

The Role of Suppression in Amblyopia: A Literature Review

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ABSTRACT

Amblyopia is a developmental vision disorder typically treated by occlusion therapy. Recent research suggests suppression is closely linked to deficits in visual acuity and stereopsis, and considerations regarding treatment should include reducing interocular suppression. The aim of this literature review is to provide an analysis of vision science research published within the past 5 years which investigates the role of suppression in amblyopia and discuss the implications to clinical practice.

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Recent research suggests binocular cells are present in the visual cortex of amblyopes, but are rendered functionally monocular by the development of a GABA inhibitory network. Suppression, or inhibition, can be quantified in both strabismic and anisometropic amblyopia by reducing contrast to the fixating eye until simultaneous perception occurs. In both strabismic and anisometropic amblyopes, higher levels of suppression are associated with lower visual acuities and absent stereopsis. In addition, the evaluation and treatment of suppression is important for the effective treatment of amblyopia, particularly in patients with deep suppression, as they may not respond as well to occlusion therapy. Variable contrast anti-suppression training improves visual acuity, reduces suppression, and improves stereopsis in both children and adults. No age trends were found, which suggests that significant neuroplasticity exists in the adult brain, and suppression may not need to be treated differently in children and adults. Incorporating variable contrast into anti-suppression therapy techniques may enhance treatment progress and promote the development of stereopsis. Existing optometric vision therapy techniques already used to treat suppression are described. Additionally, some of the computer-based tools possess variable contrast stimuli presentation capabilities. Further research is needed to evaluate the optimal length of treatment and long term stability of gains in visual acuity and stereopsis using this treatment strategy.

INTRODUCTION

The American Optometric Association defines amblyopia as a reduction in visual acuity in the absence of pathology, with an amblyogenic factor occurring before age 6 years.¹ Amblyogenic factors include uncorrected refractive error, constant unilateral strabismus, and form deprivation. Prevalence of amblyopia is estimated at 2-5%

of the population, with the majority of cases being strabismic, anisometropic, or mixed. In addition to reduced visual acuity, amblyopes can have inaccurate accommodation, reduced contrast sensitivity, unsteady fixation, poor oculomotor skills, reduced binocularity, spatial uncertainty, and discrimination of motion.² Strabismic amblyopes have abnormalities in contour interaction, or increased visual crowding, and a tendency to undercount visual features.³ Anisometropic amblyopes have worse contrast sensitivity compared to strabismic amblyopes.³

Clinically, amblyopia is typically treated with the optimal refractive error correction and occlusion therapy. However, treatment outcomes are affected by poor compliance with the prescribed patching therapy. After patching is discontinued, regression in visual acuity can be observed.⁴ The Pediatric Eye Disease Investigator Group (PEDIG) found a reduction in maximum post-treatment visual acuity in 21% of children at one year follow up.⁴ Residual amblyopia of 20/32 or worse is present in 54% of 10 year old children with history of amblyopia treatment.⁵ Occlusion therapy has limited efficacy in adults, and is rarely attempted in clinical practice.⁶ In addition, occlusion therapy is designed to treat the monocular deficits in amblyopia, and does not always result in improved binocularity.⁷

Recent research suggests binocular cells present in the visual cortex of amblyopes can be rendered functionally monocular through suppression, a GABA-mediated inhibitory process.⁸ This inhibitory network develops in response to early visual deprivation leading to the inhibition of perception in all or part of one eye's visual field during binocular viewing.^{8,9} Suppression is being actively investigated to understand its role in the evaluation and the treatment of amblyopia. The purpose of this literature review is to summarize the vision research published since 2009 and then provide clinical applications for the treatment of amblyopia with optometric vision therapy.

What Visual Pathways are Affected in Amblyopia and Suppression?

Visual Cortex

Visual information is transmitted from the retina and optic nerve to the brain by ganglion cell axons. These axons travel through the optic nerves, chiasm, tracts, into the lateral geniculate nuclei (LGN).¹⁰ From the LGN, information travels through the optic radiations to the primary visual cortex (V1), and then undergoes further processing in the dorsal and ventral streams. V1 is the first area in the visual pathway where excitatory binocular interaction occurs.¹⁰ In the dorsal stream, information about an object's location in space and movement is transmitted through V1, V2, V4 and the temporal lobe. In the ventral stream information regarding fine detail about an object, such as color and texture, travels through V1, V2, V5, V6 and the parietal lobe. Functional magnetic resonance imaging (fMRI) studies have shown that visual deficits in amblyopia occur within the primary visual cortex (V1) and in visual processing areas (V2, V4-6).^{11,8}

Repetitive transcranial magnetic stimulation (rTMS), an electrophysiological method of stimulating the visual cortex, improves high spatial frequency contrast sensitivity by 40% in amblyopic adults.¹² The excitatory effects of rTMS are greater for circuits that are inhibited, which suggests that suppression is cortical.¹² Suppression takes place at a synaptic level, and is mediated by GABA, an inhibitory neurotransmitter. The restoration of binocular response in visual cortex cells with application of a GABA antagonist suggests suppression is a cortical phenomenon.¹³ However, relay cells and interneurons in the LGN use GABA and glutamate,¹⁰ so the LGN may also be affected by the development of the GABA inhibitory network in amblyopes. It is noteworthy that any deficit in the visual processing pathway will affect processing in structures upstream in that pathway, so LGN deficits would also affect processing in the visual cortex.³

