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Stereopsis and amblyopia: A mini-review

Authors
Levi, Dennis M
Knill, David C
Bavelier, Daphne

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Corresponding Author: Dr. Dennis M. Levi,

Corresponding Author's Institution: University of California

First Author: Dennis M. Levi

Order of Authors: Dennis M. Levi; David C Knill; Daphne Bavelier

UNIVERSITY OF CALIFORNIA, BERKELEY

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DENNIS M. LEVI, O.D., PH. D.
DEAN BERKELEY, CALIFORNIA 94720-2020

SCHOOL OF OPTOMETRY

November 20, 2014

Dear Paul,

We are submitting the revised Mini-Review, invited by Susana Chung, entitled: "**Stereopsis and Amblyopia: A Mini-Review**" by Dave Knill, Daphne Bavelier and myself for consideration for publication in the Special Issue of Vision Research on Amblyopia.

We thank you and the reviewers for the insightful and constructive comments, and we have tried to address them all in the "Response to Reviews".

The aim of this mini-review is to provide a review of what is known about stereopsis and its recovery in amblyopia. Our review suggests that impaired stereoscopic depth perception is the most common deficit associated with amblyopia under ordinary (binocular) viewing conditions, and that this impairment may have a substantial impact on visuomotor tasks, difficulties in playing sports in children and locomoting safely in older adults. Furthermore, impaired stereopsis may not only negatively impact everyday activity, but may also limit career options for amblyopes. Stereopsis is much more impacted in strabismic than in anisometropic amblyopia. Our review of the various approaches to treating amblyopia suggests that there are several promising new approaches to recovering stereopsis in both ansometropic and strabismic amblyopes.

The manuscript is original, and has not been submitted elsewhere and is not under review with another journal. If accepted for publication in Vision Research, it will not be reprinted elsewhere in any language in the same form without the consent of the publisher.

Andrew Astle, Uri Polat, Suzanne McKee, Anita Simmers and Manfred Fahle would be all be highly qualified to review the paper (contact information on the next page). We would prefer that the paper not be reviewed by Robert Hess.

I would be grateful if all correspondence was directed to me at dlevi@berkeley.edu.

Thank you for your consideration.

Best Wishes,

Dennis M. Levi

Dennis

Editor suggestion: Paul McGraw

Referee suggestions:

Andrew Astle <Andrew.Astle@nottingham.ac.uk>
Uri Polat, < uri.polat@glassesoff.com>
Suzanne McKee, <suzanne@ski.org>
Anita Simmers < Anita.Simmers@gcu.ac.uk>
Manfred Fahle mfahle@uni-bremen.de

We would prefer that the paper not be reviewed by Robert Hess.

Ms. No.: VR-14-396
Title: Stereopsis and Amblyopia: A Mini-Review.
Corresponding Author: Dr. Dennis M. Levi
Authors: David C Knill; Daphne Bavelier

Dear Dennis,

I hope this message finds you well. First, let me start by expressing my condolences to you and Daphne over the sad loss of your co-author, David Knill. I was an admirer of his work; he'll be a big loss to the vision community and it's a great shame he was not able to see this important study through to completion.

Many thanks Paul – Dave was a wonderful friend and colleague, and we sorely miss him.

I have now received the Referees' comments for your manuscript and both have raised several issues that will need to be addressed before we can make a final editorial decision. The referees have clearly spent some time on this and their suggestions, if followed, should result in a stronger paper. Both reviewers express some concerns over the treatment of data used to compile table 1 and figure 5. Other issues relate to the extent to which stereopsis contributes to deficits in eye hand co-ordination (Reviewer #2) and clarification on the amelioration of stereo-deficits when a misalignment of the visual axes persists (Reviewer #1). This is a question I have had to field myself at the end of talks on PL and is clearly an issue that troubles clinicians.

We thank the reviewers for their insightful and constructive comments, and we have tried to address them as noted below.

There are a couple of minor editorial issues that will also need to be addressed in the revised ms. The highlights need some attention and crosscheck has indicated some text re-cycling issues (17%).

We have re-written the highlights, and also substantial sections of the ms in order to minimize "re-cycling" (although this is difficult to avoid in a review).

Reviewers' comments:

Reviewer #1: This is a nice review of recent studies on stereopsis and amblyopia and the effects of perceptual learning training and binocular experience on stereoacuity in amblyopia. However, the manuscript as written indiscriminately combines amblyopia and stereo deficits and lacks a cohesive and convincing theme. Instead, the manuscript waffles back and forth between amblyopia and stereoacuity deficits.

Thanks. Unfortunately, amblyopia and stereo deficits are inextricably linked. However, in the revised manuscript we have tried to clarify that given the co-occurrence of strabismus, amblyopia and reduced stereopsis in many of the subjects in these studies, it is not possible to link visuo-motor deficits to exclusively reduced stereopsis (page 8). From our perspective the theme is, however, rather clear. Persons with amblyopia have substantial deficits in stereopsis, which, on the face of the evidence results in poor visuo-motor skills, and importantly, this reduced stereopsis may be amenable to treatment.

1. It begins by describing amblyopia and why it has been the focus of so much clinical and basic research. It goes on to state that "the most common deficit associated with amblyopia under ordinary viewing conditions impaired stereoscopic depth perception." I am not sure what this means or how the Webber & Wood citation justifies such a broad conclusion - it seems more like a proclamation than an evidence-based conclusion.

The statement is a direct quote from Webber and Wood. We have tried to clarify our interpretation of this as follows:

"Under normal everyday viewing conditions, with both eyes open, the vision of persons with amblyopia is dominated by the strong eye. Thus, Webber & Wood, (2005) suggest that the most common deficit associated with amblyopia under ordinary (binocular) viewing conditions is impaired stereoscopic depth perception." (Page 4)

2. The next section continues by decreeing that "it is noteworthy that many anisometropes retain stereopsis." Why? Isn't it also noteworthy that many anisometropes have abnormal or nil stereoacuity?

We simply meant that by comparison to strabismic amblyopes. We now clarify it as follows:

"In contrast to strabismic amblyopes, many anisometropes retain stereopsis. "

3. In the same paragraph, what is meant by "the stereoacuity of anisometropic amblyopes may be as good as the resolution of the weaker eye permits"? If that were the case, shouldn't all successfully treated anisometropic amblyopes achieve normal stereoacuity? They do not.

Point well taken. We've deleted the statement.

4. The statement on page 10 that there is little clinical literature on the recovery of stereopsis is simply untrue. There are many studies that report stereoacuity outcomes following amblyopia treatment, including several randomized clinical trials in the last decade. There are also some good quality nonrandomized studies such as Agervi et al (2009), Lee & Isenberg (2003), and Steele et al (2006).

We have removed that statement, and have added details of a number of the more recent studies, as suggested by the Referee.

5. The confusion between the amblyopia and stereo deficits recurs in the section on eye hand movements on page 8. Here, data from amblyopes with stereo deficits, many of whom are also strabismic are used to argue that impaired stereopsis is the key variable in eye hand deficits. We simply cannot know that from most of these studies, where all three variables (stereoacuity, amblyopia, and strabismus may affect performance). Because of this weakness in design, most of these studies cannot show, as stated, that "observed deficits are due to impaired stereopsis, rather than visual acuity loss." These cohorts with multiple abnormalities that may affect performance are rampant in the literature and the authors would do the readers a service to make this distinction and to acknowledge the limitations that result.

We now make the distinction and acknowledge the limitations that result. Specifically, we have added:

"We note that given the co-occurrence of strabismus, amblyopia and reduced stereopsis in many of the subjects in these studies, it is not possible to conclusively link these visuomotor deficits to reduced stereopsis. However, Hrisos et al. (2006) showed that reduced binocularity significantly predicted their visuomotor results, whereas the depth of amblyopia did not. Moreover, Melmoth et al. (2009) showed similar visuomotor deficits in previously amblyopic patients who's visual acuity had been successfully corrected but with reduced stereoacuity."

6. The text on page 15 states that Table 1 and Figure 5 are limited to studies of recovery of stereo in adults. They are not. They include the studies by Polat, Knox et al, and Cleary et al. It appears that they are picking and choosing to include or exclude studies on children, depending on whether they are in agreement with the adult data.

Thanks – that statement was a holdover from an earlier version. We now make it clear that our analysis is based on data of both adults and children. However, there was no attempt to "pick and choose". We include all of the studies where we are able to assign individual data to amblyopic subjects that could be identified as anisometropic or strabismic.

7. The study by Li et al 2014, which shows no improvement in stereoacuity is not cited. Moreover, some of the data are incomplete or incorrect. For example, in dichoptic PL section, the Knox et al, Li et al 2013, and Cleary et al studies all provide info on anisometropic vs strabismic/combined amblyopia in the main text or in a supplement that would allow the authors to complete their lines in the table, yet these data are omitted. The cited Hess & Thompson paper is a review paper; the original data for these 9 patients can be found in To et al 2012 and Hess et al 2012 and the table can be completed. Once I do all of the corrections to the dichoptic PL section, about 20% of anisometropes improve and about 30% of strabismics improve. I have not gone through Table 1 section by section, but similar omissions and errors could be present there as well. I urge the authors to carefully review the data in each article's main text and tables as well as their online supplements and re-work Table 1 and Figure 5.

The Knox and Cleary studies were included. The Li 2013 study only shows mean data so there is no way to include it in our analysis. We have added a discussion of the Li 2014 paper; however, since there are no individual data, we could not include this in our analysis either. We thank the Referee for pointing to the To et al. paper.
We have gone carefully through the texts and supplements and have updated and corrected the table and figures. Fig. 5 has now been replaced by two figures. The new Fig. 5 shows a summary of all training techniques, and the new Fig. 7 shows results from each of the 5 techniques. We note that there was (and still is) some ambiguity about which of the dichoptic methods are "videogames" vs. PL. Thus we've added a new figure (Fig. 8) which collapses across all of the monocular (videogame and PL) and all of the dichoptic (videogame and PL) training. These percentages more closely match those cited by the Referee.

8. It would be a service to readers to include details of the study designs in Table 1. Some used questionable stereoacuity tests. Many of the adult studies cited suffer from a confounding of treatments. Amblyopic adults upon entry to the study often are refracted and given updated spectacle correction. We know that, in children and teenagers, this treatment alone is enough to improve visual acuity and stereoacuity in some amblyopes and it may have the same benefit for adults. Moreover, updated spectacles may be more effective as a treatment for anisometropic than strabismic amblyopes, leading to the erroneous conclusion that a PL treatment is more effective when it is really the combination of spectacles and PL that results in a larger visual acuity and stereo gain. The adults are then treated with PL, often in conjunction with a patch and no control for time spend patching. Again we now know that patching is an effective treatment for amblyopia well into the teen years and may be effective in adults. Not all study results should simply be tallied up in an undiscerning way and then conclude (page 17) that stereopsis is much more impacted in strabismic than in anisometropic amblyopia."

The Referee makes an excellent point; however, there is frequently insufficient detail in the published studies to decide how they should be weighted. Thus we have tried to address this issue in the section on caveats, as follows:

" In addition, some of the studies may have confounded treatments. For example, as noted above, in children, spectacle correction alone can improve visual acuity and stereoacuity (Richardson et al., 2005; Stewart et al., 2013). Amblyopic subjects, upon entry to a study are often refracted and given an updated spectacle correction. It is unclear whether spectacle correction has the same benefit in adults, and most adult PL studies do not include a refractive adaptation period. Additionally, monocular PL studies generally involve patching the strong eye, and few studies include a control for patching."

In addition, we have added a brief description of the task and stereo tests used in the Table.

9. Some of the studies reported good to excellent stereoacuity at outcome in patients despite the presence of a large tropia - an impossible result. This is really another elephant in the room. Most of the adult studies fail to provide detail about the angle of strabismus during treatment and testing. If the strabismic amblyopes are not well aligned, how can we expect them to improve stereo?

We agree completely, and have added the following in te section on caveats (page 19): "Another important issue is that many of the studies do not provide details about the angle of strabismus during treatment and testing. Proper binocular alignment is critical for stereopsis in strabismic subjects, and it seems important to know whether this was achieved and how."

Minor points:

1. Page 3. The authors may want to update their citation for the prevalence of amblyopia to some of the recent population-based studies (MEPEDS, BPEDS, ALSPAC, SES).

Done

2. Page 3. Please cite an original source for the statement about brain plasticity is known to peak during a critical period in early childhood rather than your own earlier review.

Done

3. Page 3. "sin qua non" should be "sine qua non"

Fixed

4. Page 4. It may be more appropriate to cite references for the effect of monocular blur on stereoacuity that use the same clinical stereo tests employed by most of the studies that you discuss in the reminder of the manuscript (Randot and Titmus circles) . Good choices might be Donzis et al Arch Ophthalmol 1983 and Menon et al Indian J Ophthalmol 1997.

Thanks – we've added these references.

5. In Fig 1 caption, please state that the Randot circles were used for 400-40 arcsec, and the Randot shapes for 250 and 500 arcsec - two qualitatively different types of test.

Only Randot circles were used in these studies.

6. Page 7. There are several tests that have been developed to quantify the range of suppression in children in the clinic - see Kwon et al 2014; Li et al 2014; Narasimhan et al 2012 for some examples.

Thanks – we've added these references.

7. Page 8: Job options may be limited for those with stereo deficits, whether or not they have amblyopia.

The sentence now reads: "While most of these studies focus on adults, the results suggest that impaired stereopsis may also negatively affect everyday activity in amblyopic children (Webber, Wood, Gole & Brown, 2008a), as well as limit career and job options."

8. The red-green color scheme of the figures is a poor choice, limiting the ability of color-deficient readers to access the material.

