Spatial and Global Sensory Suppression Mapping Encompassing the Central 10° Field in Anisometropic Amblyopia

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Submitted: July 9, 2016
Accepted: December 12, 2016

Citation: Li J, Li J, Chen Z, et al. Spatial and global sensory suppression mapping encompassing the central 10° field in anisometropic amblyopia. *Invest Ophthalmol Vis Sci.* 2017;58:481–491. DOI:10.1167/iovs.16-20298

Purpose. We investigate the efficacy of a novel dichoptic mapping paradigm in evaluating visual function of anisometropic amblyopes.

Methods. Using standard clinical measures of visual function (visual acuity, stereo acuity, Bagolini lenses, and neutral density filters) and a novel quantitative mapping technique, 26 patients with anisometropic amblyopia (mean age = 19.15 ± 4.42 years) were assessed. Two additional psychophysical interocular suppression measurements were tested with dichoptic global motion coherence and binocular phase combination tasks. Luminance reduction was achieved by placing neutral density filters in front of the normal eye.

Results. Our study revealed that suppression changes across the central 10° visual field by mean luminance modulation in amblyopes as well as normal controls. Using simulation and an elimination of interocular suppression, we identified a novel method to effectively reflect the distribution of suppression in anisometropic amblyopia. Additionally, the new quantitative mapping technique was in good agreement with conventional clinical measures, such as interocular acuity difference ($P < 0.001$) and stereo acuity ($P = 0.005$). There was a good consistency between the results of interocular suppression with dichoptic mapping paradigm and the results of the other two psychophysical methods (suppression mapping versus binocular phase combination, $P < 0.001$; suppression mapping versus global motion coherence, $P = 0.005$).

Conclusions. The dichoptic suppression mapping technique is an effective method to represent impaired visual function in patients with anisometropic amblyopia. It offers a potential in "micro-"antisuppression mapping tests and therapies for amblyopia.

Keywords: suppression, amblyopia, mapping, anisometropic

Amblyopia is a visual developmental disorder associated with deficits in the visual cortex that occurs during the "plastic" period of visual development.[1] It is the most common cause of preventable visual impairment in children with an incidence rate of up to 3.5%.[2] The amblyopic syndrome impacts amblyopes to different extents depending on differing factors, such as the status of binocular functions and the type of amblyopia. Strabismus (an eye turn), anisometropia (differences in refractive errors), or other causative factors, which occlude the visual axis (form deprivation),[1] can challenge the visual system with differing patterns of visual acuity (VA) and contrast sensitivity losses.[3,4]

There is increasing attention now, on the critical role interocular suppression has among amblyopes.[5–8] Rather than adhering to a traditional monocular therapy in the form of occlusion or penalization, which is challenged by high reoccurrences of residual amblyopia,[9,10] we now aim to provide a proper binocular visual experience during therapy.[11–14] Converging evidence has shown how amblyopes have a structurally intact binocular visual system that is functionally monocular as a result of deep suppressive mechanisms.[6,15,16] The finding that stronger suppression is associated with a greater visual acuity (VA) deficit and a poorer response to occlusion therapy suggests that suppression is the main cause of amblyopia.[8,17,18] Furthermore, a series of recent studies indicate that binocularly-based therapies, which target suppressive interactions within the visual cortex restored monocular functions (such as VA of the amblyopic eye) as well as binocular functions (such as stereopsis) for adult amblyopes who failed the patching therapy.[12,14,16,19–24] In particular, dichoptic perceptual learning, in the form of a video game, may represent a viable treatment option for patients with amblyopia, especially for those whose age already has passed the critical period with limited brain plasticity.[12,21] Thus, understanding and measuring suppression is the key to this novel binocular treatment based on antisuppression therapy.

More recently, a number of different psychophysical techniques have been devised to quantify suppression in patients with amblyopia using global motion coherence threshold,[7,25,26] orientation coherence,[27] and binocular phase

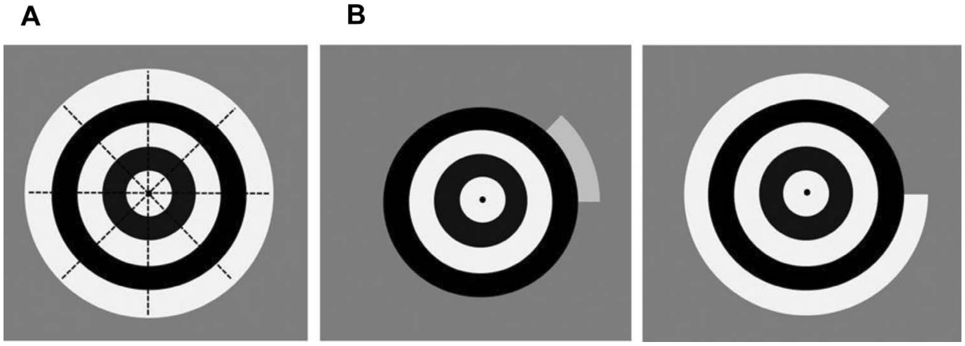

FIGURE 1. A sample stimuli used for suppression mapping task. (**A**) The 40 regions in the 10° visual field that were measured. (**B**) Dichoptic testing arrangement for region #1. The *left* sector was displayed to the dominant eye (the fellow fixing eye) and the *right* sector from the same annulus was presented to the nondominant eye (the amblyopic eye). Participants varied the contrast of each sector presented to their dominant eye (the fellow fixing eye) until it matches the perceived contrast of the nondominant eye (the amblyopic eye). The remaining rings were shown to both eyes at 80% contrast.

combination.[28–30] Although the three techniques (global motion coherence threshold, orientation coherence, and binocular phase combination) provide a rapid and precise way to assess the strength of interocular suppression and have offered more quantitative information than currently available clinical tests, they only give a "global" overview of suppression, measuring an overall and cumulative strength in a given visual field. Global processing of form and motion, which occurs in the extrastriate cortex,[31] is compromised as a consequence of disrupted vision in early amblyopic development. Suppression, however, is essentially a cumulative result that is based upon multiple spatial locations, and the nature of suppression differs fundamentally among different subtypes of amblyopia.[18,32–34] This underlines the need for a topographic suppression map of the visual system that can be integrated into new antisuppression training modules. Currently, the dichoptic mapping paradigm, which was first developed by Babu et al.,[35] precisely provides quantitative information on the distribution of suppression and indicates a topography-specific evaluation of interocular suppression within the central 10° visual field (Fig. 1). They found that the extent and magnitude of suppression was similar for patients with strabismic (n = 10) and anisometropic (n = 4) amblyopia. Suppression was strongest within the central visual field.