The amblyopic eye also has deficits in temporal processing. Amblyopes have difficulty discerning asynchrony in stimulus presentation, and reduced saccadic and visual motor reaction time when viewing with the amblyopic eye.² Farivar et al, studied the visual cortex hemodynamic response function (HRF) in subjects with strabismic and mixed amblyopia and found that the stimulus response time from the amblyopic eye was reduced by 500 msec compared to the dominant eye.¹⁴ This delay was correlated to the reduction in visual acuity of the amblyopic eye. The delay in processing increased when the dominant eye was open, suggesting a component of the processing delay is due to suppression.¹⁴

Lateral Geniculate Nuclei

The LGN regulates the flow and strength of signals to the primary visual cortex by using feedforward and feedback pathways. The feedforward pathway consists of relay cells, which utilize the excitatory neurotransmitter glutamate to transmit information to the visual cortex. The modulatory and feedback pathways use interneurons, which synapse in the LGN and use the inhibitory neurotransmitter GABA.¹⁰ Histology studies of the LGN in amblyopic humans and animals have shown abnormalities in LGN layers receiving input from the amblyopic eye.¹⁵ In both strabismic and anisometropic amblyopes, fMRI studies of the LGN have shown that the response from the LGN is reduced when driven by the amblyopic eye.¹⁵ Strabismic amblyopes have less gray matter in their LGN than normals, and reduced gray matter concentration correlates to increased fMRI V1 activity in the dominant eye.¹⁶ LGN gray matter density has not been evaluated in anisometropic amblyopes. The LGN may attenuate the signal strength of the amblyopic eye prior to binocular combination.¹⁷ However, because the LGN contains feedforward, feedback, and modulatory pathways, it is inconclusive if the

observed LGN abnormalities are caused by decreased LGN function, or by feedback from the cortex.¹⁵

Does Neuroplasticity Exist in the Adult Brain?

Perceptual learning, defined as repeatedly completing a visually demanding task, and repetitive transcranial magnetic stimulation have been shown to improve visual acuity and contrast sensitivity in amblyopic adults.^{11,12} These findings suggest neuroplasticity exists in the adult brain, specifically in areas V1-V4 of the visual cortex.^{8,11} Neuroplasticity in the adult brain likely begins as functional plasticity, which then leads to structural plasticity.⁸ Functional plasticity occurs at a neurotransmitter level, within the synapses of neurons. These alterations in neurotransmitter function enhance the activity within synapses, which leads to changes in structural plasticity. Structural plasticity refers to changes in the strength of axons and dendrites, and formation of new synapses.⁸ A reduction of GABA inhibition in V1 can reopen a period of visual plasticity, and enable modifications in higher level visual processing to occur.⁸ Epigenetics, or alterations in gene expression, fosters neuroplasticity in the brain. DNA that is not being actively transcribed into mRNA is tightly coiled around histones. DNA must be acetylated and unwrapped from histones to be actively transcribed. Transcription factors, specifically CREB, enhance transcription. MicroRNAs then target these newly transcribed RNAs for translation into protein. This is the mechanism by which new proteins are produced to execute new functions in the brain.¹⁸ Changes in mitochondrial activity within neurons can enhance synaptic activity. Mitochondria produce cellular energy in the form of adenosine triphosphate (ATP). An increase in mitochondrial activity within a neuronal dendrite will lead to an increase in the number of dendritic spines and synapses.¹⁹ The response strength of neurons is enhanced by

gene translation and mitochondrial activation. An increase in response strength causes formation of new synapses, which increases gray matter density in the brain.⁸ Refer to Figure 1 for a schematic of neuroplasticity mechanisms in the brain.

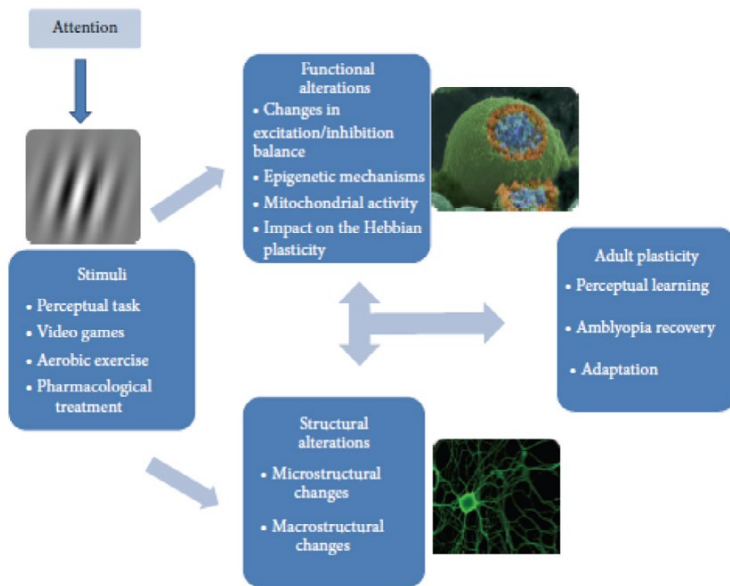


Figure 1: Flow chart highlighting mechanisms of neuroplasticity involved in amblyopia recovery.⁸

