysis was a repeated-measures multivariate analysis of variance (MANOVA). Given the small sample size and the presence of missing cells both at 10 h and 20 h evaluations, we selected the analysis with the least missing data, and focused on contrasting baseline and 20 h performance. The dependent variables were the three main tests of visual acuity (VA), stereo acuity and MN read. The MANOVA was therefore run with the within-subject factors of time (2 levels: baseline and 20 h) and test (3 tests: VA, stereo and MNREAD) and the between-subject factors of treatment type (monocular vs dichoptic) and amblyopia type (anisometropic vs. strabismic/aniso-strab). We used the Huynh-Feldt correction for the model.

For this analysis, we handled missing data at the 20 h time point by replacing it with the 10 h time point data when possible (VA, stereo and MN read data for participant A9, MN read data for participant A10) and with the group average at 20 h when the 10 h data did not exist (MNREAD data for participant A8). One participant (S7) did not have any MNREAD data (at both 10 and 20 h time points) and was therefore excluded from analyses.

We then tested our hypotheses via growth modeling, which is known to be more robust in the face of missing data points, given our focus of performance changes over time. The growth models were accomplished through multilevel modeling (e.g., Singer & Willett, 2003), which estimates individual rates of change over time by generating individual intercepts and slopes for each subject. Missing data is tolerated in growth models assuming data is missing at random, and is based in Full Information Maximum Likelihood (FIML), a "gold standard" in treating missing data, which has been shown to be superior to complete case analysis (i.e., listwise or pairwise deletion; Enders, 2010). Individual rates of change were extracted for each participant for each of the three variables of interest. These estimated rates of change were then converted to z-scores, and then we tested whether groups observed different rates of change over time using a Multivariate Analysis of Variance (MANOVA). This analysis uses the rate of change over time for each of the dependent variables rather than a within-subjects factor of time. This allowed us to retain all participants with at least 2 complete data time points, using the z scores for the 3 relevant tests (VA, stereoacuity, MNREAD). The only participant (S7), who did not have two complete data time points (S7 missed MNREAData at both 10 and 20 h time points), was excluded from the growth model analyses.

3. Results

We report descriptive statistics (Sections 3.2 and correlations) for all 21 participants who completed 20 h of training. MANOVA and growth model statistics are reported for only those participants (N = 20) who had data for all three primary outcomes – visual acuity, stereo vision and reading speed. One strabismic patient in the dichoptic group (S7 –

