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Treated amblyopes remain deficient in spatial vision: A contrast sensitivity and external noise study

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Abstract

To evaluate residual spatial vision deficits in treated amblyopia, we recruited five clinically treated amblyopes (mean age = 10.6 years). Contrast sensitivity functions (CSF) in both the previously amblyopic eyes (pAE; visual acuity = 0.944 ± 0.019 MAR) and fellow eyes (pFE; visual acuity = 0.936 ± 0.021 MAR) were measured using a standard psychophysical procedure for all the subjects. The results indicated that the treated amblyopes remained deficient in spatial vision, especially at high spatial frequencies, although their Snellen visual acuity had become normal in the pAEs. To identify the mechanisms underlying spatial vision deficits of treated amblyopes, threshold vs external noise contrast (TvC) functions – the signal contrast necessary for the subject to maintain a threshold performance level in varying amounts of external noise ("TV snow") – were measured in both eyes of four of the subjects in a sine-wave grating detection task at several spatial frequencies. Two mechanisms of amblyopia were identified: increased internal noise at low to medium spatial frequencies, and both increased internal noise and increased impact of external noise at high spatial frequencies. We suggest that, in addition to visual acuity, other tests of spatial vision (e.g., CSF, TvC) should be used to assess treatment outcomes of amblyopia therapies. Training in intermediate and high spatial frequencies may be necessary to fully recover spatial vision in amblyopia in addition to the occlusion therapy.

Keywords: Amblyopia; Treatment; Contrast sensitivity function; External noise; Perceptual template model; Internal noise; Perceptual template

1. Introduction

Amblyopia refers to a developmental visual disorder characterized by impaired spatial vision in the absence of any detectable structural or pathologic abnormalities that cannot be corrected by refractive means. Most researchers now agree that amblyopia is a cortical disorder (Barnes, Hess, Dumoulin, Achtman, & Pike, 2001; Daw, 1998; Kiorpes & McKee, 1999). Although only infant and young child amblyopes (<8 years) are treated in most clinical practice, often with the occlusion therapy (Ciuffreda, Levi, & Selenow, 1991; Hug, 2004), a number of reports suggest that perceptual learning – intensive practice in simple visual tasks – can significantly improve the contrast sensitivity and visual acuity in adults with amblyopia (Levi & Polat, 1996; Levi, Polat, & Hu, 1997; Polat, Ma-Naim, Belkin, & Sagi, 2004; Zhou et al., 2006).

Conventional evaluation of the outcome of amblyopia treatments has strongly emphasized tests of visual acuity. Most often, a treatment's success has been defined by reaching either a certain acuity, usually 6/9 or 6/12 (Cascairo, Mazow, Holladay, & Prager, 1997; Hiscox, Strong, Thompson, Minshull, & Woodruff, 1992; The Paediatric Eye Disease Investigator Group, 2002), 20/25 (Regan, 1988), and 6/6 (Fulton & Mayer, 1988; Lithander &

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Sjostrand, 1991; Mintz-Hittner & Fernandez, 2000), or a certain magnitude of acuity improvement (Kheterpal, Jones, Auld, & Moseley, 1996; McGraw, Winn, Gray, & Elliott, 2000; Stewart, Moseley, & Fielder, 2003). In China, achieving a 1.0 MAR or better visual acuity in the amblyopic eye marks an initial success; maintaining such acuity for more than three years qualifies the treatment as a complete success (Child Strabismus & Amblyopia. Prevention Group of Chinese Society of Ophthalmology, 1990).

Although visual acuity tests provide convenient and important evaluations of the resolution limits of spatial vision, it has long been recognized that simple assessments of photopic visual acuity may not predict an individual's performance in other spatial vision tasks, such as target detection or discrimination (Braddick, Campbell, & Atkinson, 1978; Pelli, Robson, & Wilkins, 1988; Watson, Barlow, & Robson, 1983). Many researchers have suggested that the contrast sensitivity function (CSF), which assesses spatial vision over a wide range of spatial frequencies and contrast levels, may be a better tool for detecting and diagnosing deficits in spatial vision (Della Sala, Bertoni, Somazzi, Stubbe, & Wilkins, 1985; Hess, 1979; Hess & Howell, 1977; Jindra & Zemon, 1989; Marmor, 1981; Marmor, 1986; Marmor & Gawande, 1988; Montes-Mico & Ferrer-Blasco, 2001; Wolkstein, Atkin, & Bodis-Wollner, 1980; Woo & Dalziel, 1981; Yenice et al., 2006). Models using the CSF as the front-end spatial frequency filter can account for normal human performance in a wide range of visual tasks, including letter identification (Pelli, Levi, & Chung, 2004) and face recognition (Kornowski & Petersik, 2003). In a recent analysis of 427 adults with amblyopia or with risk factors for amblyopia, McKee, Levi, and Movshon (2003) concluded that two orthogonal dimensions are needed to account for the variations in amblyopic visual performance: one relates to visual acuity measures (optotype, Vernier, and grating acuity) and the other relates to contrast sensitivity measures (Pelli-Robson and edge contrast sensitivity).

A number of practical measurement instruments have been developed to clinically assess contrast sensitivity in amblyopia (Della Sala et al., 1985; Ginsburg, 1984; Hyvarinen, 1985; Pelli et al., 1988; Regan, Giaschi, & Fresco, 1993). Rogers, Bremer, and Leguire (1987) measured contrast sensitivity of 14 anisometropic and 17 strabismic child amblyopes using the Vistech VCTS 6500-1 contrast sensitivity function board (Ginsburg, 1984) – a wall chart consisting of 40 patches of sinusoidal gratings (five sizes × eight contrast levels), each oriented at +15, 0, or −15° from vertical. Estimating contrast sensitivity from this three-alternative forced-choice identification task, they reported that a subgroup of five amblyopic patients, whose final visual acuity was 20/20 in both eyes after the occlusion therapy, exhibited significantly lower contrast sensitivity in the previously amblyopic eyes (pAEs) than in the previous fellow eyes (pFEs). Using a low-contrast visual acuity test developed for pediatric use, Regan (1988) examined a sample of 37 children (3–8 years old) who had completed occlusion therapy and 15 children (4–8 years old) who were still receiving occlusion therapy. Regan reported three patterns of visual loss: predominant loss at high-contrast acuity, fairly uniform loss at high, intermediate- and low-contrast acuity, and, in two patients, loss at low- and intermediate contrast levels, with relative sparing at the high-contrast level. The subjects in the last category would have been considered "treated" amblyopes, because their visual acuity in the high contrast test was normal. Using the Holladay Contrast Acuity Test (Stereo Optical, Chicago), Cascairo et al. (1997) found that a subgroup of five amblyopes (two anisometropic and three strabismic) with post occlusion-treatment Snellen acuity (measured in high contrast) of 20/20 in both eyes had lower contrast visual acuity (measured in low contrast) scores in the pAEs than the pFEs, although the difference did not reach statistical significance.