Perceptual learning may enhance the response strength of neurons by activating the above mechanisms involved in neuroplasticity. Perceptual learning trains individuals to discriminate small visual changes that can involve contrast, figure-ground, spatial judgments, or Vernier acuity.¹¹ Gains in visual function achieved through perceptual learning are typically specific for the orientation and the task trained. For example, training a patient to discriminate horizontal gratings does not improve their ability to discriminate vertical gratings. However, perceptual learning through a variety of different tasks and orientations translates to an increase in Snellen visual acuity. Of all perceptual learning techniques reviewed by Levi and Li, tasks involving contrast discrimination training showed the greatest improvements in Snellen visual acuity. Perceptual learning may affect the neural responses in the early visual cortex, visual attention and decision making

processes in the dorsal stream, or both.¹¹ Visual attention guides the brain to filter out irrelevant stimuli and process only the relevant stimuli. Tasks involving visual attention, visual perception, and visual motor integration target the dorsal stream processing pathway and may activate mechanisms involved in neuroplasticity.⁸ Perceptual learning research has demonstrated neuroplasticity exists in the adult brain, and that visual information processing may be an important factor to address during amblyopia treatment.

How Can Suppression Be Quantified?

To analyze the role of suppression in amblyopia, researchers designed unique methods to quantify suppression. Several different research groups designed protocols that manipulate contrast to quantify suppression. A random dot kinematogram is one task which utilizes the concept of signal to noise ratio (see Figure 2). Noise in this task is a population of dots moving in random directions that is presented to one eye, and the signal is a population of dots moving in the same direction that is presented to the other eye.²⁰ If binocular vision exists, the signal and noise should be perceived by both eyes. If both the signal and noise are not perceived, suppression is occurring. In subjects with amblyopia, suppression can be quantified by reducing contrast to the dominant eye until both the signal and noise are able to be perceived.²⁰ At this balance point of contrast, simultaneous perception occurs, and when the signal and noise are presented to either eye, the brain will perceive both.²⁰ The amount of contrast reduction required for the fixating eye to reach this balance point quantifies the depth of the suppression.²⁰ A more accurate method for subjects with anisometropia greater than 5 diopters is a modified version of this procedure in which the size of the dots is randomized.²¹ Randomizing dot size eliminates effects from aniseikonia and leads to a more accurate measurement of suppression.²¹

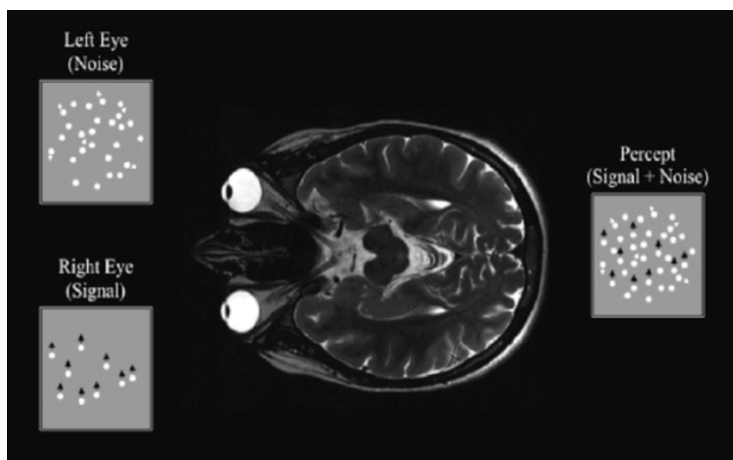


Figure 2: “Reprinted from Restorative Neurology and Neuroscience, 28, Hess, Robert, A New Binocular Approach to the Treatment of Amblyopia in Adults Well beyond the Critical Period of Development, 1-10, Copyright (2012), with permission from IOS Press.”

A random dot kinematogram. At the balance point of contrast the signal and noise are able to be perceived by the brain regardless of which eye they are presented to.⁷

Another method researchers used to quantify suppression is the push-pull learning method (see Figure 3). This method presents a horizontal sine wave grating to one eye and a vertical sine wave grating to the other eye. Contrast is reduced to the fixating eye until each eye’s image is perceived 50% of the time, which is called the balance contrast.²² The amount that the contrast must be reduced to the dominant eye quantifies the amount of suppression.

