

Endogenous attention improves perception in amblyopic macaques

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Amblyopia, a developmental disorder of vision, affects many aspects of spatial vision as well as motion perception and some cognitive skills. Current models of amblyopic vision based on known neurophysiological deficiencies have yet to provide an understanding of the wide range of amblyopic perceptual losses. Visual spatial attention is known to enhance performance in a variety of detection and discrimination tasks in visually typical humans and nonhuman primates. We investigated whether and how voluntary spatial attention affected psychophysical performance in amblyopic macaques. Full-contrast response functions for motion direction discrimination were measured for each eye of six monkeys: five amblyopic and one control. We assessed whether the effect of a valid spatial cue on performance corresponded to a change in contrast gain, a leftward shift of the function, or response gain, an upward scaling of the function. Our results showed that macaque amblyopes benefit from a valid spatial cue. Performance with amblyopic eyes viewing showed enhancement of both contrast and response gain whereas fellow and control eyes' performance showed only contrast gain. Reaction time analysis showed no speed accuracy trade-off in any case. The valid spatial cue improved contrast sensitivity for the amblyopic eye, effectively eliminating the amblyopic contrast sensitivity deficit. These results suggest that engaging endogenous spatial attention may confer substantial benefit to amblyopic vision.

Introduction

Amblyopia is a developmental disorder of vision, affecting 3%–5% of children worldwide, the neural basis for which is still unknown. It is most commonly associated with anisometropia (unequal refractive

errors), strabismus (misalignment of the visual axes), and cataracts (ocular opacities) when they exist during an early critical period of visual development. Amblyopia is primarily a disorder of spatial vision, being characterized clinically as a deficit in acuity of one eye although various disorders of motion perception have also been identified (for reviews, see Kiorpes, 2006; Levi, 2006, 2013; Grant & Moseley, 2011; Kanonidou, 2011; Wong, 2012; Birch, 2013). Importantly, numerous deficits of higher-order perception have been documented, for example, in global form and motion perception and figure–ground segregation (for a review, see Hamm, Black, Dai, & Thompson, 2014). Some of the higher-order losses persist despite “successful treatment” during childhood (Levi, Yu, Kuai, & Rislove, 2007; Rislove, Hall, Stavros, & Kiorpes, 2010; Secen, Culham, Ho, & Giaschi, 2011; Giaschi, Chapman, Meier, Narasimhan, & Regan, 2015) and may extend to the fellow eye (Kozma & Kiorpes, 2003; Ho et al., 2006; Kiorpes, Tang, & Movshon, 2006; Secen et al., 2011; Meier & Giaschi, 2017).

Investigations into the neural mechanisms that underlie amblyopia have uncovered a number of visual cortical deficits. Reduced representation of the amblyopic eye in V1 is a common finding although some amblyopic macaques show balanced or nearly balanced eye dominance (Wiesel, 1982; Movshon et al., 1987; Smith et al., 1997; Kiorpes, Kiper, O’Keefe, Cavanaugh, & Movshon, 1998; Shooner et al., 2015). An additional factor is defective signaling by neurons driven through the amblyopic eye. V1 and V2 neurons driven by amblyopic eye stimulation have reduced spatial resolution and contrast sensitivity (Movshon et al., 1987; Kiorpes et al., 1998; Bi et al., 2011); however, these effects alone are too small to explain the animals’ behaviorally measured resolution or sensitivity losses

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(Kiorpes et al., 1998; Kiorpes & Movshon, 2004; Shooner et al., 2015). A number of additional receptive field abnormalities have been identified in early visual cortical areas, for example, orientation bias, abnormal spike dynamics, and imbalance of excitation and inhibition, which in combination with abnormal binocular suppression may more completely capture the spatial vision losses (Bi et al., 2011; Hallum et al., 2017; Shooner et al., 2017; Y. Wang et al., 2017).

These results and the range of reported higher-order perceptual deficits identified in amblyopes suggest that substantial disruption of neural organization may exist beyond V1 and even V2. El-Shamayleh, Kiorpes, Kohn, and Movshon (2010) is the only investigation of a downstream area to date in amblyopia. These authors reported similar neural response properties—direction selectivity and speed tuning—for middle temporal (MT) neurons driven by the two eyes of amblyopic macaques despite the fact that they showed substantial behavioral deficits in motion perception. This mismatch further documents the lack of a commensurate neurophysiological effect at a single unit level. Alternative approaches that approximate the response of the greater population of neurons in amblyopic MT, taking into account the weak feed-forward representation of the amblyopic eye, provide a better representation of the perceptual losses (El-Shamayleh et al., 2010) but still fall short of fully accounting for them.