We have redone all of the figures.

8. Page 12: second line "refs" needs to be replaced with citations

Done

9. Page 12: "LogMar" should be "LogMAR"

Fixed

10. Page 12: I don't understand how "it is not clear whether or not stereoacuity was measured before and after training" when the author of this manuscript is one of the authors of the cited study.

Sorry, the sentence was not clear. We were not referring to the Li & Levi study, but to other studies. Sentence now reads:

"A few mention gains in stereopsis in passing (e.g. Li & Levi, 2004), but in many other published studies it not clear whether stereoacuity was measured before and after training in all subjects, or only in some."

11. Page 12: "anismetropic" should be "anisometropic"

Fixed

12. Fig 4 caption: Page 12: "anismetropic" should be "anisometropic"

Fixed

13. Fig 4: How is % improvement in stereoacuity computed for someone who begins with nil stereo? How can it vary from 30 to 85%?

As is now noted in the figure legend, individuals failing the test were assigned a threshold value of 600 arc sec in order to calculate % improvement.

14. Page 16: I don't see any reason to describe in great detail the stories of Sue and Bruce. These are already briefly discussed earlier in the manuscript and that is all that is needed.

We have greatly abbrieviated the stories of sue and Bruce

15. Page 16: The reference to the cited Astle paper is missing.

Fixed. Thanks.

17. Page 17: "Xie" should be "Xi."

Fixed. Thanks.

Reviewer #2: Before I begin, may I extend my condolences to Prof Bavelier and Prof Levi on the tragic loss of Prof Knill.

We thank the Reviewer – Dave was a wonderful friend and colleague, and we sorely miss him.

I enjoyed this review and found it a useful contribution.

Thanks.

However, I felt it overstated its case at several places, notably regarding the functional importance of stereopsis.

We have attempted to tone this down.

Major comments

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1. Importance of stereopsis for visuomotor performance:

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The paper suggests in a number of places that "impaired stereoscopic depth perception … may have a substantial impact on visuomotor tasks". I did not see the evidence for this. When the relevant studies are discussed on p. 8, it is noticeable that now the word "significant" is used instead of "substantial": "amblyopes with impaired stereopsis show deficits in visually-guided hand movements", "visually guided hand movements are significantly impaired when viewing is restricted to one eye, "poor stereopsis … significantly longer and less accurate hand movements", "walking performance is also significantly degraded", "adaptations to changes in terrain are significantly less accurate without stereopsis". I'm sure I don't need to explain to these authors the distinction between statistical and clinical significance. I think if they are going to continue to put "substantial" in the abstract and summary (even weakened as it is with the weasel word "may"!) they really need to back this up with some evidence about the size of the impairments and the likely impact in everyday life.

We would welcome suggestions from the Reviewer as to how best address his/her point. We provided the references to a large number of studies that have shown significant differences between monocular and binocular performance. The present paper being a review, we felt it was not appropriate to repeat the statistics of source papers. We have added the following clarification which we hope will help:

"For example, movements took on average 100 msec longer, and subjects made about three times as many corrective movements under monocular conditions (Melmoth & Grant, 2006). These differences between monocular and binocular conditions were highly significant."

Similarly, the Hayhoe et al study of walking showed highly significant effects, and we have qualified the statement as follows: "Walking performance is also significantly degraded, slower by about 10%, in monocular vs. binocular conditions (Hayhoe, Gillam, Chajka & Vecellio 2009)"

Additionally, the authors need to be more precise in discussing the literature, and discriminate clearly between advantages provided by binocular viewing and those provided specifically by stereopsis. For example, they write "In humans with normal binocular vision, visually guided hand movements are significantly impaired when viewing is restricted to one eye " This is true, but in normally sighted adults it is not clear that loss of stereo is the reason for this poor performance. If it were, one would expect performance in the binocular condition, or at least the binocular advantage, to correlate with stereoacuity. The evidence on this is conflicting; see for example:

Murdoch, McGhee, & Glover (1991). The relationship between stereopsis and fine manual dexterity: Pilot study of a new instrument. Eye, 5(Pt 5), 642-643.

Joy, Davis & Buckley (2001). Is stereopsis linked to hand-eye coordination? The British Orthoptic Journal, 58, 38-41.

O'Connor, Birch, Anderson & Draper (2010). The functional significance of stereopsis. Investigative Ophthalmology & Visual Science, 51(4), 2019-2023.

Read, Begum, McDonald, Trowbridge, The binocular advantage in visuomotor tasks involving tools, i-Perception, 4 (2013) 101-110.

We thank the reviewer for this comment and have added the following clarification on page 8:

"While the evidence relating binocular vision and stereopsis (not necessarily stereoacuity) to visuomotor performance in normally sighted subjects is strong, the relationship between the impairment in visually guided hand movements and stereoacuity remains somewhat controversial. For example, Read, Begum, McDonald, Trowbridge (2013) report that while subjects (aged 7 to 82) performed manual dexterity tasks faster and more accurately with both eyes open than with one eye occluded, the binocular advantage was not significantly correlated with their stereo acuity. Similarly, Murdoch, McGhee & Glover (1991) reported that while individuals with no stereopsis have difficulty in performing a task with 3D clues, there are some individuals (post-fellowship ophthalmologists) who "have better manual dexterity than one might anticipate on the basis of stereo acuity testing alone". Clearly there are substantial individual differences in performance, and it seems plausible that some individuals with poor stereopsis maybe able to compensate. However, a recent large-scale study (O'Conner, Birch, Anderson & Draper, 2010) showed that performance on motor skills pegboard and bead tasks was related to the subject's stereoacuity with those with normal stereoacuity performing best."

Related to this, Webber & Wood 2005 report the common observation that "Parents of strabismic children whose eyes have been aligned surgically have reported that the children's visuomotor skills have suddenly and vastly improved following surgery". I am not aware of any evidence showing that this is due to improved stereopsis post-surgery as opposed to, for example, normal retinal correspondence and binocular summation. If there is any such evidence, this would be important.

The referee makes a good point. We have added the following (Page 9):
"Interestingly, parents of strabismic children whose eye's have been surgically aligned sometimes report improvements in their child's visuomotor skills (Webber and Wood, 2005; von Noorden, 2005). Whether this is due to improved stereopsis or to other factors, such as binocular summation, is unknown."

My impression is that the evidence relating stereoacuity (specifically) to visuomotor performance is stronger in amblyopes than it is in normally-sighted controls. If I am correct in this, it should be made clear. I think this is important because of the question whether improving stereoacuity through training would necessarily bring about improved visuomotor performance. I would find this more plausible if stereoacuity correlated with performance in the general population. Otherwise, it might be that amblyopes with good stereoacuity show good performance because both reflect some third factor.

We feel that the evidence relating binocular vision and stereopsis (not necessarily stereoacuity) in normally sighted subjects is very strong, including some of Dave Knill's own work (Hu & Knill, 2011; Knill & Saunders, 2003; Saunders & Knill, 2004, 2005). As noted above, we have added a paragraph to address this point.

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2. Contour stereograms vs random dot:
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p.9 "Consider for example, the widely used Randot "Circles" test … there are monocular cues … Fawcett & Birch (2003) found that … the circles test progressively overestimated stereoacuity for poorer random-dot stereoacuity scores."
This reads as if the authors are implying that the reason for the mismatch was that the subjects were using monocular cues on the circles test. While this is certainly possible, I don't think it's proved. Several authors have suggested that stereograms with monocularly visible contours may be subserved by different neuronal mechanisms from cyclopean stereograms (coarse vs fine and similar distinctions), and these mechanisms may be selectively spared in strabismus, for example. See Giaschi D, Lo R, Narasimhan S, Lyons C, Wilcox LM. 2013. Sparing of coarse stereopsis in stereodeficient children with a history of amblyopia. J Vis 13.

We did not intend to imply that the reason for the mismatch was that the subjects were using monocular cues on the circles test. To clarify, we have added the following: "Whether this is due to subjects using the monocular cues or because stereograms with monocularly visible contours and cyclopean stereograms are processed by different neural mechanisms (e.g. coarse vs fine) is unclear. However, coarse stereopsis may be selectively spared in stereo deficient children with a history of amblyopia (Giaschi, Lo, Narasimhan, Lyons &Wilcox (2013)."

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3. Improvements in stereopsis due to training
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p. 12. The reported improvements in stereoacuity must be interpreted cautiously, especially as few of the studies seem to have included a control group (although I gather the unpublished Vedamurthy study cited is an exception, which I applaud). Apparent changes in stereoacuity, e.g. from 400 to 40 arcsec, may reflect the child's greater understanding of or willingness to cooperate with the test when tested on a repeat occasion, especially given the very poor test/retest reliability of such clinical tests (e.g. Adams WE, Leske DA, Hatt SR, Holmes JM. 2009. Defining real change in measures of stereoacuity. Ophthalmology 116:281-285). Thus without a control group, we cannot know how much of the change was real improvement due to the training and how much to other effects such as increased familiarity.

The point is well taken and we've added the following caution (page 22):
"In addition, for many clinical stereo tests, test-retest reliability is often poor, with 95 confidence intervals of 1 to 2 octaves (e.g., Fawcett & Birch, 2000; Adams, Leske, Hatt & Holmes, 2009). While some studies include control groups (e.g. Li et al., 2013; 2014; Vedamurthy et al., 2014a), most do not, making it difficult to interpret the changes in stereoacuity. Clearly, there is a need for better stereo tests, without monocular cues, that can be applied to patients."

I do agree that Table 1 / Fig 5 show an impressively consistent difference between anisometropic and strabismic amblyopes, which in principle could help with this. However, the baseline stereo will also be different between these two groups, which could in principle account for the difference. In these clinical tests, child keep moving through levels until they fail, either because they have reached the limit of their stereo vision, or because they have got fed up with the test. One can easily imagine that a truly stereoblind child will fail the test whenever they are tested, while a child who has stereo vision might continue through more levels when they are more familiar and happy with the test. In principle, this could produce a improvement in measured stereo, greater in the aniso group than for the strab group, even if there was no real improvement in either group. Maybe there is some different way of presenting the data to make it clear that this is not the case; for example, plotting stereoacuity after vs before training, and showing the aniso vs strab amblyopes are clearly clustered differently post-training in a way which cannot be explained by their pre-training differences. Or maybe the authors could discuss how their recent studies resolve this concern.

The reviewer raises a legitimate and important concern. We do not think the data is available to resolve it, but we've added (page 22) the following caveat:
"Whether the apparent difference between strabismic and anisometropic amblyopes reflects differences in their baseline stereopsis (i.e. many strabismic subjects fail the test or have very poor stereopsis initially), is unclear. Based on standard clinical treatment, the PEDIG studies suggest that better post-treatment stereoacuity was associated with better base-line stereoacuity and better post-treatment visual acuity in their amblyopic eyes (Wallace et al., 2011)."

Following the reviewer's suggestion, we replotted stereoacuity pre- vs. post training, from five of our studies, and now include this as Figure 6 with the following text:
"In order to look into this question more closely, we have replotted data from several of our studies, involving 94 subjects and multiple training approaches, as post- vs. pre-training thresholds (Fig. 6). What seems clear from this figure is that: i) Many more anisometropic (blue) than strabismic (red) amblyopes improve after training (symbols below the gray unity line). ii) Many more strabismic than anisometropic amblyopes have no measurable stereopsis both before and after training, and, iii) there are both anisometropic and strabismic amblyopes at *all levels of pre-training stereoacuity* (including no measurable stereopsis) who show improvements following training, many achieving stereoacuity of 140 arc sec or better (as indicated by the horizontal dashed lines)."

We thank the reviewer for this excellent suggestion.

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4. The effects of stereoblindness
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I was unconvinced by the argument that "Individuals who develop without stereopsis … develop an entirely different way of sensing the three dimensional world." On p 16, the authors liken this to the experience of blindness or deafness: "individuals deprived of a sense are not just "missing" a sense. Rather, they have developed an entirely different way of sensing the world." First, I am not sure how one would even define "an entirely different way of sensing the world". Deaf or blind people do not develop new abilities, e.g. ultrasound or infra-red vision, but they certainly can develop heightened sensitivity with their remaining senses. Additionally, cortical areas usually associated with the lost sense can be taken over by other senses, which is perhaps the strongest objective evidence supporting the claim that they have an "entirely different way of sensing the world". I am not aware of any comparable evidence for stereopsis. Barry and Bridgeman's subjective accounts are fascinating, but it is not clear what scientific status to give them. If the loss of stereopsis were as functionally significant as implied here, I would expect the visuomotor deficits associated with stereopsis to be much more significant than the literature suggests they are (see point 1). Additionally, Barry and Bridgeman's recovery of stereopsis argues against the idea that they had indeed developed an entirely different way of sensing the world. If they had, surely this would have involved the development of entirely different neuronal machinery, which would have made it unlikely that they could spontaneously recover stereopsis as Bridgeman recounts. Imagine someone raised with both eyes occluded since birth, whose area 17 becomes recruited for non-vision activities such as Braille reading (Sadato N, Pascual-Leone A, Grafman J, Ibañez V, Deiber M-P, Dold G, et al. 1996. Activation of primary visual cortex by braille reading. Nature 380:526-528). Such a person arguably has developed an "entirely different way of sensing the world", but for precisely this reason, if one were to remove the eye-covering in adulthood, it is highly unlikely that they would recover anything like normal vision. Barry & Bridgeman's stories are arguably more compatible with the idea that depth perception is achieved by combining multiple cues, including stereo disparity, motion parallax, perspective, shading etc. This makes the system robust to the removal of any individual cue, and also enables the cue to be reintegrated relatively seamlessly should it once again become available.