In this study, we investigated the efficacy of this novel suppression mapping technique in subjects with anisometropic amblyopia. Previous studies described visual field deficits in strabismic and anisometropic amblyopes.[32,33,36–39] Comparisons between nasal and temporal hemifields across the fovea along the horizontal meridian and with different eccentricities were used commonly in these studies. There are inconsistencies in the literature as to whether an asymmetry exists.[32,33,36–39] In this study, we focused on anisometropic amblyopia to provide more data, and for the sake of comparison with strabismus. Therefore, it is useful to assess the degree of suppression symmetry with this novel test using dichoptic stimuli.

We first explored the spatial distribution characteristics of interocular suppression in normal controls and anisometropic amblyopes. The relationship between conventional clinical measures and the level of suppression using the dichoptic mapping paradigm was assessed. We also compared two widely used psychophysical methods (the global motion coherence threshold and binocular phase combination tasks) to investigate their suppression outcomes to this spatial mapping task. Additionally, previous psychophysical studies have shown that neutral density (ND) filters can be placed over the fellow eye to rebalance binocular vision asymmetry in amblyopes as well as simulate amblyopic suppression in observers with normal binocular vision.[40–46] The mechanism for this simulation may be related to a reduced signal and increased noise in the normal eye,[47] or a delayed visual signal transmission to the cortex.[48] Ding et al.[46] suggested that reducing luminance would lead to attenuated gain-control energy in one eye, thereby rebalancing the binocular asymmetry in amblyopes. We have further identified the effectiveness of dichoptic mapping paradigm in anisometropic amblyopes by using ND filters to manipulate luminance.

METHODS

Participants

This exploratory study evaluated the regional extent of interocular suppression and the effect of mean luminance modulation by ND filters on suppression in visually normal observers and amblyopes. A total of 23 naive observers (controls) with normal vision (13 females, 15–32 years old, mean age = 22.65 ± 5.42) and 26 anisometropic amblyopes (13–29 years old, mean age = 19.15 ± 4.42, 13 females) with their best-corrected refractive correction participated in this experiment. Clinical details for the amblyopic group are listed in Table 1.

Inclusion criteria for control observers were best corrected VA of at least 20/20 (0.0 logMAR) in each eye; absence of any ocular disease, oculomotor, or binocular abnormalities; normal stereo acuity (at least 40 seconds of arc); and a spherical equivalent refraction (SER) between +1.00 dioptric sphere (DS) and −2.50 DS with a dioptric difference of less than 1 diopter (D) between eyes. Exclusion criteria for control observers included any history of binocular visual disorders, such as constant or intermittent tropia. Mean SER was −1.25 DS in the control group with 10 myopes. Amblyopia was defined as at least 0.2 logMAR interocular VA difference, with a logMAR acuity of at least 0.20 in the fellow eye and no history of ocular pathology. Anisometropia was defined as a spherical equivalent difference (SED) of 1.50 D or more between the two eyes as confirmed by their past medical records. The participants were recruited from the Optometry Clinic at Zhongshan Ophthalmic Center, Guangzhou, China. All enrolled participants were anisometropic amblyopes without strabismus as confirmed by reviewing their detailed medical history records. All subjects who currently have, or were previously diagnosed with amblyopia were included in this study. Subject 20 is a bilateral mixed anisometropic amblyope. Interocular suppression was noted

Table 1. Clinical Details for the Observers With Anisometropic Amblyopia

Subject	Age, y	Sex	Cycloplegic Refractive Error, OD/OS	LogMAR BSCVA, OD/OS	Stereopsis, sec arc	History
1	16	M	−8.50/−1.00 × 35	0.20	Nil	Detected at 7 y
			−2.50/−0.50 × 130	0		Patching for 1 y (2 h/d)
2	19	M	+3.50/+0.75 × 90	0.10	400	Detected at 5 y
			+1.00/+0.50 × 90	0		Patching for 2 y (4 h/d)
3	13	F	+6.00/+1.50 × 65	0.12	100	Detected at 11 y
			+2.00/+1.50 × 95	0		Patching for 2 m (6 h/d)
4	13	F	+6.25/+1.50 × 80	0.30	Nil	Detected at 12 y
			+3.50 DS	0		Patching for 3 m (all day)
5	15	F	−3.50 DS	0	40	Detected at 12 y
			+3.50/−4.00 × 15	0.10		Patching for 3 m (1 h/d)
6	16	M	+7.50/+1.50 × 90	0.86	Nil	No detection
			+4.50/+2.75 × 100	0.16		No treatment
7	16	M	−0.50 × 170	0	Nil	No detection
			+5.00/+2.00 × 82	0.92		No treatment
8	18	F	+1.00/+0.75 × 85	0.10	Nil	Detected at 15 y
			+4.50/+1.50 × 80	0.80		No patching
9	22	F	−1.00/−3.25 × 180	0.18	100	Detected at 12 y
			−4.75/−1.25 × 3	0		No treatment
10	21	F	+5.00/+1.25 × 45	0.70	Nil	No detection
			−0.75 DS	−0.10		No treatment
11	28	M	Plano DS	0	Nil	No detection
			+5.75/+1.75 × 165	0.60		No treatment
12	21	M	+7.50 DS	0.70	Nil	Detected at 7 y
			+4.5/+0.75 × 60	0		No patching
13	18	M	+2.75/+2.5 × 85	0.94	Nil	Detected at 12 y
			−1.00 × 180	−0.10		No treatment
14	29	M	Plano DS	−0.10	Nil	Detected at 12 y
			+4.25/+2.25 × 110	0.90		No treatment
15	17	F	+2.25/+2.00 × 50	0.20	Nil	No detection
			+0.75/+0.25 × 70	0		No treatment
16	16	F	−0.50/−0.50 × 165	0.04	400	Detected at 15 y
			+0.50/−0.75 × 170	0.42		No treatment
17	19	F	+4.75/+0.25 × 30	0.10	Nil	No detection
			+6.50/+2.50 × 135	1.00		No treatment
18	21	F	+1.25 DS	−0.20	Nil	Detected at 10 y
			+8.00/+1.00 × 145	1.00		No treatment
19	21	M	+1.75/+2.50 × 90	0.88	Nil	Detected at 4 y
			+1.00/+2.00 × 88	0		Patching for 2 y
20	29	M	+4.00/+1.50 × 90	0.20	Nil	Detected at 8 y
			+5.50/+1.25 × 90	0.40		Patching for 6 m
21	21	M	−0.25/−0.25 × 15	0	Nil	Detected at 12 y
			+5.25/+1.25 × 150	0.80		No patching
22	20	F	+2.50/−0.50 × 180	0	Nil	Detected at 19 y
			+5.50/−1.25 × 15	0.60		No treatment
23	22	F	+4.00/+0.50 × 70	0.26	Nil	Detected at 14 y
			+0.75 DS	0.06		No treatment
24	17	F	−2.75/−0.25 × 139	0	Nil	No detection
			+1.50/−1.50 × 2	1.00		No treatment
25	16	M	Plano DS	0	Nil	No detection
			+6.00/−1.50 × 75	0.68		No treatment
26	14	F	Plano DS	0	Nil	No detection
			+1.75/−5.75 × 170	0.44		No treatment

All the participants are amblyopes or have a history of amblyopia (as confirmed from old medical records but have undergone standard clinical treatment or lab training with perceptual learning). The original medical records of BSCVA were as follows: subject 2, OD 0.2, OS 0; subject 3, OD 0.24, OS 0; subject 5, OD 0, OS 0.3; subject 9, OD 0.22, OS 0. M, male; F, female.

in the suppression mapping measurement as well as motion and phase combination tasks. This subject had been included in our data analysis (Table 1). Prior written consent was obtained from all participants and/or their legal guardians before study enrollment. This study was approved by the Ethics Committee of Zhongshan Ophthalmic Center and adhered to the tenets of the Declaration of Helsinki.

