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Effects of Temporal Frequency on Binocular Deficits in Amblyopia

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Abstract

Amblyopia is associated with a range of well-known visual spatial deficits, which include reduced contrast sensitivity, spatial distortions, interocular suppression, and impaired stereopsis. Previous work has also pointed to deficits in processing dynamic visual information, but it is unknown whether these deficits influence performance under binocular conditions. We examined the effects of temporal modulation on contrast sensitivity and binocular interactions in a preliminary study of 8 adults with amblyopia and 14 normally-sighted control subjects. For each observer, we measured interocular balance and stereopsis thresholds with binocular flicker across a range of four temporal (0, 4, 7.5, and 12 Hz) and spatial (1, 2, 4, and 8 cpd) frequencies. Interocular balance was estimated by varying the relative contrast of dichoptic letter pairs to produce perceptual reports of each letter with equal frequency, and stereopsis thresholds were measured by determining the minimum disparity at which subjects identified a front-depth target with 75% accuracy. Consistent with previous findings, we observed greater interocular imbalance and impaired stereoacuity at high spatial frequencies in amblyopes. In contrast, the effects of temporal frequency on performance were smaller: across both groups, interocular imbalance was largest at mid-to-low temporal frequencies, and stereopsis thresholds were unaffected by temporal frequency. Our results suggest that there may be a previously unreported effect of temporal frequency on interocular balance, as well as a possible dissociation between the effects of flicker on interocular balance and stereopsis.

Keywords

Amblyopia; binocularity; stereopsis; suppression; temporal frequency; flicker; temporal contrast sensitivity

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1. Introduction

Binocular vision is important for many daily activities, as it provides the basis for stereoscopic depth perception and yields advantages for a range of visually-guided skills, such as reading, reaching and grasping, and fine motor control (Melmoth & Grant, 2006; O'Connor, Birch, Anderson, & Draper, 2010; Sheedy, Bailey, Buri, & Bass, 1986; Webber, Wood, Gole, & Brown, 2008). These critical visual functions are impaired in individuals who have amblyopia, a visual disorder characterized by an optically uncorrectable loss of visual acuity due to abnormal binocular interactions, which may be caused by unequal or uncorrected high refractive error, ocular misalignment or form deprivation (e.g., due to congenital cataracts). Amblyopia is associated with a range of visual spatial deficits (see Webber & Wood, 2005, for a review), which include reductions in contrast sensitivity (Bradley & Freeman, 1981; Hess & Howell, 1977; Levi & Harwerth, 1977), impaired stereopsis (Cooper & Feldman, 1978; McKee, Levi, & Movshon, 2003; Simons, 1981), interocular suppression (Jampolsky, 1955; Travers, 1938), and spatial distortions (Barrett, Pacey, Bradley, Thibos, & Morrill, 2003; Piano, Bex, & Simmers, 2015, 2016; Pugh, 1958; Sireteanu, Thiel, Fikus, & Iftime, 2008).

These amblyopic visual deficits have been primarily examined in the spatial domain, and have been shown to vary with stimulus spatial frequency. In many cases, contrast sensitivity loss is largest at high spatial frequencies (Hess & Howell, 1977; Levi & Harwerth, 1977), and several other deficits—including interocular imbalance (Birch et al., 2016; Kwon et al., 2015), stereopsis (Holopigian et al., 1986) and spatial distortions (Barrett et al., 2003)—tend to show deficits at high spatial frequencies as well. At the neuronal level, these impairments may be due to a loss of spatial resolution in primary visual cortex, as neurophysiological studies have demonstrated shifts in the tuning of neurons driven by the amblyopic eye toward lower spatial frequencies. (Kiorpes, Kiper, O'Keefe, Cavanaugh, & Movshon, 1998; Movshon et al., 1987).

Since amblyopia is traditionally characterized as a deficit in spatial processing, comparatively less is known about the influence of temporal factors on amblyopic visual deficits, or potential interactions between spatial and temporal processing deficits. Work examining amblyopes' sensitivity to temporal visual information has found evidence for impairments in the speed of visual processing for stimuli shown to the amblyopic eye. These include a number of studies showing increased response latencies for images shown to the amblyopic eye, based on either reaction time measures (Hamasaki & Flynn, 1981; Von Noorden, 1961), saccade latencies (Ciuffreda, Kenyon, & Stark, 1978; McKee, Levi, Schor, & Movshon, 2016), or visual evoked potentials (Levi & Harwerth, 1978; Levi & Manny, 1980; Sokol, 1983). However, these temporal deficits cannot be readily disambiguated from reductions in spatial contrast sensitivity. Since reductions in stimulus intensity are associated with increases in response latencies (Piéron, 1913), these delayed response times could be a direct consequence of reductions in effective luminance or contrast in the amblyopic eye.

In addition, several studies have measured temporal contrast sensitivity functions (TCSFs) and critical flicker frequency (CFF) thresholds in observers with amblyopia. One possibility is that impairments in the speed in processing visual information in the amblyopic eye could

result in reduced temporal contrast sensitivity and lower CFF thresholds. For example, delays in the time required to process incoming visual signals could impair an observers' ability to discriminate between consecutive stimulus cycles, and manifest as a reduction in critical flicker frequency. Consistent with this idea, several early studies showed reduced temporal contrast sensitivity at a broad range of temporal frequencies (Manny & Levi, 1982b; Wesson & Loop, 1982), as well as reductions in critical flicker frequency (Alpern, Flitman, & Joseph, 1960; Feinberg, 1956). However, these have shown significant variability between experiments and individual subjects, as many additional factors (e.g., luminance, spatial frequency, stimulus size) have been shown to influence critical flicker frequency. In particular, experiments varying the spatial component of the stimulus have shown that losses in contrast sensitivity typically depend on spatial frequency, with amblyopes often exhibiting normal temporal contrast sensitivity at low spatial frequencies (Bradley & Freeman, 1985; Levi & Harwerth, 1977; Manny & Levi, 1982a). Taken together, these results suggest that amblyopic deficits in contrast detection may depend primarily on spatial, rather than temporal frequency.

Other studies have pointed to several deficits in motion perception, including deficits in the perception of global motion (Simmers, Ledgeway, Hess, & McGraw, 2003), oscillatory movement displacement (Buckingham, Watkins, Bansal, & Bamford, 1991), motion-defined form (Giaschi, Regan, Kraft, & Hong, 1992), and motion aftereffects (Hess, Demanins, & Bex, 1997). There is also evidence that amblyopes have a reduced ability to detect and discriminate temporally asynchronous events in the amblyopic eye (Huang, Li, Deng, Yu, & Hess, 2012; St. John, 1998; Steinman, Levi, & McKee, 1988), and have impairments in grouping visual elements based on temporal information (Spang & Fahle, 2009). Although the mechanisms for these deficits have not been established, increased visual processing time could account for these deficits in motion and temporal synchrony perception. In addition, neurophysiological findings have pointed to reductions in the synchrony of neural firing in response to visual input to the amblyopic eye (Roelfsema, König, Engel, Sireteanu, & Singer, 1994). Others have proposed that the normally sustained responses of parvocellular neurons may be shortened in amblyopia (Altmann & Singer, 1986), which may account for deficits in temporal integration and temporal instability in perceptual distortions (Thiel & Iftime, 2016).

Deficits in monocular processing of temporal visual information, as indicated by these studies, would also predict impairments in binocular visual function (e.g., stereopsis) with flickering images, and variation in performance on binocular tasks as a function of temporal frequency. However, there has been little reported to date on the effects of temporal modulations on binocular function in amblyopes. In normally sighted observers, temporal modulations have been shown to influence binocular interactions. For example, high temporal frequencies are associated with increased stereopsis thresholds (Kane, Guan, & Banks, 2014; Lee, Shioiri, & Yaguchi, 2003, 2007; Norcia & Tyler, 1984; Patterson, 1990; Richards, 1972), and continuous flash suppression is largest at low temporal frequencies, depending additionally on the spatial properties of the mask (Han, Lunghi, & Alais, 2016; though see Zhu, Drewes, & Melcher, 2016). There may also be different effects of spatial and temporal stimulus frequency on stereopsis thresholds compared to interocular balance,

as evidenced by a recent study in patients with myopia (Vera-Diaz, Bex, Ferreira, & Kosovicheva, 2018).

