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## The Neurology of Amblyopia: A Further Evaluation of Data from the Eyetronix Flicker Glass Clinical Study

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## **Abstract**

**Background:** Gold standard penalization therapies for amblyopia are thankfully being challenged by new techniques and new technologies. One such technology, rapid alternate occlusion or alternating flicker was recently studied and improved visual acuity and stereopsis in anisometropic amblyopes.

**Methods:** Starting with a recapitulation of the Eyetronix Flicker Glass Clinical Study of the affect of 7Hz square-wave alternating flicker on anisometropic amblyopia, further analysis looks at how stereopsis changed through the period of the study, and possible age-related differences in outcomes and changes in reading symptomology pre- to post-therapy. A discussion of the complexity of how alternating flicker may work therapeutically is presented separately in an appendix.

**Results:** In a group of 23 anisometropic amblyopes, 12 weeks of Eyetronix Flicker Glass therapy improved BCVA of the amblyopic eye about two lines with no adverse effects to the better eye with considerably less therapy time than in penalization techniques, improved both random dot “global” and contoured “local” stereopsis and also reduced symptoms of reading problems. Age and beginning acuity were non-factors in success of the therapy.

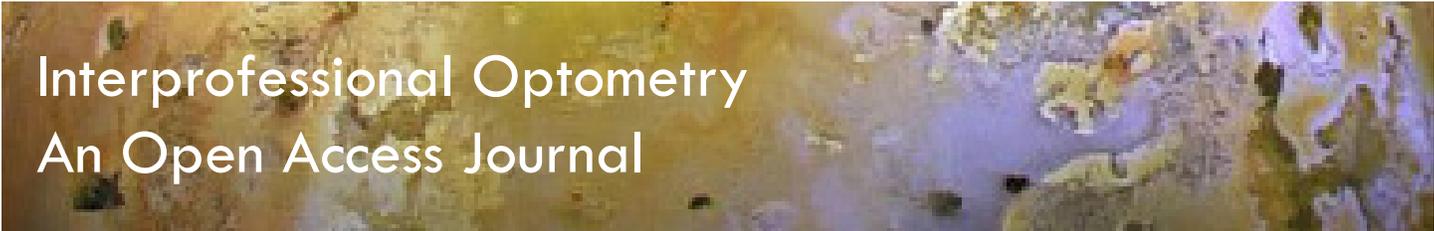
**Conclusions:** Paradoxically, square-wave rapidly alternating visual flicker may present one of the few truly bilateral therapeutic visual stimuli to the cortex. The mechanism may include the anti-masking effect of appropriately-timed on- and offset of the flickering visual stimuli, flicker as a strong visual motion stimulus driving visibility at or near the LGN, and temporal summation.

## **Keywords**

amblyopia, flicker

## **Acknowledgements and Funding**

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# Interprofessional Optometry

## An Open Access Journal

# The Neurology of Amblyopia: A Further Evaluation of Data from the Eyetronix Flicker Glass Clinical Study

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Optometry has been treating amblyopia since the inception of the profession. Amblyopia has sometimes frightened optometrists clinically, perhaps because of wanting to be sure no serious pathology is at the root of the amblyopia, or perhaps because treatment of amblyopia has historically meant patching and the fights that accompany that form of therapy. One of the traditional authorities, Gunter K. von Noorden, defined amblyopia as “a decrease of visual acuity in one eye caused by abnormal binocular interaction... for which no causes can be detected by the physical examination of the eye(s) and which in appropriate cases is reversible by therapeutic measures” (p. 246). von Noorden goes on to quote von Graefe as defining amblyopia as “the condition in which the observer sees nothing, and the patient very little” (p. 246).

Clinically, we usually define amblyopia as reduced best-corrected visual acuity with one eye in the absence of a history of active pathology, but when there has been an interruption in development during the amblyogenic period. Proper glasses or contacts don't quickly bring the poorer eye's acuity up to be on a par with the better eye, although wearing glasses can certainly help the amblyopic eye. We usually think amblyopia is a function of some binocularity-interfering condition during early visual (and general) development, often early strabismus or early anisometropia. Hyperopic and/or astigmatic anisometropia and strabismus are often found in conjunction with, or we could say they are co-morbid with, amblyopia. Deep suppression is considered part of the syndrome, although seldom is deep defined (Hess, Thompson, & Baker, 2014).

When faced with having diagnosed an amblyopic eye, eye care practitioners have to decide whether to treat it beyond suggesting glasses. Loose clinical language to facilitate a parent's agreement and cooperation with these therapies may include such prompts as “the eye will go blind without treatment.” The strength of that induced commitment might help when traditional treatments—patching—are employed: Kids, being generally smarter than adults (and maybe smarter than many doctors), rebel at the loss of the clarity of the better eye and the loss of the full panorama of vision with patching, all justified by a promise of improvement. There's a reason patching and atropine drops are called penalization, and kids don't like the penalty, short-lived though it may be. We can shorten the patching time or we can lengthen it depending on response of the eye, but it is still penalization. We can even patch

in 30-second intervals now (Pediatric eye disease investigator group, 2005; Spierer et al., 2010; Wang et al., 2015).

The world of gaming, especially when the game is presented dichoptically, shows promise in improving acuity in amblyopia (Li et al., 2015). Unsurprisingly, kids old enough to play the games are more interested in this sort of treatment than in penalization. Gaming, not being the native soil of lab scientists, would be expected to bring a wave of non-traditional sources for treatments into the arena of amblyopia care, and that's probably a good thing.

A recent study has re-introduced a different treatment vehicle into the amblyopia arena, that treatment being rapidly-alternating visual flicker. When there is an attempt to explain how alternating flicker might treat amblyopia, the explanation usually involves the suppression, again assumed to be “deep.” The recent clinical study done with Eyetronix Flicker Glass (EFG) showed rapid alternation to be a viable way to treat amblyopia, improving stereopsis as well as visual acuity (Vera-Diaz, Moore, etc, 2016). An improvement in stereopsis, stereopsis that requires two functioning retinas, overlapping visual fields, and intact neural circuitry is different than what is seen in direct occlusion (Westheimer, 2013). When we demand two retinas—eyes—to be involved for stereopsis, now the discussion moves beyond one-eyed acuity to binocularity (binocularity: “bin”—a combining form meaning “two at a time”, “ocular”—“the eyes”) (<http://www.dictionary.com/browse/binocularity>). If stereopsis improved, we must have improved binocularity. How did that happen? What does that tell us about how eyes and the visual system work? How can we explain all that?

We'll start the potential explanation with a recapitulation of the Eyetronix Flicker Glass Clinical Study. Then those data will be expanded graphically to emphasize some of the changes seen in the kids in the study as well as their responses to treatment. Following that will be a very complex explanation for how alternating flicker might work, especially when the visual stimulus itself provides no periods of bilateral simultaneous sight, and yet, we improved binocularity (Vera-Diaz et al p. 112). Finally, especially for those who skip the “why it works” section, we'll end with what this might mean for how eyes and the visual system respond to different therapeutic stimuli and some suggestions for further study.

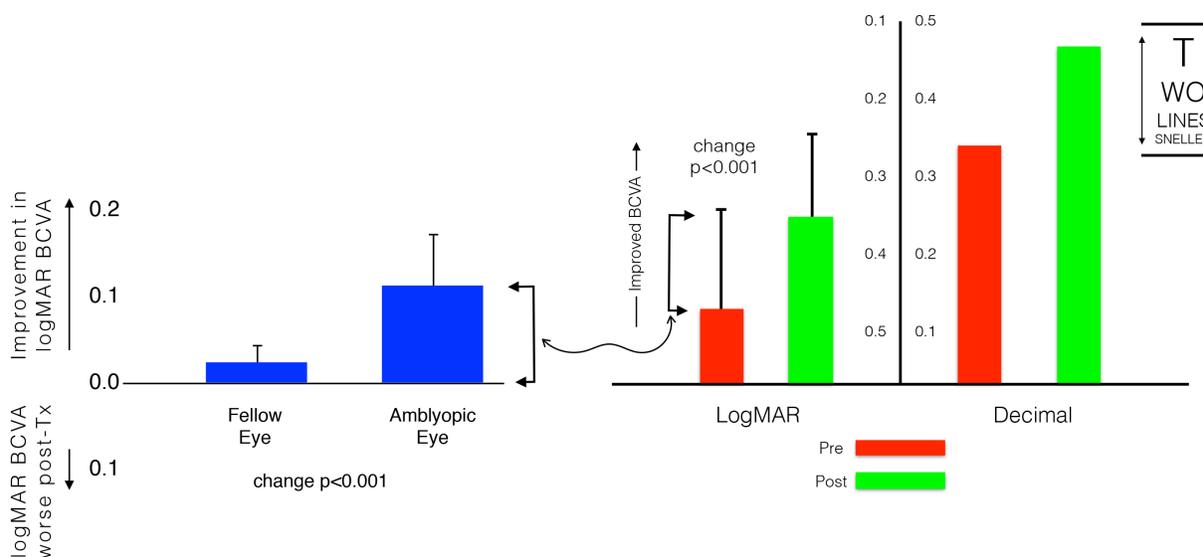
## Recapitulation: The Eyetronix Clinical Study

The purpose of the original Eyetronix Flicker Glass study was to evaluate the effect on anisometropic amblyopia of alternating flicker. The flicker came in the form of a 7 Hz square-wave directly alternating visual stimulus provided by Eyetronix Flicker Glass programmable liquid crystal shutter lenses, worn for one to two hours daily. The open/closed periods, at 7 Hz direct alternation, are 71+ msec each. Seven Hz matches Schor, Terrell & Peterson’s experimentally derived timing using acuity chart presentation as a visual stimulus (1976). However, rather than just looking at acuity charts, wearable liquid crystal shutter lenses can be used for virtually any indoor, safe visual activity since they are not tethered to any acuity charts, game interface or other defined targets (Birch et al., 2015). Kids can wear the device while reading, working puzzles, coloring, playing most video games, whenever. Outcome measures were very traditional: Best corrected VA and stereopsis, but compliance, quality of life, and reading symptomatology were also surveyed and reported.

### Subjects

Seven Hz alternation with Eyetronix Flicker Glass as a therapy for mild to moderate anisometropic amblyopia was studied (Vera-Diaz, Moore, Hussey, Srinivasan, & Johnson, 2016), and to accomplish that, twenty-three children, ages 5 to 17 years old (mean 10.6±4 years) with anisometropic amblyopia were recruited. The inclusion criteria that had to be met were: 1) age from 5 to 17 years old; 2) acuity with the amblyopic eye between +0.20 and +0.70 logMAR (20/32 to 20/100 Snellen), fellow eye acuity at least +0.20 logMAR (20/32), and minimum difference between the eyes of +0.20 logMAR (2 lines Snellen); 3) anisometropia of at least 1.00 DS or 1.50 DC; 4) no strabismus greater than 20 prism diopters on distance cover test; 5) full time best-correction glasses for at least 8 weeks prior to treatment with no subsequent improvement in BCVA found; and no improvement in BCVA was found in any amblyopic eyes with optical correction alone during the pre-therapy period; 6) no amblyopia treatment other than glasses for 1 month prior to the study or during the study.