In summary, the literature suggests that treated amblyopes can simultaneously exhibit normal Snellen acuities but deficits in contrast sensitivity. However, these studies all used either pattern or letter charts, rather than more carefully controlled psychophysical procedures. Recently, McAnany and Alexander (2005) compared contrast sensitivity functions measured with letter optotypes and grating stimuli. They concluded that the conventional letter tests can yield misleading measures of contrast sensitivity, especially under parvocellular-mediated conditions. Ginsberg (1996) also suggested that gratings are more appropriate than letter optotypes as stimuli for measuring contrast sensitivity. Because contrast sensitivity functions might offer highly valuable diagnosis and treatment information not readily provided by acuity measures, we decided to measure contrast sensitivity functions in treated amblyopes using standard psychophysical procedures with sine-wave grating stimuli.

We recruited five treated child amblyopes (three with strabismus, one with anisometropia and one with both anisometropia and strabismus), who had successfully completed occlusion therapy, all with visual acuity around 1.0 MAR in both eyes. In addition to measuring contrast sensitivity functions in both eyes of each subject, for four of the subjects we also measured threshold vs external noise contrast (TvC) functions – the amount of signal contrast required for the observer to maintain a threshold performance level in varying amounts of external noise – for signal sine-wave gratings at several spatial frequencies.

The external noise approach allows us to de-compose contrast sensitivity in terms of intrinsic limitations of the perceptual system (Burgess & Colborne, 1988; Eckstein, Ahumada, & Watson, 1997; Lu & Dosher, 1999; Pelli, 1985; Pelli & Farell, 1999). This approach has been widely used to characterize and compare system states in normal (Levi & Klein, 1990b; Pelli, 1990) as well as amblyopic vision (Kersten, Hess, & Plant, 1988; Kiorpes, Tang, & Movshon, 1999; Levi & Klein, 1990a; Nordmann, Freeman, & Casanova, 1992; Pelli et al., 2004; Wang, Levi, & Klein, 1998; Watt & Hess, 1987). Using the external noise method, Xu, Lu, Qiu, and Zhou (2006) considered three mechanisms of amblyopia based on the perceptual template model (Lu & Dosher, 1998): increased internal

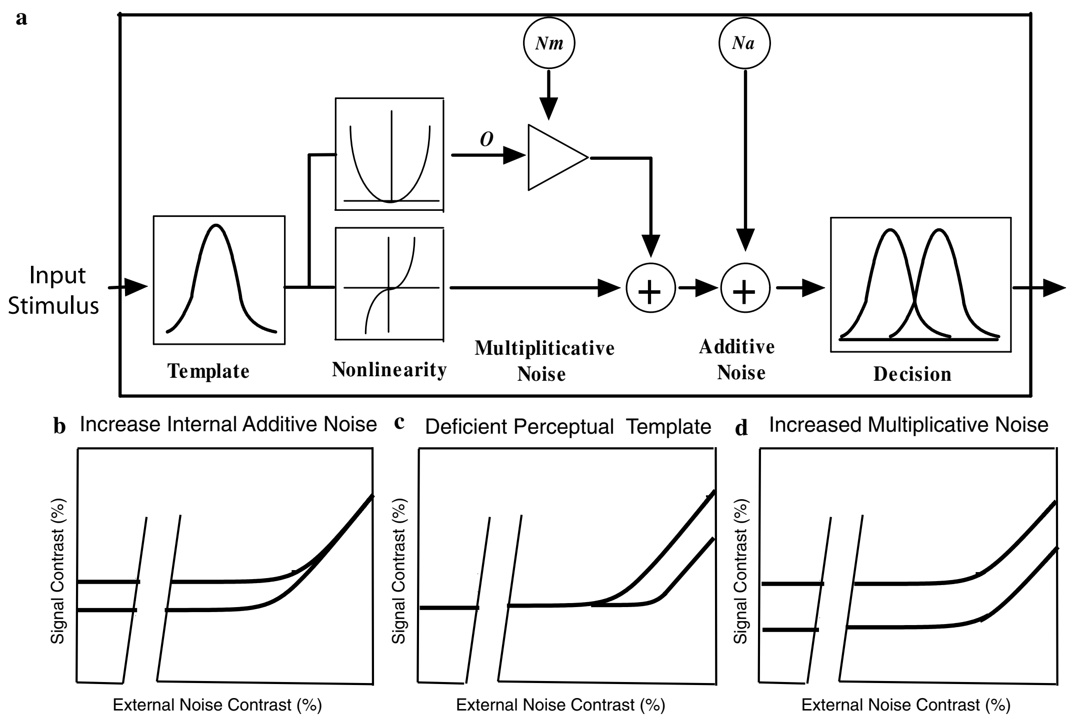

Fig. 1. (a) Perceptual template model (PTM). (b–d) Performance signatures of the three mechanisms of amblyopia deficits.

addition noise, deficient perceptual template, and increased multiplicative noise. A brief description of the PTM model and potential mechanisms of amblyopia is in Appendix A. Here we only present the signature performance patterns of the three mechanisms: *Increased internal additive noise* only impairs performance when internal additive noise dominates and is associated with performance decrements only in low or zero external noise (Fig. 1b). *Deficient perceptual template* impairs the ability of the observer to exclude external noise and therefore is associated with performance decrements only in high external noise (Fig. 1c). *Increased multiplicative noise* adds noise that is proportional to stimulus energy and is associated with performance decrements throughout the full range of external noise (Fig. 1d). In addition, the various mixtures of mechanisms can be distinguished via measurements of TvC functions at multiple performance levels (Dosher & Lu, 1999; Lu & Dosher, 1999).

Xu et al. (2006) concluded that amblyopia does not alter the multiplicative noise or the transducer non-linearity.[1] Instead, increased additive internal noise and deficient perceptual templates contribute to the spatial vision deficits in amblyopia. Whereas increased additive noise underlies performance deficits in all spatial frequencies, the degree of perceptual template deterioration increased with the spatial frequency.

Here, we applied the external noise method and the PTM framework to identify the mechanisms of visual deficits in treated amblyopia. Because it was impractical to collect TvC functions at multiple performance levels for this group of child subjects, as required by the PTM framework to distinguish mechanism mixtures, we based our theoretical interpretation on one result from Xu et al. (2006), namely, amblyopia does not change the non-linear transducer or the multiplicative noise of the visual system.

2. Material and methods

2.1. Subjects

Five naïve, treated amblyopes with natural-occurring amblyopia were recruited from the ophthalmology practice of the second author TLM at the First Affiliated Hospital of Anhui Medical University of China. The age of the observers ranged from 9 to 13 years (mean = 10.6 years; $SD = 1.8$ years). All had finished amblyopia treatment and participated in our study during their follow-up office visits. The average visual acuity of the pFEs for these subjects was 0.936 ± 0.021 MAR. Their acuities in pAE (0.944 ± 0.019 MAR acuity) had been maintained for at least three years before participating in this study. Detailed characteristics of these observers are listed in Table 1. Written informed consents were obtained from each observer and their guardians/parents.

Visual acuity, assessed with the Chinese Tumbling E Chart (Mou, 1966), was defined as the size of letters associated with 75% correct judgments. All observers, wearing their corrective lenses (if necessary) during the experiment, participated in the CSF portion of the study. Four of the observers also participated in the TvC part of the study.