Psychophysical investigations in humans have noted cognitive level deficits in amblyopia. For example, Farzin and Norcia (2011) documented decision-making and response-selection deficits that were not explained by low-level deficits in visual function; these losses extended to the fellow eye. A few studies have investigated whether deficits exist in other higher-level tasks, such as multiple-object tracking (Ho et al., 2006; Levi & Tripathy, 2006; Secen et al., 2011), numerosity judgments (Sharma, Levi, & Klein, 2000), and “attentional blink” (Popple & Levi, 2008). These authors have reported deficits under particular circumstances that again could not be accounted for based on basic visual loss. These deficits have been attributed to visual attention, but very few have directly manipulated attention rather than inferred its contributions.

Visual attention enables the observer to selectively process particular stimuli among many or a particular object in a scene. The effects of attention on typical vision have been well characterized; visual attention enhances performance in a wide variety of detection and discrimination tasks, many mediated by contrast sensitivity and spatial resolution (for reviews, see Carrasco, 2011; Carrasco & Barbot, 2015). A few studies have directly assessed whether attentional losses are evident in amblyopia with somewhat conflicting results. On the one hand, Roberts, Cymerman, Smith, Kiorpes, and Carrasco (2016) manipulated both

endogenous (voluntary) and exogenous (involuntary) spatial attention using a classic covert attention approach. They found that amblyopes were able to successfully deploy attention regardless of which eye was viewing; the benefits at the attended location and costs at an unattended location did not differ either between the amblyopic and fellow eyes or from typical adults. Sharma et al. (2000) reported undercounting of features in multiple element displays by amblyopic observers, but spatial cueing reduced the error rate across all observers and did not differentially impact amblyopic performance. On the other hand, electrophysiological studies show weaker modulation of evoked potentials through one or both eyes of amblyopes in attention versus no-attention conditions (van Balen & Henkes, 1962; Hou, Kim, Lai, & Verghese, 2016). Hou et al. (2016) noted decreased visual evoked potential modulation amplitude in response to attended versus ignored grating stimulation in the amblyopic eye compared with the corresponding difference for the fellow eye of strabismic amblyopes. Both eyes showed weaker attentional modulation in areas downstream of V1 (hV4, hMT+); only the amblyopic eye showed weaker modulation in V1. They also reported a significant correlation between the modulation deficits in V1 and the depth of amblyopia and interocular suppression, suggesting that attentional weakness may be intimately related to the more global losses seen in amblyopia.

Given the broad range of deficiencies that have been reported for amblyopic vision and the fact that no clear neurophysiological account has been identified, we investigated the integrity of voluntary, endogenous spatial attention in amblyopic macaques. No previous study has evaluated the nature in which an endogenous spatial cue impacts discrimination performance in amblyopes. In the current study, to evaluate the nature of the effect of endogenous attention on psychophysical performance in amblyopia, we measured full-contrast response functions for each eye, amblyopic and fellow, and assessed whether the effect on performance in each case corresponded to a change in contrast gain (a leftward shift of the function) or response gain (an upward scaling of the function); see Figure 1 for illustration. Many neurophysiological and psychophysical studies have assessed these attention-based shifts (e.g., reviews, Reynolds & Heeger, 2009; Carrasco, 2011). We explored whether and how the effects of spatial cueing of voluntary attention differed for the amblyopic eye compared to the fellow eye or to visually normal control eyes. In fact, we found that macaque amblyopes benefit from a spatial cue as do human amblyopes (Roberts et al., 2016). However, the effect of a valid spatial cue on the psychometric function was qualitatively different between fellow and amblyopic eyes; amblyopic eye performance exhibited changes in