Penalization had been a prior treatment for 75% of the kids. We might suggest, then that any improvements with the therapy represent something beyond what can be attained with penalization. The penalization phase is over and done. Figure 1 is a summary of acuity changes in the group. Figure 2 shows those changes individually, but also designates those who had been penalized with a “P.”



**Figure 1.** Figure 1 Change in acuity summary; amblyopic eye vs fellow eye, logMAR change and decimal change in amblyopic eye

Four locations contributed: two clinics affiliated with the New England College of Optometry (NECO) in Boston, MA, this author's private practice in Spokane, WA, and a private practice in Fort Worth, TX. All protocols were approved through the NECO IRB.

## Protocol and Procedures

The children used the Eyetronix Flicker Glass at home for 12 weeks. Surveillance and supervision included seven scheduled visits: an initial comprehensive eye and vision examination that included determination of acceptability; a dispensing visit where initial logMAR acuities were recorded with a standardized EDTS procedure; four monitoring visits at 1, 3, 6, and 9 weeks device use; and a final exit visit at 12 weeks that included a second comprehensive eye and vision examination as well as final EDTS acuities. The dispensing, monitoring and final examinations included EDTS acuities and stereoacuity using the Randot 2 stereo test, both random dot global and 3-dot forced-choice local contoured stereopsis. Weekly phone calls during the treatment period aided monitoring. Ten (43%) of subjects returned for an added-on follow-up visit an additional 12 weeks after the 12-weeks exit visit, and in that group, no regression was found and even a little further improvement.

Quality of life surveys were taken at each visit and a Symptoms Survey at the initial and Exit visits was performed, all with the idea of monitoring for problems, but also to see what real-world changes the therapy made. Any spontaneous offerings of real-world changes in quality of life were reported to the study by the examining doctor. Even before looking further at results, it's worth noting that satisfaction with the therapy was very high, especially when compared to patching. Not yet validated questions probing comfort, ease of use, and stress on the family were all 75-98% positive in this study in which 75% of the participants were patched.

## Results: Visual Acuities

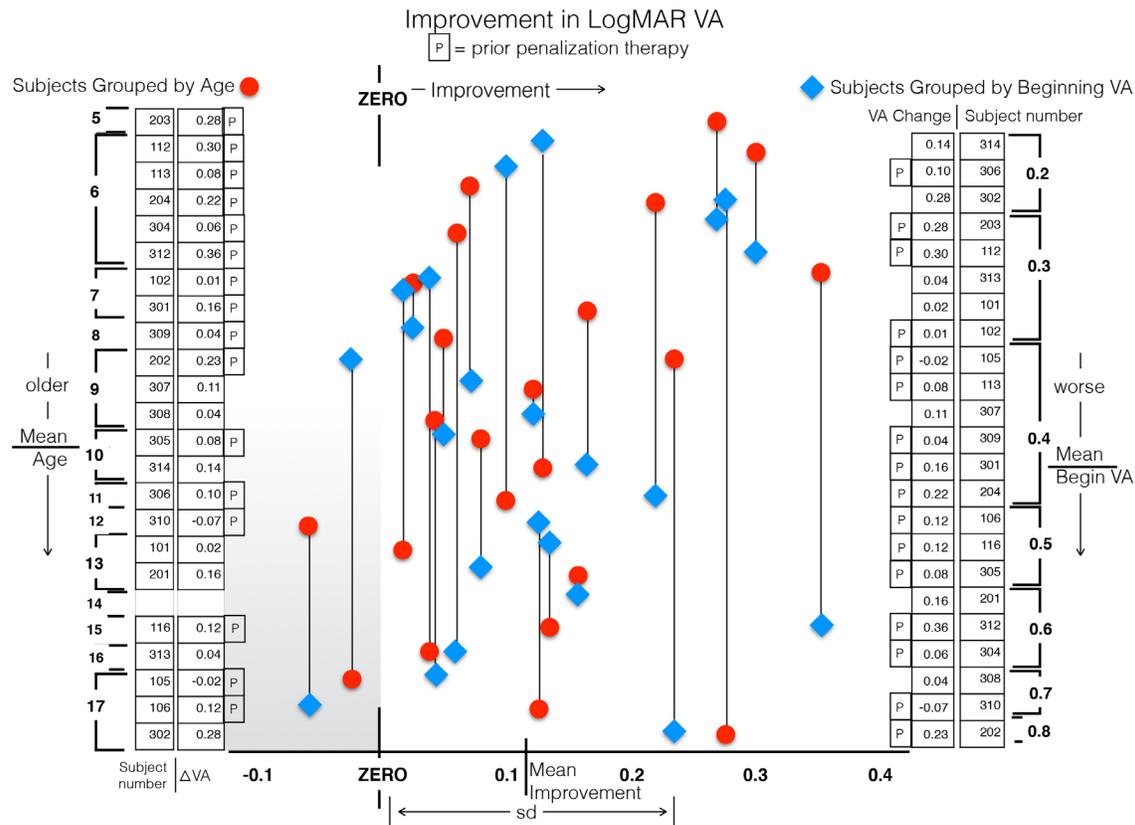
Acknowledging again that three-quarters of these kids had previously been penalized for their reduced acuity, amblyopic eye acuity improved in 21 of 23 in this current study. Overall acuity improvement is shown in figures 1 and 2. The 21 subjects who improved, gained 1 to 4 lines in BCVA in the amblyopic eye. Full-group improvement (mean  $-0.124 \pm 0.111$  logMAR,  $p < 0.001$ ) was about two lines on average. Five subjects (22%) showed improvement beyond the two lines plus a standard deviation. The legitimate

question is whether in the previously penalized kids these improvements should be added onto any prior improvements. Is this possibly a therapy that has an additive effect?

The improvement in acuity in the amblyopic eye did not come at the cost of the fellow, normal eye (change amblyopic vs. fellow eye: two-tailed t-test,  $p < 0.001$ ; fellow eye mean improvement  $-0.02 \pm 0.07$  logMAR,  $p = 0.15$ ). One of the concerns with penalization therapy is that the fellow eye is actually, measurably penalized. That is, post-patching the fellow eye is now worse, perhaps temporarily, although the effects with several months to years of patching, especially near amblyogenic periods is less clear (Odom, Hoyt, Marg (1982).

Age and degree of acuity impairment made little difference in the ability to improve children's amblyopia in this Eyetronix study. Figure 2 shows individual subjects' changes in amblyopic acuities, the individuals identified by subject number and distributed by age as well as by beginning VA for the amblyopic eye, the two data points tethered together. All but two improved in acuity. (The two who didn't improve, varied in acuity visit to visit including visits with better-than-initial acuity, but at the final visit did not show improvement. They were certainly not in a worsening trend.) But, notice that there is no other discernible grouping: No groupings of age or beginning acuities that would suggest limitations in the therapy and reinforce old suspicions of an inherent lid on the possibility of improvement in amblyopia. At least through 17 years of age, no age appears to be too old for treating amblyopia (see also Results, combined, below). Nor did beginning acuity provide an impenetrable barrier to improvement, at least from logMAR 0.2 to 0.8 (roughly 20/30 to 20/125). Age and beginning visual acuity should be rejected by clinicians as absolute barriers to treatment. Adding age and beginning acuities as non-exclusions to the other revelation that prior penalization should not be an excluding factor to further treatment should encourage clinicians to embrace current treatment trends and fear amblyopia a little less.

Calling on clinicians for new boldness in treating amblyopia begs some comparisons to prior literature and other treatment efforts. In a prior PEDIG study (Pediatric Eye Disease Investigator Group, 2005), the same improvement as this Eyetronix mean improvement—about 2 lines of acuity—was the differentiation for responder versus non-responder groupings. About one-fourth of subjects in that study improved with



**Figure 2.** Improvement in logMAR acuities, subjects grouped by age and by beginning logMAR acuities, lines link to same subject, subject's change in VA is next to each subject number. P indicates prior penalization therapy.

optical correction alone. In fact, penalization therapy in the 13- to 17-year-olds was not particularly beneficial, especially if subjects had done prior penalization therapy—the first contradictory finding versus this Eyetronix study.

We have to acknowledge the small numbers of children treated in this Eyetronix study, and the lack of a control group, and therefore proceed with a certain level of caution, but in the few 13- to 17-year-olds, almost half had prior penalization therapy, all had prior full correction (removing the optical effects as a stand-alone consideration), and yet slightly more than half of this small group met or showed more improvement than the mean improvement. Given the lack of effect in this age group with penalization (especially when penalization had been done previously) as shown in this PEDIG study, the improvements in this current study may well represent significantly greater therapy effects than penalization and optical correction have shown—and in half the therapy time (12 vs. 24 weeks).