[1] Instead of the non-linear transducer, some authors (Eckstein et al., 1997; Pelli, 1985) prefer observer models based on decision uncertainty. Although uncertainty and transducer non-linearity are rather different processes, they describe very similar mathematical properties of the TvC functions. In fact, Lu and Dosher (1999) concluded that it is rather difficult to empirically distinguish non-linear transducer based models from uncertainty-based models. Because Xu et al. (2006) did not find different non-linear transducer for the amblyopic eyes, compared to either the fellow eyes or the normal eyes, we can conclude that amblyopia does not change uncertainty in uncertainty-based model frameworks.

Table 1
Observer characteristics

Subjects	Age (years)	Gender	Acuity[a] (MAR)		Stereopsis[b] (arc second)	Refraction	Strabismus (Near)[c]	Type	Treatment[d]
SBB	13	f	LE	0.913	140	$+4.50/+2.00 \times 90$	eso $8^{\triangle}$	Strab	Occlusion/ training
			RE	0.913		$+0.50/+0.50 \times 85$		Aniso	
ZKY	10	f	LE	0.956	140	$+0.50/+0.85 \times 90$			Occlusion/ training
			RE	0.949		$+2.00/+2.25 \times 80$		Aniso	
WR	9	m	LE	0.955	140	+3.00	eso $5^{\triangle}$		Occlusion/ training
			RE	0.955		+3.00		Strab	
HZQ	12	f	LE	0.949	200	$+3.00/+1.00 \times 85$			Occlusion/ training
			RE	0.955		+3.50	eso $30^{\triangle}$	Strab	
YYQ	9	f	LE	0.944	200	$+4.00/+1.50 \times 90$	eso $10^{\triangle}$		Occlusion/ training
			RE	0.913		$+4.00/+1.00 \times 90$		Strab	

LE, left eye; RE, right eye; Strab, strabismic; Aniso, anisometropic.
[a] Visual acuity was evaluated with the Chinese Tumbling E Chart (Mou, 1966).
[b] Stereoacuity was assessed with the Titmus Stereo Test (Stereo Optical Co., Inc., Chicago, IL, USA).
[c] State of strabismus was tested right before treatment. Strabismus (accommodative esotropia) has been corrected for all observers at least half a year before our study by refractive means.
[d] Treatment includes refractive correction, occlusion and acuity exercises – dragging a thread through a pinhole, re-drawing, selecting gingeli from beans with the amblyopic eye. Training lasted for at least half a year.

2.2. Apparatus and stimuli

All stimuli were generated by a PC running Matlab programs based on version 2.50 of PsychToolBox (Brainard, 1997; Pelli, 1997), and presented on a Sony G220 Triniton monitor with a 640×480 resolution, 85 Hz refresh rate, and 27 cd/m^2 background mean luminance. Using a special circuit that combines two 8-bit output channels of the graphics card, the display system produced 14-bit gray-level resolution and was gamma-corrected using a psychophysics procedure (Li, Lu, Xu, Jin, & Zhou, 2003).

The signal stimuli were vertical $3.06° \times 3.06°$ sine-wave gratings presented in the center of the display:

$$l(x,y) = l_0\{1.0 + c\sin[2\pi f(y\cos\theta - x\sin\theta)]\}, \quad (1)$$

where l_0 is the mean luminance, c the signal contrast; f the spatial frequency; and $\theta = 90°$. To minimize edge effects, a 0.5° half-Gaussian ramp is added to each side of the stimulus to blend it to the background.

In the TvC experiment, additional external noise images with the same size as that of the signal frames were generated. The average spatial frequency spectrum of the external noise images was flat up to about 38 c/deg. The external noise images were made up of noisy pixels of $0.013° \times 0.013°$ to each, with each pixel's contrast constructed by sampling from a Gaussian distribution with mean 0 and standard deviation depending on the level of external noise. Eight standard deviations were used: 0.001, 0.02, 0.04, 0.08, 0.12, 0.16, 0.25, and 0.33.

Subjects viewed the displays monocularly in fovea in a dimly lit room at a viewing distance of 2.28 m. The eye not being tested in a given session was covered with an opaque eye patch.

2.3. Experimental design

To evaluate contrast sensitivity functions (CSF), contrast sensitivity (CS), defined as 1/threshold, was calculated from sine-wave grating detection thresholds at spatial frequencies 0.5, 1, 2, 4, 8, 12, and 16 c/deg for both eyes. The thresholds were measured in a two-interval forced-choice (2IFC) detection task using a 3-down 1-up staircase procedure that converges to the 79.3% correct performance level (Levitt, 1971). The staircase procedure decreased signal contrast by 10% (multiplied the previous value by 0.9) after every three consecutive correct responses and increased signal contrast by 10% (multiplied the previous value by 1.1) after every incorrect response. The starting contrast for each staircase was set to the expected threshold, based on results from pilot testing.

Contrast sensitivity functions for the pAEs and the pFEs were measured in separate sessions with a counterbalanced order across observers. Each session consisted of 700 trials and lasted about 35 min. Within a session, the staircases for all the spatial frequencies were interleaved. For each spatial frequency in each eye, the staircase procedure went through 100 trials. A reversal resulted when the staircase changed its direction (changing from increasing to decreasing contrast or vice versa). Following standard practice, we excluded the first three (if the number of total reversals were odd) or four (if even) reversals. The mean of the remaining reversals was taken as the contrast threshold at 79.3% correct.

Threshold vs noise contrast functions were measured in the same 2IFC paradigm. Thresholds at 70.7% correct were measured using a 2-down 1-up staircase procedure.[2] The staircase procedure decreased signal contrast (by 10% of the current contrast) after every two consecutive correct responses and increased signal contrast by 10% after every incorrect response. For each observer, TvC functions were measured in both pAEs and pFEs at two to three spatial frequencies in ascending order (i.e., from low to high spatial frequencies) in separate sessions. Observer HZQ was tested with sine-wave gratings at 1 and 8 c/deg; SBB was tested at 1, 4, and 8 c/deg; WR was tested at 1 and 4 c/deg; ZKY was tested at 4 and 16 c/deg. TvC functions at all the test spatial frequencies were measured in one eye and then the other, with the order of eye counterbalanced across observers. Within each session, all the eight staircases, corresponding to the eight external noise conditions, were interleaved. Seventy-two trials were used to estimate each contrast threshold. A session lasted around 30 min.

Prior to the data acquisition, subjects ran 700 and 800 instructional/practice trials in each eye for the CSF and the TvC tests, respectively.

[2] The 2-down 1-up instead of the 3-down/1-up staircase procedure was used to reduce the number of trials required to reach reliable threshold estimate.

2.4. Procedure

Each CSF trial started with a 259 ms fixation cross in the center of the display, followed by two 118 ms intervals. The intervals each began with a brief 80 ms tone, and were separated with a 500 ms blank screen (at the mean background luminance). The signal sine-wave grating appeared in only one of the two intervals for 118 ms. The TvC trial sequence was similar to that used in a previous report (Lu & Dosher, 1999). Briefly, each trial started with a 259 ms fixation cross in the center of the display, followed by two intervals of 175 ms each, separated by a 500 ms blank screen. Demarcated by a brief tone in the beginning, both intervals consisted of five 35 ms long images: two noise frames, one signal or blank frame and another two noise frames. All noise frames were independently sampled. In both CSF and TvC tests, observers were asked to indicate which interval contained the signal by pressing a key on the computer keyboard. A brief tone immediately followed each response, regardless of its accuracy. The response also initiated the next trial.