Comprehensive Eye Examinations

Enrolled participants underwent a complete ophthalmologic examination performed by an experienced ophthalmologist at Zhongshan Ophthalmic Center. All tests were conducted under identical lighting conditions as measured using a digital light meter (TES Electronic Corp, Taipei, Taiwan). Visual acuity was measured using a tumbling E version of the Bailey-Lovie logMAR chart at a standard luminance of 200 cd/m^2.[49] Best refractive correction was determined by subjective refraction and, if necessary, a trial frame correction was used during testing for both groups. Binocular vision was assessed using the Worth-4-Dot test,[50] the stereo acuity test (Randot Preschool Test; Stereo Optical Co., Inc., Chicago, IL, USA) and the cover/uncover test was used to ensure the absence of strabismus. Anterior segment and fundus examinations also were performed. Motor eye dominance (MED; measured using standard eye sighting tests to determine the ocular preference of control observers) was identified using the hole-in-card test.[51,52]

Measurements of Interocular Suppression

All anisometropic amblyopes underwent three psychophysical tasks to measure their amplitudes of interocular suppression. The normal control group only completed the suppression mapping task to compare its suppression regions against the anisometropic amblyopes. The same examiner performed all psychophysical measurements for all participants to ensure stability and continuity of data collection. Practice trials were provided before data collection to allow participants to familiarize themselves with the psychophysical tasks. There was no time-limit constraint. All tests were presented in a random order.

Dichoptic stimuli were presented on a computer monitor (ASUS VG278HE; refresh rate: 144 Hz; resolution; 1920 × 1080) with participants wearing polarized glasses (NVIDIA 3D shutter glasses) during viewing. Visual angles were 22° for the dichoptic global motion coherence test, 6.8° for the binocular phase combination task, and 20° for the suppression mapping task. We measured the size of the stimuli and calculated the required viewing distance. The viewing distances were 50 cm in the dichoptic global motion coherence test, 47 cm in the phase combination task and 48 cm in the suppression mapping task. A chinrest was used to maintain a constant viewing distance. Each dichoptic pair paradigm was aligned by the subject who used a computer keyboard to vary the position of the stimulus presented to the amblyopic eye until the eyes were able to fuse the stimulus. Suppression measurements started once alignment was achieved.

Suppression Mapping Test

In this dichoptic suppression mapping task, the stimulus (10° radius) was composed of five concentric rings with alternate contrast polarities (Fig. 1).[35] Each ring subtended 2° of eccentricity and was divided into eight segments. The dominant eye (or the fellow nonamblyopic eye) viewed a "target" segment of variable contrast and the nondominant eye (the amblyopic eye) viewed the seven remaining segments on the same annulus at 80% contrast. The remaining annuli were displayed to both eyes. Before the start of each task, all participants needed to achieve an alignment by fixating on a central black dot and the psychophysical task required participants to adjust a patch contrast shown to their dominant eye (the fellow eye) by using the up and down laptop arrow keys until it matched the perceived contrast of the remaining sections in the ring that were presented to the nondominant eye (the amblyopic eye). Measurements were obtained without and with ND filters worn (details described under ND-Filters Application below). Subjects knew which segment was being tested at any given time since the position of the segments evolved in a predictable manner progressing from peripheral to central, following a clockwise direction on the same ring. This procedure was repeated for each segment for each of the five concentric rings. The adaptive adjustment method (suprathreshold matching procedure) was repeated three times with a contrast step size of 10%, 5%, and 1%. Participants were allowed to take a break at any time to avoid any fluctuations caused by fatigue.

Global Motion Coherence Threshold Test

The dichoptic global motion coherence test used random dot kinematograms composed of two populations of moving dots with randomized dot size.[26] One population consisted of signal dots, which moved in coherent motion, and another population of noise dots, which moved in random directions. The task required participants to indicate the direction of signal dots in motion. During the first stage, the test measured motion coherence thresholds under conditions with both eyes viewing the same image. This procedure was repeated at least three times to provide an average binocular motion coherence threshold. During the second stage, the number of signal dots (based on binocular measurements) was fixed in the amblyopic eye at high contrast (100%), while the contrast of the noise dots presented to the fellow eye was varied using a three-down, one-up staircase procedure starting from zero contrast. The coherence thresholds (79% correct performance) were estimated based on the last five staircase reversals and each staircase was repeated a minimum of three times.

Binocular Phase Combination Task

For the binocular phase combination task, two horizontal sine-wave gratings (0.3 c/d, 6.8° × 6.8°) with phase shifts in opposite directions of the same magnitude were dichoptically presented to each eye. After completing an eye alignment task, observers were asked to adjust the height of a one-pixel sided reference line to indicate the perceived phase of the grating after binocular combination, defined as the location of the center dark stripe of the grating. The initial height of the reference line was randomly (–9–10 pixels) assigned relative to the center of the frame in each trial. The reference line was moved with a fixed step size of one pixel, corresponding to a 4° phase angle of the sine-wave grating. This program measured the phase versus interocular contrast ratio (PvR) curve eight times, divided into four-measurement blocks.[27,29,41] This balanced point is termed effective contrast ratio. The PvR curves were fitted by the previously described equation under the attenuation model and calculated in Matlab (version 7.10.0.499, R2010a; Mathworks, Natick, MA, USA).[29,30]

ND Filters Applications

Bagolini Lenses. The ability to sustain normal binocular vision (suppression resistance) was measured in normal participants using the modified Bagolini striated lens test.[50] Control observers viewed a point light source (30 cd/m^2) held at a distance of 33 cm while wearing Bagolini striated lenses under low ambient room illumination (5 lux). Neutral density filters (Kodak Wratten; ND filter bar; 0.3-log unit increments; Eastman Kodak, Rochester, NY, USA) were placed in front of the nondominant eye (determined by the hole-in-card test) to determine the least amount of ND filter strength that resulted in a sustained breakdown of binocular combination (perception of only one visible striation). To ensure endpoint accuracy, a bracketing ND filter strength presentation was used until the participants reported two separate striations (X) were visible once again. We repeated these steps until a balanced reversal had been attained. The procedure was similar for amblyopic participants, except that the filter bar was held over the fellow