Looking more deeply into the level of penalization in that particular PEDIG study, patching was done two

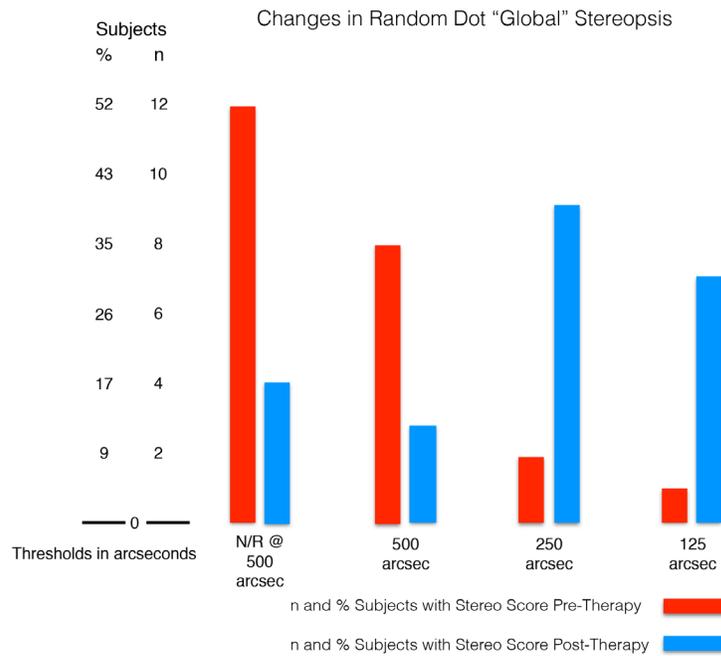
to six hours daily, or an average of four hours for a total of 24 weeks—an average of 672 hours of time the better eye was penalized. That actually pales in comparison to Spierer et al. (2010) using their original 40 second/20 second liquid crystal penalization technique with a treatment time of 2160 hours over nine months, their protocol being 8 hours use per day during which the better eye was penalized roughly 5 hours per. In the Eyetronix Flicker Glass study, the devices were worn, on average, 1.5 hours a day for 12 weeks—an average of 126 treatment-hours, or less than 20% of the total PEDIG treatment time (6% of the Spierer et al. treatment time). Just as an aid for the average family with three children, reducing treatment time by 80% (or 94%) should be a remarkable benefit. That benefit to family no doubt contributed to the positive Eyetronix satisfaction scores (above). But also, if the assertion is correct that the Eyetronix data suggest prior penalization is not a disqualifying factor for further treatment, then re-treatment is a much easier sell to a teenager at 20% of the original commitment, not to mention the broad usage alternatives with activities like video games. Since re-treatment is a viable alternative, further studies should look at how much improvement can be expected with further

rounds of EFG therapy, both with and without prior penalization therapies

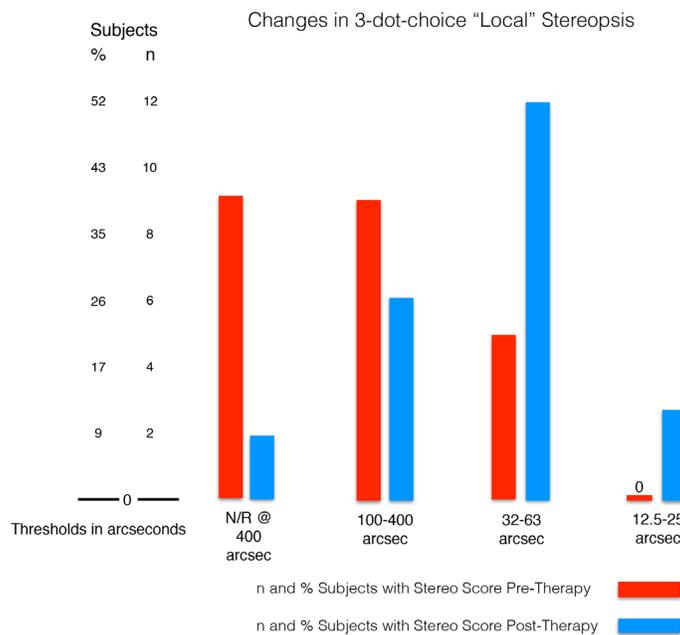
### Results: Stereopsis

The Randot 2 stereopsis test has both random dot global and 3-dot-choice contoured local stereopsis

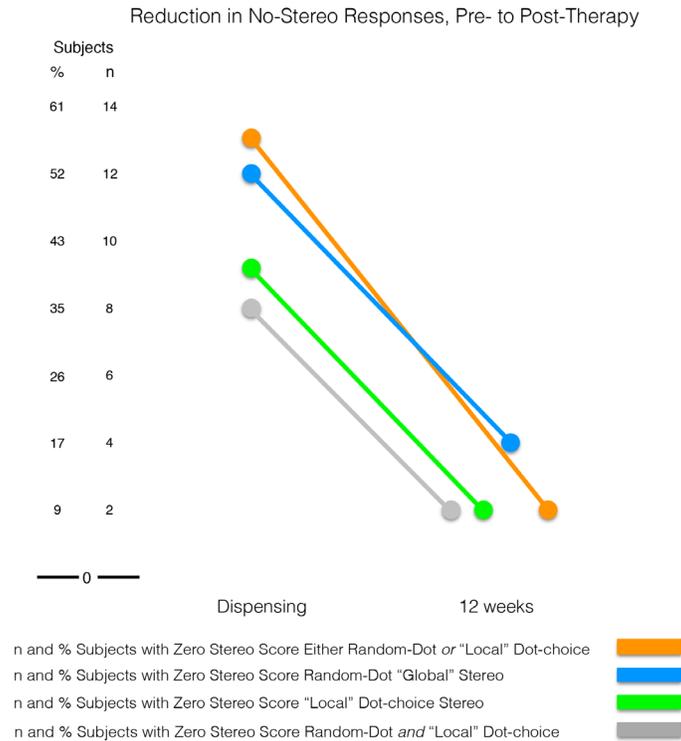
targets. The random dot “global” targets incorporate a random dot background to eliminate the contour cues that are part of the contoured “local” targets. Figure 3 shows pre- to post-treatment global stereopsis scores while figure 4 shows the pre- to post-treatment local/contoured stereopsis scores.



**Figure 3.** Changes in random dot (global) stereopsis pre- to post-therapy



**Figure 4.** Changes in contoured (local) stereopsis pre- to post-therapy



**Figure 5.** Decrease in zero-stereopsis pre- to post-therapy

Both forms of stereopsis improved in the group as a whole. The pre-therapy scores cluster toward lower (worse) stereopsis, including significant percentages showing no response/zero stereo at initial testing. The post-therapy scores cluster toward much-improved, better stereopsis.

But what about those who began with no measurable stereopsis on the Randot test? Figure 5 specifically shows zero stereo/non-responses pre- and post-therapy. These numbers, then, reflect the children who, when shown a stereo target, responded that none of the forms were discernible (random dot) or discernible as being in depth. Zero-stereopsis scores decreased post-therapy for both forms of stereopsis. The reduction in no-stereo responses means more patients developed some form of stereo where there had previously been none. Figure 6 shows the number of no-stereoacuity responses, global and local combined, as a function of time over the 12 weeks graphed against visual acuity changes over the same 12 weeks of the study. The scales for acuity and the number of no-stereoacuity responses are not precisely matchable. But, the slopes of the changes over time suggest stereoacuity responses improved more quickly than visual acuity did, the “awakening” of stereo happening in the first six weeks. This awakening of stereopsis—again, a binocular function—ap-

parently happening due to a visual stimulus that at no time is a classically binocular stimulus.

### Results: Combined

If we remove non-responders on stereo testing (since by definition they have no recordable minimum angle of resolution on this specific testing), convert stereopsis scores to log (base 10) of the minimum angle of resolution in minutes of arc, then combine stereopsis changes graphically with visual acuity changes (Log-MAR), similar patterns of change are seen. Figure 7 shows those changes over the study visits by weeks. Change slopes again suggest stereopsis changed at a faster pace than did visual acuity—and in both types of stereopsis. Standard deviations suggest a lot of variability in the group in stereopsis scores, but with that caveat, this begs the question of whether the therapy drives visual acuity, or whether it drives stereopsis somehow, which then pulls visual acuity along as stereopsis improves. Or possibly, both are true.

Figure 8 is a graph of a “yes-or-no” cumulative change score for acuity, local stereo and global stereo by age. Each factor—acuity, local stereopsis, and global stereopsis—was given a score of 1 if that factor improved between dispensing and the 12-weeks final examination.

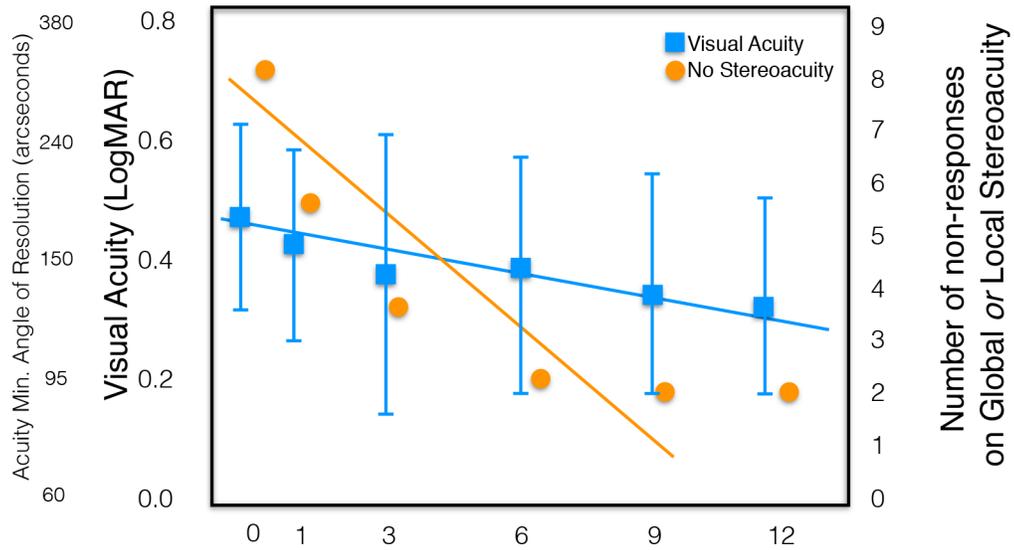


Figure 6.