2.5. Statistical analysis and model fit

Each CSF was fitted with the following function:

$$\log(S_t) = a_1 \exp\left[-\left(\frac{\log_2(f) - b_1}{c_1}\right)^2\right] - a_2 \exp\left[-\left(\frac{\log_2(f) - b_2}{c_2}\right)^2\right] - a_3 \exp\left[-\left(\frac{\log_2(f) - b_3}{c_3}\right)^2\right], \quad (2)$$

where f is the spatial frequency of the sine-wave grating, S_t is the predicted contrast sensitivity, and a_1, b_1,c_1, a_2, b_2, c_2, a_3, and c_3 are parameters. The first two terms of the function constituted a difference of Gaussian (DOG) function, often used to fit CSF functions (Rohaly & Buchsbaum, 1988; Rohaly & Buchsbaum, 1989; Zhou et al., 2006). The third term was included to estimate the magnitude and the bandwidth of the CSF deficits of the amblyopic eyes. For the fellow eyes, a_3 was set to 0. Because the largest deficit in amblyopia most often occurs in high spatial frequencies (Bradley & Freeman, 1981; Ciuffreda et al., 1991; Yang, Wu, Tian, & Wu, 1991), we set the center of the third Gaussian function, $b_3 = \log_2(16) = 4.0$, corresponding to the highest spatial frequency used in this study.

Following the suggestion from an anonymous referee of the manuscript, we also fit the CSFs in the pFE and pAE separately with DOGs, i.e., the first two terms in Eq. (2). Each pair of CSFs in the pFE and pAE of a given observer was compared by testing whether they can be modeled with the same DOG parameters. This fitting procedure as well as the original procedure described in the previous paragraph also allowed us to calculate the cutoff spatial frequencies, corresponding to the spatial frequency at which the contrast sensitivity is 2.0.

The perceptual template model (PTM; see Appendix A, also Lu & Dosher, 1999 for the formal theoretical development of the model) was fit to the TvC functions. In the PTM, log contrast threshold is modeled as a function of signal contrast and external noise level using the following equation:

$$\log(c_t) = \frac{1}{2\gamma}\left\{\log[(1 + A_m^2(k)N_m^2)A_f^{2\gamma}(k)N_{ext}^{2\gamma} + A_a^2(k)N_a^2] - \log\left[\frac{1}{d^2} - A_m^2(k)N_m^2\right]\right\} - \log(\beta), \quad (3)$$

where c_t denotes the predicted contrast threshold, N_{ext} is the standard deviation of external noises, $d' = 1.089$ is the perceptual sensitivity of the observer corresponding to 70.7% correct in the 2IFC. The rest of the symbols are model parameters: β is the gain of the perceptual template to a signal-valued stimulus, γ is the exponent of the nonlinear transducer function, N_m is the proportional constant for multiplicative noise, and N_a is the standard deviation of the additive internal noise. Following the practice in research on attention (Lu & Dosher, 1998) and perceptual learning (Dosher & Lu, 1999) as well as amblyopia (Xu et al., 2006), we used $A_a(pAE)$, $A_f(pAE)$,and $A_m(pAE)$ to model increased additive internal noise, increased impact of external noise, and increased multiplicative noise in the amblyopic eyes, as compared to the fellow eyes, for which $A_a(pFE)$, $A_f(pFE)$,and $A_m(pFE)$ were all set to 1.0.

Although we were fully aware that it is necessary to obtain TvC functions at multiple performance criteria in order to fully constrain the PTM model (Lu & Dosher, 1999), it was impractical to collect that amount of data with the relatively young observers in this study. We have therefore fixed two model parameters, based on the results of Xu et al. (2006). Specifically, we set $A_m(pAE) = 1.0$ because Xu et al. found that $A_m(pAE) = A_m(pFE) = 1.0$ in all the 18 cases in their study when they modeled TvC functions in the amblyopic and fellow eyes. We set $\gamma = 1.62$ because Xu et al. (2006) found that γ was relatively constant across eyes and different spatial frequencies (1.64 ± 0.02 at 1.5 c/deg; 1.61 ± 0.16 at 2.3 c/deg; 1.60 ± 0.49 at 4.6 c/deg). To test the generality of the modeling results, additional curve fitting with $\gamma = 1.0$ was also performed.

The model fitting procedures were implemented in Matlab using a nonlinear least- square method that minimized $\sum[\log(c_t^{theory}) - \log(c_t)]^2$. The goodness-of-fit was evaluated by the r^2 statistic:

$$r^2 = 1.0 - \frac{\sum[\log(c_t^{theory}) - \log(c_t)]^2}{\sum[\log(c_t) - \text{mean}(\log(c_t))]^2}. \quad (4)$$

For both CSF and TvC's, different variants of the models were compared using an F-test for nested models (Hays, 1988):

$$F(df_1, df_2) = \frac{(r_{full}^2 - r_{reduced}^2)/df_1}{(1 - r_{full}^2)/df_2}, \quad (5)$$

where $df_1 = k_{full} - k_{reduced}$, and $df_2 = N - k_{full} - 1$. The k's are the number of parameters in each model and N is the number of predicted data points.

3. Results

3.1. Contrast sensitivity functions

Fig. 2 depicts the contrast sensitivity functions for all five subjects. A within-subject analysis of variance (ANOVA) showed that contrast sensitivity varied significantly with both spatial frequency ($F(6,24) = 60.91$, $p < .001$) and eyes ($F(1,4) = 17.97$, $p < .05$). The interaction of the two factors was also significant ($F(6,24) = 4.58$, $p < .01$). In other words, contrast sensitivity was significantly higher in the pFEs than in the pAEs, and the difference depended on spatial frequency: highly significant at 12 and 16 c/deg (paired t-test, $t(4) = 6.884$, 4.951, both $p < 0.01$), significant at 8 c/deg ($t(4) = 3.197$, $p < .05$), and marginally significant at 2 and 4 c/deg ($t(4) = 2.515$, 2.269, $.05 < p < .10$).