The aim of the present study was to address these gaps in the literature by measuring both stereopsis and interocular balance in amblyopes across a set of spatial and temporal frequencies: do these binocular measures show a similar pattern to monocular contrast sensitivity, which is mainly spatial, but not temporal frequency dependent? Or is there variation in stereopsis and interocular balance across temporal frequency, due to impairments in the speed of visual processing in amblyopia? To examine these relationships, we measured interocular balance points and stereopsis thresholds across a broad range of spatial and temporal frequencies in a preliminary study, testing both amblyopes and normally-sighted controls. If temporal processing deficits are implicated in amblyopia, we would predict impairments in binocular vision with flickering images, beyond the variation seen in normally-sighted observers, and these impairments would be consistent across a range of spatial frequencies. Measuring both stereopsis thresholds and interocular balance points allows us to also test whether the effects of temporal frequency are consistent across different types of binocular interactions (i.e., binocular fusion and competition, respectively). In addition, we measured monocular temporal contrast sensitivity functions (TCSFs)—at each of four spatial frequencies per subject—to determine the relationship between monocular contrast sensitivity and our binocular measures.

2. Methods

2.1. Subjects

We recruited a total of 28 adults from the New England College of Optometry community to participate in the study. Subjects were assigned to the control and amblyope groups based on the criteria described below. Six subjects did not meet the acuity criteria for either group and were excluded from the final sample. The final sample consisted of 22 subjects (mean age: 25.5 years, range 18 – 50), with 8 amblyopes and 14 normally-sighted control subjects. Normally-sighted control subjects had a best-corrected visual acuity (BCVA) of 0.00 logMAR or better in each eye, and no history of accommodative or binocular anomalies. Amblyopic subjects had a BCVA of 0.00 logMAR or better in the fellow eye, and 0.10 logMAR or worse in the amblyopic eye. In addition, amblyopic subjects had an interocular BCVA difference of at least 0.16 logMAR. Subjects in the amblyope group could have refractive (anisometropic, isometropic or meridional), strabismic, or mixed amblyopia. In addition to these criteria, subjects in both groups were: (1) not using any medications that could affect their vision, (2) had no history of eye disease that could have resulted in visual consequences, (3) had no history of epilepsy or other seizures (to minimize seizure risk associated with viewing the flickering images in study), and (4) had sufficient language skills, hearing, and mental ability to understand the consent process and experiment instructions.

Procedures were approved by the Institutional Review Board at the New England College of Optometry, and followed the tenets of the Declaration of Helsinki. Subjects gave written informed consent prior to participating in the experiment.

2.2. Screening Procedures

To determine eligibility based on the above criteria, subjects completed a vision screening procedure, which included a questionnaire on their refractive, ocular, and medical history. We determined refractive errors for each eye by objective refraction with an open-field autorefractor (Grand Seiko WR5100K). This was followed by binocular subjective refraction with binocular balancing. A computerized LogMAR chart was used to evaluate each subject's best-corrected visual acuity (BCVA).

In addition, we performed several tests to evaluate binocular and accommodative function. Strabismus was assessed with an alternating cover test, and in those subjects that microtropia was suspected, it was ruled out using a four prism diopter base-out test. Subjects completed clinical stereopsis (Random Dot 3) and suppression (Worth 4-Dot and Bagolini Striated Lens Test with neutral density filters to evaluate the depth of suppression if indicated) tests at a 40 cm viewing distance. For the Worth 4-Dot and Bagolini Tests, the level of suppression was evaluated using neutral density filters placed over the fellow eye to determine the lowest filter value at which the subject reported the image in the amblyopic eye. Finally, subjects completed a hole-in-card motor eye dominance test (Pointer, 2012; Walls, 1951). The results of the screening procedures for the amblyope group are summarized in Table 1.

2.3. Stimuli and Procedures

Stimuli were shown on a gamma-corrected ROG SWIFT PG278Q Asus LCD monitor and run on a PC computer with an NVidia GeForce GTX 780 graphics processing unit. Display resolution was set to 1920 × 1080 and the refresh rate to 120 Hz. The response time of the display was measured with an Optical Transient Recorder OTR–3 (Display Metrology & Systems GmbH & Co. KG, Karlsruhe, Germany) at 10 kHz using full-field flicker. The experiment was programmed using the Psychophysics Toolbox Version 3 (Brainard, 1997; Kleiner, Brainard, & Pelli, 2007; Pelli, 1997) in Matlab (The MathWorks, Inc., Natick, MA). For the interocular balance and stereopsis measurements, subjects viewed the display binocularly through wireless LCD active shutter glasses synchronized to the refresh of the monitor (NVidia 3D Vision; 60 Hz monocular refresh). The glasses were synchronized using an infrared signal from an emitter connected to the computer over USB, and the monitor refresh rate was selected for compatibility with the shutter glasses. For the temporal contrast sensitivity measurements, the display was viewed monocularly (without shutter glasses), and the untested eye was occluded with an eye patch. A chinrest was used to stabilize head position at a viewing distance at 40 cm. At this distance, the display subtended approximately 73° horizontally and 42° vertically.

Each subject completed 1,664 trials, in which forced-choice tasks were used to measure temporal contrast sensitivity functions, stereopsis thresholds and interocular balance points as a function of temporal and spatial frequency (400, 624, and 640 trials for each of the three tasks, respectively). Stimuli consisted of spatially bandpass-filtered Sloan letters (TCSF and interocular balance point measurement) or circles (stereopsis measurement) on a uniform gray (85 cd/m^2) background. Sloan letters had a 5:1 optotype height to stroke width ratio, and circles had a 1:1 aspect ratio. All images were spatially filtered using an isotropic log exponential filter with a peak spatial frequency of 5 cycles per image and a bandwidth (full-

width at half-maximum) of two octaves. Images were scaled to 5, 2.5, 1.25, and 0.625° in height, resulting in peak spatial frequencies of 1, 2, 4, and 8 cycles per degree, respectively.

For the interocular balance and stereopsis measurements, we varied temporal frequency in separate blocks of trials, using sinusoidal counterphase flicker at one of four frequencies: 0 (static), 4, 7.5, and 12 Hz. These frequencies were selected based on the temporal frequency ranges used studies investigating the effects of temporal modulations in luminance on stereopsis thresholds (Patterson, 1990), and studies measuring binocular interactions in amblyopes (e.g., Schor, Terrell, & Peterson, 1976). For the temporal contrast sensitivity measurement, temporal frequencies were varied between trials, and selected using the adaptive procedure described in the next section. To improve the efficiency of the testing procedures, stimuli in all three tasks were arranged into charts, adapted from previous work (e.g., Birch et al., 2016; Kwon et al., 2015). Additionally, to allow subjects to attain the maximum level of performance possible within each stimulus condition, subjects were given an unlimited amount of time to view and respond to the stimuli.

2.3.1. Monocular temporal contrast sensitivity—Stimuli for the temporal contrast sensitivity measurement procedure were organized into charts consisting of four bandpass-filtered Sloan letters, one for each of the four spatial frequency conditions (Figure 1A). Letters were arranged vertically in a screen-centered column, in order of increasing peak spatial frequency from top to bottom (i.e., 1 cpd for the top letter and 8 cpd for the bottom letter). Adjacent pairs of letters had a vertical center-to-center separation of 1.5 times the height of the upper of the two letters. Each letter was centered within a black Nonius frame twice the height and width of the individual letter (line width: 0.14°), which was continuously visible. To avoid repeating letter identities within a chart, the four letters on each chart were randomly drawn without replacement from the full set of 26 letters of the English alphabet. Subjects performed a 26-alternative forced-choice (AFC) letter identification task, in which they were instructed to read the letters aloud from top to bottom. Responses were manually entered by the experimenter, and once all responses were recorded for a given chart, it was immediately replaced by the next chart.