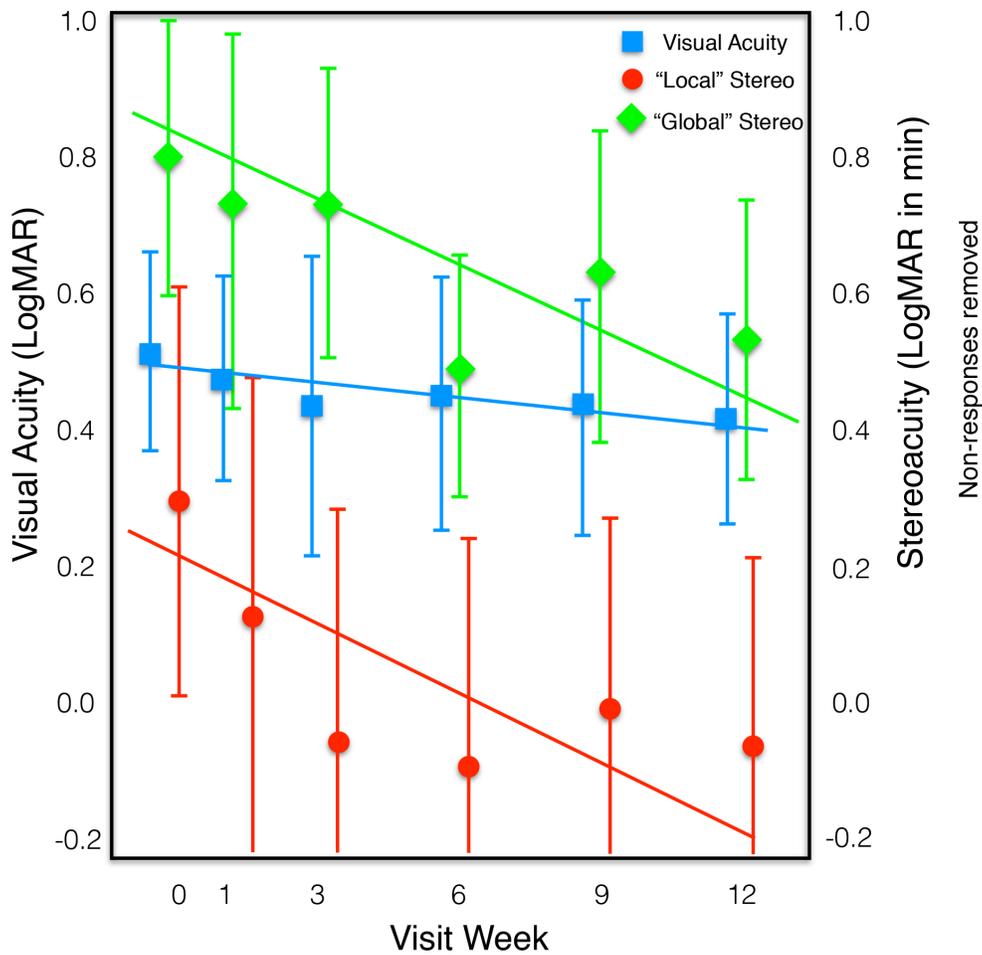
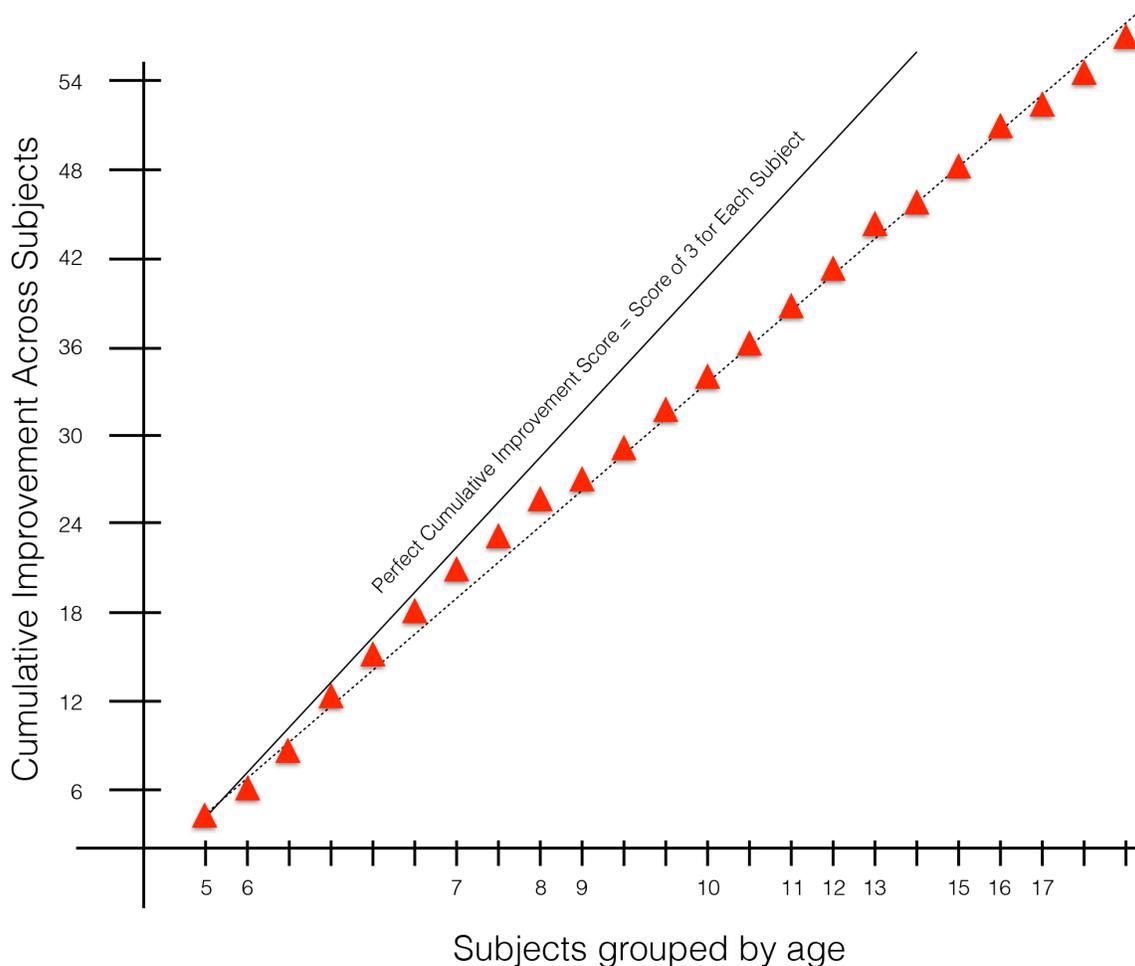


Figure 7. Changes in acuity and stereopsis over time graphed as log minimum angle of resolution (in minutes of arc)



**Figure 8.** Cumulative change score distributed across ages

Possible scores were 0 if none of these three factors improved (but as noted in the first Eyetronix Flicker Glass study, those subjects who didn't improve in acuity improved in stereopsis and vice versa, so there were no absolute non-improvers in this study), 1 if one factor improved, 2 if two improved, and if all three factors improved, a perfect score of 3 was given. These cumulative scores for each subject were then individually distributed by age, each new subject added to the last. What this scoring shows is that there is no drop-off in improvements with age, through the top age in this study of 17 years old. An age ceiling for improvement in these functions would cause the graph to plateau at that ceiling-age. The graph does vary slightly from a straight line and does not show perfection (all subjects with a perfect score of 3) for all three functions, but it does not plateau at any age. If we define improvement in amblyopia to include stereopsis in its clinically tested forms, age should not be an excluding factor for treating amblyopia with rapidly alternating visual flicker. This all underscores an older literature review suggesting less concern about age in amblyopia treatment is necessary (Birnbaum,

Koslowe, Sanet, 1977).

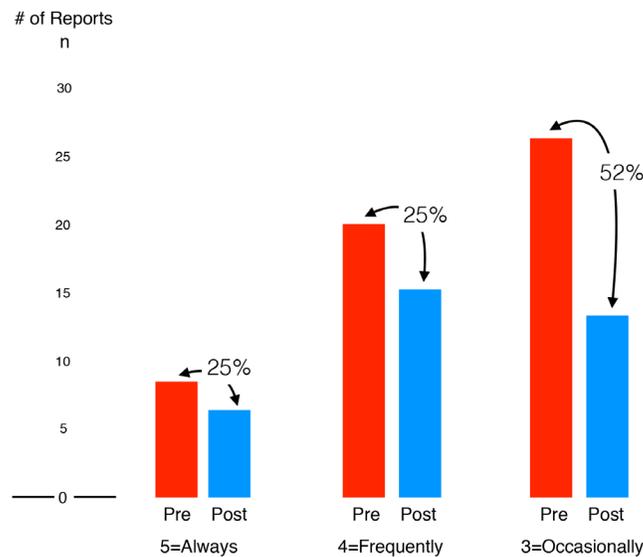
### Results: Symptomatology

Figure 9 shows the questions about symptoms given pre- and post-therapy to subjects and their parents. This question list was not pre-validated as a stand-alone questionnaire prior to the Eyetronix study, but does have considerable overlap with the fully validated COVD QOL questionnaire (Vaughn, Maples, Hoenes, 2006), the School Screening adaptation of the COVD QOL (Rasch analyzed) (Baker, Hong, Pin, 2012), and the questions are fully represented in the 16-question list of reading-specific questions in the COVD QOL questionnaire (Hussey, 2012). Looking at those symptoms as a whole across the group, pre-to post-therapy, symptoms in this group of amblyopes decreased significantly ( $p < 0.005$ , paired t-test). This is the first report of changes in reading symptoms with amblyopia treatment. This lends some support to the thesis that the therapy improved binocularity in these subjects. Hussey has shown significant improvements in reading symptoms with decrease in suppression.

Please rate these visual symptoms for your child, from 1 to 5, 1=never, 5=always

- 1) Blurry vision at near
- 2) Double vision
- 3) Headaches, eyestrain, or discomfort while reading
- 4) Loses concentration when reading
- 5) Words run together, jump or swim when reading
- 6) Skips or repeats lines when reading
- 7) Avoids near work and reading
- 8) Dizziness or nausea with near work
- 9) Head tilt or closes one eye when reading
- 10) Poor reading comprehension

**Figure 9.** Cumulative change score distributed across ages



Changes in reports of significant symptoms pre- to post-therapy

**Figure 10.** Cumulative change score distributed across ages

Specifically intermittent central suppression in non-amblyopes. However, if improved binocularity can be defined in part by reduced suppression or improved response to clinical stereopsis testing, and if improved binocularity in non-amblyopes improved reading symptoms (Hussey, 2012; Hussey, 2015a) then taken together this suggests an association between reduced suppression, improved binocularity, and

reduction in reading symptoms. Perhaps we should expect improvement in symptoms of reading difficulty to result with improved binocularity. Alternatively, this might suggest an improvement in general visual function or ocular skills with the therapy. Another suggestion for future research is to look at fixation and saccadic behaviors during reading pre- and post-therapeutic use of rapid alternation. A preliminary study

on non-amblyopes suggests improvements in fixation and saccade accuracy with 4 Hz alternation during reading (S-N. Yang, personal communication, March 26, 2015). Whatever the reason, the point remains: this is the first time such a link between improving amblyopia and improved reading symptomatology has been reported.

Figure 10 shows changes in the “worst” responses on the symptoms questionnaire, that is the symptom happens always, frequently or occasionally. Those three categories of symptoms decreased 25, 25 and 52 percent respectively.

These changes in reading symptomatology beg another comparison to at least one other current amblyopia therapy—not to penalization, but to perceptual learning. Perceptual learning uses repeated exposure to a perceptual task (commonly approximately 3500, but sometimes 20,000 to 35,000 trials) to improve acuity in amblyopia, and lately in infantile nystagmus. A criticism has been lack of transfer, or generalization of gains to behaviors beyond the training stimulus (Kiorpes, 2015), Huurneman, Boonstra, Goossens, 2016a & b). The improved reading symptoms reported here might be deemed surprising by some with familiarity with perceptual learning, especially with no reading-specific training as part of the Eyetronix study.