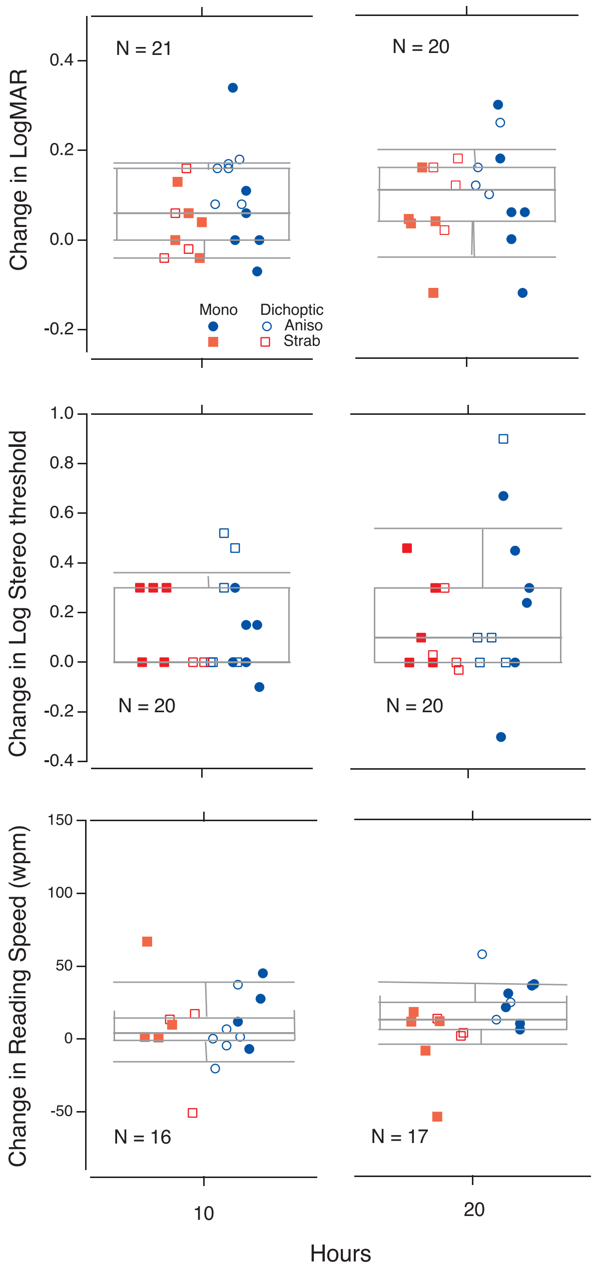

Fig. 4. Box plots showing change in performance for visual acuity (top panels), stereoacuity (middle panels) and MMNREAD (bottom panels). In each boxplot, the center horizontal bar is the median, the box shows the semi-interquartile range, and the whiskers the 9th and 91st percentile. Change scores are shown following 10 h (left plots) and 20 h (right plots) of training, relative to baseline. Changes are shown for monocular (filled symbols) and dichoptic (open symbols) training participants. Color- and shape-coding denotes amblyopia type: aniso (blue, circle) or strab (red, square). The number of participants contributing to each measurement is reported at the bottom of each plot. Note that the horizontal positions of the data points have been jittered to avoid overlap. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

see Table 1) was not included in these analyses as he lacked reading speed data. A separate analysis of the interocular ratio (IOR) included data of 9 participants who completed 10 h. IOR data for 2 observers were inadvertently not recorded.

3.1. Compliance

Drop-out rate was about 31% for the monocular group, and 23% for the dichoptic group. The main reason invoked was the substantial time commitment required for training in the lab. We note that the two groups were similar in age (9.7 ± 2.2 [se] years and 10.2 ± 4.0 [se] in the monocular and dichoptic groups, respectively), and in distribution of amblyopia type (≈45% strabismic and 55% anisometropic in each group), but differed slightly, although not significantly (p = 0.35), in their baseline VA (0.50 ± 0.16 [se] vs. 0.58 ± 0.28 [se] logMAR in the monocular and dichoptic game groups, respectively).

3.2. Descriptive results

In the sections below we provide a description of changes seen in all 21 participants for visual acuity, stereo acuity, and reading speed. Of note, we report 'raw', non-transformed data in this section, with missing values being treated as such with no imputation. Thus, means extracted at the 10 h and 20 h time point are not necessarily matched in terms of patients they include (see Fig. 4).

3.2.1. Changes in LogMAR visual acuity

The mean change in visual acuity (LogMAR) across all participants (n = 21) was 0.08 ± 0.02 [se] logMAR units following 10 h of training, and 0.095 ± 0.02 [se] logMAR units (the equivalent of one line on a letter chart or ≈26%) from baseline to 20 h (Fig. 4 – top panels).

The dichoptic training group (n = 10) improved by 0.1 ± 0.02 [se] logMAR units after 10 h and by 0.14 ± 0.02 L[se] ogMAR units after 20 h (when compared to their baseline data), whereas the monocular group (n = 11) improved on average by 0.06 ± 0.03[se] logMAR units following both 10 and 20 h of training.

Regardless of treatment group, individuals with anisometropia ('aniso') improved by 0.1 ± 0.03 [se] and by 0.11 ± 0.03 [se] logMAR units by 10 and 20 h of training, respectively. This indicates that most change was achieved following 10 h of training, and little change was seen with additional training. In contrast, individuals with strabismus ('strab') improved only by 0.04 ± 0.02 [se] logMAR units following 10 h of training (from 0.62 ± 0.07 to 0.58 ± 0.07 [se] logMAR) and by a total of 0.07 ± 0.03 [se] logMAR units following 20 h of training, indicating slow and consistent gains across each training period.

3.2.2. Changes in stereoacuity

Two of the 11 subjects in the monocular training group (18.2%) and 3 of the 10 participants in the dichoptic training group (30%) failed the Randot stereo test at the baseline visit (we label them as 'stereo blind'). None recovered stereopsis. Of those with initially measurable stereo (n = 16), 8 subjects showed improved stereo acuity; however, overall the mean change across all study participants (n = 21) was 0.08 ± 0.05 [se] log arcsec (≈20%) following 10 h of training, and 0.07 ± 0.07 [se] log arcsec (≈17%) from baseline to 20 h.

Participants in the dichoptic group improved, on average, by 0.16 ± 0.07 [se] and by 0.07 ± 0.11 [se] log arcsec (45 and 17%) following 10 and 20 h of training, respectively. (Note that because of missing data the 10 h and 20 h group differed in the participants they included. The 10 h group included one anisometrope with no data at 20 h and the 20 h group including one strabismic patient with no data at 10 h). The monocular training group improved only by 0.02 ± 0.06 [se] and by 0.06 ± 0.1[se] log arcsec (≈5 and 15%) following 10 and 20 h of training.

Across both treatment groups, 7 of the 12 individuals with anisometropic amblyopia showed improvement in stereoacuity, while only 1 of the 9 strabismic individuals improved. The average improvement for the anisometropic group was 0.15 ± 0.06 [se] log arcsec (41%) following 10 h and 0.2 ± 0.1 [se] log arcsec (58%) following 20 h of training, thus showing continued improvement with increased training. In contrast, strabismic amblyopes showed no improvement at either 10 h (0.002 ± 0.07 [se] log arcsec) or at 20 h (worse by 0.1 ± 0.06 [se] log arcsec). Log-transformed stereoacuity data are plotted in Fig. 4 (middle panel).