The discussion of Barry and Bridgeman’s cases has been much reduced and this point has been removed.

Minor comments

p. 14 "As is evident in Fig. 5A, roughly the same percentage of anisometropic amblyopes achieve a two-level improvement in stereopsis and a stereoacuity of 160" or better with monocular and dichoptic PL. However, this approach appears to be substantially more effective than monocular PL in improving stereopsis in strabismic amblyopes (Fig. 5B). More than 60% of strabismic amblyopes achieved a twolevel improvement in stereopsis and a stereoacuity of 160" or better following dichoptic PL, compared with less than 10% reported for monocular PL." Am I looking at the wrong bars? The bars labeled "monocular PL" and "Dichoptic PL" do not seem to match these numbers.

The reviewer is correct. We’ve added data to the Table and Fig. 7 (formerly Fig. 5) and revised the text accordingly:
“As is evident in Fig. 7B, none of the strabismic amblyopes achieve a two-level improvement in stereopsis and a stereoacuity of 160” or better; however, we note that the number of anisometropic amblyopes in the dichoptic PL category is very small (Table 1). However, dichoptic PL appears to be substantially more effective than monocular PL in improving stereopsis in strabismic amblyopes (compare Fig. 7 with 7A). More than 40% of strabismic amblyopes achieved a two-level improvement in stereopsis and a stereoacuity of 160” or better following dichoptic PL, compared with less than 10% reported for monocular PL."

"the detail of the visual scene [was] split between the two eyes.. it is not known whether images were perceived in depth." Presumably not in stereo 3D if detail was split between eyes.

We have deleted the statement
extra "is" in the abstract before (Webber & Wood).

Fixed. Thanks.

p. 3 "sin qua non" -> "sine qua non"
Fixed. Thanks.

Fig 4: need to say what % improvement means for initially stereoblind observers (I assume they arbitrarily set threshold to 600 arc sec as in Zhang et al). Also, I suggest different symbols be used as well as colors, to improve legibility on monochrome print-out.

We have added the following to the figure legend:
"These subjects were arbitrarily assigned a threshold value of 600 arc sec., which was used in the calculation of % improvement."
All the graphs have been re-done using different colors.

Highlights

- We review the extant literature on stereopsis and amblyopia.
- Impaired stereopsis is a very common deficit associated with amblyopia.
- Impaired stereopsis may have a substantial impact on visuomotor tasks.
- Impaired stereopsis may also limit career options for adults with amblyopia.
- Our review suggests several promising new approaches to recovering stereopsis.

Stereopsis and Amblyopia: A Mini-Review.

Dennis M. Levi[1], David C. Knill[2,3] & Daphne Bavelier[2,3,4]

[1]School of Optometry, Graduate Group in Vision Science and Helen Wills Neuroscience Institute, University of California, Berkeley. Berkeley, California, 94720-2020

[2]Department of Brain & Cognitive Sciences, University of Rochester. Rochester, New York 14627-0268, U.S.A.

[3]Center for Visual Science, University of Rochester. Rochester, New York 14627-0268, U.S.A.

[4]Psychology and Education Sciences (FPSE), University of Geneva, Geneva, Switzerland

Corresponding author: Dennis Levi
School of Optometry, Graduate Group in Vision Science and Helen Wills Neuroscience Institute, University of California, Berkeley. Berkeley, California, 94720-2020.

Phone: 510-643-8685
E-mail: dlevi@berkeley.edu

Abstract:

Amblyopia is a neuro-developmental disorder of the visual cortex that arises from abnormal visual experience early in life. Amblyopia is clinically important because it is a major cause of vision loss in infants and young children. Amblyopia is also of basic interest because it reflects the neural impairment that occurs when normal visual development is disrupted. Amblyopia provides an ideal model for understanding when and how brain plasticity may be harnessed for recovery of function. Over the past two decades there has been a rekindling of interest in developing more effective methods for treating amblyopia, and for extending the treatment beyond the critical period, as exemplified by new clinical trials and new basic research studies. The focus of this review is on stereopsis and its potential for recovery. Impaired stereoscopic depth perception is the most common deficit associated with amblyopia under ordinary (binocular) viewing conditions (Webber & Wood, 2005). Our review of the extant literature suggests that this impairment may have a substantial impact on visuomotor tasks, difficulties in playing sports in children and locomoting safely in older adults. Furthermore, impaired stereopsis may also limit career options for amblyopes. Finally, stereopsis is more impacted in strabismic than in anisometropic amblyopia. Our review of the various approaches to treating amblyopia (Patching, Perceptual Learning, Videogames) suggests that there are several promising new approaches to recovering stereopsis in both anisometropic and strabismic amblyopes. However, recovery of stereoacuity may require more active treatment in strabismic than in anisometropic amblyopia. Individuals with strabismic amblyopia have a very low probability of improvement with monocular training; however they fare better with dichoptic training than with monocular training, and even better with direct stereo training.

Introduction:

Amblyopia is a neuro-developmental disorder of the visual cortex that arises from abnormal visual experience early in life, affecting between 1 and 4% of the general population (Ciuffreda, Levi & Selenow, 1991; MEPEDS, 2009; McKean-Cowdin, Cotter, Tarczy-Hornoch, Wen, Kim, Borchert, Varma, 2013; Williams, Northstone, Howard, Harvey, Harrad & Sparrow, 2008). Amblyopia usually has its onset within the first three years of life, and is thought to reflect alterations in the properties of neurons in early cortical areas (V1 and V2), possibly even as early as the LGN (Kiorpes, 2006; Bi, Zhang, Tao, Harwerth, Smith & Chino, 2011; Hess, Thompson, Gole & Mullen, 2009; for a recent review of mechanisms see Levi, 2013). Accordingly, sensory deficits include a loss of visual acuity as well as of stereopsis, position acuity and contrast sensitivity, particularly at high spatial frequencies (Levi, 2006). Recent work suggests that the amblyopic deficit is then amplified downstream (Levi, 2006; Muckli et al, 2006). Thus amblyopes suffer not only from sensory deficits, but also from deficits not simply explained by low-level considerations (Sharma, Levi & Klein, 2000; Kiorpes, 2006; Levi, 2006; Farzin & Norcia, 2011). These include second-order processing, contour integration, and temporal, spatial and/or capacity limits of attention. Thus, amblyopia leads to deficits in basic vision, and is also detrimental to many other aspects of visual cognition.

Amblyopia is clinically important because it is the most frequent cause of vision loss in infants and young children (Sachsenweger, 1968) aside from refractive error. Amblyopia is also of basic interest because it reflects the neural impairments that occur when normal visual development is disrupted, providing an ideal model for understanding when and how brain plasticity may be harnessed for recovery of function.

Brain plasticity is known to peak during a critical period in early childhood and to decrease thereafter (Wiesel, 1982; Movshon & Van Sluyters, 1981; Bavelier, Levi, Li, Dan & Hensch, 2010). While this highlights the effectiveness of early intervention to correct developmental deficits, the assumption that plasticity effectively ends after the critical period, has had a perverse effect in clinical practice. Amblyopic patients over the age of seven are often told that they will never be able to recover visual acuity or stereovision because their visual system is beyond the critical period for binocular vision. Young brains are certainly much more plastic than older ones, yet the last 15 years have shown that significant plasticity can still be induced beyond the critical period if appropriate input is provided (Levi & Polat, 1996; Morishita & Hensch, 2008; Levi & Li, 2009; Bavelier et al., 2010; Baroncelli, Maffei & Sale, 2011; Levi, 2012; Wong, 2012; Hess, Thompson & Baker, 2014).

Over the past two decades there has been a rekindling of interest in developing more effective methods for treating amblyopia, and for extending the treatment beyond the critical period, as exemplified by new clinical trials (Repka & Holmes, 2012) and new basic research studies (for recent reviews see Levi & Li, 2009; Levi, 2012; Birch, 2013; Hess, Thompson & Baker, 2014). Concurrently, over the past decade, a number of studies have documented how rich forms of experience may trigger brain plasticity beyond the critical period (Bavelier et al., 2010; Knudsen, 2004; Hensch, 2005; Lillard & Erisir, 2011). This combination of factors is particularly exciting as treatment of amblyopia beyond the critical period appears within reach. Yet, it remains unknown which intervention is most efficient, which patients may benefit, and whether patients who have recovered have done so through similar mechanisms.

Much of the rehabilitation focus has been on restoring visual acuity, since reduced visual acuity is the sine qua non of amblyopia. However, many persons with amblyopia, particularly those with strabismus, also suffer from a large (sometimes complete) loss of stereoscopic depth perception. Recent reports of the dramatic effects of restored stereopsis have renewed interest in restoring stereopsis in affected adults. Susan Berry, a neuroscientist, recounts her recovery from strabismus and her amazement as she regained stereo-vision in her book, "Fixing My Gaze"(Barry, 2009). Vision scientist Bridgeman, who had been stereo deficient all his life also gives a vivid description of spontaneously recovering stereoscopic depth perception after viewing the 3D movie Hugo (Bridgeman, 2014) well into his sixth decade.

There is no shortage of reviews of various aspects of amblyopia over the last decade (Webber & Wood, 2005; Kiorpes 2006; Levi, 2006; Wong, 2012; Birch, 2013; Hess et al., 2014: Levi & Li, 2009; Levi, 2012; 2013; Repka & Holmes, 2012; Grant & Moseley, 2011; Barrett, Bradley & Candy, 2013). The focus of this review is on stereopsis and its potential for recovery in persons with amblyopia, specifically, we address the following issues:

i) How is stereopsis compromised in amblyopia?
ii) Why does stereopsis matter?
iii) Can stereopsis be recovered in children and adults with amblyopia?

How is stereopsis compromised in amblyopia?

Under normal everyday viewing conditions, with both eyes open, the vision of persons with amblyopia is dominated by the strong eye. Thus, Webber & Wood, (2005) suggest that the most common deficit associated with amblyopia under ordinary (binocular) viewing conditions is impaired stereoscopic depth perception. This is not surprising because it is well known that in normal vision, degrading the vision of one eye by blurring, filtering or reducing the contrast (Westheimer & McKee, 1980; Donzis, Rappazzo, Burde, Gordon, 1983; Legge & Gu, 1989; Menon, Bansal & Prakash, 1997), results in reduced stereoacuity. Moreover, stereopsis is more degraded by monocular blur (or monocular contrast reduction) than by both eyes being blurred (Westheimer & McKee, 1980; Legge & Gu, 1989). Amblyopic patients, who we discuss here, face similarly degraded conditions.

Stereopsis and Visual Acuity.

In individuals with amblyopia, the visual acuity of one eye is compromised; however, the relationship between the visual acuity of the amblyopic eye and stereoacuity is complex, as illustrated by figure 1, replotted from a large-scale study (McKee, Levi & Movshon, 2003; Levi, McKee & Movshon, 2011). Overall, worse visual acuity seems to correlate with worse stereo-acuity. However, upon close inspection this relationship seems mostly driven by anisometropic subjects (blue symbols). Indeed, over the entire range of amblyopic eye visual acuities, there are amblyopes who are essentially stereoblind (red and gray symbols plotted along the top of the graph). These are mainly strabismic amblyopes, whether purely strabismic or mixed (strabismic and anisometropic). It is worth noting that constant strabismics with good acuity in both eyes are generally stereoblind.

Indeed, while the visual acuity of strabismic amblyopes (red diamonds) and strabismic-anisometropes (gray squares) varies over more than one log unit in Fig. 1, most were stereoblind, except for eight who showed stereoacuity of 2.33 arc min (140 arc sec) or better. Clearly, strabismus, either with or without anisometropia, wreaks havoc on stereo acuity, independently of the visual acuity of the weak eye.

In contrast to strabismic amblyopes, many anisometropic amblyopes retain some stereopsis. McKee et al (2003) found that more than 50% of anisometropic amblyopes passed the Randot circles test, a standard test of stereopsis described below, compared with only about 10% of strabismic amblyopes. Holopigian, Blake and Greenwald (l986) found that anisometropic amblyopes have stereopsis at low, but not high, spatial frequencies, suggesting that while their stereoacuity is not as acute as normal, it is nevertheless functional. Among anisometropic subjects (blue symbols), there is a clear linear relationship between stereoacuity and the visual acuity of the weak eye, when plotted in log-log coordinates (blue dotted line in Fig. 1). Some inter-individual variance is clearly seen; for example, some anisometropic amblyopes have reduced visual acuity in the weak eye (up to 2.5 arc min – or 20/50), but excellent stereopsis (20 arc sec), and some with stereo acuity better than 140 arc sec have substantially reduced visual acuity (MAR up to 6 arc min or 20/120). Yet, the presence of a linear relationship between stereoacuity and visual acuity stands in contrast to the case of amblyopes with strabismus in which no such relationship is visible (red and gray symbols in Fig. 1).