The temporal frequency and contrast levels for individual letters were selected using the quick CSF (qCSF) Bayesian adaptive algorithm (Lesmes, Lu, Baek, & Albright, 2010) modified for 26AFC (Hou, Lesmes, Bex, Dorr, & Lu, 2015). Four temporal contrast sensitivity functions (TCSFs) were estimated using four independent instances of the qCSF algorithm, one for each spatial frequency condition (Figure 1B). The TCSF was described as an asymmetric log-parabola function with four parameters: (1) peak gain (γ_{max}), (2) peak temporal frequency (ω_{max}), (3) upper bandwidth (β_{hi}), and (4) lower bandwidth (β_{lo}). The initial priors for the qCSF parameters were: 2% Michelson contrast for γ_{max}, 3 Hz for ω_{ma}, and 3 octaves for β_{hi} and β_{hi}. On each trial, the qCSF algorithm selected a combination of contrast level and temporal frequency to maximize the expected information gain over the parameters of the TCSF. The temporal frequency and contrast levels were updated one chart at a time, and the selected stimulus properties for a given chart reflected responses from all preceding charts within a block of trials. Temporal frequencies selected by the qCSF algorithm were adjusted by rounding the number of frames in one full cycle to the nearest

integer. The dominant and non-dominant eyes of each subject were tested in separate blocks of trials, consisting of 50 charts (200 trials) each.

2.3.2. Interocular balance points—Stimuli and procedures were based on the dichoptic letter charts described by Kwon et al. (2015). Each letter chart consisted of 40 Sloan letters, grouped into 20 spatially overlapping dichoptic pairs. Letters were arranged into four lines (Figure 2A), each line consisting of five letter pairs from a single spatial frequency condition. The four lines on each chart were arranged in order of increasing spatial frequency from top (1 cpd) to bottom (8 cpd). Letters within a given line were evenly spaced, with a horizontal center-to-center spacing of twice the letter height in the corresponding line. Vertical center-to-center separation between adjacent lines was set to 1.5 times the letter height on the upper of the two lines. To avoid duplicate letters within the same line, the letter identities for each line were selected by randomly drawing ten letters without replacement from the 26 letters of the alphabet, which were then arranged into five pairs. To promote stable vergence, a binocular, screen-centered black rectangular Nonius frame (52.20° width × 20.95° height; line width: 0.55°) surrounded each chart. The four temporal frequency conditions (0, 4, 7.5, and 12 Hz) were tested in separate blocks of trials, and all letters within a chart flickered at the same temporal frequency. Phases were randomly selected for each letter within a pair, resulting in a net absence of any temporal delays between the two eyes

Subjects performed a 2AFC task for each letter pair, in which they were instructed to report the dominant percept by reading the letters on the chart out loud from left to right, starting with the top line. As before, the entire chart was continuously visible, and subjects were given an unlimited amount of time to respond. Responses were recorded manually by the experimenter using a keyboard.

The level of interocular balance was quantified by varying the relative contrast of the letters in each pair to find the balance point (BP)—the relative contrast at which subjects reported the two letters within a pair with equal frequency (Figure 2B). Contrast levels within each pair were constrained such that the peak Michelson contrast of the letter in the left eye was equal to 100% minus the peak Michelson contrast of the letter in the right eye. Within a block of trials, contrast levels were controlled using a modified version of the QUEST staircase algorithm (Watson & Pelli, 1983). Four independent, simultaneous instances of the QUEST algorithm were used to vary the contrast levels, one staircase for each spatial frequency condition. Staircases were set to converge on an equal proportion (50%) of left eye and right eye responses. On the first chart, the contrast levels on each line were fixed at five linearly spaced levels from 10% to 90% contrast in the right eye. On the remaining charts, the five contrast levels were calculated from −2, −1, 0, +1, and +2 standard deviations around the mean of the posterior probability density function (pdf). Within each line, the five contrast levels were always randomly assigned to one of the five letter positions. To avoid abruptly changing the contrast levels partway through a chart, the posterior pdf was only updated once the all responses for a given chart had been entered. As a result, contrast levels were updated one chart at a time, taking into account responses from all preceding charts within a block of trials.

Subjects completed the four temporal frequency conditions in separate blocks of trials, in a random order. Each block consisted of 8 charts (160 dichoptic letter pairs across all four lines). Each subject completed 40 trials (i.e., letter pairs) for each unique combination of spatial frequency and temporal frequency condition (640 trials in total).

2.3.3. Stereopsis Thresholds—As with the other two tasks, the stimuli used for stereopsis measurement were arranged into charts (Figure 3B), each chart consisting of 36 stereoscopic circles, grouped into 12 sets of three (referred to as triplets). Charts were organized into four lines, arranged in order of increasing spatial frequency condition, each line containing three triplets from a single spatial frequency condition. Triplets were arranged in evenly-spaced triangular configurations. Within a triplet, circles were arranged with a center-to-center separation equal to 2.2 times the circle height for the corresponding line. Within a given line, triplets alternated between upward pointing and downward pointing triangles, starting with a downward pointing triangle for the leftmost triplet in each line. Triplets were evenly spaced within a line with a horizontal center-to-center separation equal to four times the individual circle height in the corresponding line. Vertical center-to-center separation between adjacent lines was equal to four times the circle height on the upper of the two adjacent lines.

Each triplet was composed of one randomly chosen front-depth circle and two back-depth circles. Crossed and uncrossed disparities were produced by equal but opposite horizontal displacements of the left-eye and right-eye images by half the total disparity. The absolute disparity was the same for each circle within the triplet. In the flicker conditions, all circles had the same temporal frequency, and each triplet was assigned a randomly selected phase. All circles within a triplet (including the separate left-eye and right-eye images) were identical in phase, producing no temporal lag between the images in the two eyes. Peak Michelson contrast for each circle was 100%.

Subjects performed a 3AFC task in which they were instructed to click on the front-depth circle (or the oddball target, if unsure of the sign of depth) within each triplet using a cursor, from left to right within each row, and from top to bottom on the chart. The triangular configurations of the triplets were selected to minimize the influence of monocular cues, such that the task could not be performed based on a simple Vernier or bisection judgment. Separate testing confirmed poor performance on the stereopsis test under monocular viewing conditions, with accuracy at the largest disparity level between 32.1% and 39.7% across all spatial frequency conditions. As with the other procedures, subjects viewed the charts freely and were given an unlimited amount of time to respond. The triplet that the subject was instructed to respond to on each trial was centered within a black, binocular Nonius frame, 2.15 times the circle height on the corresponding line (line width of 0.05 times the circle height). This frame also highlighted the subject's progress within a chart, moving to the next item after each response.

Stereopsis thresholds were quantified by determining the smallest binocular disparity necessary to identify the front-depth target with 75% accuracy. As with the binocular balance task, the disparity levels were controlled by four simultaneous, independent QUEST staircases, with one staircase for each spatial frequency condition, each set to converge on

75% accuracy. The disparity levels on the first chart within a block of trials were set by the screening procedure described below. On each subsequent chart, the three disparity levels were calculated from −2, 0, and +2 standard deviations around the mean of the posterior pdf, and were always randomly assigned to one of the three triplet positions. As before, disparity levels were updated one chart at a time, taking into account responses from all preceding charts within a block of trials. To prevent the staircase from increasing the disparity level beyond the subject's fusion limit, the disparity was constrained to not exceed 1.5 times the initial disparity setting from the screening procedure.

The initial disparity level for each staircase was determined by a brief screening procedure performed at the beginning of each block of trials (Figure 3A). This screening stage was implemented to increase the efficiency of the test given the high variability of stereoacuity among even normally-sighted participants (Hess, To, Zhou, Wang, & Cooperstock, 2015). Subjects viewed a chart consisting of 24 individual stereoscopic front-depth circles, arranged in four lines, one for each spatial frequency condition. Within a line, circles had a horizontal center-to-center spacing equal to twice the circle height, and adjacent pairs of lines had a vertical center-to-center separation of 1.5 times the circle height for the upper line. The flicker rate of each circle matched the temporal frequency condition for the subsequent block, and each circle had a randomly selected phase. Circles within a given line were arranged in order of decreasing disparity from left to right, in logarithmic steps. The disparity of the rightmost circle of each line was 39 arcseconds, and the disparity of the leftmost circle was either 3750, 2193, 1268, or 717 arcseconds for the 1, 2, 4, and 8 cpd conditions, respectively. For each individual line, starting from the top, subjects were instructed to click on the rightmost circle that still appeared to be in front of the display. The line that the subject was instructed to respond to was surrounded by a rectangle, scaled to 12.31 times the width and 2.31 times the height of an individual circle in the corresponding line (line width scaled to 0.05 times the circle height). After each response, the rectangle moved to highlight the line directly below it.