3.2.3. Changes in reading speed

We examined changes in reading speed (words read per minute, WPM) using the MNREAD chart-based test. Overall, children were able to read slightly more words per minute in their AE following training. The mean change across all study participants was 7.5 ± 6.5[se] WPM following 10 h of training (n = 16), and 11.7 ± 5.9 [se] WPM following 20 h of training (n = 17; Fig. 4, bottom panels).

The dichoptic training group's reading speed was reduced following 10 h (n = 8), by 4.6 ± 7.3 WPM, but did improve, by 18.8 ± 8.4 WPM after 20 h of training (n = 6). The monocular group improved on average by 19.6 ± 8.9 [se] WPM following 10 h (n = 8), but only by 10.8 ± 7.7 [se] WPM following 20 h of training (n = 11).

Regardless of treatment group, anisometropic amblyopes improved by 6.8 ± 6.5 WPM following 10 h (n = 9) and by 26.1 ± 5.4 [se] WPM following 20 h of training (n = 9). In contrast, strabismic amblyopes improved by 8.4 ± 13 [se] WPM following 10 h (n = 7), and did not improve at all following 20 h of training (change of -0.45 ± 8.2 [se] WPM; n = 8).

3.3. Statistical analyses

3.3.1. Omnibus MANOVA results

We next examined the statistical robustness of the numerical trends described above using a MANOVA. The omnibus MANOVA (n = 20) yielded a significant effect of time ($F(1,16) = 16.79$, $p < .001$, partial $\eta^2 = 0.51$), but no other significant main effects (test: $F(2,32) = 1.3$, $p = .28$, partial $\eta^2 = 0.076$; group: $F(1,16) = 0.07$, $p = .79$, partial $\eta^2 = 0.005$; amblyopia type: $F(1,16) = 2.68$, $p = .12$, partial $\eta^2 = 0.14$). Additionally, there were significant interactions between time and amblyopia type ($F(1,16) = 4.94$, $p = .041$, partial $\eta^2 = 0.24$), and between test and amblyopia type ($F(2,32) = 3.2$, $p = .048$, partial $\eta^2 = 0.17$). All other interactions, including time by treatment group, were non-significant.

These results indicate that both modes of playing the action game (monocular and dichoptic play modes) yielded statistically similar changes across all three tests, but that these changes over time were different for the two patient populations, anisometropic and strabismic amblyopes. The interaction between test and amblyopia type implies that the two patient populations differed in their test scores. A closer look at the data shows that this was particularly true for stereoacuity. Results of the Omnibus MANOVA on the z-scores are provided in Supplementary materials (Fig. S1).

3.3.2. Growth model results

To take into account all data points in our analysis (baseline, 10 h, and 20 h), we conducted a growth model analysis, yielding a single 'change' score for each participant for each measure. We then converted the change scores into z-scores, and ran a MANOVA analysis with the 3 tests (VA, stereo, MNREAD). In terms of overall growth, we found significant change over time for visual acuity ($b = -0.049$, $se = 0.012$, $|t| = 4.16$, $p = .001$, 95% CI = −0.074, −0.024) and a trend for significant growth for MN read ($b = 6.397$, $se = 3.044$, $|t| = 2.10$, $p = .051$, 95% CI = −0.022, 12.815) but not for stereoacuity ($b = -0.042$, $se = 0.037$, $|t| = 1.13$, $p = .270$, 95% CI = −0.120, 0.036).

The normalized z-score changes for the growth model are presented in Supplementary Materials (Table S2). In the subsequent MANOVA, the only additional significant effect was found for amblyopia type, for stereoacuity ($F(1,16) = 9.6$, $p = .007$), Indicating larger stereoacuity changes over time in the anisometropic than in the strabismic patients.