Lai et al.²³ calculated an interocular interaction index to quantify suppression. Visual acuity, contrast sensitivity, and alignment sensitivity were measured under full and partial (central) occlusion conditions. In the partial occlusion condition, a central occluder is placed in front of the dominant eye, and a grating pattern in front of the amblyopic eye, which creates binocular rivalry. If inhibition is stronger under the rivalry condition than the full occlusion condition, this indicates stronger suppression. The interaction index is calculated by using the following formula: Interaction index = (acuity partial – acuity full)/(acuity partial + acuity full). A positive interaction index means inhibition of the amblyopic

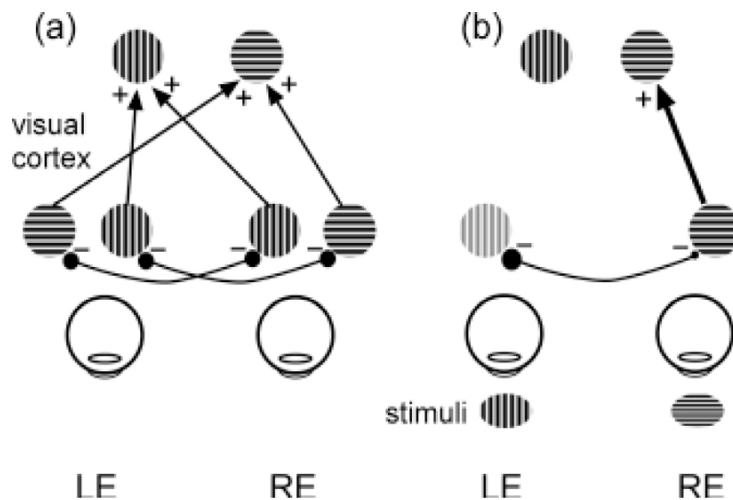


Figure 3: The push pull learning method. A horizontal sine wave grating pattern is presented to one eye, and a vertical sine wave grating is presented to the other eye. Contrast is reduced to the fixating eye until each image is perceived 50% of the time.²²

eye was stronger under partial occlusion conditions than monocular conditions. A positive interaction index indicates stronger suppression.

Ding et. al. quantified suppression by using dichoptically presented images in which different images or sine waves were presented to each eye.²⁴ Initially, the dichoptically presented sine waves were phase shifted, so the peaks and troughs of the wave were seen in different positions by either eye. Contrast between the dominant eye and non-dominant eye was varied, and subjects were asked to judge the perceived phase, or position of peaks and troughs, of the sine wave. The contrast ratio at which the perceived phase shifted to the non-dominant eye quantified the amount of suppression.

Is Suppression in Anisometric Amblyopia Due to Optical Blur?

Lai et al.²³ evaluated interocular inhibition in anisometropes with and without amblyopia. They found that children with anisometric amblyopia had higher levels of suppression compared to children with anisometropia only. Li et al. attempted to simulate suppression in normal subjects, and found that suppression could not be simulated with optical defocus.²⁰

These findings suggest that suppression is a separate factor associated with amblyopia, and not just a consequence of optical blur.

Li et al.²⁰ used a random dot kinematogram method to quantify suppression in 45 children with anisometropic amblyopia. Forty-five children without amblyopia were

used as a control group. Suppression was higher in subjects with amblyopia than in the control group. Stronger suppression was associated with lower visual acuity, absent Randot stereopsis, and higher degrees of anisometropia. Li et al.²¹ also measured levels of suppression in 11 adults between the ages

Table 1: Suppression Characteristics of Amblyopes

Author/ Citation #	Subjects	Methods	Findings
Lai XJ. et al 23	Children 5-11 yrs, mean age 9.2 17 anisometropic amblyopes 17 anisometropes No history of treatment	<ul style="list-style-type: none"> Measured low contrast acuity, contrast sensitivity, and alignment sensitivity under full and partial occlusion conditions Calculated interaction index to measure suppression 	<ul style="list-style-type: none"> Anisometropic amblyopes had higher interocular inhibition than anisometropes without amblyopia Higher suppression associated with lower visual acuity, higher anisometropia, and lower stereoacuity
Li J.et al. 20	45 children age 6-12 with anisometropic amblyopia	<ul style="list-style-type: none"> Suppression measured using random dot kinematogram method, and Bagolini lenses with neutral density filter 26 kids assigned to patching subgroup 19 kids assigned to RGP subgroup, all had >5D of anisometropia 	<ul style="list-style-type: none"> Suppression stronger in anisometropic amblyopes than controls Depth of suppression correlates to reduction in visual acuity Depth of suppression correlates to higher amounts of anisometropia Decreased stereopsis associated with higher suppression In all subjects, suppression was lower while wearing RGPs than spectacles
Li J.et al. 26	43 Strabismic, anisometropic, and mixed Amblyopes ages 9-56	<ul style="list-style-type: none"> Suppression measured using random dot kinematogram method, worth 4 dot, and Bagolini striated lens with neutral density filter test 	<ul style="list-style-type: none"> Deeper suppression associated with higher suppression and reduced stereoacuity No differences in suppression between strabismic and anisometropic amblyopes No age trends
Narasimhan S. et al 9	39 amblyopes: 19 anisometropic, 14 strabismic, 6 aniso- strabismic with prior history of amblyopia treatment	<ul style="list-style-type: none"> Measured suppression levels using random dot kinematogram method 	<ul style="list-style-type: none"> Lower visual acuity associated with higher suppression Stronger suppression in strabismics, but also stronger suppression in subjects with no stereopsis
Li et. al 21	11 adults between the ages of 15-35	<ul style="list-style-type: none"> Measured suppression levels using random dot kinematogram method Varied dot size to account for aniseikonia 	<ul style="list-style-type: none"> Randomizing dot size more accurately measures suppression in patients with >5D anisometropia Deeper suppression associated with lower visual acuity, higher anisometropia, and reduced stereopsis
Babu et al 25	10 strabismic amblyopes 4 anisometropic amblyopes 10 normal controls	<ul style="list-style-type: none"> Suprathreshold contrast matching in central 20 degree visual field-reduced contrast to fixating eye until appeared equal between eyes 	<ul style="list-style-type: none"> No differences in suppression patterns between strabismic and anisometropic amblyopes Depth of central suppression was found to correlate to the reduction in visual acuity Suppression is strongest centrally and extends throughout the central 20 degrees Stronger central suppression is related to stronger peripheral suppression Method of quantifying suppression correlates well to Bagolini and worth 4 dot