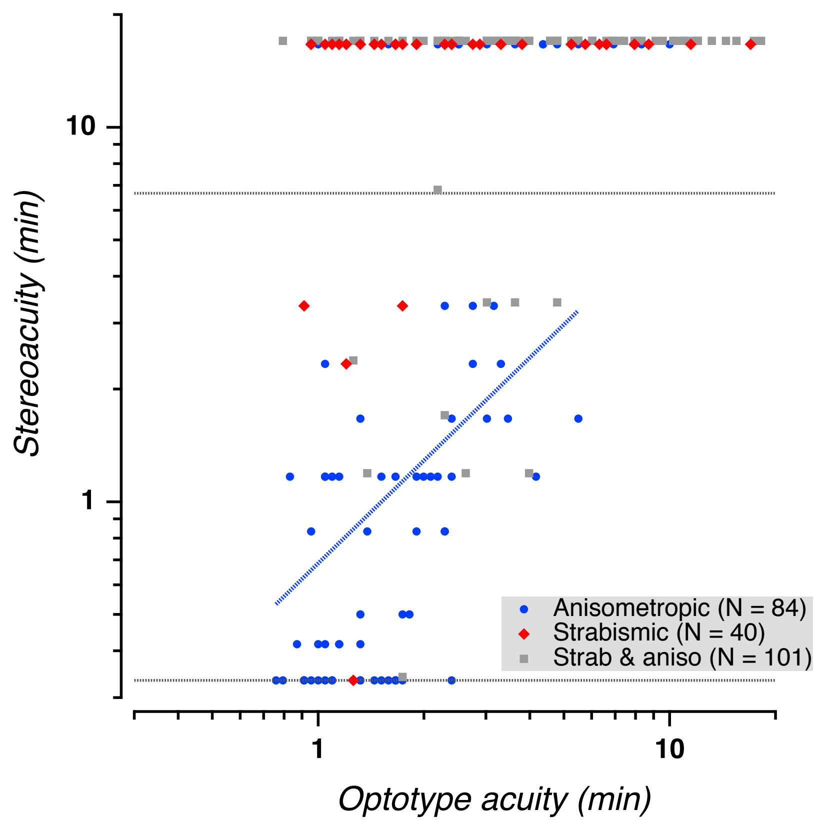

Fig. 1. Stereoacuity vs. Visual Acuity. The dotted lines show the upper and lower limits of the test. The data for strabismic anisometropes (gray squares) have been slightly displaced for clarity. Data replotted from Levi, McKee & Movshon, 2011. The blue regression line suggests that worse visual acuity goes hand in hand with worse stereoacuity in anisometropic amblyopes; however this relationship does not hold in strabismic amblyopes or strabismic anisometropes.

Stereopsis and Crowding.

An important characteristic of amblyopia is crowding – the effect of nearby contours on object recognition (see Levi, 2008 for a review). Indeed, crowding limits object recognition in individuals with strabismic amblyopia (Levi, Song & Pelli, 2007; Song, Levi & Pelli, 2014). Interestingly, there appears to be a close linkage between high crowding and abnormal stereopsis. The amount of crowding distinguishes strabismic from purely anisometropic amblyopia, in nearly perfect agreement with lack of stereopsis (Fig. 2). Song, Levi & Pelli (2014) found high agreement between the presence of strabismus, absence of stereopsis, and a high degree of crowding (as quantified by the spacing Acuity (S/A) ratio). This linkage between crowding and stereoacuity has also been reported in amblyopic children (Greenwood, Tailor, Sloper, Simmers, Bex & Dakin, 2012), and we speculate that both the increased crowding and the reduced stereopsis may be related to when in the course of development, the impairment occurred (Levi & Carkeet, 1993). Whether crowding and stereopsis have some functional relationship in their underlying physiology is an interesting but unanswered question.

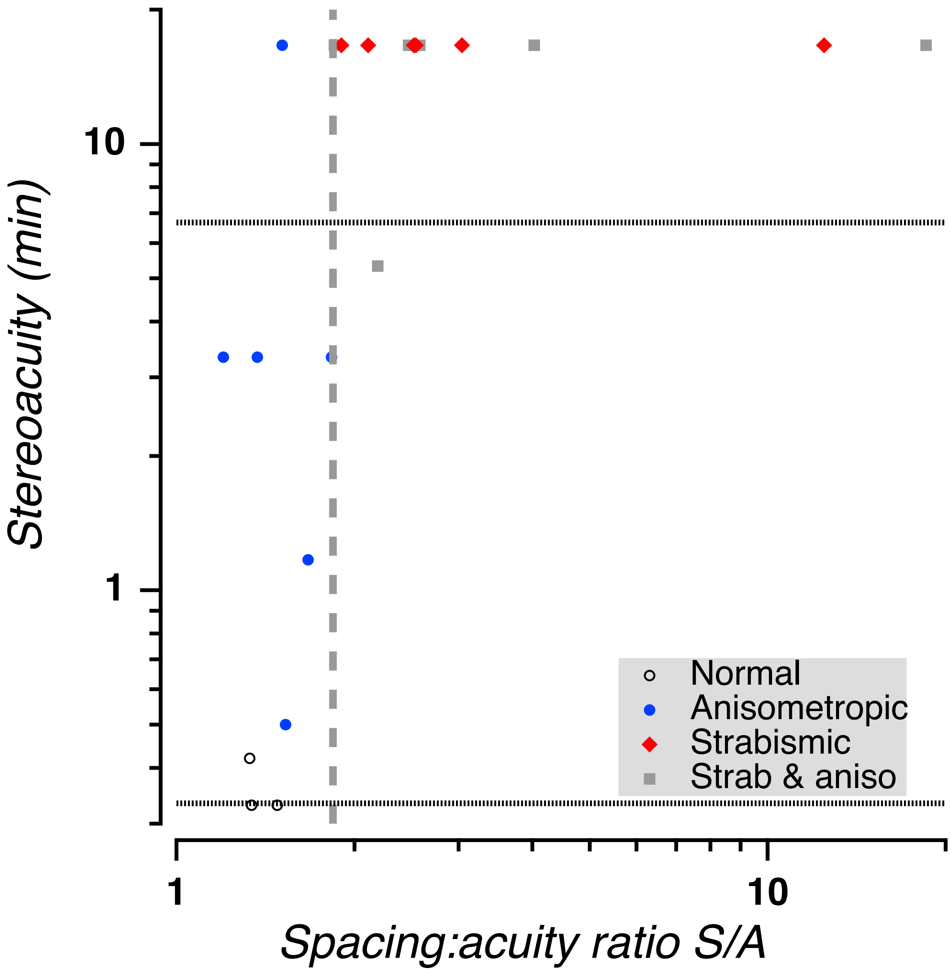

Fig. 2. Stereoacuity and crowding, as quantified by the Spacing:acuity ratio (S/A). Data points above the upper horizontal dotted line at stereoacuity = 6.67 min "Fail" the test. The vertical dashed line, *S/A* = 1.84, divides amblyopic patients into two groups with large and small spacing:acuity ratio, or in other words high crowding or low crowding. High levels of crowding appear systematically associated with loss of stereo-acuity. Indeed, all but one amblyopic patient with a small S/A ratio pass the test, and all but one with a large S/A ratio fail. Data replotted from Song, Levi & Pelli, 2014.

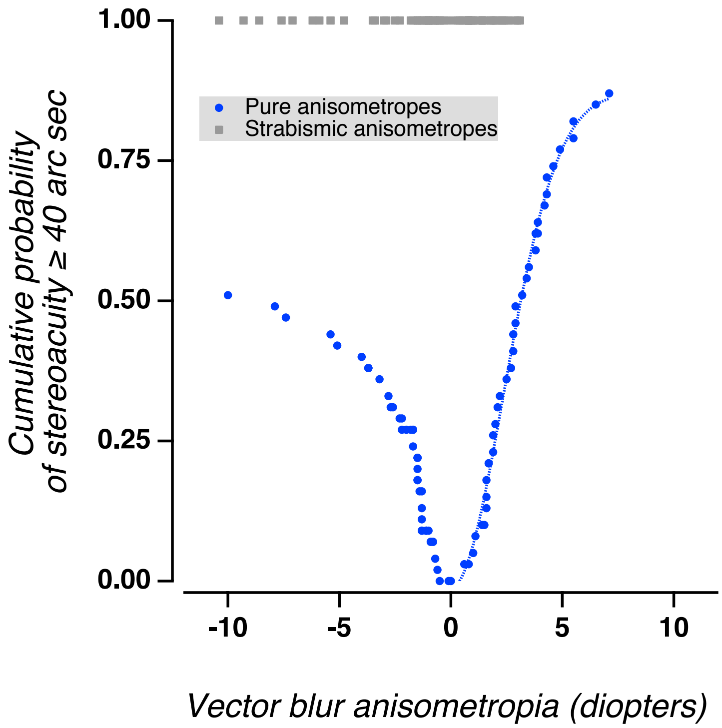

Fig. 3. The cumulative probability of stereo-acuity being 40 arc seconds or worse. Cumulative probabilities for positive and negative values of vector blur anisometropia were computed separately, beginning at 0. Data replotted from Levi, McKee & Movshon, 2011.

Since stereopsis in normal vision is degraded by monocular blur, it is not surprising that in anisometropic amblyopes, the loss of stereopsis depends on the amount of anisometropia. Fig. 3 shows the effect of unequal refractive error in the two eyes on stereopsis. Specifically, this figure shows the cumulative probability of stereoacuity being 40 arc seconds or worse (a factor of two worse than "normal" for this test). With 3 diopters of pure anisometropia (blue circles), 40% of both hyperopic and myopic anisometropes have reduced stereopsis. For hyperopic anisometropes, increased anisometropia results in an increasing proportion of the population with reduced stereopsis. In contrast, the data for the myopic anisometropes saturate, so that even with as much as 10 D of anisometropia, more than 50% of the myopic anisometropes retain stereoacuity of better than 40 arc sec. In contrast, 99% of strabismic anisometropes (gray squares) fail to meet the 40 arc sec criterion regardless of the amount of anisometropia. Thus, the loss of stereoacuity appears to be a general feature accompanying strabismus, while it occurs in anisometropia only when there is substantial unilateral defocus.

Stereopsis and Suppression.

For more than a century, suppression, or inhibition of the amblyopic eye by the strong eye has been implicated as a feature, and possibly a cause, of amblyopia (Worth & Chevasse) and loss of stereopsis, and there is strong clinical (von Noorden, 1990), psychophysical (Levi, Harwerth & Smith, 1979; 1980; Smith, Levi, Manny, Harwerth & White, 1985; Hess, 1991; Harrad & Hess, 1992; Baker, Meese & Hess, 2008; Maehara, Thompson, Mansouri, Farivar & Hess, 2011; Mansouri, Thompson & Hess, 2008; Ding, Klein & Levi, 2013; Ding & Levi, 2014; Hess, Thompson & Baker, 2014) and physiological (Harrad, Sengpiel & Blakemore, 1996; Sengpiel & Blakemore, 1996; Bi et al., 2011) evidence for this point of view. However, the role, occurrence and nature of suppression in amblyopia has been somewhat controversial

(Barrett, Panesar, Scally and Pacey, 2012; Holopigian, Blake & Greenwald, 1986). Moreover, it has been suggested that suppression may take on different forms in anisometropia and strabismus – passive in anisometropia (where the amblyopic eye's image is blurred) but active in strabismus, in order to avoid diplopia.

Some of the disagreements over the role of suppression undoubtedly reflect the many different types of tests used to measure suppression. It is well known in the clinical literature that the artificial situations used to test suppression will often influence the very suppression that one is attempting to measure (von Noorden, 1996). Moreover, suppression may depend strongly on the nature of the targets and their similarity in the two eyes, target locations in the visual field, and other factors (Schor, 1977; Hess, 1991).

While there are several new approaches to quantifying suppression (e.g. Mansouri, Thompson & Hess, 2008; Huang, Zhou, Lu & Zhou, 2011; Ding, Klein & Levi, 2013), it seems important to develop a battery of psychophysical tests that might allow one to better quantify the range and diversity of suppression most relevant to every day functioning. To be of clinical relevance, these tests should be developed with constraints from the clinic in mind. We are encouraged by several recent efforts in this direction (Narasimhan, Harrison & Giaschi, 2012; Kwon, Lu, Miller, Kazlas, Hunter & Bex, 2014; Li et al., 2013).

Why does stereopsis matter?

We review here the functional consequences of the loss of stereopsis for individuals with amblyopia, drawing on the extant literature. Stereopsis seems to provide a unique sensation of depth in the world, as evidenced by normal observer's experience when viewing 3D displays or movies and by the remarkable changes in the qualia of depth perception reported by people who have recovered stereopsis. However, stereopsis is just one of many cues that the brain uses to infer 3D spatial relationships in visual scenes (Howard and Rogers, 2008). We first review the role of stereopsis in normal vision. For persons with normal binocular vision, binocular depth thresholds in natural scenes can be a factor of 10 better than monocular thresholds (McKee & Taylor, 2010). This difference in performance is due to stereopsis.

In observers with normal binocular vision, studies of visual cue integration consistently demonstrate that stereoscopic disparities contribute strongly to depth and shape perception when presented in conjunction with others depth cues (Johnston, Cumming and Parker, 1993; Knill and Saunders, 2003; Vuong, Domini & Caudek, 2006; Hillis, Watt, Landy & Banks, 2004; Lovell, Bloj and Harris, 2012). Despite these laboratory demonstrations, the functional importance of stereopsis remains much debated.

The most studied behavior in relation to stereopsis is probably driving. While early studies seemed to show some correlation between stereoscopic acuity and accident rates (Humprhiss, 1987, Gresset & Meye, 1994), more recent studies have found little correlation between stereopsis (or more generally, intact binocular vision) and driving performance (McKnight, et. al. 1991; Bauer, et. al. 2001; Oladehinde, et. al. 2007). Thus it remains unclear just how important stereopsis is for safe driving. Interestingly, the emerging story is different for visually guided control of one's own body movements.

In humans with normal binocular vision, visually guided hand movements are significantly impaired when viewing is restricted to one eye (Fielder & Moseley, 1996; Servos, Goodale & Jakobson, 1992; O'Conner, Birch, Anderson & Draper, 2010; Melmoth & Grant, 2006). Movements take longer and are less accurate under monocular viewing. For example, movements took on average 100 msec longer, and subjects made about three times as many corrective movements under monocular conditions (Melmoth & Grant, 2006). These differences between monocular and binocular conditions were highly significant. Planning hand movements in depth is clearly more uncertain under monocular viewing, since visual information about the distance of a target from the observer is significantly degraded when stereoscopic information is removed.