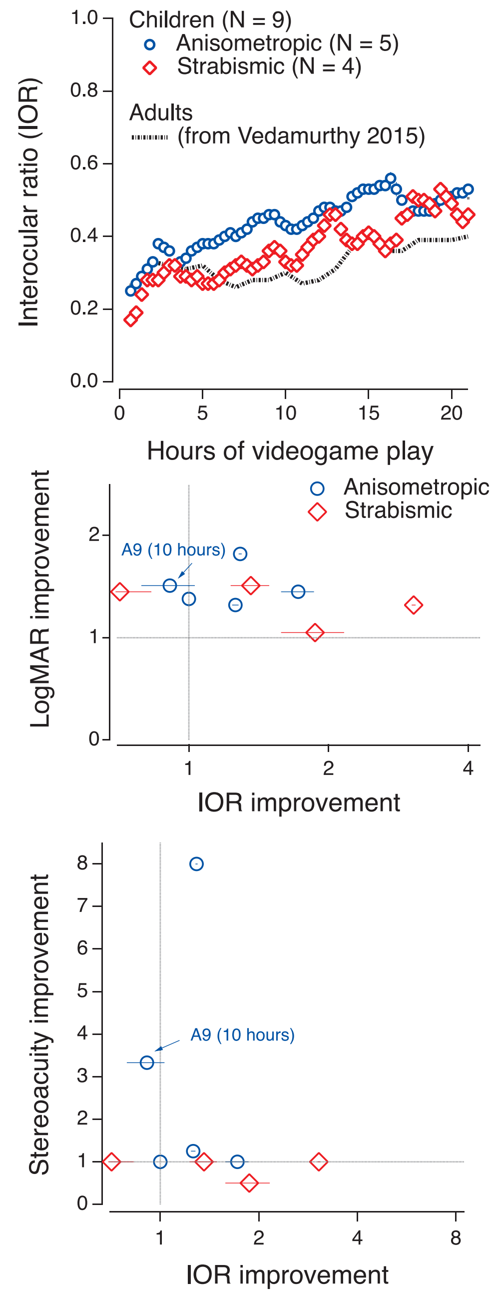

Fig. 5. In-game IOR Data. Top: IOR as a function of hours of video game play for anisometric (N = 5 out of 6) and strabismic (N = 4) patients separately as well as for comparable data from our recent study in adults (dotted line - Vedamurthy et al., 2015). Middle: Improvement in VA as a function of changes in IOR from 0 to 20 h of game play (except for A9). Bottom: improvement in stereo acuity as a function of changes in IOR from 0 to 20 h of game play. Blue – data from anisometric participants. Red – data from strabismic participants. The data of observer A9 is highlighted in the two lower panels because IOR was only recorded for the first 10 h). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

All other effects, including group, were non-significant.

3.3.3. Change between outcome measures not correlated

Although we found little difference between our two groups, both groups improved over time. It is thus of interest to ask whether a participant who improved in VA may be more likely than someone who showed no VA improvement to display gains in stereo or reading speed. Interestingly, none of the dependent measures were correlated: VA/

Stereo: $R^2 = 0.19$, $p = 0.43$; VA/WPM: $R^2 = 0.29$, $p = 0.2$; Stereo/WPM: $R^2 = 0.29$, $p = 0.2$.

3.4. Exploratory analyses

3.4.1. In-game interocular suppression (IOR)

Interocular suppression (IOR) was reduced during dichoptic game play. Ten children completed 20 h of dichoptic game play: 4 strabismic and 6 anisometropic amblyopes. IOR data for one anisometropic observer (A13) was not recorded at all, and for another, (A9), was inadvertently not recorded for the last 10 h. For the 9 children with some IOR data, IOR increased steadily and significantly - by, on average about a factor of 2.4, about twice that of adult amblyopes over the same 20 h of training (Vedamurthy et al., 2015). The symbols in Fig. 5 (top panel) show the running average IOR (blue circles for anisometropic and red diamonds for strabismic). The dot-dashed line shows comparable data from adults (from Vedamurthy et al., 2015). However, as reported for adults, there was no significant relationship between decreased suppression as measured by increased IOR and improved visual acuity (Fig. 5, middle panel) or stereo acuity (Fig. 5, bottom). Furthermore, similar to the data of adults, it is clear that the two participants with the greatest improvement in stereoacuity show little or no change in IOR.

3.4.2. Follow-up assessments

Study participants were asked to return to follow-up assessments 6–10 weeks following completion of training. However, only 12 of the 20 participants returned (6 for each of the monocular and dichoptic training group). We therefore conducted an exploratory MANOVA with effects of time (baseline and follow up) and test (VA, and stereo only, since MNREAD did not have enough data points) and between-subject effects of group and amblyopia type. Follow-up data is summarized in Supplementary Fig. S3.

We found that VA and stereo improvements were maintained at follow-up (significant effect of time: $F(1,8) = 68.4$, $p < .0005$, partial $\eta^2 = 0.895$), and that those improvements did not differ between the training groups (no significant effects of group or time X group interaction). However, improvements at follow-up were overall larger for VA than for stereo acuity, indicated by a significant effect of test ($F(1,8) = 34.2$, $p < .0005$, partial $\eta^2 = 0.81$) and a significant interaction of time X test ($F(1,8) = 39.4$, $p < .0005$, partial $\eta^2 = 0.83$). Specifically, for VA, when only the children that returned for a follow-up were included (n = 12) the 0.11 [+ 0.04 logMAR gain seen from baseline to post-20 h was numerically maintained at follow-up. For stereo acuity, the mean change from baseline to follow-up was 0.044 ± 0.10 [se] log units.