of 15-35 years with anisometropic amblyopia. All subjects with greater than five diopters of anisometropia had no measureable Randot stereopsis, while subjects with less than five diopters of anisometropia had between 400-800 arcseconds of Randot stereopsis. Consistent with their previous research, stronger suppression was associated with lower visual acuity in the amblyopic eye, absent Randot stereopsis, and greater than five diopters of anisometropia. Suppression levels were compared while wearing spectacle or RGP correction in 19 anisometropes with greater than five diopters of anisometropia. Suppression was lower while wearing RGP lenses than spectacles.²⁰ It is clinically relevant that these relationships were present in both children and adults, as it suggests their amblyopic visual systems are functionally similar.

Are Characteristics of Suppression Different in Strabismic and Anisometropic Amblyopia?

Historically, suppression is thought of as weaker in anisometropic amblyopia, and localized to a central scotoma corresponding to the dominant eye's fovea in strabismic amblyopes.²⁵ Three research groups compared suppression characteristics between strabismic and anisometropic amblyopes. Li et al.²⁶ measured suppression using a random dot kinematogram method in 43 anisometropic, strabismic, and mixed amblyopes between the ages of 9-56 years. No differences were found between the suppression patterns of anisometropic and strabismic amblyopes. In all three types of amblyopia, deeper suppression was associated with the degree of reduction in Randot stereoacuity and the degree of reduction in visual acuity. There were also no differences in suppression patterns between children and adults. No relationship existed between the size or the direction of the strabismic angle and the suppression patterns.

Narasimhan et al.⁹ analyzed suppression in 39 children between the ages of 5-16 years

using the random dot kinematogram method. All subjects had a prior history of amblyopia treatment, so a complete history regarding each child's pre-treatment visual acuity and occlusion regimen was taken. Higher levels of suppression were found in children with strabismic amblyopia than in children with anisometropic amblyopia. Subjects with absent Randot stereopsis, the majority of whom were strabismic, had higher levels of suppression.

Babu et al.²⁵ used a suprathreshold matching technique to map suppression patterns in strabismic and anisometropic amblyopes. The central visual field was divided into 40 sections; within each section subjects reduced contrast to their dominant eye until equal contrast was perceived. No difference in suppression patterns were found between strabismic and anisometropic amblyopes. In both types of amblyopia, depth of central suppression correlated with the reduction in visual acuity. Suppression was present throughout the central 20 degrees in all amblyopes, and the deepest suppression was found in the central 6 degrees. Stronger central suppression was correlated with stronger peripheral suppression. Refer to table 1 for a summary of suppression characteristics in strabismic and anisometropic amblyopes.

Is Suppression Stronger in Cases that Do Not Respond to Patching Therapy?

Three groups analyzed the relationship between suppression and improvement in visual acuity from occlusion therapy. Lai et al.²³ found that subjects with higher levels of suppression responded best to occlusion therapy; however, only 4 of 15 subjects showed any improvement in visual acuity. Li et al.²⁰ found that children with lower levels of suppression had the most improvement in visual acuity. Narasimhan et al.⁹ found that children whose visual acuity improved after patching treatment had lower levels of suppression than those who did not improve. Conflicting evidence exists, but in Lai's²³ study

Table 2: Occlusion Therapy and Suppression

Author/ Citation #	Subjects	Methods	Findings
Lai XJ. et al 23	Children 5-11 yrs, mean age 9.2 17 anisometric amblyopes 17 anisometropes No prior history of amblyopia treatment	<ul style="list-style-type: none"> Subjects underwent 6 hours of daily patching for 6 months 	<ul style="list-style-type: none"> Only 4/15 subjects improved with patching therapy Subjects with higher levels of suppression improved most
Li J. et al. 20	45 children age 6-12 with anisometric amblyopia BCVA: 20/40-20/63 (11) 20/70-20/100 (25) < 20/100 (9) Degree of anisometropia < 5.00 16 > 5.00 D 29 Measurable stereoacuity Yes 18 No 27	<ul style="list-style-type: none"> 26 kids assigned to patching subgroup, Occlusion regime unspecified by article 	<ul style="list-style-type: none"> Children with lower levels of suppression improved the most
Narasimhan, S. et al 9	39 amblyopes: 19 anisometric, 14 strabismic, 6 aniso-strabismic amblyopes with prior history of patching treatment	<ul style="list-style-type: none"> Retrospectively reviewed history of patching treatment 	<ul style="list-style-type: none"> 24 children improved in VA with occlusion therapy 11 children showed no improvement from patching therapy Children who improved with patching therapy were found to have lower levels of suppression

only four subjects had any improvement with occlusion therapy. Therefore, the majority of the evidence suggests that patients with lower levels of suppression respond best to occlusion therapy. This may be particularly important clinically, as in-office vision therapy aimed at reducing suppression should be recommended as the better treatment option for patients with high levels of suppression. Refer to table 2 for a comparison of suppression characteristics and patching outcomes.