Table 2. Mean Matching Contrast Values (%) and Multiple Comparisons for the Different Central Field Sectors in Controls

Sector	Control Group	*P* Value	Control Group With Filter	*P* Value
0–2°	54.67 ± 18.00	–	31.34 ± 14.16	–
2–4°	68.88 ± 16.98	<0.001*	52.58 ± 23.47	<0.001*
4–6°	60.33 ± 17.41	0.132*	41.84 ± 20.19	0.015*
6–8°	75.15 ± 13.74	<0.001*	57.98 ± 20.75	<0.001*
8–10°	68.29 ± 14.45	<0.001*	44.09 ± 17.06	0.003*
Upper visual field	64.59 ± 15.10	0.418	44.29 ± 15.14	0.140
Lower visual field	66.33 ± 9.72		46.83 ± 14.98	
Left visual field	65.03 ± 13.30	0.522	45.68 ± 15.57	0.866
Right visual field	65.89 ± 10.71		45.44 ± 14.21	
Mean	65.46 ± 11.45	–	45.56 ± 14.52	–
Other comparisons				
2–4° vs. 4–6°	–	0.024	–	0.013
2–4° vs. 6–8°	–	0.095	–	0.206
2–4° vs. 8–10°	–	0.875	–	0.048
4–6° vs. 6–8°	–	<0.001	–	<0.001
4–6° vs. 8–10°	–	0.035	–	0.597
6–8° vs. 8–10°	–	0.068	–	0.001

All values are given as mean ± SD. In the control group, the mean strength of ND filter was 2.17 log units (SD, 0.31 log units; Details seen in the method section).

* *P* values are shown for comparison between 0° and 2° and other eccentricities (univariate ANOVA were performed, and the least significant difference (LSD) test was used to conduct multiple comparisons).

eye and the outcome was to achieve an ND filter strength that resulted in a perceived line intensity seen by the amblyopic eye as the same or slightly stronger than the line seen by the fellow fixing eye.[17] The appropriate ND filter strength using the above method was worn to penalize the nondominant eye of the control observers in the suppression mapping task (Table 2).[8,50] For the amblyopic group, a 2.0 strength ND filter was placed in front of the fellow fixating eye during the psychophysical measurements (Table 3). Before testing, all participants wore the ND filter for at least 5 minutes for dark adaption. Participants were allowed to take a break at any time to avoid any fluctuations caused by fatigue. After each break, the participant had to dark adapt again.

Novel Suppression Mapping Test. Neutral density filters (using the strengths determined by the Bagolini striated lens test method described above) were worn by all normal observers during the dichoptic suppression mapping task to achieve a luminance reduction. All anisometropic amblyopes were tested with a 2.0 ND strength filter worn in front of their fellow fixating eye during all three psychophysical suppression measurements.

Statistical Analysis

A paired *t*-test analysis was used to compare the symmetric effect and the contrast ratio at the balance point with and without a 2.0 strength ND filter worn over the fellow eye during the three psychophysical tasks. An independent sample test was used to compare the extent of suppression between anisometropic amblyopes with and without stereopsis, and between amblyopes who had no reported history of treatment versus those who had a history of previous treatment. To define average suppression maps, the mean values of 40 regions (one mean per region) were calculated and data were analyzed using a mixed model ANOVA. The relationship between the degree of suppression measured using the mapping test and clinical parameters (i.e., VA and stereo acuity), and comparisons of the measured effective contrast ratios among three psychophysical paradigms in observers with anisometropic amblyopia were assessed using Pearson's *R* correlation coefficient. Repeated measures within-subject ANOVA was performed to compare the effective contrast ratios (Effective Contrast Ratio = Matching Contrast/Base Contrast on Suppression Mapping) among the three psychophysical tasks, whereby the Bonferroni test was used to conduct pairwise comparisons, correcting for multiple comparisons.

Table 3. Mean Matching Contrast Values (%) and Multiple Comparisons for the Different Central Field Sectors in Anisometropic Amblyopes

Sector	Amblyopia Group	*P* Value	Amblyopia Group With Filter	*P* Value
0–2°	14.44 ± 16.82	–	35.64 ± 28.00	–
2–4°	20.05 ± 17.66	0.084*	41.92 ± 28.10	0.136*
4–6°	25.87 ± 21.17	0.001*	46.02 ± 26.45	0.014*
6–8°	31.22 ± 18.43	<0.001*	53.54 ± 24.47	<0.001*
8–10°	45.74 ± 22.79	<0.001*	68.31 ± 26.75	<0.001*
Upper visual field	26.98 ± 16.91	0.445	48.87 ± 23.69	0.749
Lower visual field	27.94 ± 16.73		49.30 ± 23.11	
Left visual field	27.61 ± 17.36	0.754	49.13 ± 23.28	0.953
Right visual field	27.31 ± 16.00		49.04 ± 23.68	
Mean	27.46 ± 16.52	–	49.09 ± 23.16	–
Other comparisons				
2–4° vs. 4–6°	–	0.073	–	0.328
2–4° vs. 6–8°	–	0.001	–	0.006
2–4° vs. 8–10°	–	<0.001	–	<0.001
4–6° vs. 6–8°	–	0.099	–	0.075
4–6° vs. 8–10°	–	<0.001	–	<0.001
6–8° vs. 8–10°	–	<0.001	–	0.001

All values are given as mean ± SD. In amblyopia group, 2.0 ND and without any ND filter were placed on the fellow eye.

* *P* values are shown for comparison between 0° and 2° and other eccentricities (univariate ANOVA were performed, and the LSD test was used to conduct multiple comparisons).