3.4.3. Participant factors

Given the mixed results of previous studies, we examined whether participant factors such as the child's age and baseline level of visual acuity could be related to improvement on visual assessments. We found no relationship between age and VA improvement ($R^2 = 0.01$, $p = .62$), nor between baseline VA in the AE and VA improvement ($R^2 = 0.01$, $p = .70$). We also found no correlation between both participant factors (age and baseline VA) and stereoacuity change (age/stereo change: $R^2 = 0.04$, $p = .39$ and baseline VA/stereo change: $R^2 = 0.20$, $p = .09$). Similarly, there was no relationship between improvement in reading metrics and age (WPM: $R^2 = 0.02$, $p = .55$; CPS: $R^2 = 0.12$, $p = .17$) or baseline VA (WPM: $R^2 = 0.01$, $p = .67$; CPS: $R^2 = 0.01$, $p = .70$).

In contrast, *treatment history* was significantly correlated with the degree of improvement. Participants were classified as previously patched in the previous 6 months (n = 6), not patched (n = 12), or unknown treatment history (n = 3). Those with unknown history were excluded from this analysis. The recently-patched group was slightly younger (mean age 8.33 ± 0.61 [se] years old) than the non-patched group (11.66 ± 1.06 [se] years old, $t = 1.80$, $p = .05$). However, both groups had similar starting VAs in their AE (0.53 ± 0.17 [se] logMAR in the recently-patched group, 0.57 ± 0.22 [se] logMAR in the non-patched group, $t = 0.41$, $p = .34$). While the recently-patched group had little to no improvement in VA (0.02 ± 0.05 [se] logMAR on average), the non-patched group had significantly more improvement (0.12 ± 0.03 [se] logMAR, $t = 1.97$, $p = .03$). Differences in stereoacuity (0.04 ± 0.09 [se] log units vs. 0.16 ± 0.11 [se] log units for the recently-patched and non-patched groups, respectively), and reading (WPM: 15.08 ± 19.49 [se] words vs. 16.50 ± 6.98 [se] words) were not significant.

While not all children demonstrated a significant improvement in VA, we looked to see if there was improvement in at least 2 of the 3 visual functions assessed. Our criteria for this was, an improvement of: 0.1 log unit or more in VA and stereo, or an increase of 20 wpm in reading speed. Eight of the twenty-one children achieved at least two of these criteria by the end of training. Seven were anisometropic (4/6 for monocular training vs. 3/6 for dichoptic training); however, only one strabismic child in the dichoptic group met at least 2 of the improvement criteria, and none of the strabismic children in the monocular group did so.

4. Discussion

The goal of this study was to evaluate a custom-made action video game for treatment of children with amblyopia, and to determine whether dichoptic game playing is more effective than playing the game monocularly with the amblyopic eye while the fellow eye is patched. Another goal was differences in outcomes between the two subgroups of amblyopia, anisometric and strabismic patients.

Our dichoptic approach, presenting a weak but visible stimulus to the dominant eye, receives some physiological support from a recent study of dichoptic masking in amblyopic monkeys (Shooner et al., 2017). Specifically, it provides evidence that the plasticity required to restore normal binocular function "need not include a weakening of amblyopic-eye suppression, but rather a strengthening of the amblyopic eye's suppressive influence over the dominant eye" (Shooner et al., 2017, p. 16). Thus, presenting a weak but visible stimulus to the dominant eye may provide the requisite target signal for modulation of the dominant eye by the amblyopic eye, while sidestepping the reciprocal suppression that would otherwise reduce the amblyopic eye's signals in the cortex.

We found that both groups benefitted from video game training, whether played dichoptically or monocularly with the fellow eye patched, and that these gains were largely maintained following a no-contact period of 6–10 weeks. Although VA, stereo acuity and reading speed improved slightly more for the dichoptic training group, these differences did not reach statistical significance, potentially given our small sample. Furthermore, these improvements were independent of one another, with no covariation among any of these 3 measures.

Amblyopia type had a significant effect on gains made following training, with anisometropic amblyopes showing greater gains on all measures compared with strabismic amblyopes. Most notable differences were seen for stereo acuity, where anisometropic individuals improved while the majority of strabismic amblyopes did not. In the sections below we discuss these results in light of similar studies in both adults and children with amblyopia.

4.1. Relationship to previous studies in children

Our main findings were that following 20 h of training, VA improved on average by 0.14 logMAR (≈38%) for the dichoptic group and only by 0.06 logMAR (≈15%) for the monocular group. Improvements in stereoacuity were similar across training groups, with average improvement of 0.07 log arcsec (≈17%) following dichoptic training, and of 0.06 log arcsec (≈15%) following monocular training.