To compare the CSFs in the pFE and the pAE for each observer and to estimate the bandwidth of the deficits, we fitted Eq. (2) to the CSFs of both eyes for each observer and tested whether including the deficit for the pAE (the 3rd term in Eq. (2)) provided a statistically better fit to the CSFs. The results are listed in Table 2. For four observers and the average of all the observers, the model with a pAE deficit provided significantly better fits to the data (all $p < .025$). For one observer, the model with a pAE deficit provided marginally better fit to the data ($p = .09$). The maximum contrast sensitivity difference occurred at the

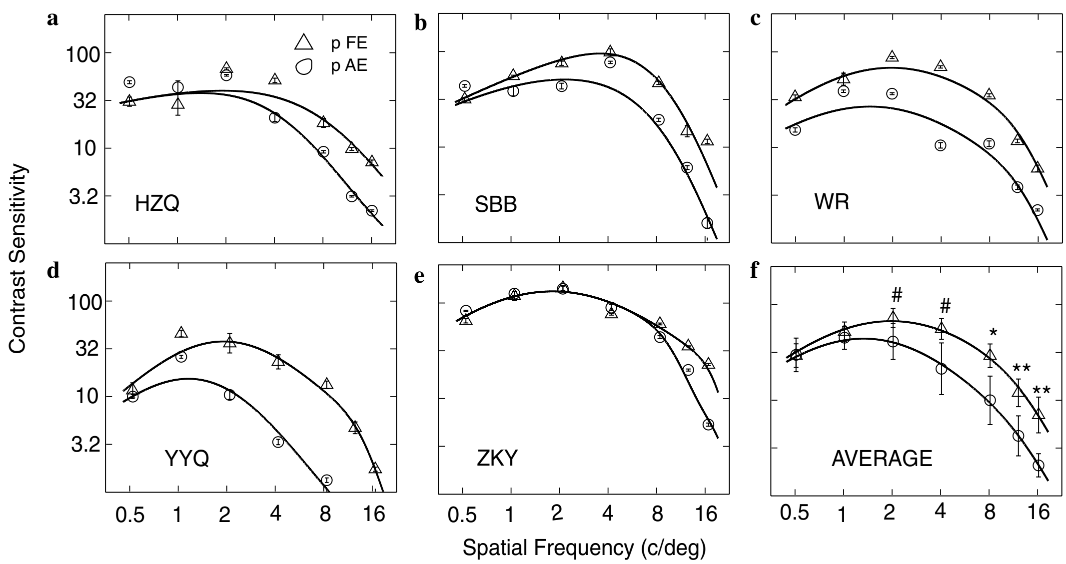

Fig. 2. Individual (a–e) and average (f) contrast sensitivity functions (CSF). The CSFs were fitted with the DOG model (Eq. (1)). Triangle, pFE; circle, pAE. The average CSFs for the pAEs and pFEs are shown with the *p*-value of the paired *t*-test at each spatial frequency. $^{\#}0.05 < p < 0.10$; $^{*}p < 0.05$; $^{**}p < 0.01$. The differences are significant mostly in intermediate to high spatial frequencies.

highest spatial frequencies and ranged from 10.40 to 21.74 dB across observers (mean = 12.90; SE = 2.22; median = 10.81). The bandwidth at half height of the CSF deficit also varied across observers, ranging from 0.58 to 4.82 octaves (mean = 2.48; SE = 0.72; median = 2.56). For the average observer, the maximum contrast sensitivity difference was 10.26 dB with a bandwidth of 2.73 octaves.

Using the alternative fitting procedure – modeling each pair of CSFs of each observer using separate DOGs, we found that independently fitting any one of the parameters of the second Gauss in the DOG while keeping all the other parameters the same between the two eyes (Eq. (2)) can significantly ($p < .01$) improve the quality of the fits for all the observers and their average. In other words, the two CSFs in the pFE and the pAE of each observer were significantly different.

Both fitting procedures were used to estimate the cutoff spatial frequency of each CSF. In the pAE, the average cutoff spatial frequency was estimated to be 14.8 ± 2.5 c/deg using the first procedure, and 14.9 ± 2.6 c/deg using the second procedure. In the pFE, the average cutoff spatial frequency was estimated to be 22.3 ± 2.4 c/deg using the first procedure, and 24.5 ± 3.0 c/deg using the second procedure. The results from the two procedures are virtually the same.

3.2. Identifying mechanisms of the deficits

To identify the mechanisms of perceptual deficits, the PTM model (Eq. (3)) was fit to the pair of TvC functions (pAE and pFE) measured in each spatial frequency condition. The best fitting model parameters (with $\gamma = 1.62$ and 1.0) are listed in Tables 3 and 4; the corresponding predictions with $\gamma = 1.62$ are graphed in Fig. 3. We describe the results with $\gamma = 1.62$ in the text. A similar pattern of results was obtained with $\gamma = 1.0$.

Subject HZQ was tested at 1 and 8 c/deg. At 1 c/deg, no significant deficit was found in the pAE: the model positing no amblyopic deficit (all A's = 1.0) accounted for 83.6% of the variance in the data and was statistically equivalent to the more saturated models (all $p > .10$). At 8 c/deg, the model with both mechanisms of amblyopia, increased internal noise and increased impact of external noise, provided the best fit to the data: It accounted for 98.5% of the variance with about 300% increase of internal additive noise and 118% increase of the impact of external noise

Table 2
Best fitting DOG parameters

	HZQ	SBB	WR	YYQ	ZKY	AVG
a_1	1.65	2.18	1.82	1.57	2.15	1.84
b_1	1.65	3.91	0.98	0.88	0.79	0.96
c_1	9.00	8.00	4.45	3.28	5.02	4.47
a_2	1.47	2.96	1.00	1.01	6.84	1.00
b_2	6.16	5.83	5.11	4.75	5.65	5.62
c_2	2.49	2.10	1.10	0.78	0.80	1.50
a_3	0.519	0.54	0.56	1.09	0.52	0.51
c_3	1.91	3.07	5.79	3.46	0.69	3.29
R^2_{full}	0.89	0.97	0.94	0.96	0.98	0.99
R^2_{reduced}	0.72	0.85	0.70	0.56	0.91	0.81
$F(2,5)$[a]	4.08	9.11	10.77	16.56	10.01	95.87
p	.09	.02	.02	.02	.018	0.001
SF_{cutoff} pFE[§] (c/d)	30.23	21.17	21.71	15.42	22.86	24.54
SF_{cutoff} pAE (c/d)	16.54	15.51	15.22	5.83	21.05	16.45

[a] For subject YYQ, we did not obtain accurate measurements of the last two data points in his pAE. We discarded these two data points in fitting the DOGs. So the degree of freedom should be 2 and 3 in the *F*-test.

[§] Cutoff spatial frequency SF cut off was defined as the spatial frequency at which observer's contrast sensitivity was 2.

Table 3
Parameters of the best fitting PTM model ($\gamma = 1.62$ for both eyes)

Parameters	HZQ		SBBQ			WR		ZKY	
	1 (c/d)	8	1	4	8	1	4	4	16
γ	1.62	1.62	1.62	1.62	1.62	1.62	1.62	1.62	1.62
N_a	0.006	0.010	0.008	0.020	0.034	0.083	0.002	0.013	0.15
N_m	0.78	0.63	0.67	0.054	0.39	0.62	0.73	0.38	0.29
β	1.21	1.70	2.31	4.26	3.02	1.74	2.13	3.41	3.48
A_a		4.00		2.70	5.78	1.53	3.96		5.92
A_f		2.18			1.81				6.23
R^2	0.840	0.985	0.953	0.927	0.944	0.968	0.927	0.927	0.932
$F_{\text{full vs reduced}}$	1.420	82.162***	0.965	16.599***	53.331***	12.155**	4.929*	0.260	64.320***
$F_{\text{Af vs reduced}}$	1.372	30.255***	0.413	0.241	6.585*	0.348	2.998	0.550	13.440**
$F_{\text{Aa vs reduced}}$	2.727	16.331**	1.308	36.135***	63.176***	26.309***	7.027*	0.050	53.378***
$F_{\text{full vs Af}}$	1.416	36.481***	1.499	32.272***	62.976***	23.257***	5.605*	0.020	52.399***
$F_{\text{full vs Aa}}$	0.290	60.160***	0.663	0.0811	7.301*	0.116	2.117	0.473	13.689**

* $p < .05$.
** $p < 0.01$.
*** $p < .001$.