In each block of trials, subjects completed 13 charts following the screening procedure. Each subject completed the four temporal frequency conditions in separate blocks of trials, in a random order. Subjects completed 39 trials for each unique combination of spatial and temporal frequency condition, for a total of 624 trials.

2.4. Data Analysis

Data from the qCSF procedure (Figure 1B) was summarized by calculating the area under the log temporal contrast sensitivity function (AULTCSF). This served as an estimate of overall contrast sensitivity, and was calculated using trapezoidal integration between 1 Hz and the high-frequency cutoff. Statistical comparisons were performed using a 4 × 2 × 2 mixed-model analysis of variance (ANOVA), with spatial frequency and viewing eye (dominant vs. nondominant) as within-subject factors and subject group (amblyope vs. control) as a between-subject factor.

Interocular balance points and stereopsis thresholds were calculated by fitting the staircase data to a logistic function with two parameters—threshold (α), and slope (β)—using maximum likelihood estimation. The 50% and 75% thresholds were calculated from the

resulting fits, to estimate interocular balance point and stereopsis thresholds, respectively. In the interocular contrast data, contrast values were analyzed with respect to contrast in the amblyopic eye (or non-dominant eye, for control subjects) for each subject. A balance point of 0.5 indicates perfect balance, and values above 0.5 are consistent with suppression, or reduced sensitivity in the amblyopic (or non-dominant eye). Statistical comparisons were performed using a 4 (spatial frequency) × 4 (temporal frequency) × 2 (group: amblyopes vs. control) mixed-model ANOVA using the Satterthwaite approximation for denominator degrees of freedom. Effect sizes are reported as partial eta-squared (η_p^2). Relationships between the three measures (AULTCSF, stereoacuity, interocular contrast) were quantified using Pearson's correlation coefficient.

In the stereopsis data, the 1 cpd spatial frequency condition was removed from the analysis for all subjects, due to high variability in subject responses and reported difficulty with the test (across all subjects, 40.9%, or 36 out of the 88 observations in the 1 cpd condition had an overall accuracy of 50% or less). Stereopsis threshold values for a given subject and stimulus condition were otherwise taken to indicate a lack of stereopsis if they met at least one of the following criteria: no stereopsis in the screening procedure, fitted thresholds > 5,000 arcsec, or overall proportion correct not significantly better than chance (using a binomial test), and these values were replaced with 10,000 arcsec. This is intended to capture the variation in performance (i.e., stereopsis vs. no-stereopsis) across task conditions, rather than to allow inferences from the threshold values themselves. An additional 3 out of 264 observations that did not meet these criteria were removed from the analysis due to unreliable threshold estimates (overall accuracy ≥ 87.5%, or negative fitted slopes). In the binocular balance task, one subject with dense amblyopia (subject A5) was unable to complete the 12 Hz condition, and another (subject A7) reported difficulty seeing the letters in the 8 cpd condition. The observers' data from these conditions were not included in the analysis.

The full data set is available on the Open Science Framework online (https://osf.io/rf7c8).

3. Results

3.1. Monocular Temporal Contrast Sensitivity

Figure 4 shows AULTCSFs for each spatial frequency condition, separately for amblyopes and controls and for each eye tested. A three-way mixed model ANOVA on AULTCSF values showed a significant main effect of spatial frequency, $F(3,60) = 245.4$, $p < .001$, $\eta_p^2 = 0.92$. As expected, across both groups, and across each eye tested, temporal contrast sensitivity was lower at higher spatial frequencies. In the amblyope group, we observed spatial-frequency dependent decrements in AULTCSF values in the amblyopic eye, consistent with significant interactions between spatial frequency and group, ($F(3,60) = 4.03$, $p = 0.01$, $\eta_p^2 = 0.17$), spatial frequency and viewing eye ($F(3,60) = 3.17$, $p = 0.03$, $\eta_p^2 = 0.14$), as well as viewing eye and group, $F(1,20) = 5.34$, $p = 0.03$, $\eta_p^2 = 0.21$. Importantly, these effects were qualified by a significant three-way interaction between spatial frequency, viewing eye, and group, $F(3,60) = 6.75$, $p < 0.001$, $\eta_p^2 = 0.25$. As shown in Figure 4, control subjects showed similar contrast sensitivity between the two eyes across all spatial frequencies. In contrast, amblyopes showed large interocular differences in contrast

sensitivity, but only at high spatial frequencies. Pairwise post-hoc contrasts (with a Bonferroni-corrected alpha, α_B, of 0.013) indicated that interocular differences in contrast sensitivity were significantly greater in amblyopes compared to controls at 8 cpd ($t(37.3) = 3.18$, $p = 0.003$), and at 4 cpd ($t(37.3) = 3.07$, $p = 0.004$). Interocular differences in AULTCSF values were not significantly different between amblyopes and controls at 1cpd ($t(37.3) = 0.28$, $p = 0.78$) and 2 cpd ($t(37.3) = 1.84$, $p = 0.07$), indicating that the amblyopes had a preserved ability to process temporal information at low spatial frequencies, consistent with previous literature (e.g., Bradley & Freeman, 1985; Levi & Harwerth, 1977; Manny & Levi, 1982a).

3.2. Interocular balance points

Figure 5A shows interocular balance points across spatial and temporal frequency, in separate plots for amblyopes and control subjects. A three-way mixed-model ANOVA showed a significant main effect of group, $F(1,19.96) = 79.25$, $p < .001$, $\eta_p^2 = 0.80$. As expected, subjects with amblyopia showed greater interocular imbalance compared to control subjects, with mean interocular balance points of 0.796 and 0.504, respectively. In addition, as shown in Figure 5B, we observed significant main effects of both spatial frequency $F(3, 58.89) = 16.09$, $p < .001$, $\eta_p^2 = 0.45$ and temporal frequency $F(3, 59.99) = 3.12$, $p = 0.03$, $\eta_p^2 = 0.14$. As shown in Figure 5A, interocular imbalance was largest at mid to high spatial frequencies, increasing from 0.75 at 1 cpd to 0.84 at 4 cpd in amblyopic subjects. Pairwise post-hoc contrasts with Tukey HSD tests, averaged across groups, indicated significant differences between 1 cpd and each of the remaining frequencies (2 cpd: $t(59.4) = 3.75$, $p = 0.002$, 4 cpd: $t(59.4) = 6.45$, $p < .0001$; 8 cpd: $t(59.4) = 5.38$, $p < .0001$), as well as a significant difference between 2 and 4 cpd: $t(59.4) = 2.70$, $p = 0.04$. The remaining comparisons were not significant (p-values > 0.31). Interocular balance points were also largest at low- to mid-temporal frequencies, with the largest binocular imbalance in amblyopes at 4 Hz (balance point of 0.81), and lowest at 12 Hz (0.77). Averaged across both groups, post-hoc contrasts showed significantly greater binocular imbalance at 4 Hz compared to 12 Hz, $t(59.6) = 2.79$, $p = 0.03$. None of the other pairwise comparisons reached significance (for 4 vs. 7.5 Hz, $t(59.6) = 2.45$, $p = 0.08$; all other p-values > 0.31). We also observed a significant spatial frequency × group interaction, $F(3,58.89) = 8.78$, $p < .001$, $\eta_p^2 = 0.31$. As shown in Figure 5B, there was a larger spatial-frequency dependent increase in interocular imbalance in amblyopes compared to controls. The spatial × temporal frequency interaction, the temporal frequency × group interaction, and the three-way interaction were all non-significant (all p-values > 0.22).

We note that while these interocular balance point estimates do not directly account for interocular differences in contrast sensitivity, these estimates include conditions were there are no interocular differences in contrast sensitivity (e.g., low spatial frequencies), as well as conditions in which there are differences (e.g., high spatial frequencies). We find significant differences in the interocular balance point between amblyopes and controls across all spatial frequencies, which demonstrates that the results are not fully accounted for by impaired contrast sensitivity in the amblyopic eye. This is consistent with previous work showing increased interocular suppression (Birch et al., 2016) and elevated stereopsis thresholds (Levi, 2006; Levi, Knill, & Bavelier, 2015; Stewart, Wallace, Stephens, Fielder, &

Moseley, 2013) in subjects who have been previously treated for amblyopia, who show similar contrast sensitivity between the two eyes.