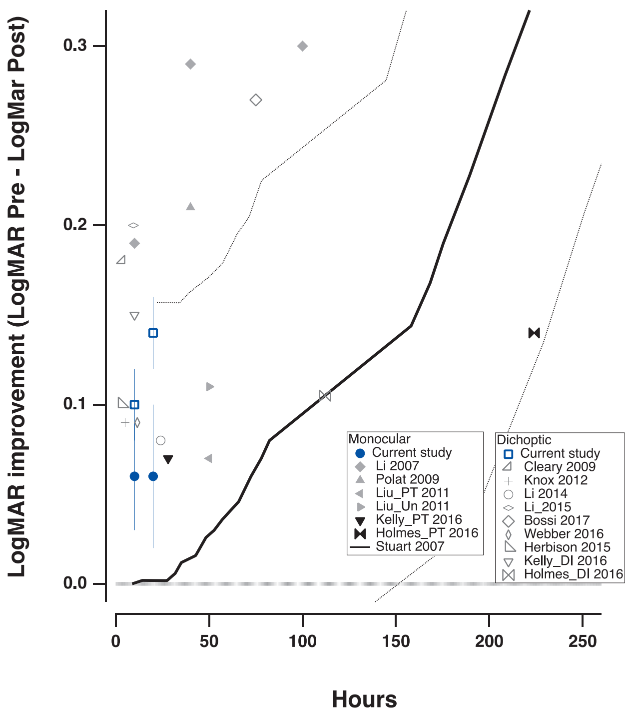

Fig. 6. VA improvement data (pre-post) from previous studies examining treatments in children with amblyopia, as a function of hours of treatment. Solid gray symbols represent monocular perceptual learning or video game treatment. Black symbols show patching treatment; open symbols indicate dichoptic/binocular treatment. The blue symbols are from the current study. The lines in Fig. 6 show the time course of monitored occlusion (solid line) and the 95% confidence intervals (dotted lines – from Stewart et al., 2007). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Across both treatment groups, 7 of the 12 individuals with anisometropic amblyopia showed improvement in stereoacuity, while only 1 of the 9 strabismic individuals improved.

4.1.1. Gains in visual acuity

A review of the extant studies of video game play and PL in childhood amblyopia suggests about sixteen studies with almost 700 patients. A summary of these data is presented in Fig. 6 (see also Table 1). On average, despite wide variations in training paradigms, training duration and participants age, both monocular and dichoptic training yielded an average improvement of about 0.15 LogMAR (1.5 lines on an eye chart) in VA, with a range of benefit of ≈0.08 to 0.3 logMAR (see Table 1). Our results, showing improvement of 0.14 and 0.06 logMAR for the dichoptic and monocular groups, respectively, are consistent with those of previous studies.

There are several potential accounts for this range of results. First, one major factor in our study was treatment history, where children that had recently undergone occlusion therapy were much less likely to show improvements in visual function. This has also been noted in several other children's studies. For example, Holmes et al. (2016) report an improvement of 0.12 logMAR for all of the children that played a dichoptic game in their study; however, when including only children that had not recently patched, the mean improvement more than doubled to 0.25 logMAR. Similarly, Liu, Zhang, Jia, Wang, and Yu (2011) reported a substantial difference in the response to perceptual learning in untreated children (see Liu_Un 2011 in Fig. 6) compared to those who had been previously patched (see Liu_PT 2011 in Fig. 6). This was also the case in the present study, with the recently patched children showing improvements of only 0.02 logMAR, but the non-patched ones showing an average improvement of 0.12 logMAR.

Two very recent studies should also be considered. First, the BRAVO RCT (Gao et al., 2018), which included both adults (up to 55 years of age, N = 49) and children (7–18 years of age, N = 58), many of whom had prior treatment. Patients were randomized into two groups. The active group played a dichoptic Ipod touch falling blocks video game with game elements split between the two eyes, and a contrast offset between the two eyes, for 1 h per day for 16 weeks. The placebo group played the same game with identical images to the two eyes. Compliance was generally poor, especially in the younger age groups. VA improved by 0.06 LogMAR in the active group and by 0.07 LogMAR in the placebo group. Both groups showed small and similar reductions in suppression and improvements in stereopsis. Interestingly, the authors report no significant influence of age.

A second recent study is a PEDIG RCT (Manh et al., 2017), which included older children (13 to < 17 years of age) and hence is not included in Fig. 6 or Table 1. Patients were randomized into two groups: a 'binocular' group, which received the same treatment as in the BRAVO RCT above, and a 'patching' group, which wore a patch (prescribed for 2 h/day) for 16 weeks. The mean VA improved by ≈0.07 LogMAR in the binocular group and by ≈0.13 LogMAR in the patching group. However, compliance here too was poor, with only 13% of participants in the binocular group completing more than 75% of the prescribed treatment.