RESULTS

Distribution Characteristics of Interocular Suppression Among Normal Observers

During normal viewing, mean matching contrast values for the five central field eccentricities are shown in Table 2. A univariate ANOVA conducted on the dichoptic suppression mapping measurements showed significant effects of eccentricity ($F_{[4,88]} = 9.284$, $P < 0.001$). Our data showed that there were significant differences among five eccentricities. There was a trend that suppression appeared to be less along greater eccentricities, the 0° to 2° eccentricity had the lowest mean matching contrast compared to other eccentricities in normal observers (Table 2). Similarly, with ND filters in place, there also were statistically significant differences in the mean matching contrast values between different eccentricities; a minimum mean matching contrast at the 0° to 2°eccentric sectors was detected compared to other eccentricities ($F_{[4,88]} = 11.740$, $P < 0.001$; Table 2). We also explored whether there was a performance asymmetry between the upper and lower visual fields, left and right visual fields along the horizontal and vertical meridians in normal observers. The paired *t*-test analysis revealed that there were no significant asymmetries

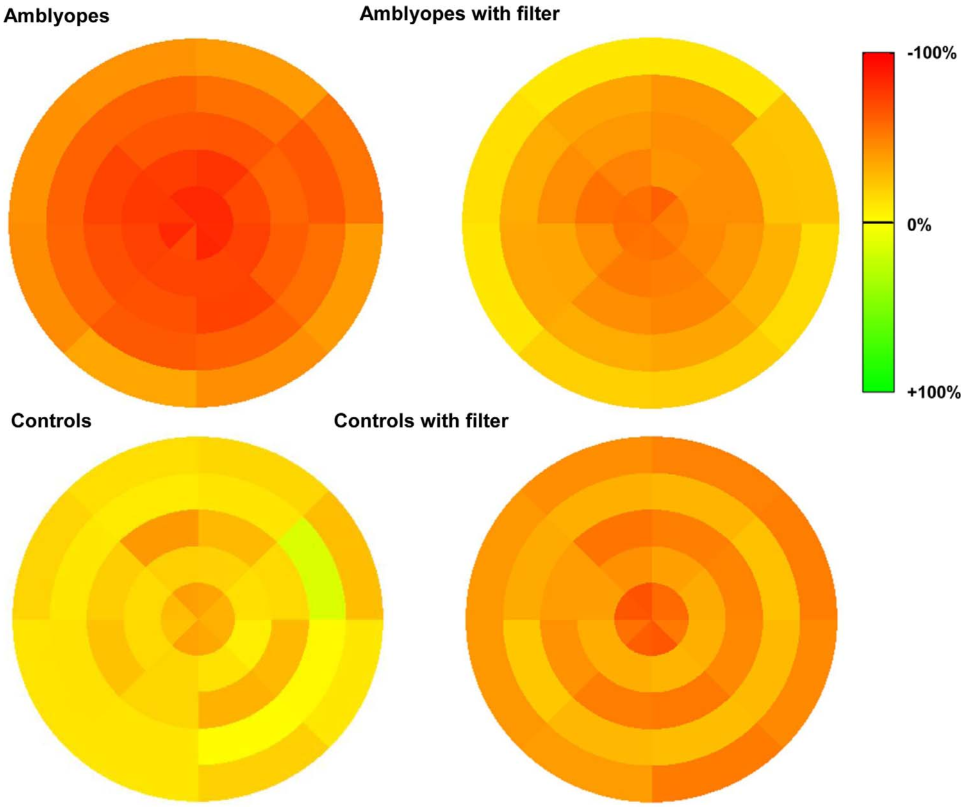

Figure 2. Average suppression maps without and with ND filters over the fellow eye across the central field in normal observers and observers with anisometropic amblyopia. Each section on the color map corresponds to a sector in the suppression mapping stimulus (Fig. 1). The degree of the contrast mismatch between the two eyes is presented using a color code with *red* indicating contrast underestimation (suppression), *green* indicating contrast overestimation (facilitation), and *yellow* indicating a perfect match. Reduction of the fellow eye's mean luminance could alleviate interocular suppression in amblyopic observers. Controls with ND filters had significantly stronger suppression than those without.

between the upper and lower visual fields (no filter, $t_{22} = -0.825$, $P = 0.418$; with ND filter, $t_{22} = -1.530$, $P = 0.140$), or between the left and right visual fields (no filter, $t_{22} = -0.651$, $P = 0.522$; with ND filter, $t_{22} = 0.171$, $P = 0.866$).

Distribution Characteristics of Interocular Suppression in Amblyopic Observers

A univariate ANOVA conducted on the dichoptic suppression mapping measurements indicated significant effects of eccentricity ($F_{[4,100]} = 27.827$, $P < 0.001$). The amblyopic group showed stronger suppression within the foveal region even though interocular suppression was evident throughout the whole 10° visual field (0°–2°eccentric sectors compared to other eccentricities; all $P < 0.05$, except for 2°–4°; comparisons between other eccentricities are shown in Table 3). With a 2.0 strength ND filter worn over the fellow eye, our data indicated that a reduction of mean luminance in the non-amblyopic eye reduced its suppression on the amblyopic eye, but it remained pronounced within the central most part (0°–2°eccentric sectors compared to other eccentricities: all $P < 0.05$, except for 2°–4°; other multiple comparisons are presented in Table 3). There were no significant asymmetric performances along the horizontal and vertical meridians, between the upper and lower visual fields (no filter, $t_{25} = -0.775$, $P = 0.445$; with ND filter, $t_{25} = -0.323$, $P = 0.749$), or the left and right visual fields (no filter, $t_{25} = 0.317$, $P = 0.754$; with ND filter, $t_{25} = 0.059$, $P = 0.953$).

Comparison Between Amblyopic and Normal Observers

The average spatial color maps for normal observers and anisometropic amblyopes (with or without ND filters) are presented to provide a visual illustration of the mean matching contrast of each segment of the stimulus (Fig. 2). A mixed model ANOVA factoring in eccentricities (five central field sectors: 0°–2°, 2°–4°, 4°–6°, 6°–8°, and 8°–10°) and observer groups (anisometropic amblyopes with and without ND filters, controls with and without ND filters) showed a significant main effect of the group ($F_{[3,94]} = 20.117$, $P < 0.001$; Tables 2, 3). Post hoc Bonferroni tests (corrected for multiple comparisons) indicated significant differences between anisometropic amblyopes and controls ($P < 0.001$), between anisometropic amblyopes and anisometropic amblyopes with an ND filter ($P < 0.001$), and between controls and controls with an ND filter ($P = 0.001$). As illustrated under Figure 2, the magnitude of suppression measured in amblyopic participants could be simulated by mean luminance reduction in normal observers, as well as alleviated by wearing ND filters over the fellow eye. There was a significant overall effect of eccentricity with suppression ($F_{[3,281]} = 44.375$, $P < 0.001$), whereby the level of suppression reduced with increasing eccentricity among all subgroups. We also found that there was a statistically significant interaction between group and eccentricity ($F_{[9,281]} = 6.311$, $P < 0.001$). This signifies that the effect of eccentricity on the degree of suppression was more pronounced for the amblyopic group than for the control group.