Also reported in the prior paper (Vera-Diaz, Moore, Hussey, etc (2016), were spontaneous reports by the children in treatment of improvements in sports: hockey, field hockey, and ping-pong. Although a literature search did not uncover them, perhaps specific tests for generalization after amblyopia therapy exist. But, if those tests do not exist, certainly these spontaneous reports and improved reading symptoms very strongly suggest changes beyond acuity into the “real world.” Further, consider the potentially large number of repetitions in perceptual learning paradigms (think about 5-year-olds and thousands of trials) versus the ability to use Eyetronix Flicker Glass for books, coloring, or playing with Legos. Those activities certainly have some value in the real world of a child.

### **Discussion: When is a monocular stimulus actually a binocular stimulus?**

We might define binocularity as both eyes having intact visibility of central images that are combined into one percept without loss of visibility of either central image, with that combined intact visibility sustained over time (Hussey, 2015). However, we lack

a recognized “gold standard” test for binocularity as defined. Often stereopsis is used as a test of binocularity—perhaps more accurately as a surrogate for binocularity (Medicinenet.com, 2016; Blake & Wilson, 2011). Clinical stereopsis tests are limited as complete descriptors of binocularity, first in not being threshold tests, but rather measurements in discreet steps. Further, if we have defined binocularity as a visual function maintained over time, stereopsis is not typically evaluated over time in the same sense that a heart monitor might provide continual readouts over time, but is a “snapshot” only at different clinic visits. Stereopsis has no continuous readout over seconds, minutes, hours, or days. It is usually a number recorded at most, as in this study, every three weeks. So, in conditions such as intermittent central suppression, where sensation varies over time, stereopsis gives an incomplete measure of binocularity.

If we acknowledge its weaknesses, then use stereopsis as it is often used as a surrogate for binocularity, the next question is how does a rapidly directly alternating visual stimulus as in this Eyetronix study drive binocularity and improve this measure of binocularity? Since the liquid crystal lenses occlude either eye alternately, the stimulus is actually a series of very short (in this study just over 71 msec) monocular stimuli. So, how does a rapidly alternating monocular stimulus induce or increase binocularity?

Hypotheses to explain this might fall into three basic groups, and the closest-to-correct hypothesis may be an amalgam of some or all of these: 1) facilitation of the visual signal to the cortex, 2) correlations of the 71 msec open timing to known visual functions, 3) viewing on-off flicker as a series of transient on-off stimuli (on a stimulus level, time-dependent brightness changes) equivalent to a pooled, non-directional motion stimulus (Borst, Egelhaaf, 1993; DeHaan, Lee, Norstrom, 2013) perhaps best viewed in combination with masking theories.

An early hypothesis of facilitation was championed by Allen and based on the Bartley phenomenon (Allen, 1995). At about a 9 Hz flash rate, brightness of lights observably increases, suggesting facilitated transmission to the cortex. Allen’s improved transmission to the cortex is certainly an appealing explanation, although with an alternating stimulus we still have to explain improvements in a binocular function like stereopsis. The Bartley phenomenon is observable, but this explanation would not allow other alternation rates to be useful.

Timing correlations offer two possibilities to explain

changes. The 71 msec open time of 7 Hz was suggested by Schor et al. as matching the stimulus asynchrony that supports masking, presumably in the cortex (Schor et al., 1976). And, Schor et al.'s data showed that binocular acuity in amblyopia improved best at 7 Hz. So, the suggestion was logical that masking, perhaps as the mechanism of suppression, was being reduced at 7 Hz. Only going that far leaves some of the mechanism unexplained since the anti-masking stimulus is equally presented to both sides. So, how does matching the stimulus asynchrony of masking experiments bilaterally reduce masking thought to occur on one side? If Schor et al. is correct that suppression is from masking and reduction in masking reduces suppression, then an increase in stereopsis is understandable. In this view, although the stimulus is an alternating monocular stimulus, the effect is a binocular effect. Reduced stereopsis is considered a function of suppression (and masking), so could improve.

Another hypothesis based on timing correlations has been suggested by Yang (2015). That is that improved binocular coordination is possible when the visual system clearly registers the difference between left and right images: When a flicker rate is too low, the left and right images will encode images formed during different fixations; no binocular fusion is expected from monocular images in different fixation positions. When a flicker frequency is too high, monocular images are either fused or suppressed at the cortical level. The average fixation time between saccades is about 225 msec. At 7 Hz, or 71 msec per open period, each fixation might have two to three presentations of the package of information for the brain to link together at that position. But, different frequencies such as 5 Hz (100 msec per open period) could still provide two image packages in a fixation to link together.

The fourth hypothesis is an explanation of the stimulus based in visibility, potentially positioning an alternating stimulus as functionally a binocular stimulus. To picture sustained visibility by analogy, consider the mouse and the computer: If the computer mouse is moved, the screen stays "awake." Stop moving the mouse and the screen goes blank—the computer switches to screen-saver. That is a picture of how visibility is maintained, with the visual percept the computer screen and visual motion or flicker as the computer mouse (for a fuller discussion of the possible role of visibility in suppression, (Hussey, 2015b). An explanation based in visibility may in part support Schor et al.'s sugges-

tion that masking was involved when he alternated at 7 Hz.

The visibility hypothesis positions anti-suppression as a function of stimuli that drive sustained visibility of a target. Vision science shows increasing visibility of a target especially with repetitive stimulation to motion-detecting neurology. For example, with repetitive flashing near 5 Hz, termed continuous flash suppression, a target to one eye can be made to dominate the other eye's target (Tsuchiya, Koch, Gilary, & Blake, 2006). Also, at that pace, temporal summation and/or temporal fusion (Kauffman, 1974; Rieiro, Ledo, Martinez-Conde, & Macknik, 2012) will merge flashes, so that in the special case of rapid alternation both sides will be continuously driven by the "barrage of transients" that forces visibility in continuous flash suppression paradigms. Temporal summation (or temporal fusion) provides the carry-over in the central vision, similar to the smooth action in a movie, to keep both sides driven to remain visible, even though the stimulus is actually alternating (Kauffman, 1974; Rieiro et al., 2012).

At least seven parts may be involved in this visibility-based explanation:

Visual images are kept alive via the transient-sensitive neurology; the polar opposite to this is that lack of motion signal produces (Troxler) fading of visual perception at or near the lateral geniculate nuclei (LGN) (Hussey, 2015b). Even though we think of the transient-sensitive neurology as detecting motion, abruptly turning an image "on" is a particularly strong stimulus to transient-detecting neurology (Martinez-Conde; Macknik, & Hubel, 2004). Turning a stimulus "off" is the important signal in masking experiments and also in temporal fusion (Rieiro et al., 2012; Macknik & Livingstone, 1998). Abrupt "on" or "off" of a stimulus increases the number of spikes in the transient-sensitive neurology for about 100 msec (Tsuchiya et al., 2006). Repetitive flashing of one eye's image can override the other eye's image for extended periods (Tsuchiya et al., 2006). Temporal summation of flashed images lasts about 100 msec, and probably occurs in the cortex. Temporal summation is thankfully useful in seeing smooth motion in movies (Kauffman, 1974).

According to Wiesel and Hubel (1965) competition between monocular inputs is a crucial factor contributing to plasticity of the developing visual system. These seven stimulus characteristics, potentially working as a cohesive mechanism to treat suppres-

sion will be developed in more detail in the appendix.

## Conclusion

Paradoxically, rapid alternation of visual stimuli (alternating flicker) has improved stereopsis, a two-eyed—maybe the term “binocular” could be used—phenomenon as well as improving acuity in amblyopic eyes in this group of 23 children. Flicker can be considered motion in stimulus form, driving visibility at the LGN and inhibiting masking at the cortex. By alternating and taking advantage of temporal summation, we are both driving the visibility of the two sides against each other, satisfying Wiesel and Hubel’s demand for competing inputs to produce plasticity, as well as driving both sides simultaneously, or “binocularly.” The neural plasticity produced by this bilateral stimulus is the likely culprit in improving binocular function in these children.

Despite driving visibility and overriding masking, normal acuity is not immediately produced. Assuming preventing drop-out of visibility at the LGN might be a significant part of the treatment, the converse in visual development is that the same signal dropout must also be considered as a factor in producing the acuity defect. Dropout of visibility early in the visual development of each of these children would negatively affect acuity development on a synapse level since it would be unlikely that the image would somehow regenerate beyond the drop-out point—possibly the LGN. Neurons beyond the LGN may be deprived of a signal during their early development. So, when we have residual acuity deficits, it is possible that what we’re left with reflects a form of deprivation—internally “created” deprivation from signal dropout prior to the cortex.

A surprising additional result of treatment was the positive effect on reading symptomatology. This is the first amblyopia trial to report such an effect and suggests some commonality with, or perhaps adds legitimacy to studies suggesting improved binocularity has positive effects on reading (Hussey, 2012; Hussey, 2015a).

Future studies should expand numbers of subjects and look at how much improvement can be expected with further rounds of EFG therapy, both with and without prior penalization therapies. How much additional effort is necessary for more improvement should be examined. Those efforts should include expansion of the age-range since age, beginning

amblyopic acuity, and prior penalization all were ruled out as exclusions for amblyopia therapy with EFG. Also, looking at fixation and saccadic behaviors during reading pre- and post- therapeutic use of rapid alternation use might help with understanding the role of fixation in amblyopia (Shaikh, Otero-Millan, Kimar, Ghasia (2016). A comparison of generalization of post-therapy improvements compared to perceptual learning might clarify what kinds of improvements to expect with both. But, in answer to the question “When is a monocular stimulus actually a binocular stimulus?” When that monocular stimulus is a square-wave alternation at the appropriate frequency.

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## References

- Allen, M. J. (1995). Understanding suppression. *Journal of Optometric Vision Development*, 26(2), 50-52.
- Bakar, Abu, Nurul Farhana, Chen Ai Hong, and Goh Pik Pin 2012COVD-QOL Questionnaire: An Adaptation for School Vision Screening Using Rasch Analysis. *Journal of Optometry* 5(4): 182–187.
- Birch, Eileen E., Simone L. Li, Reed M. Jost, et al. (2015). Binocular iPad Treatment for Amblyopia in Preschool Children. *Journal of American Association for Pediatric Ophthalmology and Strabismus* 19(1): 6–11.
- Birnbaum, M. H., Koslowe, K., & Sanet, R. (1977). Success in amblyopia therapy as a function of age: A literature survey. *Optometry and Vision Science*, 54(5), 269-275. <https://doi.org/10.1097/00006324-197705000-00001>
- Blake, R., & Wilson, H. (2011). Binocular vision. *Vision Research*, 51(7), 754-770. <https://doi.org/10.1016/j.visres.2010.10.009>
- Borst, A., & Egelhaaf, M. (1993). Detecting visual motion: Theory and models. In *Visual motion and its role in the stabilization of gaze*.