Table 4
Parameters of the best fitting PTM model ($\gamma = 1.00$ for both eyes)

Parameters	HZQ		SBB			WR		ZKY	
	1	8	1	4	8	1	4	4	16
γ	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
N_a	0.046	0.061	0.057	0.097	0.14	0.077	0.020	0.068	0.38
N_m	0.82	0.53	0.73	0.025	0.27	0.44	0.74	0.19	0.031
β	2.17	1.89	3.58	4.90	3.47	1.35	3.09	3.57	4.45
A_a		2.37		1.82	2.93	1.53	2.48		2.97
A_f		2.15			1.75				7.01
r^2	0.880	0.986	0.959	0.918	0.950	0.968	0.943	0.905	0.928
$F_{\text{full vs reduced}}$	1.689	86.977***	1.072	14.822**	59.368***	12.155**	7.246*	0.231	61.362***
$F_{\text{Af vs reduced}}$	1.855	32.670***	0.429	0.324	7.939*	0.348	3.111	0.499	14.943**
$F_{\text{Aa vs reduced}}$	2.946	23.704***	1.216	30.452***	83.260***	26.309***	10.977**	0.066	55.819***
$F_{\text{full vs Af}}$	1.447	36.336***	1.689	28.512***	64.771***	23.257***	9.092*	0.009	46.276***
$F_{\text{full vs Aa}}$	0.552	48.307***	0.936	0.520	5.0234*	0.116	2.259	0.401	11.850**

* $p < .05$.
** $p < .01$.
*** $p < .001$.

in the pAE. The model is statistically superior to all its reduced versions (all $p < .001$).

Subject SBB was tested at 1, 4, and 8 c/deg. At 1 c/deg, no significant deficit was found in the pAE: The PTM without any amblyopic deficit (all A's = 1.0) accounted for 95.3% of the variance in the data. It was statistically equivalent to the more saturated models (all $p > .10$). At 4 c/deg, performance differences in the pAE and the pFE can be accounted for by a single mechanism of increased internal additive noise in the pAE: the corresponding PTM model accounted for 92.7% of the variance with 170% increase of internal additive noise in the pAE. The model was statically equivalent to the most saturated model ($p > .25$) and superior to its reduced version ($p > .001$). At 8 c/deg, a mixture of two mechanisms, increased internal additive noise and increased impact of external noise, was required to account for the data: the corresponding PTM accounted for 94.4% of the variance with 478% increase in internal noise and 81% increase in the impact of external noise. It was statistically superior to all its reduced versions ($p < .05$).

Subject WR was tested at 1 and 4 c/deg. At both spatial frequencies, a single mechanism of increased internal additive noise provided the best account of the data. The corresponding PTM provided statistically equivalent fits to the data when compared with more saturated models (all $p > .10$) and superior fits to the data when compared with reduced models (all $p < .05$). At 1 c/deg, the corresponding PTM accounted for 96.8% variance with about 53% increase of internal additive noise in the pAE; at 4 c/deg, the PTM accounted for 92.7% of the variance with 296% increase of internal additive noise.

Subject ZKY was tested at 4 and 16 c/deg. At 4 c/deg, no deficit was found in the pAE: the PTM with all the A's set to 1.0 provided a statistically equivalent account ($r^2 = 0.9265$) of the data when compared to all the more saturated models (all $p > .10$). At 16 c/deg, a mixture of two mechanisms, increased internal additive noise and

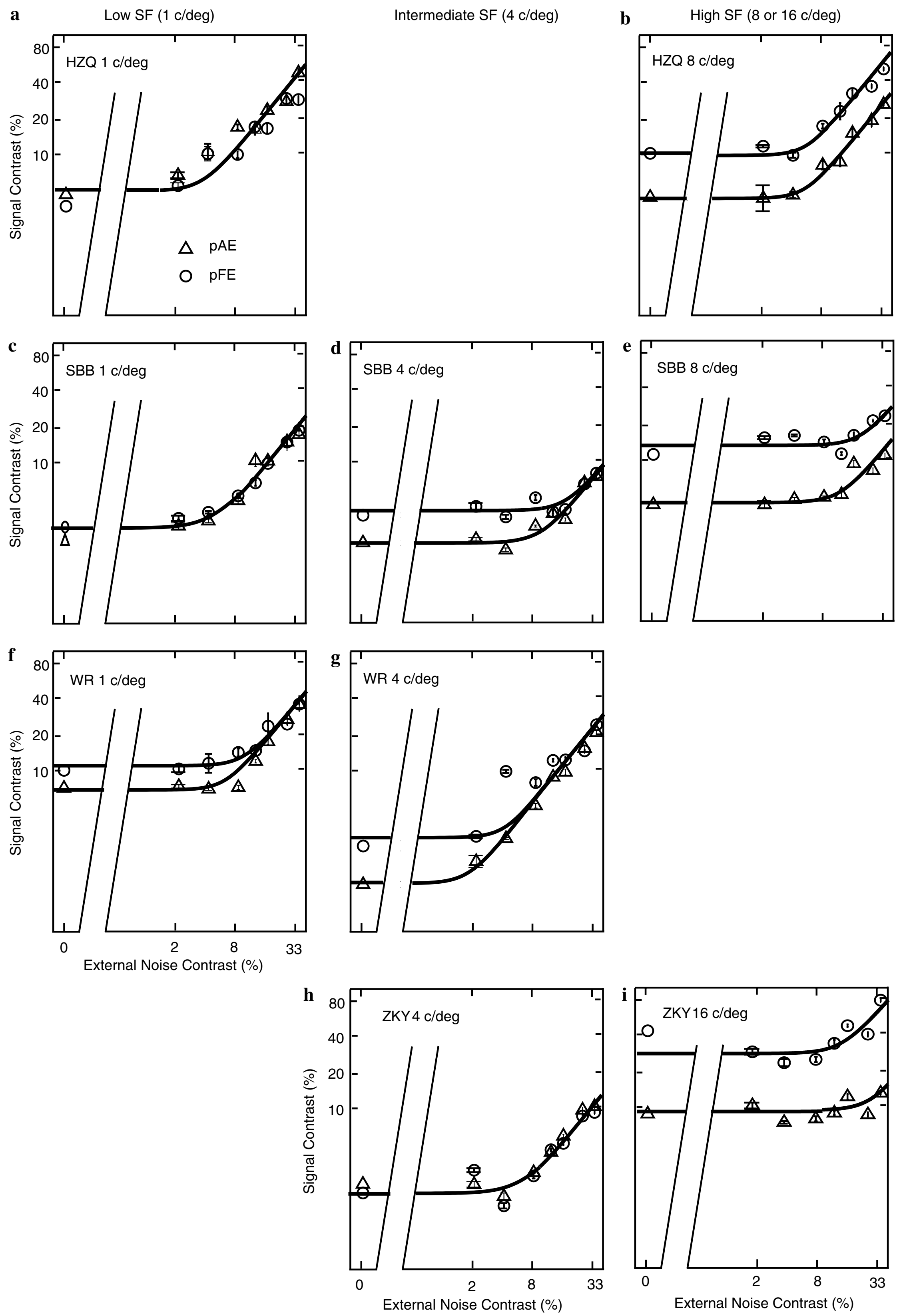

Fig. 3. TvC curves at two or three spatial frequencies for each observer. Smooth curves represent the predictions of the best fitting PTM models. Triangle, pFE; circle, pAE.

increased impact of external noise, was required to account for the data: the corresponding PTM accounted for 93.2% of the variance with 492% increase in internal noise and 523% increase in the impact of external noise. It is statistically superior to all its reduced versions ($p < .01$).