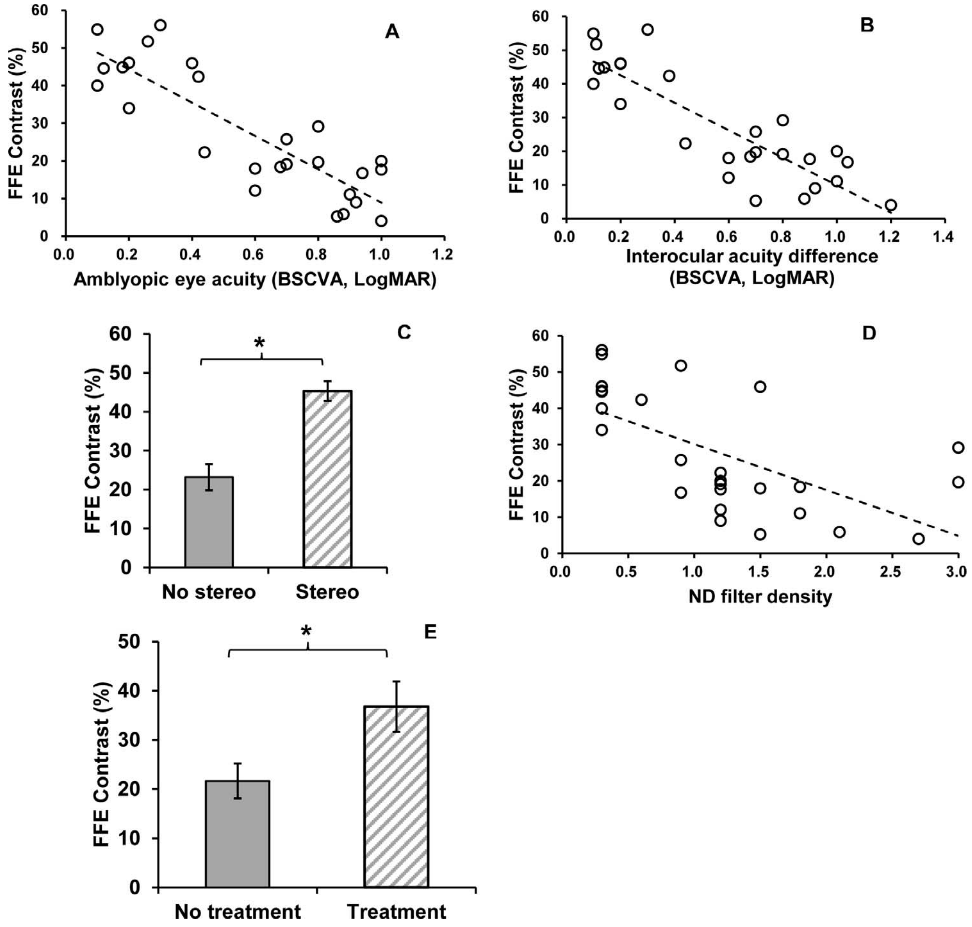

Figure 3. Graph showing the relationship between interocular suppression measured using the suppression mapping test and clinical parameters. Suppression is shown on the *y*-axes with lower values signifying stronger suppression. Deeper suppression was significantly correlated with (**A**) poorer amblyopic eye acuity, (**B**) interocular acuity difference. (**C**) Patients with measurable stereo had significantly lower suppression than those with no measurable stereo. (**D**)The degree of suppression was significantly correlated with measurements made using the combination of Bagolini striated lenses and ND filters. (**E**) Anisometropic amblyopes who had never received treatment showed stronger suppression than the treated group. *Statistically significant difference ($P < 0.001$). *Error bars*: ±1 SEM.

Relationships Between Suppression and Standard Clinical Measures

We examined the relationships between the magnitude of suppression evaluated by the suppression mapping test and clinical measures of traditional visual function, such as VA and stereo acuity. The results revealed that best spectacle-corrected VA (BSCVA) in the amblyopic eye was significantly correlated with the magnitude of suppression, whereby a deeper suppression was associated with a poorer amblyopic eye BSCVA ($r = -0.858$,95% confidence interval [CI], –0.884 to –0.827, $P < 0.001$; Fig. 3A). If interocular acuity difference was considered, the relationship also held (BSCVA, $r = -0.865$; 95% CI, –0.890 to –0.835; $P < 0.001$; Fig. 3B). In this study, five amblyopic participants had measurable stereo acuity (mean matching contrast = 45.32% ± 5.70%) while the other participants ($n = 21$) had no measurable stereo acuity (23.21% ± 15.36%). These results showed that amblyopes with measurable stereo acuity had a significantly lower suppression than those with no measurable stereo acuity ($t_{24} = -3.126$, $P = 0.005$; Fig. 3C).

In addition, the severity of suppression was in good agreement with measurements made using the combination of Bagolini striated lenses and ND filters ($r = -0.628$; 95% CI, –0.689 to –0.558, $P = 0.001$; Fig. 3D). Finally within our sample, for the 16 participants who had never received treatment and 10 participants who had received treatment (including wearing spectacles), those anisometropic amblyopes who had never received treatment showed a stronger suppression relative to the treated group (21.64% ± 14.24% vs. 36.78% ± 16.23%, $t_{24} = -2.500$, $P = 0.02$; Fig. 3E). We compared the amblyopic eye acuity of the untreated group with the treated group, and found no significant difference (0.67 ± 0.30 vs. 0.44 ± 0.32, $t_{24} = 1.858$, $P = 0.076$). These findings demonstrated that our novel measure of the level in binocular imbalance covaried with conventional clinical measurements of monocular or binocular visual functions such as vision acuity and stereo acuity as well as treatment history.

Interocular Suppression in Three Psychophysical Tasks

We examined the relationship between the dichoptic suppression mapping task and the other two psychophysical tasks. A repeated measures within-subject ANOVA demonstrated that effective contrast ratios for amblyopes were no different among the three different psychophysical tasks (acuity difference between the eyes as covariates, $P = 0.705$). Comparisons of the effective contrast ratios at the balance point among these three paradigms are shown in Figure 4.