- de Haan, R. de, Lee, Y.-J., & Nordström, K. (2013). Novel Flicker-Sensitive Visual Circuit Neurons Inhibited by Stationary Patterns. *Journal of Neuroscience*, 33(21), 8980–8989. <https://doi.org/10.1523/JNEUROSCI.5713-12.2013>
- Hess, R. F., Thompson, B., & Baker, D. H. (2014). Binocular vision in amblyopia: Structure, suppression and plasticity. *Ophthalmic and Physiological Optics*, 34(2), 146-162. <https://doi.org/10.1111/opo.12123>
- Hussey, E.S. (2002). Binocular visual sensation in reading II: Implications of a unified theory. *Journal of Behavioral Optometry*, 13(3):66-70.
- Hussey, E.S. (2003). Speculations on the Nature of Motion with Optometric Implications. *Journal of Behavioral Optometry*, 14(5):115-119.
- Hussey, E. S. (2012). Remote treatment of intermittent central suppression improves quality of life measures. *Optometry, Journal of the American Optometric Association*, 83(1), 19-26. <https://doi.org/10.1016/j.optm.2011.05.009>
- Hussey, E. S. (2015). Increases in binocularity periods with treatment of intermittent central suppression contradict suppression as solely inhibitory. *Optometry and Visual Performance*, 3(1).
- Hussey, E. S. (2015). Is anti-suppression the quest for visibility? *Optometry and Visual Performance*, 3(1).
- Huurneman, B., Boonstra, F. N., & Goossens, J. (2016a). Perceptual learning in children with infantile nystagmus: Effects on visual performance. *Investigative Ophthalmology & Visual Science*, 57, 4216–4228. <https://doi.org/10.1167/iovs.16-19554>
- Huurneman, B., Boonstra, F. N., & Goossens, J. (2016b). Perceptual learning in children with infantile nystagmus: Effects on reading performance. *Investigative Ophthalmology & Visual Science*. 57,4239–4246. <https://doi.org/10.1167/iovs.16-19556>
- Kaufman, L. (1974). *Sight and Mind: An Introduction to Visual Perception*. New York: Oxford University Press.
- Kiorpes, L., & Mangal, P. (2015). “Global” visual training and extent of transfer in amblyopic macaque monkeys. *Journal of vision*, 15(10), 14-14. <https://doi.org/10.1167/15.10.14>
- Li, S. L., Reynaud, A., Hess, R. F., Wang, Y. Z., Jost, R. M., Morale, S. E., ... & Birch, E. E. (2015). Dichoptic movie viewing treats childhood amblyopia. *Journal of American Association for Pediatric Ophthalmology and Strabismus*, 19(5), 401-405. <https://doi.org/10.1016/j.jaapos.2015.08.003>
- Macknik, S. L., & Livingstone, M. S. (1998). Neuronal correlates of visibility and invisibility in the primate visual system. *Nature neuroscience*, 1(2). <https://doi.org/10.1038/393>
- Macknik, S. L., & Martinez-Conde, S. (2004). Dichoptic visual masking reveals that early binocular neurons exhibit weak interocular suppression: Implications for binocular vision and visual awareness. *Journal of Cognitive Neuroscience*, 16(6), 1049-1059. <https://doi.org/10.1162/0898929041502788>
- Martinez-Conde, S., Macknik, S. L., & Hubel, D. H. (2004). The role of fixational eye movements in visual perception. *Nature reviews. Neuroscience*, 5(3), 229. <https://doi.org/10.1038/nrn1348>
- Odom, V. J., Hoyt, C. S., & Marg, E. (1982). Eye patching and visual evoked potential acuity in children four months to eight years old. *Optometry & Vision Science*, 59(9), 706-717. <https://doi.org/10.1097/00006324-198209000-00002>
- Pediatric Eye Disease Investigator Group (2005). Randomized trial of treatment of amblyopia in children aged 7 to 17 years. *Archives of ophthalmology*, 123(4), 437-447. <https://doi.org/10.1001/archophth.123.4.437>
- Pokorny, J. (2011). Review: Steady and pulsed pedestals, the how and why of post-receptoral pathway separation. *Journal of Vision*, 11(5), 7–7. <https://doi.org/10.1167/11.5.7>
- Rieiro, H., Ledo, M., Martinez-Conde, S., & Macknik, S. (2012). The Temporal Fusion Illusion and its neurophysiological correlates. *Journal of Vision*, 12(9), 132-132. <https://doi.org/10.1167/12.9.132>
- Schor, C., Terrell, M., & Peterson, D. (1976). Contour interaction and temporal masking in strabismus and amblyopia\*. *Optometry and Vision Science*, 53(5), 217-223. <https://doi.org/10.1097/00006324-197605000-00001>
- Shaikh, A. G., Otero-Millan, J., Kumar, P., & Ghasia, F. F. (2016). Abnormal fixational eye movements in amblyopia. *PloS one*, 11(3), e0149953. <https://doi.org/10.1371/journal.pone.0149953>
- Spierer, A., Raz, J., BenEzra, O., Herzog, R., Cohen, E., Karshai, I., & BenEzra, D. (2010). Treating amblyopia with liquid crystal glasses: a pilot study. *Investigative Ophthalmology & Visual Science*, 51(7), 3395-3398. <https://doi.org/10.1167/iovs.09-4568>
- Tsuchiya, N., Koch, C., Gilroy, L. A., & Blake, R. (2006). Depth of interocular suppression associated with continuous flash suppression, flash suppression, and binocular rivalry. *Journal of Vision*, 6(10), 6-6. <https://doi.org/10.1167/6.10.6>
- Vaughn W, Maples W, Hoenes R. (2006). The association between vision QOL and academics as measured by the College of Optometrists in Vision Development QOL questionnaire. *Optometry* 77, 116-123.
- Vera-Diaz, F., Moore, B., Hussey, E. S., Srinivasan, G., & Johnson, C. (2016). A flicker therapy for the treatment of Amblyopia. *Vision Development & Rehabilitation*, 2(2), 105-14.
- von Noorden, G. K., & Campos, E. C. (Eds.). (2002). *Binocular Vision and Ocular Motility; Theory and Management of Strabismus*. Mosby, St. Louis.

Wang, J., Neely, D., Galli, J., Schliesser, J., Damarjian, T., Smith, H., ... & Plager, D. (2015). A Randomized trial of Amblyz-TM intermittent occlusion glasses vs traditional patching for treating children with moderate unilateral amblyopia. *Investigative Ophthalmology & Visual Science* 56(7).

Westheimer, G. (2013). Clinical evaluation of stereopsis. *Vision research*, 90, 38-42. <https://doi.org/10.1016/j.visres.2012.10.005>

Wiesel, T. N., & Hubel, D. H. (1965). Comparison of the effects of unilateral and bilateral eye closure on cortical unit responses in kittens. *Journal of neurophysiology*, 28(6), 1029-1040.

## Appendix

When is a monocular stimulus actually a binocular stimulus? And how does a 7Hz flicker differ from occlusion?

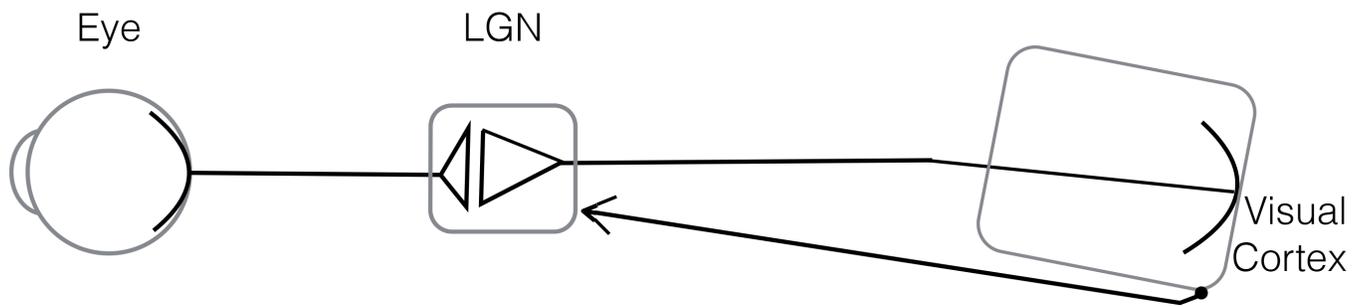


Figure A1.

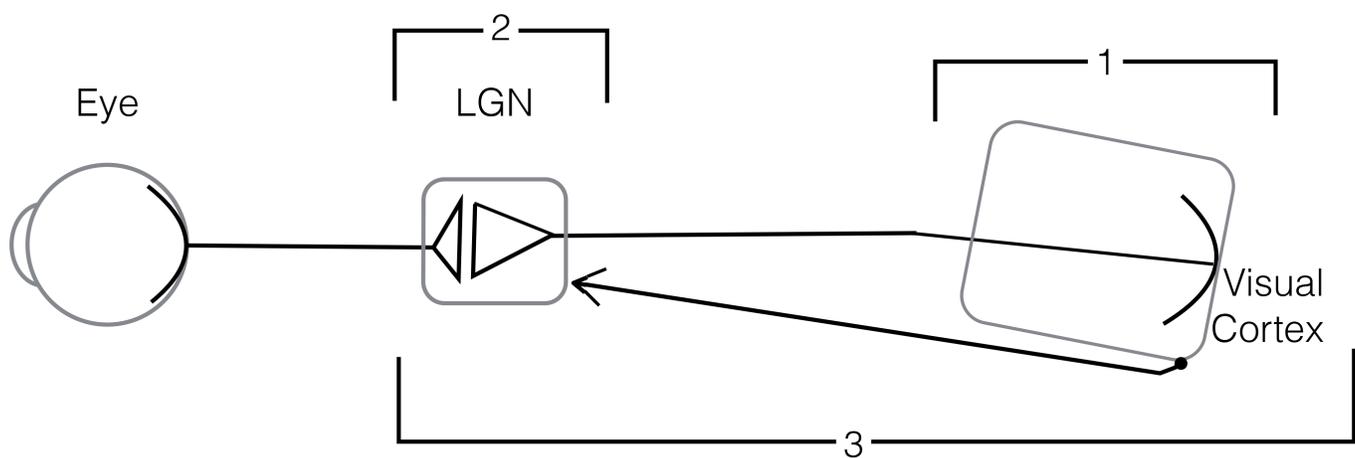
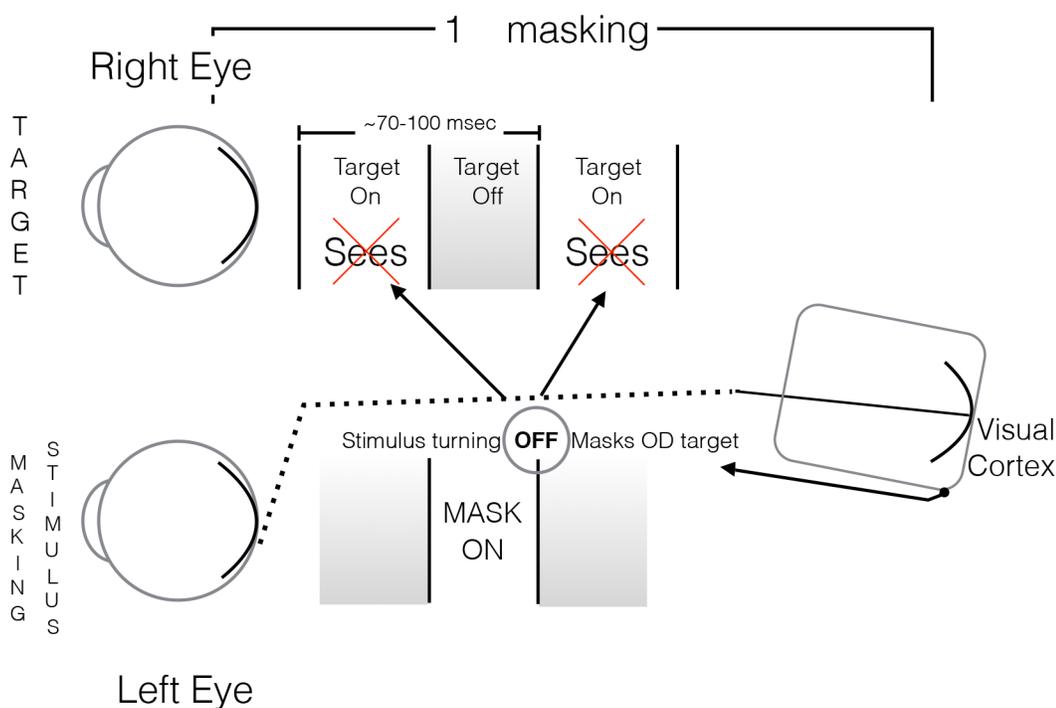