Online visual feedback from the moving hand is also critical to motor control (Keele & Posner, 1968; Connolly and Goodale, 1999; Saunders and Knill, 2004; 2005). A recent study showed that, even when monocular cues about the position and movement of the hand in depth are available, online corrections to hand movements in depth are significantly impaired under monocular viewing (Hu and Knill, 2011). Online corrections effectively disappeared during the fast phase of movements. Thus, deficits in both planning and online control likely contribute to impairments in motor control caused by the removal of binocular information. This is almost certainly due to the removal of stereoscopic information.

Walking performance is also significantly degraded, slower by about 10%, in normal subjects under monocular vs. binocular conditions (Hayhoe, Gillam, Chajka & Vecellio 2009).

While the evidence relating binocular vision and stereo information (not necessarily stereoacuity) to visuomotor performance in normally sighted subjects is strong, the relationship between the impairment in visually guided hand movements and stereoacuity remains somewhat controversial. For example, Read, Begum, McDonald, Trowbridge (2013) report that subjects (aged 7 to 82) performed manual dexterity tasks faster and more accurately with both eyes open than with one eye occluded, but the binocular advantage was not significantly correlated with their stereoacuity. Similarly, Murdoch, McGhee & Glover (1991) reported that while individuals with no stereopsis have difficulty in performing a task with 3D clues, there are some individuals (post-fellowship ophthalmologists) who "have better manual dexterity than one might anticipate on the basis of stereoacuity testing alone". Clearly there are substantial individual differences in manual dexterity performance, and it seems plausible that some individuals with poor stereopsis maybe able to compensate, while others, with excellent stereoacuity, may be "klutzes". However, a recent large-scale study (O'Conner, Birch, Anderson & Draper, 2010) showed that performance on motor skills pegboard and bead tasks was related to the subject's stereoacuity with those with normal stereoacuity performing best.

These results are mirrored in amblyopic patients. A number of studies have shown that amblyopes with impaired stereopsis show deficits in visually-guided hand movements similar to those caused by occluding vision of one eye in normally-sighted subjects. These deficits are thought to be due to impaired stereopsis, rather than to reduced visual acuity (Suttle, Melmoth, Finlay, Sloper and Grant, 2009; Melmoth, Finlay, Morgan and Grant, 2009; Niechwiej-Szwedo, Kennedy, Colpa, Chandrakumar, Goltz, & Wong, 2012; Grant, Melmoth, Morgan and Finlay, 2007), fixation instability (Subramanian, Jost and Birch, 2013), or impaired vergence control (Melmoth, Storoni, Todd, Finlay, & Grant, 2007). We acknowledge that given the co-occurrence of strabismus, amblyopia and reduced stereopsis in many of the subjects in these studies, it is not possible to conclusively link these visuomotor deficits to reduced stereopsis per se. However, Hrisos et al. (2006) showed that reduced binocularity significantly predicted visuomotor deficits in their patients, whereas the depth of amblyopia did not. Moreover, Melmoth et al. (2009) showed similar visuomotor deficits in amblyopic patients whose visual acuity had been successfully corrected but stereoacuity remained impaired.

Consistent with the findings in normally sighted adults, poor stereoacuity in amblyopic patients seems to particularly impair visual feedback control of movements, leading to significantly longer and less accurate hand movements (Grant, Melmoth, Morgan & Finlay, 2007). The effects of losing stereopsis extend beyond hand movements. In addition, adaptations to changes in terrain (e.g. steps) are significantly less accurate without stereopsis both in normally sighted subjects viewing monocularly, and in subjects with amblyopia and reduced stereoacuity or absent stereopsis (Buckley, Panesar, MacLellan, Pacey& Barrett, 2010; Helbostad, Vereijken, Hesseberg & Sletvold, 2009).

While most of these studies focus on adults, the results suggest that impaired stereopsis may also negatively affect everyday activity in amblyopic children (Webber, Wood, Gole & Brown, 2008a), as well as also limit career and job options. For example, surgeons, pilots or architects are all professions in which excellent stereoacuity is vital. In addition, while quantitative studies are needed, it has been suggested that expert athletes such as soccer players or tennis players rely heavily on their ability to properly estimate depth, as they predict the trajectory of the ball they just impacted. Finally, we should not forget the impact of amblyopia in young children and stigmatizing cost of being labeled as a clumsy kid with a patch (Webber, Wood, Gole & Brown, 2008b). Interestingly, parents of strabismic children whose eyes have been surgically aligned sometimes report improvements in their child's visuomotor skills (Webber and Wood, 2005; von Noorden, 1996). Whether this is due to improved stereoacuity or to other factors remains unknown, and is an important topic for future studies.

Can stereopsis be recovered in children and adults with amblyopia?

In children with amblyopia, having some measurable stereopsis (vs. having none) significantly influences the outcome of treatment. Children with no measurable stereopsis have a more than two-fold increase in risk for persistent amblyopia (Birch, 2013). Thus the status of stereopsis and whether it can be recovered appear critical when considering treatment.

It is important to note that stereopsis is not a single entity. First, there are thought to be distinct mechanisms for processing coarse vs. fine (or first vs. second-order) disparity signals (Wilcox & Allison, 2009; Tsutsui, Taira & Sakata, 2005) and for processing motion in depth (e.g. Rockers, Cormack & Huk, 2009). Second, stereoscopic functions vary along a number of important stimulus dimensions in the normally-sighted population, including eccentricity and spatial frequency (Siderov & Harwerth, 1995). Third, the multi-faceted nature of stereopsis is reflected by variability in patient etiology. Some patients who are categorized as stereo-blind using standard clinical tests evidence a variety of residual stereoscopic functions, including preserved sensitivity to second-order disparity signals (McColl, Ziegler & Hess, 200; Harris et al., 2000), preserved sensitivity to motion in depth in peripheral vision (Sireteanu, Fronius & Singer, 1981). Recent work suggests that coarse stereopsis may be selectively spared in stereo deficient children with a history of amblyopia (Giaschi, Lo, Narasimhan, Lyons &Wilcox (2013). In the sections below we focus primarily on stereopsis measured with standard, static, clinical tests. However, it would clearly be helpful to study stereopsis, and its recovery, using methods that tap the wide range of stereoscopic capacities.

Quantifying Stereopsis:

In order to address recovery, it is important to briefly discuss the methods used for measuring and quantifying stereopsis. As Westheimer (2013) notes, it is critical to make the distinction between "stereopsis and the ability to judge the three-dimensional disposition of objects in the visual field from other cues." Unfortunately, many of the clinical tests fail to fully eliminate cues to such judgment. Consider for example, the widely used Randot "Circles" test (Stereo Optical Co, Chicago, IL), a test recommended by Simons (1981) for use with amblyopic patients. The Randot circles test, like most clinical stereopsis tests, is a test of the ability to distinguish differences in perceived distance of static targets – in this case circles – based on the relative disparities of the targets. Polarized targets and polarizing viewers provide separate images of the targets to the two eyes. The Randot Circles test presents contoured circles at 10 discrete disparity levels (from 20 to 400 arc sec). The patient task is to choose which of the 3 circles at each disparity level appears closer than the other two - a simple 3 alternative forced choice. Note that this is not a cyclopean (Julesz, 1963) random dot stereogram. The circles are presented on a background of random dots, but are highly visible monocularly, which may be helpful for amblyopic patients with poor vision (Simons, 1981). Despite the random dot background, for large disparities, there are monocular cues, based on the image displacement that creates the retinal disparity. Indeed, Fawcett & Birch (2003) found that stereoacuity scores derived using the Randot Circles test showed good agreement with those measured with random-dot stereograms (with no monocular contours) when stereoacuity was 160 seconds of arc or better, but the Randot Circles test progressively overestimated stereoacuity for poorer random-dot stereoacuity scores. Whether this is due to subjects using the monocular cues or because stereograms with monocularly visible contours and cyclopean stereograms are processed by different neural mechanisms (e.g. coarse vs fine) is unclear.

There are other clinical tests (e.g. the Frisby test – see Simons, 1981 for a comparison of clinical tests); however, all of these have caveats. For example, all of the tests have a maximum disparity. Subjects who initially fail to detect the largest disparity are often labeled as "stereoblind", or as having a stereo sensitivity (1/stereo threshold) equal to zero. For these subjects, quantifying the amount of improvement that may occur as a result of treatment is problematic, since the "zero" may not actually be zero! Clinical tests also have a smallest disparity, and thus may underestimate improvements in stereo acuity, since patients may improve beyond the test's finest disparity.

Some consider the appreciation of depth in genuine random-dot stereograms to be the gold standard for stereopsis because the stereograms contain no monocular information (Julesz, 1963). On the other hand, failure to achieve stereopsis with random dot stereograms may occur because the dots are small and dense, low in contrast, and static, making them less than optimal for a strabismic observer to detect depth (Simons, 1981; Ding & Levi, 2011; Westheimer, 2013). We note that McKee et al. (2003) reported a nearly perfect agreement between passing (or failing) the Randot circles test (described above) and a psychophysical measure of binocular function known as the binocular motion integration in a large group of amblyopic subjects.

Although measures of stereopsis and stereo-acuity are not without weaknesses, there is enough convergence to ask whether stereopsis when absent can be recovered or stereo-acuity when poor retrained.

Is it possible to recover stereopsis?

Several recent reports suggest that it may indeed be possible to recover stereopsis, even in adulthood. As noted in the Introduction, Susan Barry acquired stereoscopic vision following successful unconventional visual therapy begun at 48 years of age, resulting in a dramatic improvement of her perception of depth or the appreciation of "the space between" objects (Barry, 2009). Her new stereoscopic vision brought much more to her life than just depth perception: Objects became clearer, motion perception more veridical, her ability to move around the world more confident. Even more dramatic is the experience of Bruce Bridgeman who recovered stereopsis after watching the 3-D movie Hugo (Bridgeman, 2014). Whether this sort of immersive experience with very large disparities, along with many other depth cues will be an effective treatment for abnormal stereopsis, remains to be tested. Moreover, we note that neither Barry nor Bridgeman were amblyopic. However, these case studies, along with lab studies of perceptual learning resulting in the recovery of stereopsis (Ding & Levi, 2011 –

discussed further below), call into question the notion that recovery of stereopsis can only occur during a "critical period" of development when the visual system is still plastic. This idea, dating back to the last century, led a number of practitioners to tell Susan and her mother that "nothing can be done" about her vision (and one to suggest that she might need a psychiatrist). Since binocular neurons are present in the visual cortex of primates within the first week of life, Barry surmises that some of the innate wiring of her binocular connections remained intact, and that vision therapy taught her to move her eyes into position for stereovision, "finally giving these neurons the information they were wired to receive". Although this is one possible explanation, other plausible explanations exist, including compensatory mechanism and new wiring giving rise to the recovery of binocular information through different pathways.

Below we review studies of recovery of stereopsis in both children and adults with amblyopia. We present analyses of extant studies (below – see Table 1 and Figure 5) where we consider: i) reports of any improvement in stereopsis; ii) reports of patients with no measurable stereopsis prior to treatment who have measurable stereopsis following treatment; and iii) reports of at least a 2-level improvement on a test (e.g. from 200 arc sec to 100 arc sec on the Randot Circles) and a post training stereoacuity of 160 arc sec or better. We regard the latter criterion as providing reasonable evidence for genuine recovery of stereoacuity . Our analysis is based on published studies in which we were able to identify data (stereo thresholds or stereo sensitivity) for individual subjects (adults and children) that could be identified as anisometropic or strabismic amblyopes. Note that in the following sections we have combined purely strabismic amblyopes and amblyopes with both anisometropia and strabismus, referring to them as "strabismic"

Standard clinical treatment:

The standard clinical treatment for amblyopia for the last two centuries consists of: i) correcting any refractive error, and ii) patching or "penalizing" the strong eye, in order to "force" the weak eye to do the work. This treatment is almost exclusively applied to children, adults being considered past their critical period for recovery of vision.

In young children, simply correcting the refractive error results in improved visual acuity and stereo acuity. For example, Richardson et al. (2005), found that refractive correction alone resulted in an ≈ 30 arc sec improvement in stereoacuity in non-strabismic amblyopic children between the ages of 3 and 4 years, 9 months. This improvement in stereopsis from refractive correction alone (often referred to as refractive adaptation) has been confirmed by other studies (Stewart et al., 2013). Importantly the improvement is not limited to anisometropic amblyopia, but also extends to strabismic amblyopia.

Patching or penalization also results in improved stereoacuity both in young children (less than 7 – Lee and Isenberg, 2003; Steele et al. 2006; Agervi et al., 2009; Wallace et al., 2011) and in older children (7 to 12 years of age - PEDIG, 2008). Specifically, for the older group, combining patching and penalization (using atropine to blur the strong eye at near) treatment resulted in an improvement of 2 or more levels on the Randot Preschool stereoacuity test in about 22% of the patients. Fig. 4 shows a small decrease in the percentage of pediatric patients with very poor stereo acuity (800 arc sec or worse) – and a modest increase in the percentage of patients with good stereo acuity (100 arc sec or better) after patching – 12% of anisometropic amblyopes and 5% of strabismics.