3.3. Stereopsis Thresholds

Figure 6 shows stereopsis thresholds across spatial and temporal frequency for both amblyopes and control subjects. A three-way mixed-model ANOVA showed a significant main effect of group, $F(1,20) = 31.63$, $p < .001$, $\eta_p^2 = 0.61$; as expected, subjects with amblyopia had reduced performance in the stereopsis task compared to controls. We note that both groups showed elevated stereoacuity values compared to common clinical tests (e.g., Random Dot 3, Titmus, see Table 1). This elevation in thresholds is likely due to the absence of sharp edges and high-spatial frequency content in our bandpass-filtered stimuli, consistent with previous findings (e.g., Westheimer & Mckee, 1980). In addition, we observed a main effect of spatial frequency, ($F(2,39.9) = 4.21$, $p = .022$, $\eta_p^2 = 0.17$), with higher stereopsis thresholds at higher spatial frequencies. Pairwise post-hoc contrasts using Tukey HSD tests indicated significantly larger stereopsis thresholds in the 8 cpd condition compared to the 2 cpd condition, $t(40.2) = 2.81$, $p = 0.02$. The other comparisons (2 vs 4 cpd and 4 vs 8 cpd) were not significant (p-values > 0.12). As with the interocular balance points, we observed a significant spatial frequency × group interaction, $F(2,39.9) = 5.63$, $p = .007$, $\eta_p^2 = 0.22$. As shown in Figure 6B, amblyopes showed a larger effect of spatial frequency on stereopsis thresholds compared to control subjects. However, unlike the interocular balance points, there was no main effect of temporal frequency, $F(3,60.8) = 0.13$, $p = .94$, $\eta_p^2 = 0.01$. The spatial × temporal frequency interaction, the temporal frequency × group interaction, and the three-way interaction were all non-significant (all p-values > 0.40).

3.4. Correlations

To examine the relationship between the two binocularity measures, and to determine whether monocular contrast sensitivity was related to performance in the two binocular tasks, we performed pairwise correlations between each of the three measures (stereopsis thresholds, interocular balance points, and interocular difference in AULTCSF), with a Bonferroni-corrected alpha for three comparisons ($\alpha_B = 0.017$; Figure 7). Interocular differences AULTCSF values were normalized to account for individual variation in overall contrast sensitivity. Reported values were calculated by subtracting the AULTCSF value in the fellow/dominant eye from the amblyopic/non-dominant eye, and then dividing by the mean contrast sensitivity across the two eyes. Negative values indicate lower contrast sensitivity in the amblyopic/non-dominant eye. As expected, higher levels of interocular imbalance were associated with higher stereopsis thresholds, $r(20) = .74$, $p < .001$. In addition, lower AULTCSF difference scores were associated with greater interocular imbalance, $r(20) = -0.70$, $p < .001$. Lower AULTCSF difference scores were also associated with higher stereopsis thresholds, though this correlation was somewhat lower, $r(20) = -.53$, $p = .012$ ($\alpha_B = 0.017$).

However, we note that these results include one observer who may have possible pathological retinal changes as a consequence of high myopia (A5). We therefore repeated our analyses with this observer removed. Two of the correlations reported in Figure 7 are

significant with A5 removed from the analysis: the correlation between stereopsis thresholds and interocular balance points ($r(19) = 0.71$, $p < .001$), as well as the correlation between AULTCSF difference scores and interocular balance ($r(19) = -0.69$, $p < .001$). The correlation between AULTCSF difference scores and stereopsis thresholds did not reach significance when corrected for multiple comparisons ($r(19) = -0.46$, $p = .037$, $\alpha_B = 0.017$). Together, these results indicate an association between our measures of binocular performance across the amblyope and control groups together, with a weaker or absent relationship between AULTCSF difference scores and stereopsis thresholds. Finally, we repeated all the remaining analyses for this experiment (Sections 3.1 – 3.3) with A5 removed from the analysis, and observed similar results (see Supplemental Materials for details).

4. Discussion

The purpose of our study was to examine the effects of temporal stimulus modulation on binocular visual function in amblyopes by measuring stereopsis thresholds and interocular balance points across a broad range of temporal and spatial frequencies. Our results can be summarized as three main findings. First, the monocular TCSF data indicates that amblyopes have a preserved ability to process temporal information at low spatial frequencies, consistent with previous work showing that amblyopes have normal temporal contrast sensitivity when stimulus spatial frequency is sufficiently low (Bradley & Freeman, 1985; Levi & Harwerth, 1977; Manny & Levi, 1982a). Second, in measuring interocular balance points, we replicated previous findings of spatial-frequency dependence (Birch et al., 2016; Kwon et al., 2015), and we observed a previously unreported, smaller effect of temporal frequency on interocular contrast ratios in amblyopes, with subjects showing the largest degrees of imbalance at low-tomid temporal frequencies. However, the absence of an interaction between subject group and temporal frequency suggests that this effect of temporal frequency on interocular balance points is similar between the two groups. Finally, stereopsis thresholds were influenced by stimulus spatial frequency, as has been reported in both amblyopes (Holopigian et al., 1986) and normally-sighted observers (Schor & Wood, 1983; Schor, Wood, & Ogawa, 1984; Tyler, 1974). However, any variation in thresholds across temporal frequencies appears to be much smaller than the variation across spatial frequency, with no clear relationship between temporal frequency and stereopsis thresholds across groups. While our results here suggest that, compared to the effect on interocular balance, flicker has a weaker effect on stereoacuity, we note that additional experiments would be necessary to confirm the absence of any effect.

Together, our findings are broadly consistent with the characterization of amblyopia as a primarily spatial deficit. We observed no deficits in temporal contrast sensitivity at low spatial frequencies, indicating that amblyopes may have a preserved ability to process temporal information when sensitivity to the spatial component of the stimulus is sufficiently high. Comparisons to the binocular measures showed that reduced monocular contrast sensitivity in the amblyopic eye was associated with higher stereopsis thresholds and larger degrees of interocular imbalance, consistent with the finding that monocular reductions in contrast sensitivity are associated with impairments in stereo performance (Halpern & Blake, 1988; Legge & Gu, 1989). Consistent with the TCSF data, our binocular measures also indicated primarily spatial deficits: interocular balance and stereopsis

performance were largely influenced by spatial, rather than temporal stimulus frequency. However, we found that temporal frequency influenced interocular balance points across the two groups, and together with the spatial frequency manipulation, our results showed the largest degrees of binocular imbalance in amblyopes at mid-temporal frequencies (4 Hz) and mid-to-high spatial frequencies (4 and 8 cpd; Figure 5A). Given individual variability in binocular interactions in amblyopes (e.g., Zhou et al., 2018), and given known differences between subtypes of amblyopia (e.g., Asper, Crewther, & Crewther, 2000; Eggers & Blakemore, 1978; Hess, Bradley, & Piotrowski, 1983; Levi & Klein, 1982), further work is necessary to extend these preliminary findings and separately measure the effects of temporal frequency on binocular deficits for strabismic, anisometropic, and mixed amblyopia.

Although few results have been reported on the effects of simultaneous binocular flicker on interocular balance, other work has examined the temporal-frequency dependence of continuous flash suppression (CFS) in normally-sighted observers, in which a flickering image shown to one eye suppresses a different, static image shown to the other eye (Tsuchiya & Koch, 2005; Tsuchiya, Koch, Gilroy, & Blake, 2006). Recent results indicate that CFS may be largest at lower temporal frequencies, near 1 Hz, suggesting that interocular suppression may be mediated by input to the parvocellular pathway (Han et al., 2016). A number studies have proposed that deficits in parvocellular function are implicated in amblyopia (Davis et al., 2006; Hess, Li, Lu, Thompson, & Hansen, 2010; Hess, Thompson, Gole, & Mullen, 2010; Miki, Siegfried, Liu, Modestino, & Liu, 2008). To the extent that amblyopia involves selective impairment in this channel, the temporal-frequency dependence of interocular balance points may be different between amblyopes and normally sighted observers within these low temporal frequency ranges.