How Can Suppression Be Treated?

Hess et al.⁷ used random dot kinematograms therapeutically with adults with strabismic amblyopia. Subjects were trained for 2 to 6 weeks, with one training session consisting of 100 balance point of contrast threshold measurements, or repeatedly reducing contrast to the dominant eye until simultaneous perception occurs. At the end of training subjects could perceive the signal and dots at equal contrast between eyes. In all subjects, monocular visual acuity increased. The subject

with the worst visual acuity improved the most. This is particularly important, because subjects with lower visual acuity tend to have higher levels of suppression.^{9,20-24} Many patients also showed gains in Randot stereopsis, which is noteworthy because many patients did not demonstrate measurable Randot stereopsis at the start of the experiment.

Xu et al.²² used a push-pull learning protocol to reduce suppression. A horizontal sine wave grating was presented to one eye and a vertical sine wave grating was presented to the other eye. Initially, contrast was reduced to the dominant eye's grating pattern in accordance to the previously measured balance contrast. The amblyopic eye was flashed with a priming signal 100 msec prior to exposure of the grating patterns. The priming signal served as an attentional cue, causing the amblyopic eye's image to be perceived and the dominant eye's image to be inhibited. Contrast was increased to the dominant eye through the training procedure until it was equal to that of the amblyopic eye's grating pattern. Using this

method, suppression was reduced, Randot stereopsis and monocular contrast sensitivity increased. Training was most effective at foveal and parafoveal locations.²⁷

Li et al.⁶ used a head-mounted goggle version of Tetris® to train 18 adults with amblyopia (strabismic or anisometropic is not specified by the study). Nine adults played the game monocularly with their amblyopic eye, and another nine adults played the anti-suppression version of the game with variable contrast. This study design was chosen because monocular video game playing has been shown to be effective at improving visual acuity in amblyopic adults.²⁸ The authors wanted to evaluate if anti-suppression with variable contrast video game play was more effective than monocular video game play. Subjects played the game for one hour a day over a period of two weeks; after which time the monocular group was switched over to the binocular game. Binocular training improved monocular visual acuity, reduced suppression, and improved Randot stereopsis more than monocular training. Of the initial nine patients, five patients attended a three-month follow up and their gains remained stable. These results suggest anti-suppression variable contrast videogames are a more effective treatment for adult amblyopia than monocular videogames.

What Anti-Suppression Devices Can Be Used as a Home Treatment for Amblyopia?

Adults

Because dichoptic Tetris was found to be an effective amblyopia treatment method in adults,⁶ an iPod® gaming platform was developed. Hess et al²⁹ used a variable contrast anti-suppression iPod® Tetris treatment on 14 adults with anisometropic, strabismic, and mixed amblyopia between the ages of 13-50. To play the iPod® game, the subjects wore anaglyphic glasses with the green filter placed over the amblyopic eye. The amblyopic eye saw high-contrast red blocks and the

dominant eye saw reduced-contrast green blocks. Visual acuity (VA), Randot stereopsis, Worth Dot, Bagolini, and dichoptic global motion tests were used before and after the video game play. Contrast was initially set at 100% for the amblyopic eye and the dominant eye's contrast was set at the point of balance contrast measured using the dichoptic global motion test. Contrast was increased by 10% every 24 hours if the game was played at the threshold level. Home video game play for 10-30 hours improved visual acuity by 0.11+/- 0.8 logMAR (Snellen equivalent 1-2 lines). All subjects reached the 100% contrast setting within 30 days, restoring simultaneous perception. Randot stereo acuity improved in 11 of 14 subjects and two stereo blind subjects developed Randot stereo acuity.

Children

Because the dichoptic Tetris® home training game was an effective amblyopia treatment in adults,²⁹ the game was studied by two research groups as a potential home treatment option in children. Li et al,³⁰ compared variable contrast anti-suppression iPad game play to sham iPad play with 50 children age 4-12 years with strabismic, anisometropic, or mixed amblyopia. Subjects were prescribed four hours of play per week for four weeks. VA, Randot stereopsis, and suppression using the motion coherence threshold were measured at four weeks, eight weeks and three months. Approximately three quarters of subjects had a history of patching therapy prior to enrollment in the study. Half of the subjects were currently undergoing two hours of patching therapy at a different time of day. Visual acuity improved from an average of 0.47 log MAR to 0.39 log MAR (Snellen equivalent 20/60 to 20/50) at four weeks. No improvement was found in suppression or Randot stereopsis measurements. There was no clinically significant difference in VA outcomes between subjects who patched while playing the video game and those who played the video game only. Children ages 4-7