Second, results may have been affected by compliance with treatment, which varied widely among different studies, from near 100% for DIGRUSH, an action-adventure video game developed specifically to be played dichoptically (Kelly et al., 2016) to 22% for a Tetris style game (i.e., only 22% of the children achieved greater than 75% of the prescribed play time – Holmes et al., 2016). Several groups send participants home with an iPad and anaglyphic glasses, or have the children complete the training on a computer at home (see Table 1). This design results in a wide variation in compliance, both within and between studies, causing large differences in dosage, despite approximately the same time period between assessments. Studies that report better compliance tend to have better outcomes (Bossi et al., 2017; Li, Provost, & Levi, 2007; see full list in Table 1). In the current study, compliance was ensured by having the subjects play the game or watch movies under supervision. However, the difficulty of coming to the lab several times per week led to attrition. Thus, 21 of 29 subjects (72%) completed 20 h of training, with number of weeks to completion varying widely between participants (from 3 to 20 weeks).

Importantly, our study, and many of the others illustrated in Table 1 and Fig. 6 suggest that the most important benefit of perceptual learning and video game play in children is that 1 to 2 lines of improvement can be achieved in 10 to 20 h of play, in contrast to more than 100 h of occlusion (Stewart et al., 2007 – solid black line in Fig. 6).

Finally, since most of the experimental treatments have been tested over short durations (some only for a few hours, and none over 100 h), it is not clear whether the maximum improvement possible is more limited than that obtained with prolonged patching.

4.1.2. Dichoptic vs. monocular training

As previously mentioned, it is important to understand whether dichoptic training provides an additional benefit beyond monocular training, as it is logistically more challenging. Also, the development of diplopia is an added concern with dichoptic training, although few if any cases have been reported. The present study allowed us to investigate the direct effect of dichoptic training since our two groups played the same game, but one monocularly and the other dichoptically. The dichoptic group showed larger improvements in VA; however, because our sample size was small, the difference is not statistically significant. This was also true for the main three outcome measures used in the study, that is not only VA, but also stereoacuity and reading speed. Interestingly 6/12 anisometropic subjects showed at least a 2-step improvement in stereoacuity and a final stereoacuity of better than 140arc sec (Levi et al., 2015) – 4/6 in the monocular group

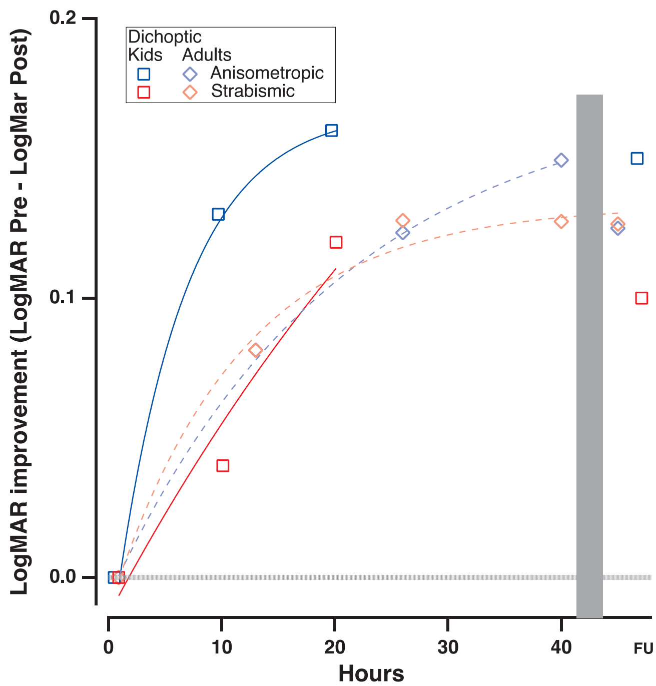

Fig. 7. Comparison of children and adult gains following action video game play. Gains in visual acuity (pre-post) as a function of hours of training for current study in children (square symbols) and for our previous study in adults (diamond symbols; Vedamurthy et al., 2015).

and 2/6 in the dichoptic group. In contrast, none of the nine strabismic patients met this criterion.

It is also evident in Fig. 6 that the range of improvement in children with amblyopia is similar for monocular PL, monocular video game training and dichoptic training. Indeed, the studies showing the largest improvements are those of Li et al. (2007) who had children perform extensive PL monocularly and Bossi et al. (2017) who had children watching dichoptic movies. Note that the subjects in both studies were previously untreated.

4.2. Action video game training in children vs. adults

The adult study most similar to the current study is that of Vedamurthy, Nahum, Huang et al. (2015). In this study, adults with amblyopia either played a dichoptic action video game, or watched action movies while patching their NAE for 40 h. They found that visual acuity (VA) improved on average by ≈0.14 logMAR (≈28%) in the action video game group, and 0.07 logMAR in the action movies group. Interestingly, patients with anisometropic amblyopia in the movies group showed similar VA improvements to those of the video game group, while subjects with strabismic amblyopia improved only following game play. Stereoacuity and reading speed, and contrast sensitivity improved more for the video game group participants compared with the movies group participants.