Combining data from seven PEDIG (Pediatric Eye Disease Investigator group) clinical trials, Wallace et al. (2011) evaluated stereoacuity before and after treatment in a large sample (633) of anisometropic children amblyopes. As expected, even before treatment, amblyopes with better initial visual acuity and less anisometropia had better stereoacuity. Better post-treatment stereoacuity was associated with better base-line stereoacuity and better post-treatment visual acuity in their amblyopic eyes; however, among patients with normal or nearly normal visual acuity following treatment, stereoacuity remained impaired compared to children of the same age with normal vision.

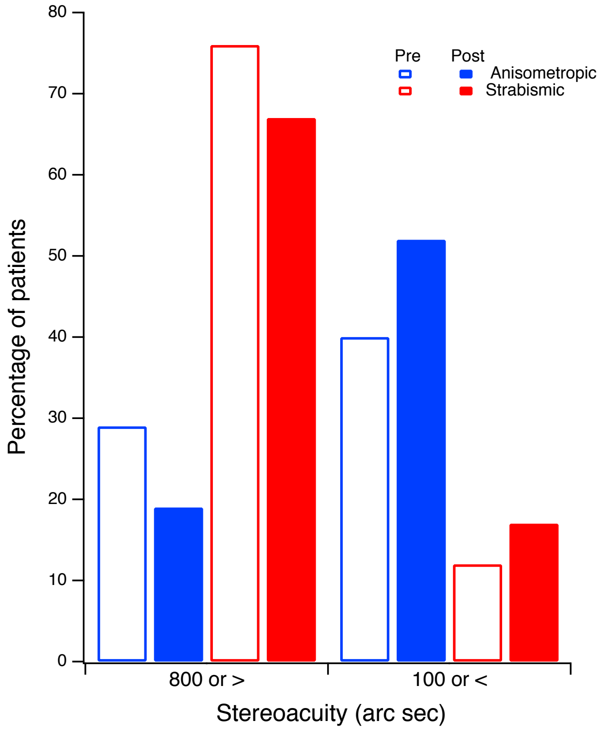

Fig. 4. The effect of patching on stereopsis recovery in children. The percentage of patients with very poor or no stereopsis (800 arc sec or >) decreases, and there is a modest increase in the percentage of patients with good stereo acuity (100 arc sec or <). Based on data in PEDIG, 2008.

Early onset strabismus is a major obstacle to the development of good stereoacuity. In an extensive review, Birch & Wang (2009) reported that only about 30% of infantile esotropes who underwent early surgery in the first year of life showed coarse stereopsis (100 to 3000 arc sec) at age 5, and less than 0.5% of this cohort developed normal stereoacuity. Early botulinum toxin treatment resulted in a better outcome, with 50% showing coarse stereo, and 20% achieving stereo acuity of less than 60 arc sec. Yet this still means that half of the patients fail to recover coarse stereopsis. How to best treat those individuals that do not respond to patching has been the focus of the experimental treatments considered below.

Experimental treatments:

The results of the clinical treatment presented to date are in pediatric populations because adults have generally been considered to be beyond the critical period for recovery. In the following sections we review data based on experimental treatments in adults as well as children. These data suggest that while adults are more difficult to treat, there are solid reasons to believe that adult treatment can be effective. Note that here we only review those studies where we are able to assign individual data to amblyopic subjects that could be identified as either anisometropic or strabismic. Thus, our survey (Table 1 and Figs. 5 and 7) does not reflect the adult data of Li et al., 2013 where only average stereo sensitivity data are provided, or the children's data of Li et al., 2014 where only 5/45 (11%) of the subjects improved, but it is unclear whether these 5 were anisometropic or strabismic, or by how much they improved.

Nonetheless, taken together, these studies reveal greater plasticity in stereopsis than previously thought. They also point to the greater advantage of dichoptic approaches when it comes to retraining stereo vision.

Combined across all of the experimental studies reviewed below (see Table 1), we find that 55% of anisometropic amblyopes and 26% of strabismic amblyopes show substantial improvement in stereoacuity after intervention (Fig. 5). Below we look in more detail at the specific classes of treatment.

Table 1 near here

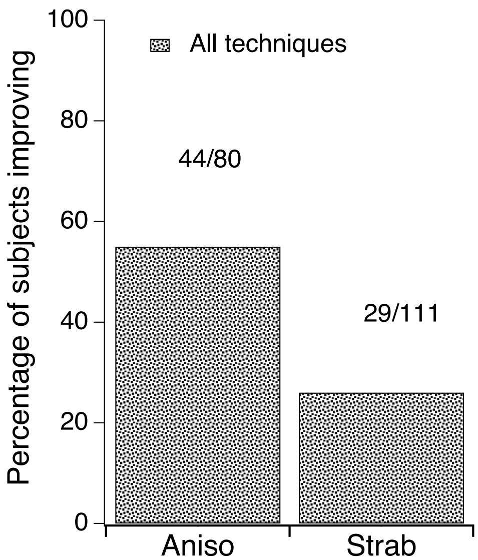

Fig. 5. The percentage of anisometropic and strabismic amblyopes achieving at least a two-level improvement in stereoacuity and a stereoacuity of 160" or better with all methods of treatment (based on the studies in Table 1). The numbers above each bar show the number of subjects achieving this improvement/the number of participants in that category.

Monocular Treatment:

Traditionally, the aim of amblyopia treatment (both clinical and experimental) has been to improve first and foremost visual acuity of the amblyopic eye and check other visual functions.

"Supervised patching"

To date there are no randomized clinical trials of patching in adults with amblyopia; however, the study of Vedamurthy et al. (2014) included a control group who watched action movies with their amblyopic eye, while the strong eye was patched. Surprisingly, 43% (3/7) of their anisometric amblyopes, and 22% (2/9) of strabismic amblyopes met our criterion for improvements in stereopsis, that is at least a 2 level improvement and a stereoacuity of 160 arc sec (considered to be clinically significant – Fawcett & Birch, 2003).

Monocular Perceptual learning (PL):

It is well known that practicing challenging visual tasks can lead to dramatic and long-lasting improvements in performing them, i.e., practice makes perfect! In adults with normal vision, practice can improve performance on a variety of visual tasks (see Sagi, 2011 for a recent review). This learning can be quite specific (to the trained task, orientation, eye, etc., – but recent work shows that this apparently specific learning can be made to generalize using the appropriate training protocol (Xiao et al., 2008; Zhang et al., 2010) even in amblyopic patients (Zhang et al., 2014). Over the last two decades or so, there has been a great deal of interest in applying PL to patients with amblyopia, and to date there have been more than thirty published studies, involving more than 400 amblyopic subjects and a wide range of tasks.

Most of these studies have been conducted in adult amblyopes and involve monocular PL with the amblyopic eye while the strong eye is patched. The results of many of these studies have been reviewed elsewhere (Levi & Li, 2009; Levi, 2012), with the focus on the amount of learning in the trained task, and any transfer to the visual acuity of the amblyopic eye. On average, these studies show that amblyopic subjects improve by about a factor of two on the trained task, and that their visual acuity also improves by about a factor of ≈ 1.6, roughly two lines on a LogMAR acuity chart (Levi & Li, 2009; Levi, 2012). Unfortunately few of these studies report on transfer of learning to stereopsis. A few mention gains in stereopsis in passing (e.g. Li & Levi, 2004), but in many other published studies it not clear whether stereoacuity was measured before and after training in all subjects, or only in some. One recent exception is the study of Zhang et al., (2014) who performed extensive monocular PL in a group of 19 adult amblyopes. Their results, summarized in Fig. 6, show substantial improvements in stereoacuity in adults with both anisometropic and strabismic amblyopia, including several who were "stereoblind" (i.e., unable to see a disparity of 500 arc sec, the largest disparity tested – data in the blue rectangle) initially.

Based on the data reported in the extant studies (Table 1), roughly 18% of both strabismic and anisometropic amblyopes with no measurable stereopsis initially, demonstrated measurable stereopsis following monocular PL. Importantly, more than 60% of anisometropic amblyopes met or surpassed our criterion for improvements in stereopsis by the end of training. In contrast only 9% of strabismic amblyopes achieved the same criterion, despite showing equivalent improvement in visual acuity as anisometropic amblyopes (Table 1 and Fig. 7A). Thus simply improving monocular visual processing may result in improved stereopsis in anisometropic, but much less so in strabismic amblyopes.

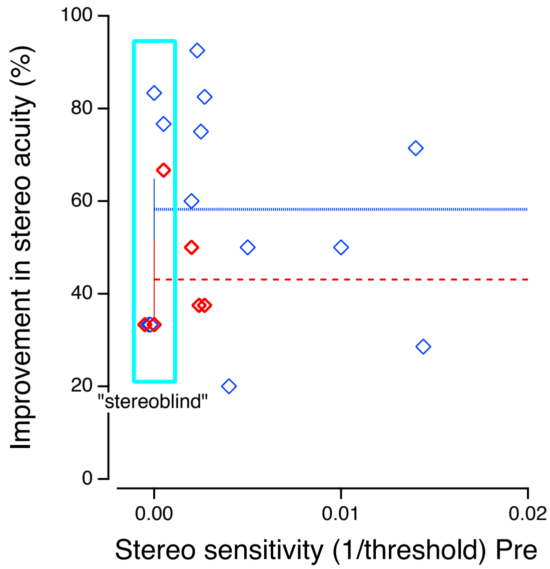

Fig. 6. The effect of extensive monocular PL on stereoacuity in adult amblyopes. Both anisometropic (blue) and strabismic (red) amblyopes, including several who were "stereoblind" (i.e., unable to see a disparity of 500 arc sec, the largest disparity tested – data in the turquoise rectangle) initially show improved stereo sensitivity after PL (replotted from Zhang et al., 2014). These subjects were arbitrarily assigned a threshold value of 600 arc sec., which was used in the calculation of % improvement.

Monocular Videogame Play

PL clearly can result in improved visual capacities even in adults with amblyopia, however, there are two major drawbacks to PL for clinical use – specificity and tedium. PL is often highly specific to the stimulus, task, retinal location etc. However, a crucially important goal in rehabilitation is to have the learning generalize. While there are learning protocols that do aid in generalizing learning (e.g. double training – Xiao et al., 2008; Zhang et al, 2010, 2014), they still require several thousands of trials. Moreover, standard PL is highly repetitive and considered tedious by many subjects. Thus, an alternative approach is to use highly engaging and motivating videogames.

In the first such study (Li, Ngo, Nguyen & Levi, 2011), 20 adult amblyopes played an off the shelf videogame (Medal of Honor) with their amblyopic eye (AE), while the non-amblyopic eye (NAE) was patched. Both strabismic and anisometropic amblyopes showed improved visual acuity. Stereopsis, however, improved in the five anisometropic amblyopes, but in none of the 15 strabismics participants (Fig. 7B).

<u>Dichoptic Treatment:</u>

A more recent trend involves dichoptic treatment, in which different images are presented to the two eyes at the same time. The key aim of this approach is to try to eliminate or reduce interocular suppression.

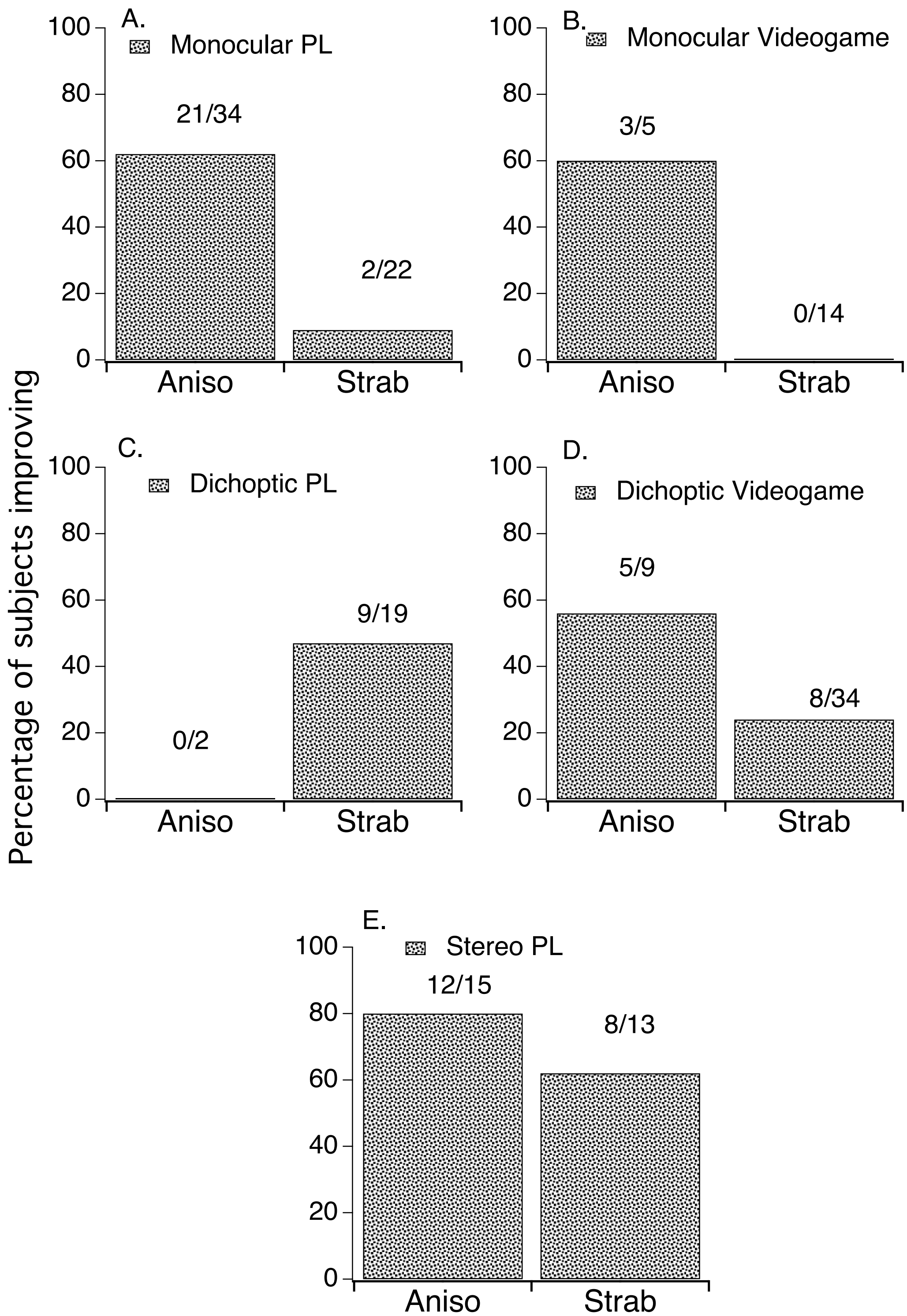

Fig. 7. The percentage of anisometropic amblyopes (A) and strabismic amblyopes (B) showing improved stereopsis with various methods of treatment. The selected criterion for stereopsis improvement is achieving at least a two-level improvement in stereopsis and a stereoacuity of 160" or better (data plotted based on the studies in Table 1).