Table 3: Home iPad Training Results

Author/ Citation #	Subjects	Methods	Findings
Birch et al 31	50 preschool children with strabismic, anisometropic and mixed amblyopia with prior history of amblyopia treatment	4 hours of video game play per week for 4 weeks	Children who played for at least 8 hours improved VA by 1-2 lines
Li et al 30	50 children age 4-12 with strabismic, anisometropic, and mixed amblyopia	4 hours of video game play per week for 4 weeks	VA improved from 20/60 to 20/50 and improvement remained stable at 3 month follow up
Hess et al 29	14 adults age 13-50 with anisometropic, strabismic, and mixed amblyopia	4 hours of video game play per week for 4 weeks	10-30 hours of video game play improved VA by 1-2 lines

had the same amount of VA improvement as children ages 7-12. There were no difference in outcomes between strabismic, anisometropic, and mixed amblyopes. No additional VA improvement was found at eight weeks. Stable VA was noted in 21 subjects after three months.

Birch et. al.³¹ used the same iPad® game setup in 50 preschool children with strabismic, anisometropic, and combined-mechanism amblyopia. Initially, the amblyopic eye's contrast was set to 100% and the dominant eye's contrast was set to 15%. When the child achieved a certain criterion score, the contrast to the dominant eye was increased by 10%. In the sham iPad® group, the anaglyphic glasses were reversed so the amblyopic eye saw green, low contrast shapes. Researchers prescribed four hours of video game play per week for four weeks. The majority of subjects had a history of patching treatment for 3-18 months prior to the study. 20 of 28 children who played the variable-contrast, anti-suppression iPad® game for at least eight hours improved an average of 1-2 lines in visual acuity, no differences were found in VA response between strabismic, anisometropic, and mixed amblyopes. Randot stereopsis did not improve. Some children in the treatment group were concurrently undergoing two hours per day of patching treatment, which limits the conclusions able to be drawn from this study. However, among the 28 children who played for at least eight hours, no significant

difference in improvement was found between those who patched and those who did not.

All three research groups using the home based iPad® treatment found an improvement in VA over a short treatment duration (8-30 hours of play).²⁹⁻³¹ Refer to table 3 for a comparison of these studies. An additional benefit of this treatment concept is the program tracks the patient's progress, giving the managing doctor a reliable compliance log.²⁹⁻³¹

Rapid Alternate Occlusion

Rapid alternate occlusion is another method to reduce suppression that is currently being investigated by researchers. Rapid alternate occlusion treats the temporal processing aspects of suppression, rather than the depth of suppression.³² Because temporal processing deficits may play a role in suppression mechanisms, change in the amount of suppression over time is another way to quantify suppression. Periods of suppression can be timed while a patient is viewing a vectographic near card, and compared pre and post therapy.³² The Eyetronix flicker glasses, liquid crystal glasses that administer rapid alternating occlusion, were used to treat anisometropic amblyopia in 20 children between ages 6-17.³³ Subjects wore the Eyetronix flicker glasses, set to a 7 Hz flicker frequency, for one hour each day while doing near work, and kept a compliance log. Subjects were followed over a 12 week period. Nineteen subjects improved VA in

the amblyopic eye by an average of one line of Snellen acuity. Stereopsis improved in eighteen subjects.³⁴

How Can This New Research be Incorporated into Amblyopia Therapy?

Suppression is an important component of the amblyopic syndrome and should be actively addressed during amblyopia therapy. Treating suppression may be particularly beneficial in cases that do not respond to patching and in adults.^{6,7,9,20} Because reducing GABA inhibition in the visual system activates mechanisms involved in functional plasticity,⁸ a treatment regimen emphasizing suppression reduction as a first step and monocular visual processing tasks as a second step may be the most beneficial treatment in adults.³⁵ However, caution should be exercised with prescribing anti-suppression therapy for patients with mono-fixation syndrome. Because these patients typically have absent fusion, there is risk of developing irretractable diplopia.³⁶ In addition to improved monocular visual acuity, a reduction in suppression and improved Randot stereopsis should be considered goals of amblyopia therapy. Amblyopic deficits in stereopsis and visual motor integration have been shown to affect performance at several tasks including grasp accuracy, walking, driving, and reading speed.³⁷ Amblyopes tend to perform these tasks slower, less accurately, and with more caution than their peers with stereopsis. Performance in these tasks correlates to the reduction in stereopsis rather than the reduction in monocular visual acuity.³⁷ Stereopsis influences motor planning and decision-making, and reduced stereopsis can contribute to errors and inaccuracies in motor planning. Stereopsis and suppression should be evaluated at all amblyopia follow-ups, and an improvement in either characteristic should be considered an improvement in the condition, even if visual acuity does not improve.

Because perceptual learning has been shown to increase VA in amblyopic adults,¹¹

visual processing tasks should be emphasized during monocular occlusion. Tasks involving visual attention, visual motor integration, figure-ground discrimination, spatial orientation, and contrast discrimination activate functional plasticity in the brain,¹¹ and should be emphasized during monocular occlusion.