Figure A2.

A bare-bones schematic of the parts of the visual system we're discussing might look like Figure A1. The arrow from the cortex back toward the LGN represents the perceptual filling-in that occurs in a Troxler's fade (Hussey, 2015b). The cortex calculates a fill-in that is surround; that is, a visual percept that is a color and texture that fills in an area left blank by loss of the visual signal from perceptual fading. That fill-in is strong enough that it can create rivalry with the percept from the non-faded eye (Hussey, 2015b). The strength of that fill-in is something clinical science has not recognized. This schematic will be discussed in three segments to show how rapid alternation might affect binocularity: 1. masking, 2. visibility at the LGN, 3. temporal summation or image carry-over (Fig A2).

### 1. Masking (and Visibility)

On- and off-set of a stimulus increases neural activity keeping images "alive," that increase in neural activity being around 100 msec. The eyes are seldom stationary, so visual stimuli move on and off photoreceptors and receptive fields constantly, and it is the transient neurology responding to that on- and off- that keeps the image awake (Macknik and Livingstone, 1998). On-set may be a particularly strong stimulus, creating seven times the neural activity of a moving bar stimulus (Martinez-Conde, Macknik, Hubel, 2004). But, off-set of the target also works to keep vision awake, and again via the transient-detection motion neurology (Kaufman, 1974).



**Figure A3.**

Masking of—or rendering invisible—a target stimulus requires interfering with those on- and off-set signals in the visual transient neurology (Martinez-Conde, Macknik, Hubel, 2004; Macknik, Martinez-Conde, 2004). Masking can be produced between eyes; that is, an image in one eye can mask or essentially eliminate the image in the other eye, a concept held to be an integral part of amblyopic suppression and also suggesting this type of masking is cortical (Schor, Terrell, Peterson, 1976; Macknik, Martinez-Conde, 2004). One caution here: Evidence suggests inter-ocular masking at the cortex is actually weak (Macknik, Martinez-Conde, 2004). Masking on the same side is much stronger, suggesting perhaps an interrelationship to driving visibility (see section 2, Visibility).

The on-set transient of a target is most effectively negated by turning a masking stimulus off just before the target stimulus is shown. The target off-set transient signal is most effectively negated by turning a masking stimulus off about 100 msec after the target is turned off (Figure A3).

Applying this understanding to a continuously alternating on-off visual signal as in the current study, one possibility is that alternate signals might alternately mask the signal on the other side, producing continuous masking, that is, eliminating the visual signal cortically on both sides rendering both sides invisible (ignoring for the moment how weak interocular masking might be). But, experience with these subjects as well as others (Schor, Terrell, Peterson, 1976; Hussey, 2012), shows that subjects can see through the alternating liquid crystal lenses. This suggests masking of the stimulus might actually be negated in rapid alternation. Therefore, rapid alternation does deliver a non-masked bilateral stimulus to the cortex. However, it is still an alternating stimulus. Fig. A4 shows a schematic of how the offset neural signal on one side might negate the masking actions of the other: When one side's stimulus turns "off" it should have masking effects on the other side's prior stimulus (open period) as well as the immediately following stimulus (second open period). However, the same masking effect is occurring with the opposite side's turning-off, or offset, acting toward its fellow eye. So, the combination of opposing masking stimuli should mask both sides simultaneously, or if the subject can see with the flicker, suggests the opposing stimuli negate each other. The consequence at the cortex, since amblyopic masking has been suggested to occur in the cortex, is a non-maskable stimulus at the cortex. Suppression, if

it is at least in part masking at the cortex, is negated bilaterally, and the visual cortex is “driven” by that bilateral signal.

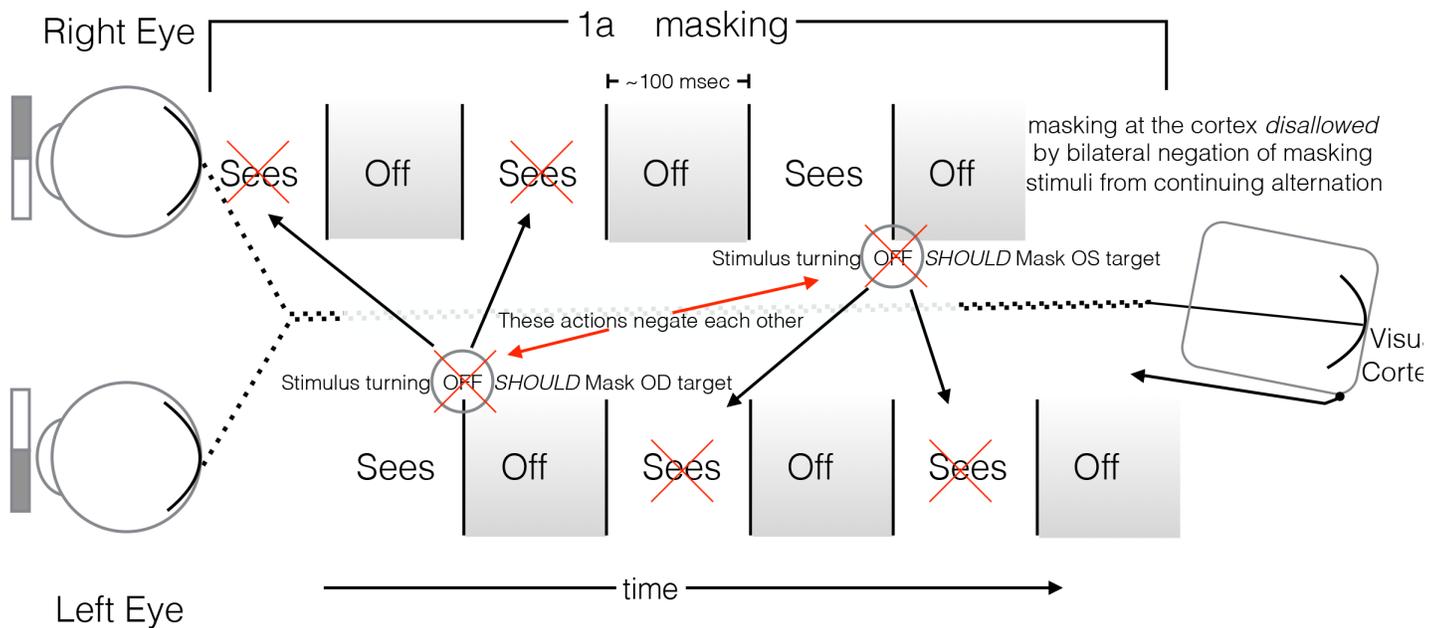


Figure A4.