To summarize, in low and intermediate spatial frequencies (1 and 4 c/deg), no deficit or a single mechanism of increased additive internal noise was observed between pAEs and pFEs. In relatively high spatial frequencies (8 and 16 c/deg), a mixture of two mechanisms, increased additive internal noise and increase impact of external noise, was found in the pAE, relative to the pFE. The results are completely consistent with those of Xu et al. (2006).

4. Discussion

The current study demonstrates that treated amblyopes with normal visual acuity may remain deficient in other aspects of spatial vision. Irrespective of amblyopia type (anisometropic, strabismus or both), the deficiencies are reflected in reduced contrast sensitivity, especially at relatively high spatial frequencies, and in elevated TvC functions. Similar to Xu et al. (2006), two mechanisms of amblyopia deficits were identified: increased internal noise at low to medium spatial frequencies, and increases in both internal noise and impact of external noise at high spatial frequencies.

The finding of deficient contrast sensitivity functions in the pAEs of treated amblyopes is consistent with other reports in the literature (Cascairo et al., 1997; Regan, 1988; Rogers et al., 1987). One important question is whether the observed spatial vision deficits in treated amblyopes reflect residual amblyopia – poorer visual acuity in the pAEs. This is clearly not the case because (1) the average visual acuity of pAE and pFE were 0.944 ± 0.019 and 0.936 ± 0.021 MAR acuity, respectively, and (2) visual acuity in the pAE of each observer had been stabilized for at least three years prior to our experiments.

Compared to previous studies on treated amblyopia, the psychophysical procedure used in the current study provided better control over stimulus presentation. This allowed us to rule out certain potential explanations for the observed CSF deficits. Two contending alternative explanations relate to eye fixation and accommodation. Many amblyopes have inaccurate or unsteady fixation (Ciuffreda et al., 1991; Schor & Hallmark, 1978). Although direct evidence is lacking, it is possible that fixation remains abnormal in the treated pAEs. Is the observed CSF abnormality a consequence of unsteady fixation in the pAEs? Although unsteady fixation can reduce contrast sensitivity, it cannot fully explain our results. First, this study used briefly presented sinusoidal gratings, covering relatively large areas of the retina, which were more robust to retinal motion than broad-band letters. Second, Westheimer and McKee (1975) showed that the spatial resolution of the visual system was immune to retinal image motion up to 2.5 deg/s, which was faster than most fixational eye movements of amblyopes (Schor & Hallmark, 1978). And, in fact, contrast sensitivity does not improve even when retinal image motion is eliminated via image stabilization (Asper, Crewther, & Crewther, 2000). Also, superimposing simulated amblyopic retinal image motion on the central field of normal adult does not produce contrast sensitivity losses (Higgins, Daugman, & Mansfield, 1982).

Decreased accommodative amplitude and increased accommodative lag have also been associated with amblyopia (Asper et al., 2000). Ciuffreda, Hokoda, Hung, Semmlow, and Selenow (1983) found slight defects in accommodation remained in "former amblyopes" who had successfully completed orthoptic therapy. Can abnormal accommodation account for the observed deficits in CSF? This explanation can be ruled out by the procedure and pattern of results in our study. First, accommodation in all the observers should have become stabilized (at least to a very high degree) after the subjects finished the 700 instructional trials prior to the data collection. Second, image blur associated with poor accommodation would have affected contrast sensitivity over a broad range of spatial frequencies (Campbell & Green, 1965; Marmor & Gawande, 1988; Thorn, 1990). However, we showed that contrast sensitivities at low and medium spatial frequencies are relatively spared.

Although visual acuity tests are often thought to exam the cutoff spatial frequency of the visual system, the task in fact involves a range of spatial frequencies. This is illustrated in the Fig. 4 – the Fourier power spectrum of the template for the tumbling *E* test (an "*E*" at a single orientation minus the average of four oriented *E*) is nearly flat in a wide spatial frequency range, including low-to-medium spatial frequencies. It is possible that amblyopes can cope with many tasks (e.g., reading) using low and intermediate

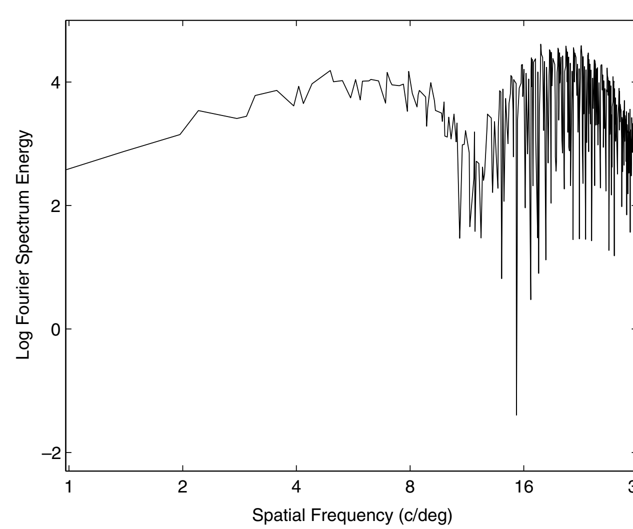

Fig. 4. The Fourier power spectrum of template for the tumbling E test (a single E – the average of four oriented E). The E used in generating the Fourier power spectrum is up-oriented and with the stroke width of 0.9625′, corresponding to the observers' visual acuity.

spatial frequency channels when their fellow eyes are patched. The relatively larger deficits in high spatial frequencies exhibited by observers who have completed occlusion therapy and practice in acuity tasks suggest that selective training in relatively high spatial frequencies might be necessary to reduce high spatial frequency deficits in amblyopia. Recently, Zhou et al. (2006) found that training in grating detection near the pre-training cutoff spatial frequency of amblyopes greatly enhanced their contrast sensitivity and visual acuity, and the performance improvements in the amblyopic eyes were broadly tuned in spatial frequency and generalized to the fellow eyes. It would be interesting to repeat the Zhou et al. study with treated amblyopes, using similar perceptual learning procedures to examine whether perceptual learning can provide additional improvements in high spatial frequencies. According to McKee et al. (2003), monocular contrast sensitivity might be related to the binocularity of neurons in the early visual pathway. That CSF remains deficient in amblyopes treated with occlusion therapy suggests that explicit training on binocular functions may be necessary following largely monocular training/exposure therapies.