Our findings, in conjunction with previous work, also suggest a possible dissociation in the temporal-frequency dependence of stereopsis thresholds compared to interocular balance points. Previous work has suggested that the neural mechanisms underlying stereopsis and binocular rivalry are similar (Hochberg, 1964; Harrad, McKee, Blake, & Yang, 1994). This would predict that the spatial and temporal frequency conditions that produce the largest elevations in stereopsis thresholds would also produce larger degrees of interocular suppression and binocular imbalance. A number of studies in normally-sighted observers have shown impairments in stereoacuity at high temporal frequencies, when measured with temporal modulations in either luminance (Lee et al., 2003, 2007; Patterson, 1990) or disparity (Kane et al., 2014; Norcia & Tyler, 1984; Richards, 1972). In contrast, interocular imbalance may be largest at lower temporal frequencies (Han et al., 2016; Vera-Diaz et al., 2018). Although the mechanisms underlying these differences have not been examined, previous results have pointed to other conditions in which interocular suppression and stereopsis can be dissociated, such as the co-occurrence of stereopsis and rivalry within the same image (Ogle & Wakefield, 1967; Julesz & Miller, 1975). In addition, there is evidence that strabismic suppression and suppression in normal binocular rivalry have different underlying mechanisms (Smith, Levi, Manny, Harwerth, & White, 1985). The present findings also suggest that the effects of temporal stimulus factors may differ between binocular fusion and competition.

As variations in binocular function across both spatial and temporal frequency have not been previously reported in amblyopes, we note that these results are preliminary in nature, and that further work with larger samples would be necessary to confirm the effect of temporal frequency on interocular balance, as well as the dissociation we observed between stereopsis and interocular balance. Additional experiments would also be necessary to determine how these effects vary between strabismic, anisometropic, and mixed amblyopia. Future investigations into how these spatial and temporal factors interact in binocular vision may also help to identify domains of spared binocular function in amblyopia, and guide the development of sensitive assessments. While our study examined these relationships in the context of simultaneous binocular flicker, the effects of binocular temporal asynchronies in amblyopia warrant further investigation. In particular, asynchronous flicker could be used to compensate for interocular differences in the speed of visual processing in amblyopia, and provide a basis for future treatments. Asynchronous dichoptic flicker has been shown to reduce contour interactions in amblyopia (Schor, Terrell, & Peterson, 1976), and recent work has investigated potential flicker-based treatments for amblyopia utilizing shutter glasses that alternately occlude each eye (Vera-Diaz, Moore, Hussey, Srinivasan, & Johnson, 2016). An understanding of these temporal factors in binocular vision and the time course of suppression in amblyopia would shed light on potential future therapies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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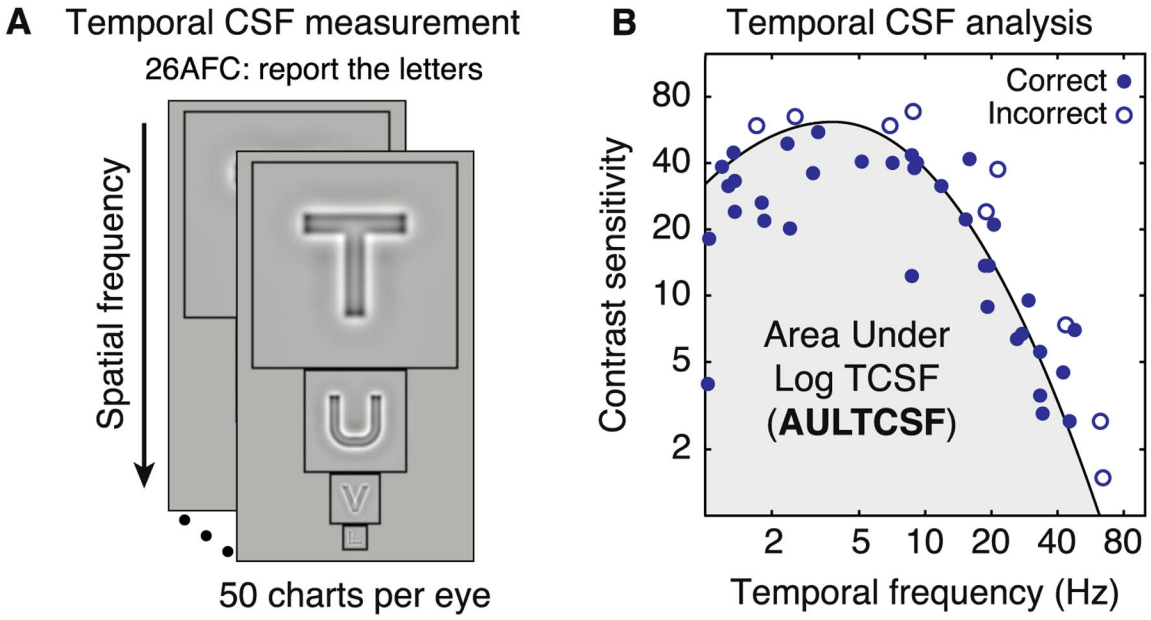

Figure 1.

(A) Stimuli used for the contrast sensitivity task. Letters were shown at a variable temporal frequency and contrast determined by the quick CSF algorithm. Subjects were instructed to read the letters from top to bottom on each chart, and their responses were manually recorded by the experimenter. (B) Example of one observer's TCSF, with scatter points showing correct and incorrect responses on individual trials (filled and empty symbols, respectively). The area under the log TCSF (AULTCSF) was calculated from each function to estimate overall contrast sensitivity.

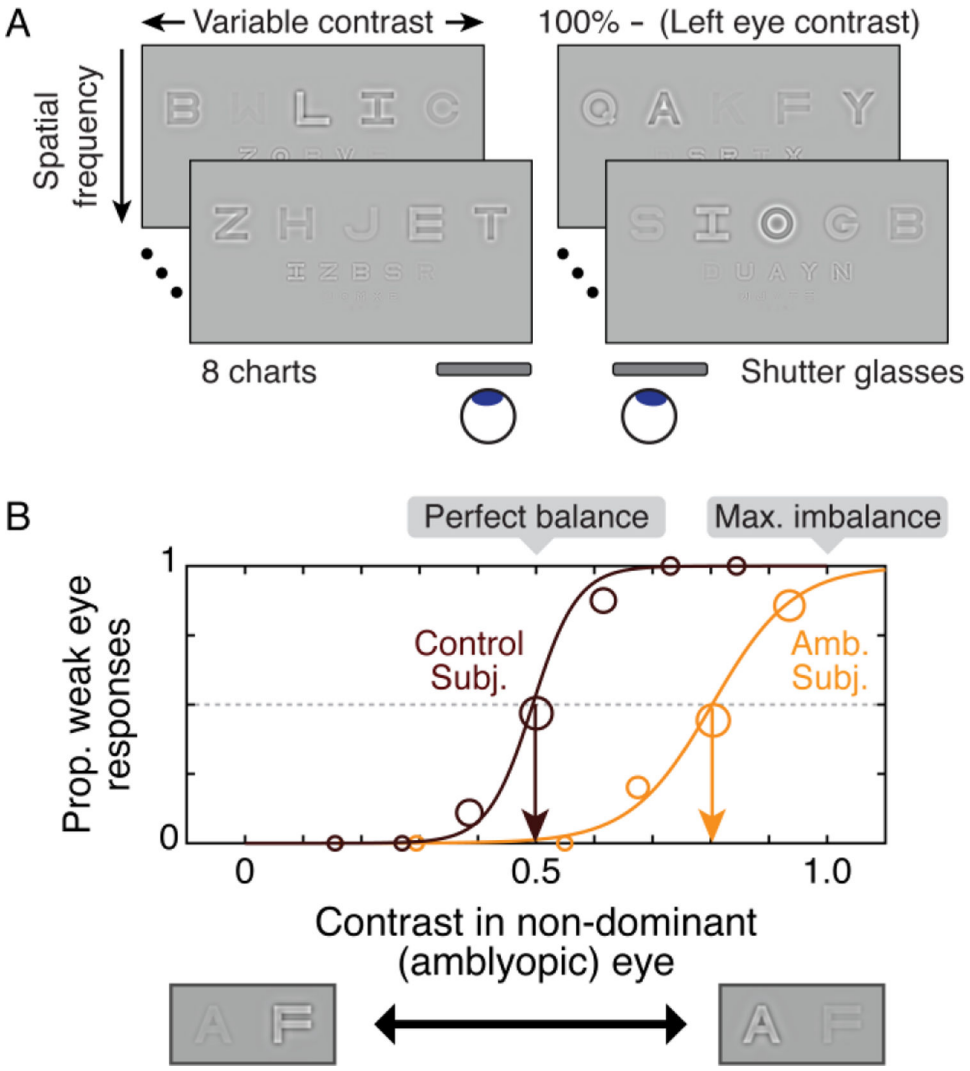

Figure 2.