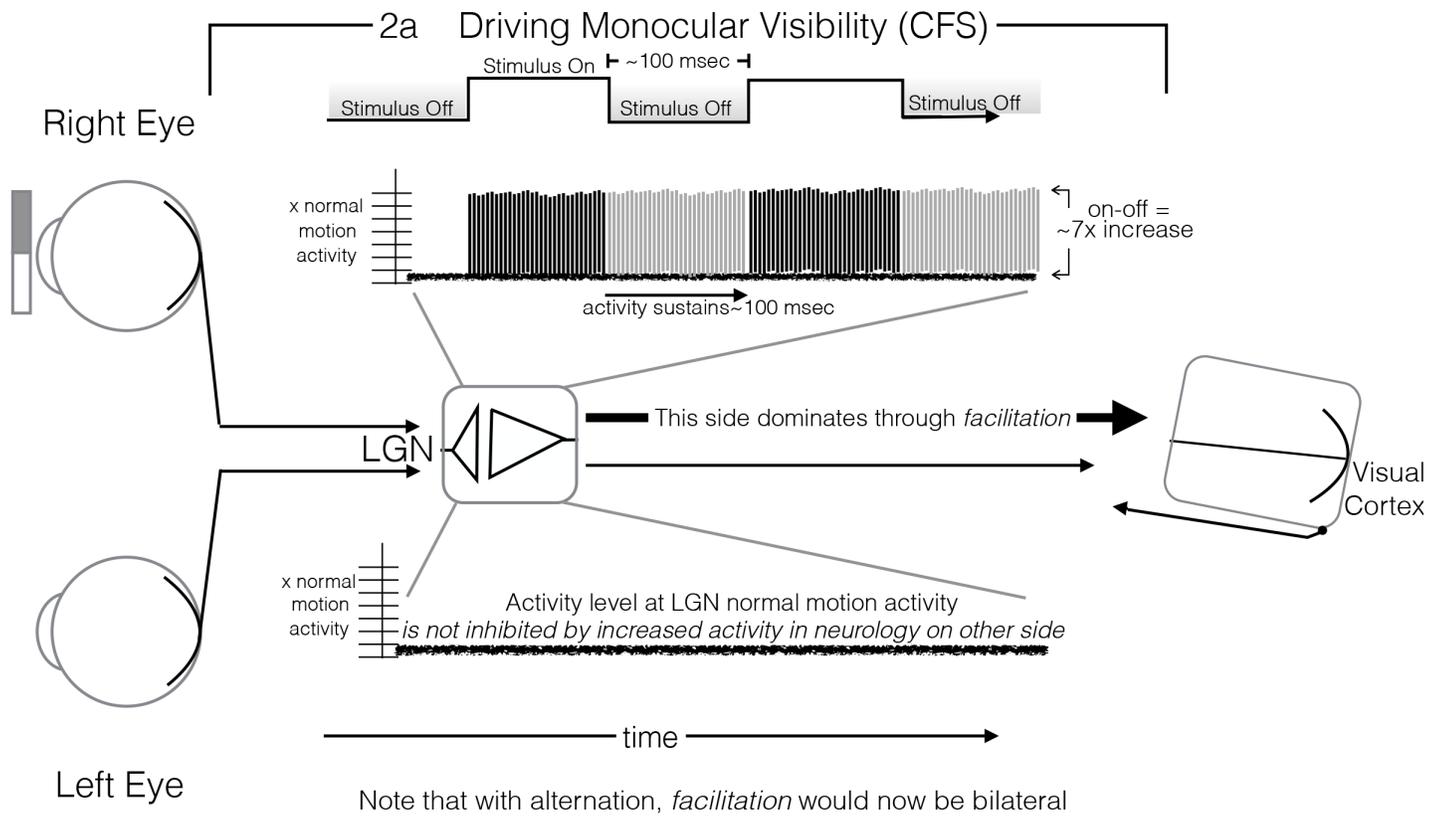


Figure A5.

## 2. Visibility and perceptual filling-in (and continuous flash suppression)

Visibility of visual percepts is facilitated at the LGN by visual motion. Lack of visual motion produces fading at the LGN, called Troxler's Perceptual Fading. Motion keeps the visual signal "awake" and in normal sight stimulus motion happens constantly across receptive fields as eyes are constantly moving. For those receptive fields, visual motion is on-off as visual edges move across receptive fields (Martinez-Conde, Macknik, Hubel, 2004; Macknik, Livingstone, 1998). The vision science uses the term "spatio-temporal edges (Macknik, Martinez-Conde, 2004). On-off flicker of the whole visual field is a transient-neurology stimulus, basically a pooled, non-directional motion stimulus (Borst, Egelhaaf, 1993; deHaan, Lee, Nordstrom, 2013; Hussey 2003).

Repetitive square-wave flashing at 5 Hz (or 7 Hz) is a positive drive to visibility on the flashed side. That is, on-off flashing at 5 Hz especially, can dominate the non-flashed side, in experiments on continuous flash suppression, for several seconds (Figure A5). It is the "sustained barrage of transients" that creates that dominance, perhaps through a cooperative inhibition [of the other side] among multiple flashes (Tsuchiya, Koch, Gilroy, Blake, 2006). But when the other, non-flashed side does show through, its period of dominance does not change, suggesting continuous flash suppression positively pushes visibility on the flashed side without immediately changing any inhibitory behavior on the other side. This may be a key observation when we consider amblyopia as one-sided, but we address it with an equal stimulus to both sides. Both sides are "driven" to strengthen synapses, versus the penalization of the stronger side with patching. In rapidly alternating flicker, the weaker side improves without penalizing the stronger side; the weaker side may just have more room to grow to approach normalcy, especially in earlier developmental epochs.

As the phrase "barrage of transients" implies the stimulus is carried in the transient-detecting neurology, the motion-sensing Magnocellular pathway. If this drive to dominate with 5 (or 7) Hz flashing is now alternated, Wiesel and Hubel's demand for one visual side to be driven against the other for plasticity—and in this study to develop binocularity—is now satisfied, apparently with stimulus masking overridden (Wiesel, Hubel, 1965, above). But, foundationally, visibility is driven by the on-off-on flicker stimulus and, with alternation, both sides are driven to be visible and both sides are driven to dominate, in essence, simultaneously. The term "visible" aptly suggests this driving of the motion neurology serves to keep the Parvocellular detail pathway "awake." Tsuchiya has suggested at five flashes neural learning occurs, explaining lasting changes in visual behavior (Tsuchiya, Koch, Gilroy, Blake, 2006). Figure A6 is a schematic of flicker as a motion stimulus, showing individual receptive field responses to a moving *spatial* edge as very much the same as a moving *temporal* edge over a broader area (Hussey, 2003). Note that both conditions stop or reverse the perceptual fill-in from the cortex. Further, with the flickering pooled, non-directional motion stimulus, adjacent neurons are driven to "fire together" so should "wire together," strengthening synapses.

## 3. Temporal summation (and masking/temporal fusion)

Added to this bilateral but alternating stimulus for visibility is temporal summation. Temporal summation is a "carry-over" of a flashed visual stimulus, suggested to last about 100 msec. This very-handy-for-the-movie-industry visual input carry-over over time will merge two flashed stimuli separated by about 100 msec (Kaufman, 1974). Flashing closer in time than 100 msec might improve temporal summation.

At least some evidence suggests temporal summation is cortical, and Parvocellular, but apparently the science is a bit unsettled in that a similar phenomenon, temporal fusion, may be masking-related (Rieiro et al., 2012; Pokorny, 2011). So, Magnocellular stimuli prevent masking and drive visibility, both subserving sustained detail visibility and perhaps fused-over-time sensation, which the Parvocellular pathway holds over time as simultaneous visual inputs. The stimulus presented to the cortex, then, despite alternating at its source, may well be summated as bilateral, maybe "binocular," at the cortex. This also leaves open the possibility that Yang is correct that bilateral encoding of images can occur now that both sides are present during a fixation.

## Summary

In the surprisingly complex visual stimulus that we term alternating flicker or rapid alternation, then, both eyes' images are being driven to stay visible by a very strong (7x the strength of a simple moving bar stimulus) non-directional, pooled motion-neurology stimulus while temporal summation (and/or temporal fusion) adds stimuli

together without interference through masking of one eye against the other. Oddly enough, as we look at overriding masking, temporal summation and carry-over of stimuli, and the stimulus to motion neurology that on-off flicker is, rapid alternation at the appropriate frequency may not just be a strong anti-suppression visual stimulus, but, paradoxically may be one of the few actually completely bilateral— “binocular”—stimuli available to rehabilitate the suppression of the central vision. As a binocular stimulus, with plasticity driven by the two sides driven against each other, neurons are firing together, therefore they are wiring together. With that repetitive bilateral visual stimulus, the cortex now has the opportunity to develop actual binocular summation (Hussey, 2002).

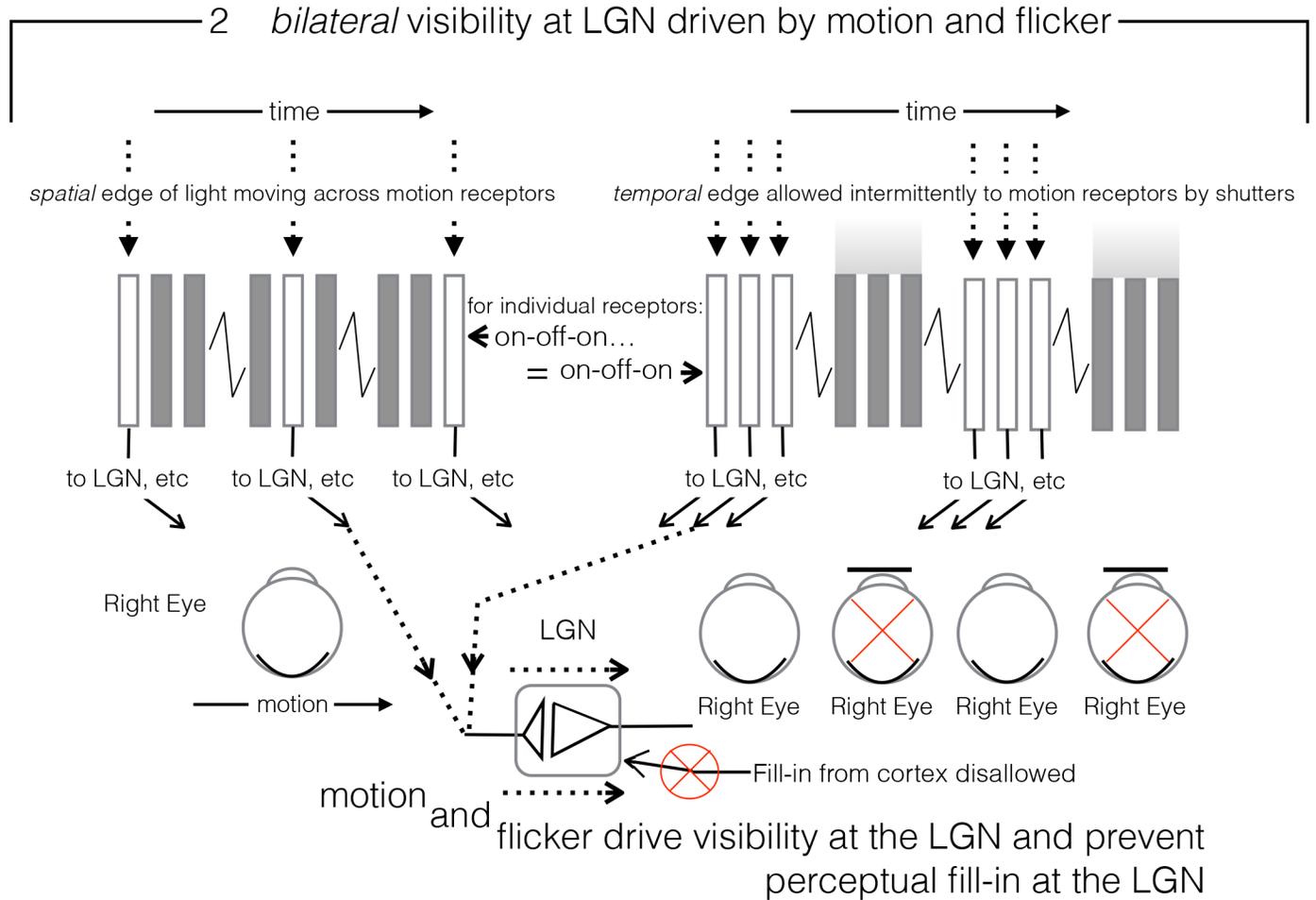


Figure A6.