If a patient has reached a plateau with patching therapy, suppression should be evaluated and treated. To properly evaluate suppression, the depth of suppression must be quantified. Because the aforementioned methods used by vision scientists are not available commercially, in a clinical setting the Worth Dot test^a and Bagolini striated lenses^b can be used to quantify suppression. These methods were found to be in high agreement with both the random dot kinematogram and contrast matching methods of measuring suppression, as detailed below.^{20,25,26} In subjects with greater than five diopters of anisometropia, a contact lens should be prescribed as the optimal refractive correction because contact lens wear alone has been found to reduce suppression.²⁰

The Worth Dot test^a can be used to quantify peripheral suppression when presented at 40 cm, and central suppression when presented at 10 feet.³⁸ Babu et al. found that suppression is strongest centrally in all amblyopes, and strong central suppression is associated with the presence of peripheral suppression.²⁵ Clinically, strabismic and amblyopic patients often are able to develop peripheral fusion before central fusion. Eliminating peripheral suppression may be an important step in treatment as developing peripheral fusion may reduce central suppression.

A modified Bagolini lens^b procedure, in which a neutral density filter was placed in front of the fixating eye and adjusted until suppression was eliminated, was used by Li et al.^{20,26} This modified procedure allows the clinician to quantify how much the contrast needs to be reduced to the fixating eye to allow for simultaneous perception to occur,

which is the concept researchers were using to measure suppression.^{9,20,25,26} The specific power of the neutral density filter^c could then be used to supplement traditional anti-suppression and monocular fixation in a binocular field techniques by placing it over the dominant eye to reduce contrast. As the patient progresses through therapy, the power of the neutral density filter could be reduced as the visual acuity increases or the level of suppression decreases.

Monocular fixation in a binocular field (MFBF) techniques, an anaglyphic set up where the amblyopic eye sees the object of interest and the dominant eye's filter eliminates the object of interest, are commonly used during optometric vision therapy to treat suppression. Anaglyphic setups were used by several research groups to treat suppression, giving evidence for the effectiveness of this technique.^{6,7,9,22,24,26,29-31} Employing the set up with activities emphasizing visual discrimination, visual figure-ground, and visual motor integration may be particularly effective as it incorporates anti-suppression training and visual processing training into therapy. Neutral density filters^c could be placed over the dominant eye during MFBF therapy techniques to incorporate contrast variability.

Several new computerized therapy programs can be used to incorporate variable contrast into anti-suppression therapy. The Sanet Vision Integrator (SVI),^d a computerized vision therapy program, has many modules which utilize an MFBF setup. Contrast of stimuli can be manipulated on many of the modules, allowing a clinician to create and MFBF setup with contrast variability. The Vision Therapy Solutions 4 (VTS4),^e a computerized program for building sensory fusion, has a feature that enables a clinician to change contrast between eyes during fusion tasks. Contrast could be reduced to the dominant eye initially, and increased as fusional vergence ranges improve. Vivid Vision,^f a computerized virtual reality system designed for treating amblyopia,

allows contrast to be reduced to the dominant eye or increased to the amblyopic eye. The Eyetronix flicker glasses⁹ can be used during nearpoint activities to aid in the reduction of suppression.

CONCLUSIONS

Variable contrast anti-suppression training is a promising new concept in amblyopia treatment. The relationships between higher levels of suppression, reduced Randot stereopsis, and reduced visual acuity were the same in both children and adults. No age trends were found, which suggests that suppression may not need to be treated differently in children and adults. Incorporating variable contrast anti-suppression techniques into therapy may decrease the duration of occlusion therapy. Minimizing occlusion time may increase compliance with therapy, leading to a better treatment outcome.

PEDIG ATS-18 is a randomized large-scale clinical trial comparing two hours of daily patching to one hour of variable contrast anti-suppression play in children age 5-17.³⁹ The Hess falling blocks game has developed three levels of difficulty to engage all ages of children in the study. Results of the study are anticipated in 2017, and may significantly influence and standardize future amblyopia treatment guidelines.

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Source List

- a. Worth 4 Dot Test
Bernell Corporation
4016 North Home Street Mishawaka, IN 46545
<https://goo.gl/dmMp6R>
- b. Bagolini striated lenses
Bernell Corporation
4016 North Home Street Mishawaka, IN 46545
<https://goo.gl/3SbZX5>
- c. LEE Filters 4x4" Neutral Density Polyester Filter Set (0.3, 0.6, & 0.9)
BH Photo and Video
420 9th Ave
New York, NY 10001
<http://goo.gl/cK69mY>
- d. Sanet Vision Integrator
HTS Inc.
6788 S. Kings Ranch Rd. Suite 4
Gold Canyon, AZ 85118
<http://www.svivation.com/>
- e. VTS4
HTS Inc.
6788 S. Kings Ranch Rd. Suite 4
Gold Canyon, AZ 85118
<http://goo.gl/X1iFL0>
- f. Vivid Vision
Vivid Vision Inc.
<http://goo.gl/Qt0O9D>
- g. Eyetronix Flicker glasses
Manufactured by Eyetronix Inc, sold through Bernell Corporation
<http://goo.gl/RmjxOI>



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