Our interpretation of the mechanisms of amblyopia is based on a theoretical framework derived from the perceptual template model (Lu & Dosher, 1998). Others in the literature have based their interpretations of the TvC functions on the linear amplifier model (LAM) of the human observer (Pelli, 1981). In the LAM, contrast threshold is described as a function of external noise by the following equation:

$$c_\tau = \sqrt{\frac{N_{\text{ext}}^2 + N_{\text{eq}}^2}{E_\tau}}, \tag{6}$$

where c_τ is the contrast threshold at performance criterion τ (e.g., 75% correct), E_τ is the sampling efficiency associated with the performance criterion, N_{ext}^2 is the variance of the (experimenter-controlled) external noise, and N_{eq}^2 is the variance of the equivalent intrinsic noise. Using the LAM framework, some studies attributed amblyopic deficits to reduced sampling efficiency; others attributed them to increased additive internal noise; and still others attributed them to increased stimulus-dependent noise. It is worth noting that attributing amblyopia to a single mechanism of lower sampling efficiency in the LAM leads to very strong predictive constraints on the relative magnitudes of amblyopic deficits in high and low external noise conditions: the threshold ratio between the amblyopic and fellow/normal eyes should be the same in high and low external noise conditions. We fitted the data in this study with the LAM. Because we have only measured TvC functions at one criterion performance level, as many other studies in the literature, the LAM fits were comparable to those of the PTM. The LAM account modeled amblyopia deficits with two mechanisms: increased additive noise (equivalent input noise) in low and intermediate spatial frequencies, and decreased calculation efficiency in high spatial frequencies.

On the other hand, as detailed in Lu and Dosher (2004) and Xu et al. (2006), the LAM used by Pelli imposes various limitations on the theoretical interpretations of the TvC functions. This is reflected in the lack of stimulus-dependent internal noise in the model construct, as well as the paradoxical, decreased internal noise in amblyopia found in some of the conditions in Pelli et al. (2004). In fact, many studies have concluded that the LAM is an inadequate observer model for human performance (Burgess & Colborne, 1988; Eckstein et al., 1997; Lu & Dosher, 1999; Lu, Lesmes, & Dosher, 2002; Pelli, 1985; Pelli et al., 2004; Tjan, Chung, & Levi, 2002). Given all the theoretical issues with LAM, we favor the PTM account of the data.

The pattern of results in the current study is completely consistent with that of Xu et al. (2006). It is surprising that treated amblyopes showed similar patterns of TvC deficits as the un-treated amblyopes. The perceptual template in the PTM represents the "receptive field" at the observer system level. Increased deficits in high external noise in the high spatial frequency conditions suggest deficient perceptual templates in those conditions, potentially associated with mis-wiring of cortical neurons ("topographical jitter") in any (or all) of the stages of visual processing (Hess & Field, 1994). It is also possible that deficient perceptual templates result from down-weighting of the high spatial frequency channels of the amblyopic eyes in the decision stage. Much new research is necessary to distinguish these two possibilities. One the other hand, increased additive noise might result from modest reduction of the effective input (Kiorpes, Kiper, O'Keefe, Cavanaugh, & Movshon, 1998) or increased variance of neuronal activities in the amblopic cortex (Tolhurst, Movshon, & Dean, 1983).

Research on perceptual learning (Dosher & Lu, 2005; Lu, Chu, & Dosher, 2006) has documented independent learning mechanisms in low and high external noise conditions. The results of the current study suggest that we probably need to develop training protocols that focus on high spatial frequency tasks in both low and high external noise conditions.

Measuring contrast sensitivity functions and threshold vs contrast functions have so far required a large investment in data collection. Although various charts have been developed in the past to estimate CSF in clinical settings, the results are still not as reliable as those from psychophysical procedures. With the wide availability of good personal computers, it has become relatively inexpensive to develop efficient computer procedures to measure these functions. In a recent publication, Lesmes, Jeon, Lu, and Dosher (2006) developed a novel Bayesian adaptive procedure, the "quick *TvC*" or "*qTvC*" method, to rapidly estimate multiple *TvC* functions. By adapting a strategy originally developed to estimate psychometric threshold and slope (Cobo-Lewis, 1997; Kontsevich & Tyler, 1999), they showed that less than 300 trials were needed to estimate *TvC* functions at three widely separated criteria with good accuracy (bias < 5%) and precision (mean rms error <1.5 dB). Efficient procedures based on the same algorithm are being developed to quickly estimate contrast sensitivity functions (<200 trials).

In conclusion, the contrast sensitivity functions of all the treated amblyopic eyes in this study remained abnormal following the "successful" completion of their occlusion therapy treatment, long after their tumbling "*E*" visual acuity had become normal. We suggest that other tests of spatial vision (CSF, TvC for example) should be used in addition to visual acuity at various stages of the treatment to assess the outcomes of amblyopia therapies. Additional training in high spatial frequency in both low and high external noise conditions may be necessary to eliminate CSF deficits in amblyopia.

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Appendix A

The perceptual template model (PTM; Fig. 1a) is an elaborated version of the simple LAM, which consisted of a linear amplification stage, an internal equivalent input noise source and a decision stage. The PTM models system performance with two additional components: a non-linear transducer function and a multiplicative noise (stimulus-dependent) source and predicts the performance of an observer, d', as

$$d' = \frac{(\beta c)^{2\gamma}}{\sqrt{N_{\mathrm{ext}}^{2\gamma} + N_{\mathrm{add}}^2 + N_{\mathrm{mul}}^2((\beta c)^{2\gamma} + N_{\mathrm{ext}}^{2\gamma})}}, \tag{A1}$$

where c is the signal contrast; β is the gain on a signal-valued stimulus processed through the template; γ characterizes system's non-linearity, N_{add} is internal additive noise (stimulus-independent), N_{ext} is external noise level that applied, and N_{mul} is multiplicative noise (stimulus-dependent). To fully characterize the PTM, measuring TvC function at a minimum of three performance levels (d') is required.

Solving for the contrast threshold, C_{t} in log form, required to reach a particular accuracy level, we have:

$$\log(C_t) = \frac{1}{2\gamma}\log((1 + N_{\mathrm{m}}^2)N_{\mathrm{ext}}^{2\gamma} + N_{\mathrm{a}}^2) - \frac{1}{2\gamma}\log(1/d'^2 - N_{\mathrm{m}}^2) - \log(\beta). \tag{A2}$$

Within the PTM framework, there can be three possible variations (mechanisms) to the system: changes in internal additive noise, perceptual template, and multiplicative noise. These three mechanisms can be modeled as modifiers of the corresponding model parameters:

$$\log(c_t) = \frac{1}{2\gamma}\left\{\log[(1 + A_{\mathrm{m}}^2(k)N_{\mathrm{m}}^2)A_f^{2\gamma}(k)N_{\mathrm{ext}}^{2\gamma} + A_{\mathrm{a}}^2(k)N_{\mathrm{a}}^2] - \log[\frac{1}{d^2} - A_{\mathrm{m}}^2(k)N_{\mathrm{m}}^2]\right\} - \log(\beta). \tag{A3}$$

These three mechanisms exhibit signature patterns when we compare TvC functions measured in the previous amblyopic and fellow eyes (Fig. 1).

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