Dichoptic Perceptual learning (PL):

Hess and his colleagues have used several variants of a dichoptic motion coherence task in a series of studies in adults (Hess, Mansouri & Thompson, 2010a and b; 2011; Li et al., 2013; Hess, Babu, Clavagnier, Black, Bobier & Thompson, 2014) and children (Knox, Simmers, Gray and Cleary, 2012; Birch, 2013; Li, Jost, Morale, Stager, Dao, Stager & Birch, 2014). The method essentially consists of presenting 'signal' dots, all moving coherently in the same direction to one eye, and 'noise' dots, all moving in random directions, to the other. For amblyopic subjects, threshold was determined either by the ratio of signal to noise dots required to determine the coherent motion direction (Hess et al., 2010), or by determining the ratio of AE to NAE contrast required to determine the coherent motion direction (Li et al., 2013). As is evident in Fig. 7C, none of the anisometropic amblyopes showed improved stereopsis; however, we note that the number of anisometropic amblyopes in the dichoptic PL category is very small (only 2, and one showed excellent stereoacuity at Pre-Test). However, dichoptic PL appears to be substantially more effective than monocular PL in improving stereopsis in strabismic amblyopes (compare Fig. 7A with 7C). More than 40% of strabismic amblyopes showed improved stereopsis, compared with less than 10% reported for monocular PL. For an extensive review of these studies see Hess et al., 2014.

Ooi, Su, Natale & He (2013) used a different approach – a sensory dominance "push-pull" task, to achieve the same goal (reducing suppression), in three adults with amblyopia. Their push-pull protocol is designed to "excite the weak eye, while completely inhibiting the strong eye's perception to recalibrate the interocular balance of excitatory and inhibitory interactions." They report improved contrast thresholds and stereopsis in their three subjects; however only one (S2) met our 2-level/160 arc sec criterion. That subject showed an impressive ≈ 4 fold improvement in stereo acuity.

Dichoptic Videogame Play:

One of the earliest dichoptic videogame studies used the I-BiT system, which "invokes a three-dimensional image in those with normal single binocular vision by stimulating both eyes simultaneously". Cleary et al. (2009) tested this system in 12 amblyopic children who did not comply or respond to occlusion. Specifically, in each of 8 sessions, the children viewed a 20-minute video clip with the "detail" viewed by the amblyopic eye and the surrounding frame by the fellow eye, and spent 5 minutes playing an interactive videogame with the detail of the visual scene split between the two eyes. The authors report that the subjects perceived the images projected to the two eyes. Seven of the 12 children showed improvement in high contrast visual acuity and 8 showed improvement in low contrast visual acuity (3-18 months after the treatment). Most interestingly, 4 of the 12 children showed an improvement in stereoacuity (one from 400 to 40 arc sec)!

A variant of the dichoptic PL method described above, is a Tetris-like dichoptic videogame, which requires players to arrange falling blocks into a pattern[1]. Some of the blocks are seen by the amblyopic eye at high contrast and others to the strong eye at a lower contrast, tailored to each patient's level of suppression (To et al., 2011; Li et al., 2014;). This method has been applied to both children and adults with amblyopia. In their recent review, Hess et al (2014) report that averaged across all of the studies acuity improved by ≈ 2 lines, a result that mirrors the outcome of most interventions studies. Interestingly, one-third of patients showed improved stereopsis regardless of amblyopia type (anisometropic, 31%; strabismic, 37%).

[1] We note that the boundary between dichoptic PL and dichoptic videogames is not always clear.

A different approach, described in this issue (Vedamurthy et al., 2012a, 2014; Bayliss et al., 2012; 2013), uses a customized dichoptic action video game designed to reduce suppression, promote fusion and increase attention by the amblyopic eye under binocular conditions. The game, viewed in a stereoscope, presents identical images to the two eyes, with the luminance/contrast of the image seen by the strong eye decreased to perceptually match that of the weak (amblyopic) eye. This is an effective method for balancing the input to the two eyes (Baker, Meese & Hess, 2008; Ding & Levi, 2014; Zhou, Jia, Huang & Hess, 2013), and frequent alignment and suppression checks ensured successful fusion. Following 40 hours of videogame play, observers showed similar improvements in visual acuity to those seen with monocular videogame play, but stereoacuity improved in about half of study participants, with average overall improvements being significant for the videogame group (Table 1).

Combined across the dichoptic videogame studies, 56% of anisometropic amblyopes and 24% of strabismic amblyopes showed an improvement of at least 2-steps and stereoacuity better than 160 arc sec. (Fig 7D).

<u>Direct Stereo Training:</u>

A recent case report documented substantial improvements in two anisometropic adults who had undergone refractive adaptation and monocular PL followed by stereo training (Astle, McGraw & Web, 2011), and several laboratory studies support the notion that it is possible to improve stereopsis in adults with abnormal binocular visual experience through visual training or perceptual learning of stereopsis per se. For example, Nakatsuka et al.(2007) reported that adult monkeys reared with prisms had mild stereo deficiencies that improved through PL after 10,000 - 20,000 trials.

Ding & Levi (2011) provided the first evidence for the recovery of stereopsis through perceptual learning in human adults long deprived of normal binocular vision. They used a novel training paradigm that combined monocular cues that were perfectly correlated with the disparity cues. Following PL (thousands of trials) with stereoscopic gratings, adults who were initially stereoblind or stereoanomalous showed substantial recovery of stereopsis. Importantly, these subjects reported that depth "popped out" in real life, and they were able to enjoy 3-D movies for the first time, similar to the experiences of Stereo Sue and Bruce Bridgeman. Their recovered stereopsis is based on perceiving depth by detecting binocular disparity, but has reduced resolution and precision. Similar improvements were recently reported in a group of anisometropic and ametropic amblyopes who were trained with anaglyphic textures with different disparities (Xi, Jia, Feng, Lu & Huang, 2014).

More recently, Vedamurthy et al. (In Preparation) have developed a virtual-reality (VR) system for training stereopsis in amblyopes (both anisometropic and strabismic) and in strabismics (both with and without amblyopia) that embeds the training in a natural visuo-motor task whereby patients have to squash a small virtual bug with a hand-held cup . Some stimuli contained monocular texture cues to slant as well as stereoscopic cues, some contained only stereoscopic cues and some contained conflicting monocular and stereo cues, enabling Vedamurthy et al. to compute the relative weights given to stereo and monocular slant cues. Following training, 8 of 11 subjects gave increased weight to stereo cues relative to monocular cues, 6 showed significant improvement on separate stereopsis tests, 5 showed improved visual acuity, and all 11 showed reduced suppression.

Combined across studies, the gains for direct stereo training (Fig. 7E) appear to be greater than the gains obtained through either monocular or dichoptic (2D) training, particularly for strabismic amblyopes. This can be more clearly seen in Fig. 8, which compares monocular training, dichoptic training (combining PL and VGP studies) and direct stereo training. This figure shows clearly that patients with strabismic amblyopia have a very low probability of improvement with monocular training; however they fare better with dichoptic training than with monocular training, and even better with direct stereo training.

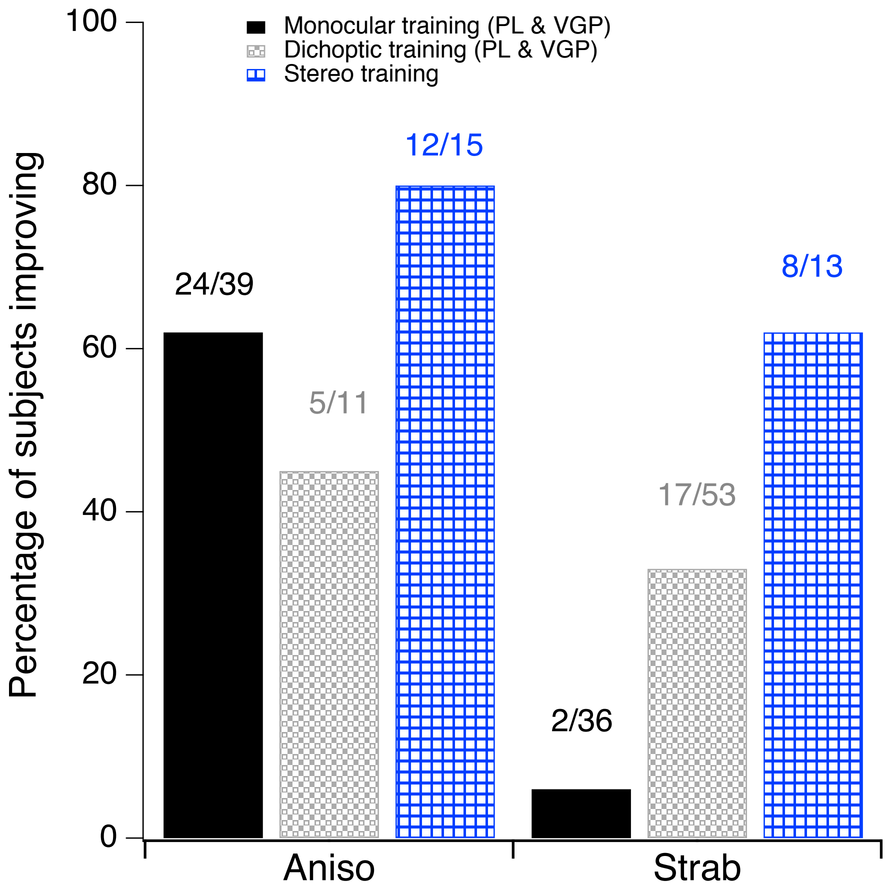

Fig. 8. Experimental training summary. The percentage of anisometropic (left 3 bars) and strabismic (right three bars) achieving the criterion improvement in stereopsis based on monocular training (combining PL & VGP – black bars), dichoptic training (combining PL & VGP – gray bars) and direct stereopsis training (blue bars).

<u>Mechanisms of Improvement</u>

A discussion of the mechanisms of improvement is beyond the scope of this review. A good deal of evidence, both physiological and behavioral, suggests that changing the balance of neural excitation and inhibition by either reducing inhibition or boosting excitation may be crucial in recovery of visual functions (Morishita & Hensch, 2008; Bavelier et al., 2010; Baroncelli, Maffei & Sale, 2011). All approaches to retraining the amblyopic eye, whether monocular videogame play (Li et al., 2011), perceptual learning (Levi & Li, 2009), the "push-pull" method (Ooi et al., 2013) or dichoptic training (Knox et al., 2012; Hess et al., 2014; Vedamurthy et al., 2014) seek to achieve this altered balance by increasing signal, reducing noise, or modulating attention in the amblyopic eye.

One possible explanation for the greater success of dichoptic and stereo training in the recovery of stereopsis, particularly in strabismic patients, is that these techniques also train binocular fusion, by placing the images on corresponding areas in the two eyes. Indeed, Ding &

Levi (2011) reported on one subject who recovered stereopsis following extensive fusion training.

Finally, we note that training stereopsis directly (Ding & Levi, 2011; Astle et al., 2011; Vedamurthy et al., in preparation) may provide a useful scaffold for integrating information from the two eyes, and may therefore present a more efficient way to restore stereovision in amblyopic patients, while simultaneously fostering improved visual acuity.

Summary, caveats, and conclusions

Figures 5, 7, 8 and Table 1 summarize the reported improvements in stereopsis for each of the approaches discussed above, based on the extant studies for which we had access to individual subject stereo data – a total of more than two hundred subjects. Across all methods, more than one fourth of amblyopes with no measurable stereopsis prior to training showed at least some measurable stereopsis after training (Table 1), and more than 50% of anisometropic and about 26% of strabismic amblyopes showed at least a 2-level improvement in visual acuity and stereoacuity of 160 arc sec or better (Fig. 5).

There are many caveats that should be kept in mind. First, the numbers of subjects in each study are generally small, and we have only included those studies that provide the individual results, as opposed to just mean results. Second, different studies use different tests to quantify stereopsis and many of the tests have such a limited range of tested disparities, that patients may be labeled as "stereoblind" simply because the test did not provide sufficiently coarse disparities (see quantifying stereopsis above). In addition, for many clinical stereo tests, test-retest reliability is often poor, with 95 confidence intervals of 1 to 2 octaves (e.g., Fawcett & Birch, 2000; Adams, Leske, Hatt & Holmes, 2009). While some studies include control groups (e.g. Li et al., 2013; 2014; Vedamurthy et al., 2014a), most do not, making it difficult to interpret the changes in stereoacuity. Clearly, there is a need for better stereo tests that can be applied to patients.