Fig. 7 compares the VA data of the two studies. As can be seen in the figure, the children in the dichoptic group in the current study had VA improvements numerically similar to those of the adults who played the dichoptic action game in the Vedamurthy, Nahum, Huang et al. (2015) and Vedamurthy, Nahum, Bavelier et al. (2015). Interestingly, the anisometropic children appear to improve slightly faster than the anisometropic adults (blue squares vs. blue diamonds in Fig. 7) and faster than both the strabismic adults and children (red symbols in Fig. 7).

4.3. Training effects in anisometropic vs. strabismic amblyopes

Vedamurthy, Nahum, Huang et al. (2015) reported very different outcomes for their adult anisometropic and strabismic groups. Their anisometropic group improved in both the control condition (watching action television shows while wearing an eye patch), and the experimental condition (playing the dichoptic action video game), while the strabismic group only improved in the experimental condition.

The results of our current study suggest tantalizing differences between anisometropic and strabismic children. Indeed, there were significant interactions between time and amblyopia type. Accordingly, anisometropic amblyopes showed greater improvements following 20 h in each of the 3 measures than did strabismic amblyopes. In addition, the growth model indicated larger stereoacuity changes over time in the anisometropic than in the strabismic patients. The most notable differences were seen for stereo acuity, where anisometropic individuals seemed to improve while the majority of strabismic amblyopes did not as documented in previous works (for a review of this point, see Levi et al., 2015).

4.4. Feasibility and other limitations of the study

Due to the challenging nature of visiting the lab 2 to 3 times a week, we had some drop-out in both training groups, for an overall drop-out rate of 28%. More work is needed to simplify the experimental treatment so that the training is portable and engaging. Several groups have looked into this. For example, Hess's group developed a dichoptic Tetris game that can be played on an iPad with anaglyph glasses at home (Birch et al., 2015; Li et al., 2014, 2015), and the Nottingham group (Hussain, Astle, Webb, & McGraw, 2014), developed a game that can be played on a computer at home with a patch over the NAE. Although certainly a great improvement, there remain a number of weaknesses with these designs. In both of these cases, compliance can still be an issue as the games can be played without the glasses, or without the patch. As Stewart et al. (2004) found with their occlusion-monitoring device, self or parental reports of wear time frequently do not match up with actual usage. Although our design was challenging in that it required children to travel to the lab after school or on weekends, we were able to directly monitor game play to make sure the children were following the rules and difficulty levels could be adjusted to maintain engagement.

As noted previously, children are more challenging to motivate in training studies, even when games rather than PL regimes are used. As such, several studies have noted more variability in results. Interestingly, there is also a great deal of variability in the response of children with amblyopia to patching, even when compliance is taken into account (Holmes et al., 2011). Therefore, although several of our assessments did not show significant differences between training types, or patient group, it does not rule out the possibility that these differences may exist. We recognize our sample size remains quite small in the face of such potential variability.

4.5. Conclusions

The emphasis of our study was on the feasibility of using action video games for children with amblyopia, with the ultimate goal of determining whether the intervention was feasible and whether the dichoptic approach may have some added benefits compared to monocular training. While both forms of active video-game training (monocular and dichoptic) resulted in rapid improvements in visual acuity, our study indicates little advantage to a dichoptic approach, and calls for caution in running large RCTs contrasting two active video games one played dichoptically and the other not. This conclusion is very much in line with a recent RCT including 115 older children, adolescents and adults which also found no advantage of a dichoptic video game over a binocular one (Gao et al., 2018).

Our study adds to the growing body of work showing that using active treatments (PL and video games) to treat amblyopia can be as effective (if not more) as traditional occlusion therapy. While we have made progress in understanding how video games can be used as a treatment for patients with amblyopia in the 7 years since Li et al. (2011) first reported on this topic, there are still many important questions that remain unanswered. In particular, we need to understand how video game play affects oculomotor control. Eye movements skills are important for proper development of spatial attention and learning activities such as reading. Children with amblyopia have reading impairments, even when using both eyes (Kelly et al., 2015), thus understanding how to improve these functions is important to the clinical outcome of these patients. Binocular fixation stability and bifoveal alignment and fusion may be key to unlocking a holistic treatment for this developmental condition. Additionally, incorporating stereo cues, as was done in Vedamurthy et al. (2016) may lead to greater overall improvement, as this provides an additional cue to aid in sustained binocular fusion. Finally, easier set-ups, that include an assortment of engaging action video games in a portable unit, and the ability of researchers and clinicians to track the data regarding a patient's compliance and progression, will be essential to future iterations of this work.

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Author contributions

CG and MN share co-first authorship. Study design and conceptualization: DB & DL; Video Game Development and Design: primarily JB with contributions from DB, IV, and DL; Video Game play test during game development: IV with contributions from DB & DL & MN; Piloting and fine-tuning of vision experiments: primarily IV with contributions of SH, MN and CG; Running the Study: IV, MN, and CG; Data analysis: MN, CG and JJ; Writing: primarily CG, DL and MN with all authors contributing. Figures: DL.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.visres.2018.04.005.

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