(A) Stimuli used for measurement of interocular balance points. Subjects were shown dichoptic letter charts, and read the letters from left to right, reporting the dominant percept for each pair in a 2AFC task. Interocular contrast was varied to determine the contrast level at which the two letters were reported with equal frequency (the interocular balance point). Stimulus contrast in the right eye was set to 100% minus the contrast in the left eye. (B) Balance points for two example subjects. The proportion of responses corresponding to the letter shown in the amblyopic (or non-dominant) eye is plotted as a function of the interocular contrast, where 0 and 1 correspond to 0% and 100% amblyopic eye contrast, respectively. Balance points (indicated by the arrows) were estimated from the contrast levels at which letters in the amblyopic and fellow eyes were reported with equal frequency (dashed line).

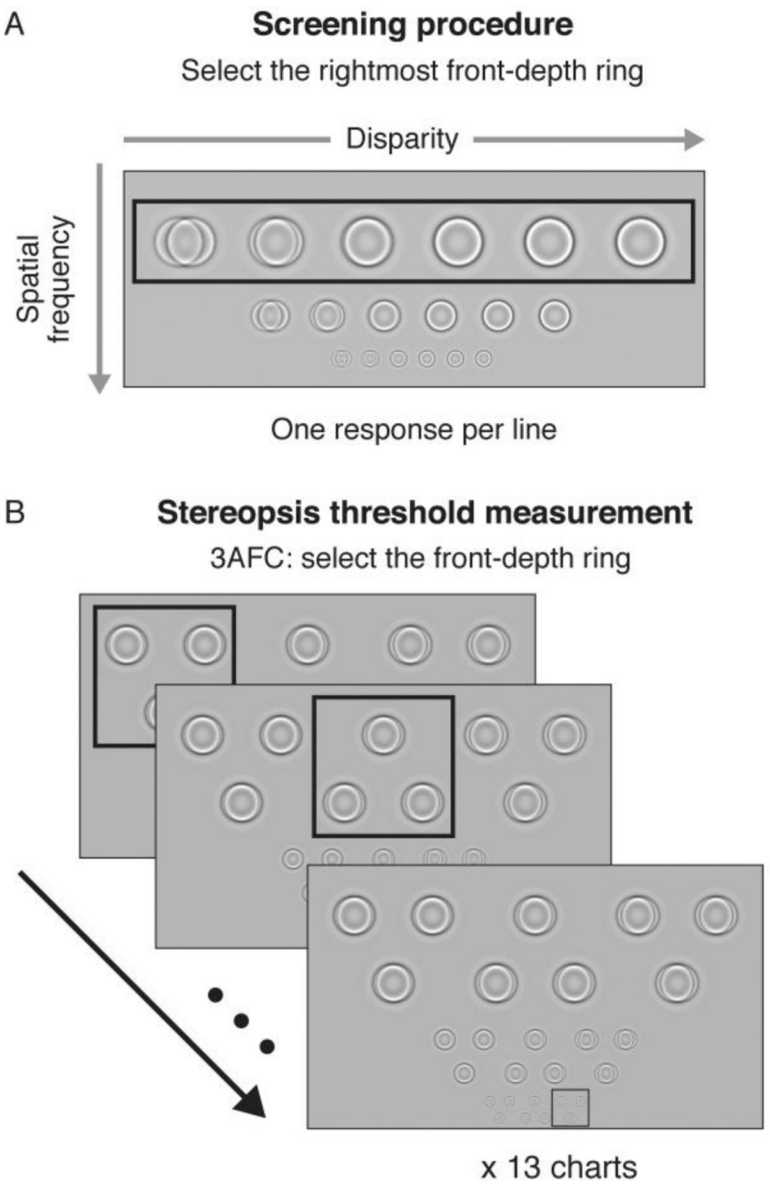

Figure 3.

(A) Screening procedure used to determine the initial disparity levels for the staircases in the stereopsis threshold task. All circles had crossed disparity (front depth) and were arranged in order of decreasing disparity from left to right. On each line, subjects were instructed to select the rightmost circle that appeared to have front depth. (B) Stimuli used to measure stereopsis thresholds. Charts consisted of triplets (one randomly selected front-depth circle and two back-depth circles), and subjects reported the front-depth circle using a mouse click. For illustrative purposes, only three stimulus rows (three spatial frequency conditions) are shown. Left and right-eye views are superimposed to show the degree of binocular disparity.

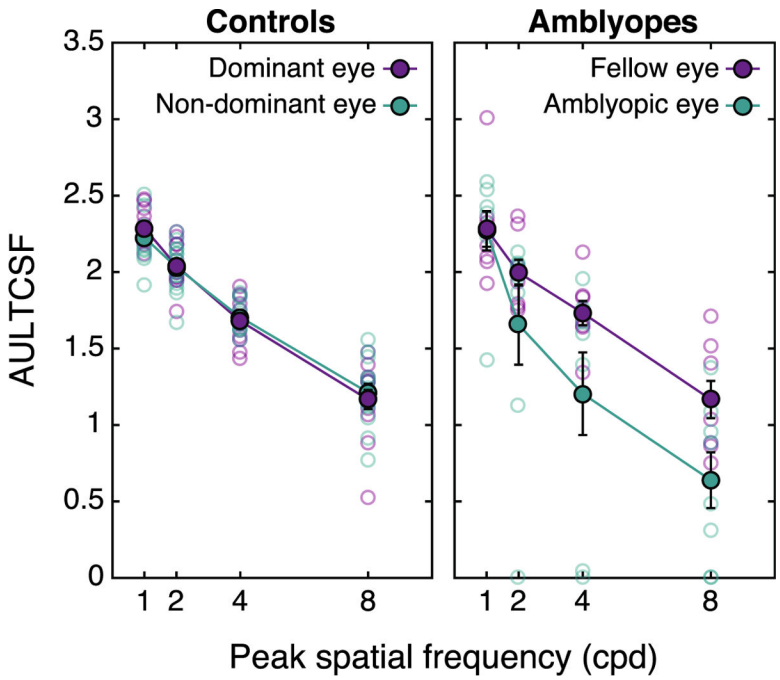

Figure 4.

Temporal contrast sensitivity, calculated from mean AULTCSF values, for control subjects and amblyopes (left and right panels, respectively) as a function of stimulus peak spatial frequency. Purple and green lines represent fellow and amblyopic eyes, respectively (or dominant and non-dominant eyes for control subjects), and scatter points represent individual subjects. Error bars represent ± 1 SEM.

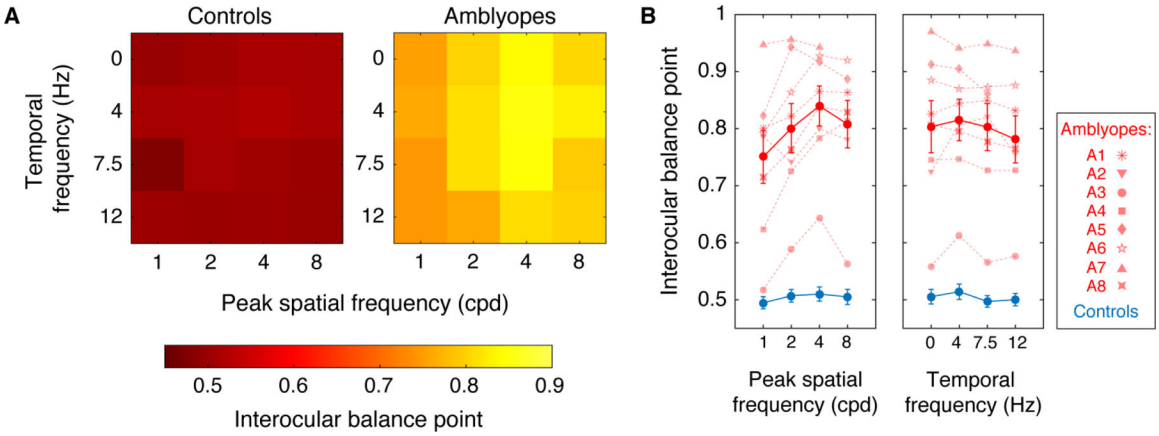

Figure 5.