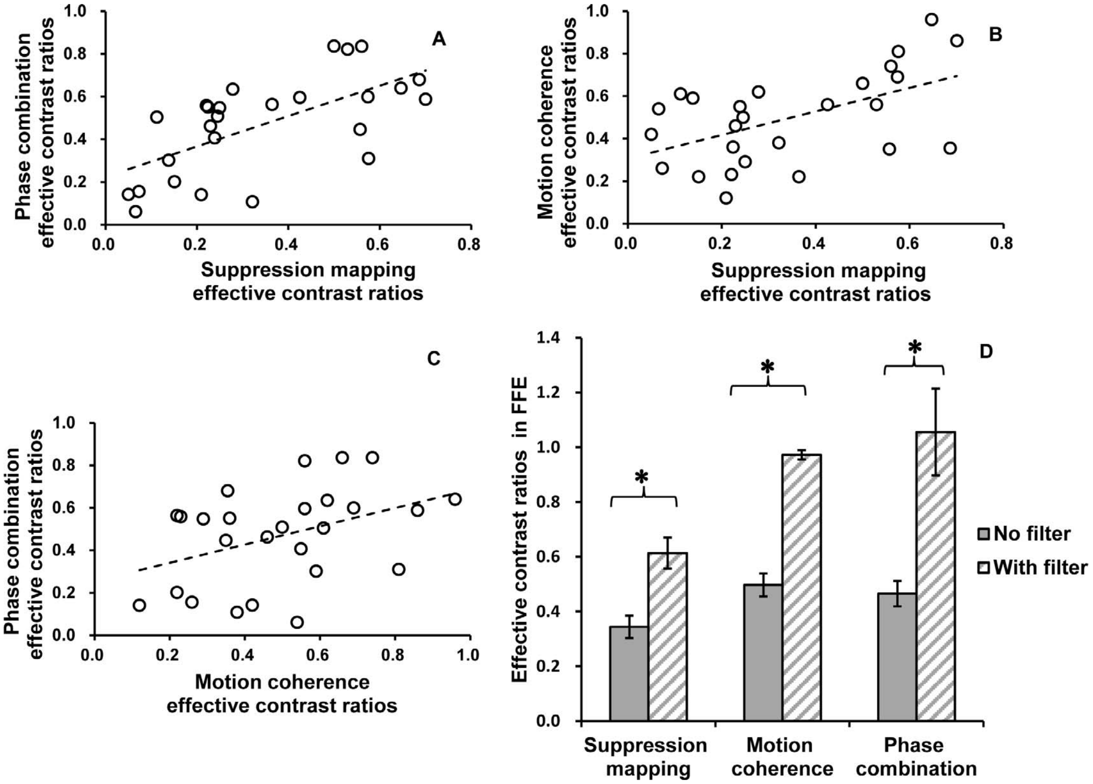

Figure 4. Comparisons of the measured effective contrast ratios in observers with anisometropic amblyopia (Effective Contrast Ratio = Matching Contrast / Base Contrast on Suppression Mapping) at the balance point in three paradigms. (**A**) Comparisons between the results in the suppression mapping task and in the phase combination task. (**B**) Comparisons between the results in the suppression mapping task and in the motion coherence task. (**C**) Comparisons between the results in the motion coherence task and in the phase combination task. The *dashed line* represents a linear fitting. (**D**) Comparisons of the measured effective contrast ratios at the balance point of three paradigms in patients without and with ND filter in front of the fellow fixing eye (FFE). Subject 24 did not finish the measurement in phase combination task with filter, we excluded the data in our analysis. *Statistically significant difference ($P < 0.001$). *Error bars*: ±1 SEM.

While the correlation test showed that there was a significant positive correlation between the results among these three paradigms (suppression mapping versus binocular phase combination, $r = 0.638$; 95% CI, 0.570–0.698; $P < 0.001$, Fig. 4A; suppression mapping versus global motion coherence, $r = 0.535$; 95% CI, 0.454–0.607; $P = 0.005$, Fig. 4B; global motion coherence versus binocular phase combination, $r = 0.406$; 95% CI, 0.312–0.492; $P = 0.039$, Fig. 4C). For the three psychophysical paradigms, the results indicated that with a 2.0 strength ND filter worn over the fellow eye, the contrast ratio at the balance point of all the amblyopes improved significantly (suppression mapping, 0.34 ± 0.21 vs. 0.61 ± 0.29; $t_{25} = -8.869$, $P < 0.001$; global motion coherence, 0.5 ± 0.22 vs. 0.97 ± 0.09; $t_{25} = -11.282$, $P < 0.001$; binocular phase combination, 0.47 ± 0.23 vs. 1.06 ± 0.79; $t_{24} = -4.055$, $P < 0.001$; Fig. 4D).

DISCUSSION

The aim of this study was to verify the efficacy of a novel dichoptic mapping paradigm to estimate visual function in anisometropic amblyopes. First, our study showed that the distribution of suppression was symmetric and appeared to be less at greater eccentricities, and deepest at the foveal area in the amblyopic and control groups. We then investigated suppression changes across the visual field by mean luminance modulation between amblyopic and normal observers. Based on simulation and elimination of visual suppression, we identified a novel method that could effectively reflect suppression distribution in anisometropic amblyopes. In addition, we found this novel suppression test correlated well with standard clinical measures of VA and stereo acuity. There were good consistencies between the results of interocular suppression with dichoptic mapping paradigm and results of the two prior psychophysical tests.

All participants showed some degree of suppression. Four participants from the control group showed pattern facilitation (mean matching contrast value >80%) or very weak pattern suppression. This mean value reflected a suppression map that did not always correspond to the same eye dominance found in the sighting eye dominance test. In normal individuals, a balanced binocular system has an equally-weighted contribution to the binocular neural network. The right and left eyes support binocular functions, such as binocular summation, fusion, and stereopsis. Excitatory and inhibitory binocular interactions exist between the two eyes. Once this mutual inhibition is unbalanced, normal binocular vision will be disrupted, resulting in SED. The clinical population with amblyopia is identified as an extreme example of normal subjects with SED, which suggests a substantial role of interocular suppression in the amblyopic and normal visual systems.[5,50,52,53] The suppression mapping test has a useful application in quantitative perimetry of suppression in normal individuals.

In addition, our results showed a symmetric suppression change across the field, where suppression reduction was observed with increasing eccentricity, 10° from the center in normal and amblyopic observers. This was consistent with the report of Babu et al.[35] In their study, however, they tested only

10 normal subjects and provided a trend figure without exact values. The regional distribution of suppression after luminance reduction with ND filters also was similar to the findings of Babu et al.[35] on anisometropic and strabismic amblyopes and the results of Xu et al.[52] on normals within the central 4° field. Babu et al.[35] reported an extensive suppression throughout the visual field in strabismic and anisometropic amblyopes, whereby strongest suppression was found within the central most region of the binocular field. They did not perform a statistical analysis of symmetry and the number of anisometropic amblyopes enrolled was limited ($n = 4$). In the study of Xu et al.,[52] the stimulus comprised of a pair of dichoptic vertical and horizontal sinusoidal grating disks on a gray background. They measured SED locally in 17 locations (at retinal eccentricities 0°, 2°, and 4°). Their study revealed that the observer's SED varied gradually across the binocular visual field. There was no significant upper/lower or left/right field asymmetry for local SED (we used the same statistical analysis approach in this study). It was concluded that an imbalance of interocular inhibition was a significant factor impeding binocular visual perception. This imbalance also can reflect the amblyopic condition as well, which is in agreement with our findings. Moreover, previous literatures reported that anisometropic amblyopes showed weaker suppression effects than strabismic amblyopes.[18,54] This was different from the results of Babu et al.[35] and needs further investigation.