We note too that the studies considered here represent a wide range of ages, study durations, training methods and measurements. However, even confining our analysis to only those studies that tested adult patients, we find that 43% showed the criterion improvement. In addition, some of the studies may have confounded treatments. For example, as noted above, in children, spectacle correction alone can improve visual acuity and stereoacuity (Richardson et al., 2005; Stewart et al., 2013). Amblyopic subjects, upon entry to a study are often refracted and given an updated spectacle correction. It is unclear whether spectacle correction has the same benefit in adults, and most adult PL studies do not include a refractive adaptation period. Additionally, monocular PL studies generally involve patching the strong eye, and few studies include a control for patching.

Another important issue is that many of the studies do not provide details about the angle of strabismus during treatment and testing. Proper binocular alignment is critical for stereopsis in strabismic subjects, and it seems important to know whether this was achieved and how. Finally, it is quite likely that negative results (failure to find improvements) are either underreported, or not reported at all. Despite these caveats, overall the results appear promising. Perhaps in the not too distant future eye doctors will tell their adult patients with amblyopia and impaired stereopsis that something can be done.

Bearing in mind the many caveats (discussed below), it is interesting to compare the effects of each of the different approaches, and to compare anisometropic vs strabismic amblyopes (Fig. 7). Between ≈ 40% and 80% of anisometropic amblyopes, achieve at least a 2-level/160" or better improvement for all approaches, except for dichoptic PL (this is probably an artifact of the small N). Direct stereo training results in the highest percentage of both strabismic and anisometropic amblyopes reaching this level.

Unsurprisingly, strabismic amblyopes do not fare as well as anisometropes in recovering stereoacuity. Whether the apparent difference between strabismic and anisometropic amblyopes reflects differences in their baseline stereopsis (i.e. many strabismic subjects fail the test or have very poor stereopsis initially), is unclear. Based on standard clinical treatment, the PEDIG studies suggest that better post-treatment stereoacuity was associated with better base-line stereoacuity and better post-treatment visual acuity in their amblyopic eyes (Wallace et al., 2011). Clearly strabismic amblyopes require an approach that is more actively aimed at normalizing binocular interactions and/or directly targeting disparity sensitive mechanisms in order to regain stereopsis, than do anisometropic amblyopes.

In order to look into this question more closely, we have replotted data from several of our studies, involving 94 subjects and multiple training approaches, as post- vs. pre-training thresholds (Fig. 9). What seems clear from this figure is that: i) Many more anisometropic (blue) than strabismic (red) amblyopes improve after training (symbols below the gray unity line). ii) Many more strabismic (40/57 – 70%) than anisometropic (12/37 – 32%) amblyopes have no measurable stereopsis both before and after training, and, iii) there are both anisometropic and strabismic amblyopes at *all levels of pre-training stereoacuity* (including no measurable stereopsis) who show improvements following training, some achieving stereoacuity of 140 arc sec or better (as indicated by the horizontal dashed lines). This figure, based on 94 adults, shows clearly that despite the dogma, many adults with amblyopia can recover, at least partially, stereoacuity.

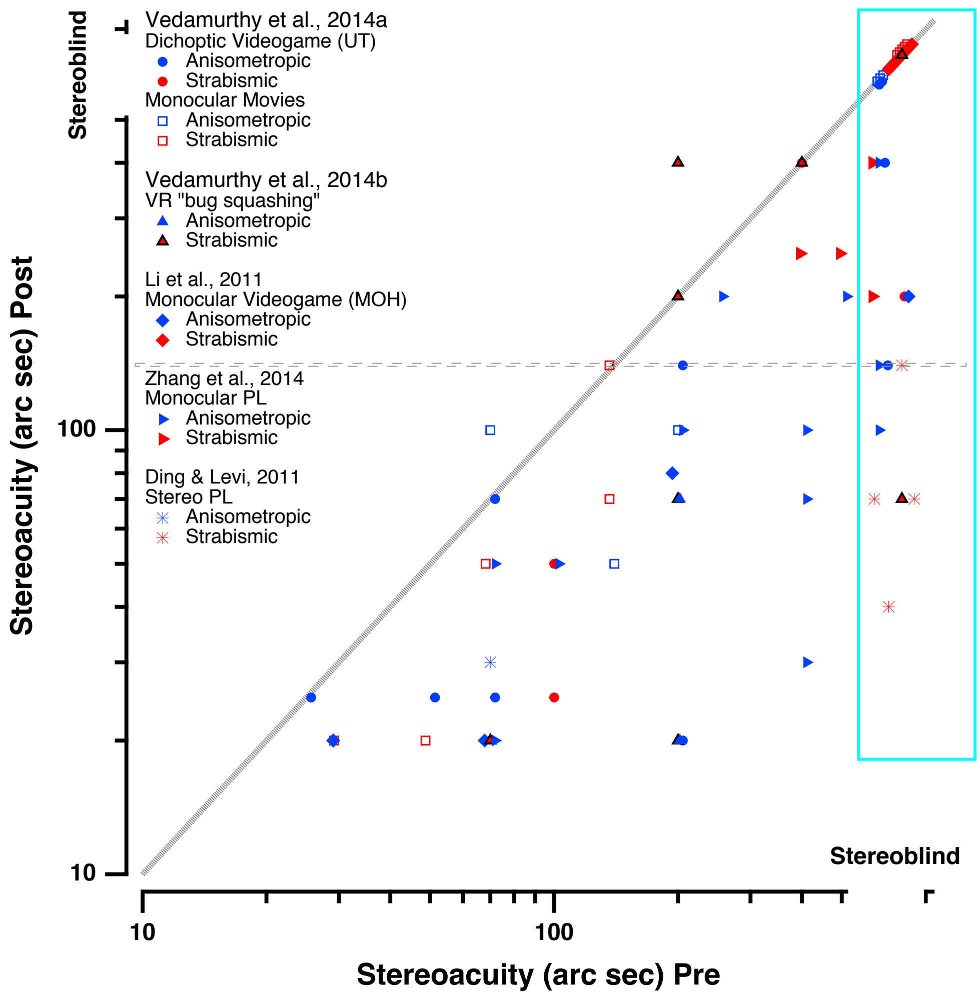

Fig. 9. Post vs Pre- training stereo thresholds. This figure replots data from several of our studies, involving 94 subjects and multiple training approaches. Blue symbols - Anisometropic amblyopes; Red symbols – strabismic amblyopes. The diagonal gray line indicates no improvement. Symbols below the line show improved performance following training. Data below the dashed horizontal lines indicate a post-training stereothreshold of 140 arc sec or better. Data within the turquoise rectangle indicate no measurable pre-training stereopsis.

Our review of the literature suggests that impaired stereoscopic depth perception is the most common deficit associated with amblyopia under ordinary (binocular) viewing conditions (Webber & Wood, 2005), and that this impairment may have a substantial impact on visuomotor tasks, difficulties in playing sports in children and locomoting safely in older adults. Furthermore, impaired stereopsis may not only negatively impact everyday activity, but may also limit career options for amblyopes. Stereopsis is much more impacted in strabismic than in anisometropic amblyopia, and recovery may require more active treatment in strabismic than in anisometropic amblyopia. Importantly however, despite the many caveats, the present review shows there are reasons to be optimistic. Clearly, recovery of at least some degree of stereopsis in patients with amblyopia, even beyond the critical period, is possible. Indeed, this is in line with a number of recent animal studies showing that recovery of visual function can be extended well beyond the critical period by a variety of methods (Morishita & Hensch, 2008; Bavelier et al., 2010; Baroncelli, Maffei & Sale, 2011; Kaneko & Stryker, 2014; Montey, Eaton & Quinlan, 2013; Duffy & Mitchell, 2013). Thus, the time may have come to re-evaluate patching as the standard clinical approach, as treatment with close to a 50% success in adults is likely to be even more successful in young children. In parallel, the large variance in outcome across patients certainly calls for further studies to unpack the factors that may predict treatment success.

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Our dear friend and colleague David Knill died tragically while this manuscript was under review. We, and indeed the entire vision community, will miss him sorely, and we dedicate this paper to his memory.

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Table

Table 1

Study	N subjects	age	Duration (hours)	Any improvement N aniso	N strab	ALL	Stereo Post/not pre N aniso	N strab	ALL	2 steps + 160" or better N aniso	N strab	ALL	Task	Stereo test
Patching														
Vedamurthy et al., 2014a	16	39	40	3/7	4/9	7/16	0/7	0/9	0/16	3/7	2/9	5/16	Supervised patching	RDC
MONOCULAR TRAINING														
Perceptual learning														
Polat et al., 2009	5	7	33		1/5	1/5					1/5	1/5	Contrast sensitivity	RDS
Li et al., 2007	2	11	100	1/1	1/1	2/2	1/1	1/1	2/2	1/1	1/1	2/2	Position discrimination	RDC
Liu et al., 2011 NPT	13	12	53	9/11		9/11	0/9	0/2	1/13	7/9	0/4	7/13	Grating acuity	RDC
Li & Levi 2004	7	37	20	1/7		1/7	1/2	0/5	1/7	1/2	0/5	1/7	Position discrimination	RDC
Liu et al. 2011 PT	10	12	53	3/9		3/9	0/9	0/1	0/10	4/9	0/1	4/10	Grating acuity	RDC
Zhang et al., 2014	19	19 - 27	>40	13/13	6/6	19/19	4/13	3/6	7/19	8/13	0/6	8/19	Multiple TPE	RDC
Total	56			27/41	8/12	35/53	6/34	4/22	11/51	21/34	2/22	23/56		
%				66	67	66	18	18	22	62	9	41		
ACTION VGP (monocular)														
Li et al., 2011 (MOH)	20	30	40	5/5	0/15	5/20	1/1	0/2	1/3	3/5	0/14	3/19	Action videogame	RDC
MONOCULAR TOTAL	**76**			**32/46**	**8/27**	**40/73**	**7/35**	**4/24**	**12/54**	**24/39**	**2/36**	**26/75**		
%				**70**	**30**	**55**	**20**	**17**	**22**	**62**	**6**	**35**		
DICHOPTIC TRAINING														
Perceptual learning														
Knox et al., 2011	14	9	5		7/12	7/14	0/1	3/7	3/8	0/2	2/7	2/14	Dichoptic Tetris	TNO/Frisby
Hess et al., 2010	9	40	48		8/9	8/9	0/0	6/9	6/9	0/0	6/9	6/9	Dichoptic motion	RDC
Li et al., 2013	9	22	10	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Dichoptic Tetris	Randot Preschool
Ooi et al., 2013	3	29	19	-	3/3	3/3	-	-	0	0/0	1/3	1/3	Push-Pull	RDS & CS
Hess et al., 2014	14	33	10-30	-	-	11/14	N/A	N/A	2/5	N/A	N/A	5/14	IPOD	RDC
Total	49				18/24	29/38	0/1	9/16	11/22	0/2	9/19	14/40		
%					75	76	-	56	50	0	47	35		
VGP (dichoptic)														
To et al. 2011	9	36	10-20	-		5/9	-	3/6	3/6	N/A	3/9	3/9	Dichoptic motion	RDC
Cleary et al., 2007	12	8	4	-	4/12	4/12	N/A	0/1	0/1	N/A	3/12	3/12	Dichoptic video and game	N/A
Vedamurthy et al., 2014a	23	39	40	5/10	3/13	8/23	2/9	1/13	3/22	5/9	2/13	7/22	Dichoptic videogame	RDC
Li et al., 2014	45	4-12	16-32	N/A	N/A	5/45	N/A	N/A	N/A	N/A	N/A	N/A		
Total	89			5/10	7/25	22/89	2/9	4/20	6/29	5/9	8/34	13/43		
%				50	28	25	22	20	21	56	24	30		
DICHOPTIC TOTAL	**138**			**5/10**	**25/49**	**51/127**	**2/10**	**13/36**	**17/51**	**5/11**	**17/53**	**27/83**		
%				**50**	**51**	**40**	**20**	**36**	**33**	**45**	**32**	**33**		
STEREO TRAINING														
Ding &Levi 2011	5	25	>40	1/1	4/4	5/5	0/0	4/4	4/4	1/1	4/4	5/5	Stereo PL	RDC & custom
Vedamurthy et al., 2014b	11	35		2/2	4/9	6/11	0/0	1/3	1/3	2/2	4/9	6/11	VR “bug squashing”	RDC
Astle et al., 2011	2	27	2	2/2	0/0	2/2	0/0		0/0	2/2		2/2	Monocular & Stereo PL	Custom
Xie et al., 2014	11	21	<10	10/10	-	11/11	0/0		0/0	7/10		8/11		
Total	**29**			**15/15**	**8/13**	**13/18**	**0/0**	**5/7**	**5/7**	**12/15**	**8/13**	**21/29**		
%				**100**	**62**	**83**		**71**	**71**	**80**	**62**	**72**		
Grand Total	**259**			**55/78**	**45/100**	**122/247**	**9/52**	**22/76**	**34/128**	**44/80**	**29/111**	**79/203**		
%				**71**	**45**	**49**	**17**	**29**	**27**	**55**	**26**	**39**		

The Table shows for each study (left column) the mean age (in years), duration of training (hours) and the number of Anisometropic, Strabismic and All subjects out of the total number in that category who show: i) any improvement in stereopsis; ii) no measurable stereopsis prior to treatment and who have measurable stereopsis following treatment; and iii) at least a 2-level improvement on a test (e.g. from 200 arc sec to 100 arc sec on the Randot Circles) and a stereoacuity of 160 arc sec or better.