(A) Interocular balance points for control subjects and amblyopes, as a function of spatial and temporal frequency. Balance points at 0.5 indicate perfect balance, and values above 0.5 are consistent with suppression, or reduced sensitivity in the amblyopic (or non-dominant eye). (B) Interocular balance points as a function of spatial frequency, averaged across temporal frequency, or vice versa (left and right panels, respectively) for amblyopes (red) and controls (blue). Each data point represents the average of four thresholds. Dashed lines represent data from individual subjects in the amblyope group (open symbols: anisometropic, asterisk symbol: strabismic, filled symbols: mixed amblyopia). Error bars represent ± 1 SEM.

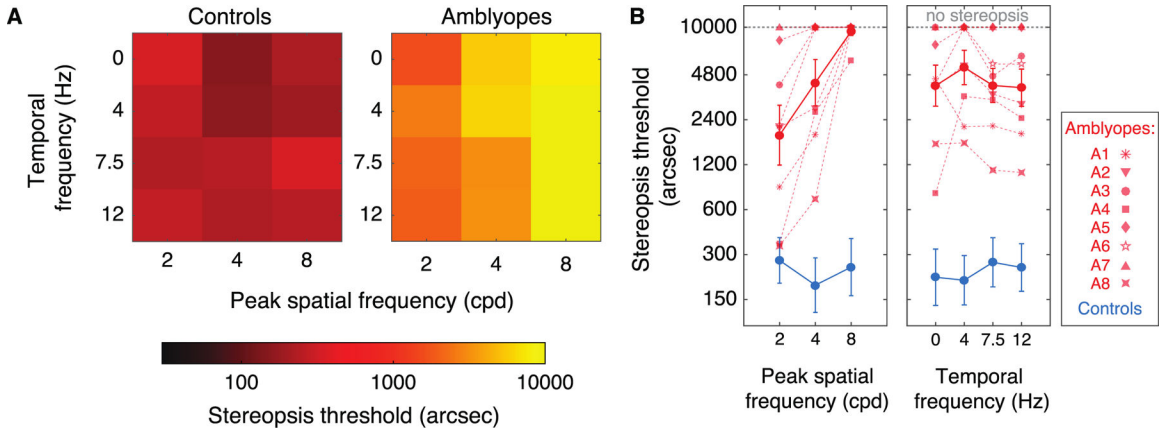

Figure 6.

(A) Stereopsis thresholds for control subjects and amblyopes, as a function of spatial and temporal frequency. Values at 10,000 arcsec indicate a lack of stereopsis in that condition. (B) Stereopsis thresholds as a function of spatial frequency, averaged across temporal frequency, or vice versa (left and right panels, respectively) for amblyopes (red) and controls (blue). Dashed lines represent data from individual subjects in the amblyope group (open symbols: anisometropic, asterisk symbol: strabismic, filled symbols: mixed amblyopia). Error bars represent ± 1 SEM.

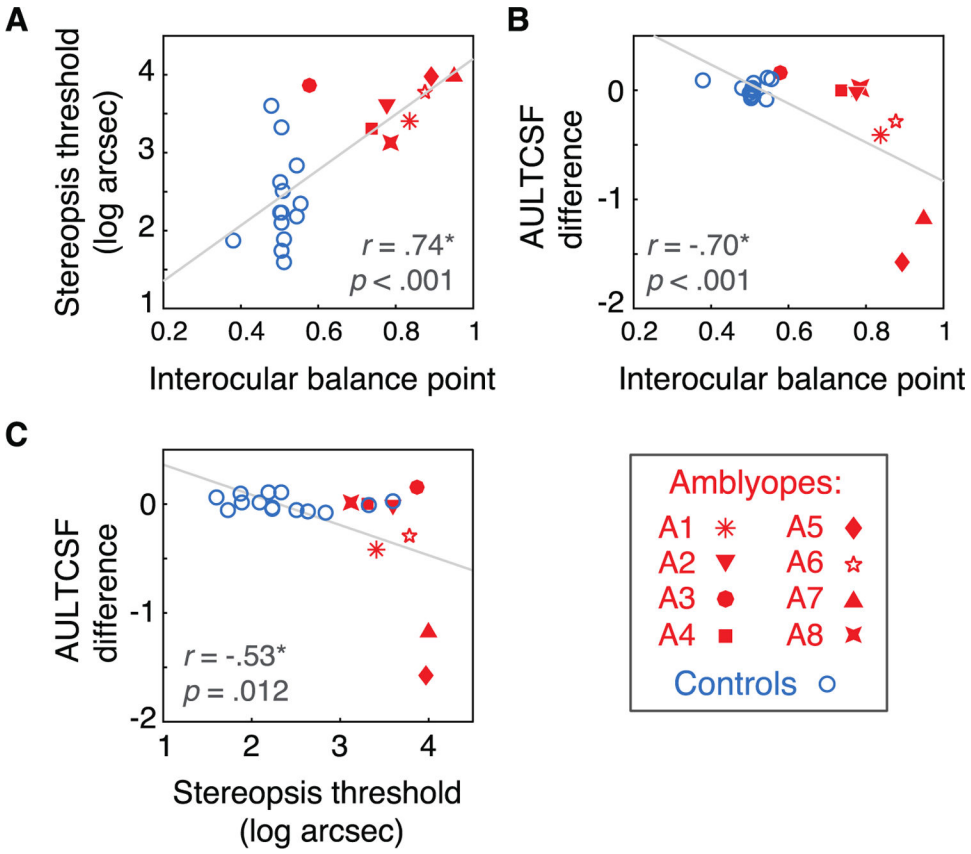

Figure 7.

Correlations between: (A) the two binocularity measures (stereopsis thresholds and interocular balance points), (B) normalized interocular difference in AULTCSF and interocular balance points, and (C) normalized interocular AULTCSF difference and stereopsis thresholds. Scatter points represent individual subjects, with amblyopes and controls shown separately (red and blue points, respectively; for the amblyope group, open symbols: anisometropic, asterisk symbol: strabismic, filled symbols: mixed amblyopia). Each point represents the mean of all conditions tested for the corresponding measure. Correlation values are calculated using Pearson's correlation coefficient, and asterisks (*) denote significant correlations with a Bonferroni correction for three comparisons (α_B = 0.017)

Table 1.

Clinical data from subjects in the amblyope group, CT = Cover test, 4BO = Four-diopter base-out prism test.

Subject	Age	Type of amblyopia	Best-Corrected Visual Acuity (LogMAR)		Refractive Error (D)		Clinical Stereo-acuity (arcsec)	Worth 4-Dot Test (40 cm)	Bagolini Test (40 cm)	Eye alignment (CT and 4BO if tested)
			OD	OS	OD	OS				
A1	50	Strabismic	−0.10	0.10	+0.75SPH	+0.75SPH	900	Diplopia	Diplopia	Constant Left Esotropia
A2	27	Mixed	0.00	0.16	+1.25SPH	+6.75/−0.75×043	900	Diplopia, no suppression	Left Suppression	Constant Left Esotropia
A3	25	Mixed	0.00	0.20	+3.00/−3.25×170	+4.00/−4.75×170	600	Left suppression	Left suppression	CT Ortho. Left microtropia in 4BO prism test
A4	24	Mixed	−0.10	0.10	Piano	+3.25/−1.00×045	32	Fusion	Fusion	CT Ortho. Left microtropia in 4BO prism test
A5	20	Mixed	0.00	1.3	−2.50/−2.25×011	−19.00/−3.00×176	500	Left suppression	Left Suppression	Constant Left Exotropia
A6	23	Refractive	−0.10	0.34	+1.00SPH	+3.25/−1.75×075	400	Fusion	Fusion	Ortho. No microtropia
A7	35	Mixed	−0.10	1.1	Piano	+7.50/−1.50×160	900	Left suppression	Left suppression	Constant Left Exotropia
A8	24	Mixed	−0.10	0.36	+3.75SPH	+5.50SPH	900	Left suppression	Left suppression	CT Ortho. Left microtropia in 4BO prism test