Based on previous reports, there is an ambiguity regarding visual field symmetry deficits. Sireteanu and Fronius[32] found that VA of the nasal retina was significantly more reduced than the temporal retina in the central 20° visual field of esotropic amblyopes using vertical grating resolution. It was suggested that the fovea of the fellow eye may be suppressing the nasal retina in esotropes. Their results also showed a uniformity in suppression distribution (without any obvious asymmetry or foveal preference) among anisometropic amblyopes, which was different from our analysis of eccentricity. Phillipp et al.[36] detected central scotomas in over 80% of their patients with strabismic and/or anisometropic amblyopia. By means of Humphrey 30-2 static perimetry, Donahue et al.[37] found different types of amblyopia were associated with a generalized light sensitivity depression, which was proportionately greatest at the fovea. A greater relative depression was noted at the temporal hemifield compared to the nasal hemifield in strabismic amblyopes.[37] Joose et al.[33] reported three types of suppression in a group of consecutive divergent strabismus: total suppression, nasal hemisuppression, and panoramic viewing without suppression. In addition, Greenstein et al.[38] compared the visual field results obtained from multifocal visual evoked potential (mfVEP) and Humphrey Visual Field Analyzer (HVFA) in strabismic amblyopes. The data from both tests were analyzed in terms of superior and inferior hemifields. It was noted that mfVEP was more sensitive than HVFA in detecting defects across the visual field. Asymmetry was not, however, investigated in their study. Hence, our analysis of symmetry is important and necessary.

In accordance with previous investigations, our results indicated that amblyopia could be simulated in normal observers by using ND filters. In addition, interocular suppression could be alleviated by wearing an ND filter over the nonamblyopic eye in amblyopic observers.[6,8,40–42,46,47] By establishing and alleviating interocular suppression using mean luminance modulation, we verified that the dichoptic suppression mapping technique could, indeed, provide topographically specific evaluation of interocular suppression in the central visual field of anisometropic amblyopes. The luminance stimuli in our study were used as first-order targets even though the amblyopic visual system also is sensitive to second-order image characteristics, such as contrast modulations. Recently, Chima et al.[55] measured interocular suppression depth and its extent in binocularly normal participants with one eye blurred using noiseless luminance (L), luminance-modulated noise (LM), and contrast-modulated noise (CM) stimuli across the central 24° visual field.[55] They found significantly deeper suppression in CM compared to LM stimuli by increasing differences in interocular blur, which suggests that CM stimuli may be processed by later mechanisms receiving binocular input. This may reflect greater extrastriate rather than striate deficits in amblyopia. It was speculated that CM stimuli may be a more sensitive method to detect suppression in suspected amblyopes. These views should be tested further in the near future.

The results of this study indicated that the level of suppression tested using the suppression-mapping paradigm significantly correlated with the depth of amblyopia and stereo acuity loss. That is, the deeper suppression, the poorer binocular and monocular visual functions will be. These results are consistent with previous results of similar studies in amblyopia using global motion coherence paradigms.[8,17,18] The findings from Barrett et al.[39] were opposite to ours. They documented that the weaker eye of strabismic amblyopes was not suppressed in 70% of strabismic amblyopes. This discrepancy is likely due to the differences in measurement methods and the fact that most subjects tested in their study had very mild amblyopia. Nevertheless, in this study we cannot fully separate the depth of amblyopia from binocular function because four of five participants with measurable stereo acuity were subjects who are currently not amblyopes, but with a previous history in our study. The lack of VA deficit, rather than measurable stereo acuity, could be the reason for lower suppression. Our sample size of participants with measurable stereo acuity was small. Furthermore, our study showed that the Bagolini test result also was in accordance with the outcome of our novel technique.[8] These provided further evidence that dichoptic mapping paradigm is in good agreement with conventional clinical measures.

Previous studies have confirmed that binocular phase combination (6.8° visual angle) and global motion coherence paradigms (22° visual angle) could accurately offer quantitative information relating to the magnitude of suppression.[8,17,56] In our research, the suppression mapping paradigm provided a topographically comparable evaluation of interocular suppression. In amblyopic observers, we did not find statistical difference among the three different psychophysical tasks, but a significant positive correlation among the results in these three paradigms was evident. In addition, reduction of mean luminance in the nonamblyopic eye can weaken suppression in these three methods. This is not in agreement with the research of Zhou et al.[27] It was documented that motion-based processing was more affected than comparable spatial-based estimation, with each task targeting a different cortical function and location.[27] Suppression appears to affect spatial and global processing quite differently.[31] The possible reason for our failure to reveal difference of suppression among the three psychophysical tasks may be due to different amblyopia subtypes and/or different degrees of suppression. In the study of Zhou et al.,[27] only one of the included 11 adult amblyopes had anisometropic amblyopia. Averaged across all 11 observers, the contrast ratio at the balance point was 0.137 ± 0.102 in the dichoptic global motion coherence paradigm (0.5 ± 0.22 in our data).

There also were certain limitations in this study. First, as with all perimetry-related tests, unsteady fixation could have influenced perimetric results, even though subjects were reminded to fixate on a central black dot during this test. To improve this condition, an eye tracking device should be included in future tests. Second, this test lasted a little less than 15 minutes, which may render the results less meaningful if the participant had a short attention span. The testing time needed to optimize the threshold value for suppression mapping should be minimized as much as possible. Third, the testing feasibility and reliability cutoff age is not well investigated at this time. Only observers with anisometropic amblyopia were enrolled in our study. Finally, suppression was only mapped across the central 10°. We aim to extend our measurements to more peripheral regions of the visual field in the future. However, our current model has established a good applicable foreground in furthering evaluation and binocular treatment of amblyopia in terms of targeting the suppression mechanics.

The dichoptic suppression-mapping paradigm is a promising technique. It can provide an overall assessment on the severity of amblyopia, and follow-up monitoring. In the future, "micro-" perimetric mapping of suppression zones can be targeted toward amblyopia therapy. Furthermore, our future work will recruit a more diverse group of amblyopic, strabismic observers to explore the neural mechanisms underlying suppression.

In summary, the dichoptic suppression mapping technique provides a precise, topography-specific evaluation of interocular suppression of the central 10° field in anisometropic amblyopes. It is an effective method to identify visual functional damages in anisometropic amblyopes, laying a clinical application in future amblyopia diagnosis and treatment. Moreover, suppression mapping may be of value in predicting treatment outcomes because it incorporates a spatial mapping measure that may supplement the current predictive values of VA and stereopsis alone.

Acknowledgments

The authors thank Robert Hess and Jiawei Zhou from McGill University for providing the program in this study.

Supported by grants from Young Teacher Training Project of Sun Yat-sen University to Jinrong Li, the Guangdong Natural Science Foundation (2015A030312016), and the Science and Technology Planning Projects of Guangdong Province (2014B030301040) to Minbin Yu. The authors alone are responsible for the content and writing of this paper.

Disclosure: **J. Li**, None; **J. Li**, None; **Z. Chen**, None; **J. Liu**, None; **J. Yuan**, None; **X. Cai**, None; **D. Deng**, None; **M. Yu**, None

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