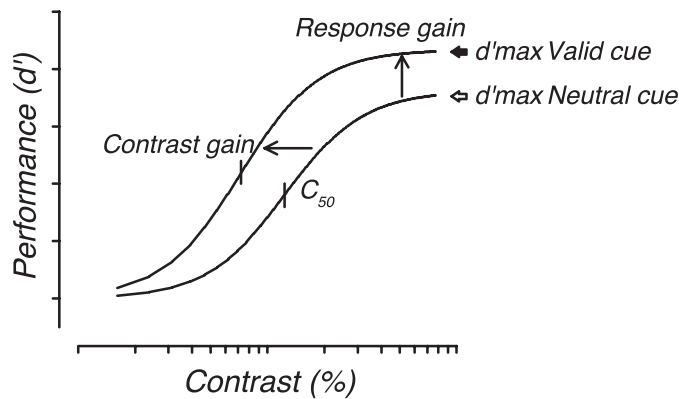


Figure 1. Illustration of covert attention effects. Two typical effects of a valid cue on the psychometric function are illustrated: a change in maximum d' ($d'max$), which reflects a response gain change; and a change in contrast sensitivity (C_{50}), which reflects a shift in contrast gain.

both contrast and response gain whereas the fellow eyes and the control eyes only showed changes in contrast gain.

Methods

Subjects

We tested six pig-tailed macaque monkeys, *Macaca nemestrina*: five amblyopic subjects (two females and three males) and one visually normal control (female), aged 3 to 7 years. Given that most tested visual functions reach maturity by 2 to 3 years after birth (Kiorpes & Bassin, 2003; Kiorpes & Movshon, 2004; Kiorpes, Price, Hall-Haro, & Movshon, 2012), we chose this age range to ensure that the subjects' vision had reached adult levels prior to the beginning of the experiment. Monkeys were born either at the Washington National Primate Research Center or at New York University's animal facilities. They were hand-reared in the nursery facility in the Visual Neuroscience Lab of New York University. Their daily activities included enrichment with various visual and tactile toys as well as regular opportunities for interaction with other monkeys and humans.

Amblyopia was induced in one of two ways. Anisometric amblyopia developed in two monkeys following rearing with extended-wear soft contact lenses (MedLens Innovations, Front Royal, VA) with a blurring -8.0 D lens in one eye and a plano lens in the other to create a unilateral defocus, beginning about 3 weeks after birth for a duration of 6–7 months. In two monkeys, strabismic amblyopia developed after surgical misalignment of the visual axes, induced by

transection of the lateral rectus muscle and resection of the medial rectus muscle of one eye, resulting in unilateral esotropia (crossed eyes), at about 3 weeks of age. Detailed procedures for inducing amblyopia experimentally can be found in previous publications from the lab (see Kiorpes, Kiper, & Movshon, 1993). The fifth amblyopic monkey was a natural amblyope. All animal care and husbandry as well as experimental methods were conducted in accordance with protocols approved by the New York University Animal Welfare Committee and conformed to the National Institutes of Health *Guide for the Care and Use of Laboratory Animals*.

Apparatus

The stimuli were generated with a Cambridge Research System's VSG 2/3 graphics card and displayed on a 21-in. EIZO FlexScan FX-E8 CRT monitor with a refresh rate of 100 Hz and a mean luminance of 30 cd/m^2 . Eye position was monitored using an infrared video camera system (ISCAN ETL-200 running DQW version 1.11); subjects were required to fixate throughout the trial. Fixation window size was adjusted as needed for each subject. The size varied due to the greater instability of fixation with the amblyopic eye of some strabismic subjects. All subjects were able to maintain fixation with either eye within a window of maximum diameter 3.5° throughout the trial.

Monkeys were tested in a dimly lit room. The experimental setup was identical for the visually normal controls and the amblyopic subjects. Subjects were placed in a cage in which they were free to move around between trials, which was 100 cm away from the monitor. A face mask containing sensors was positioned at the front of the cage, aligned with the center of the monitor. Subjects were trained to fixate using the eye-tracker camera with an infrared light source while keeping their face in the mask. They were tested monocularly with the nontest eye occluded (eye patch or physical occluder). Optical correction was provided as needed. Trials were initiated by simultaneous activation of the eye tracker and diode sensors in the face mask when the subject acquired and held fixation on a central fixation target. If the subject failed to hold fixation throughout stimulus presentation or removed his or her face from the mask, the trial was immediately terminated, and a new trial began with the target in a new location. A bar box was positioned below the mask on the testing cage, allowing the subjects to respond by pulling one of two grab bars to indicate their choice on each trial. A juice tube attached to a mouth port in the face mask delivered precalibrated juice rewards.

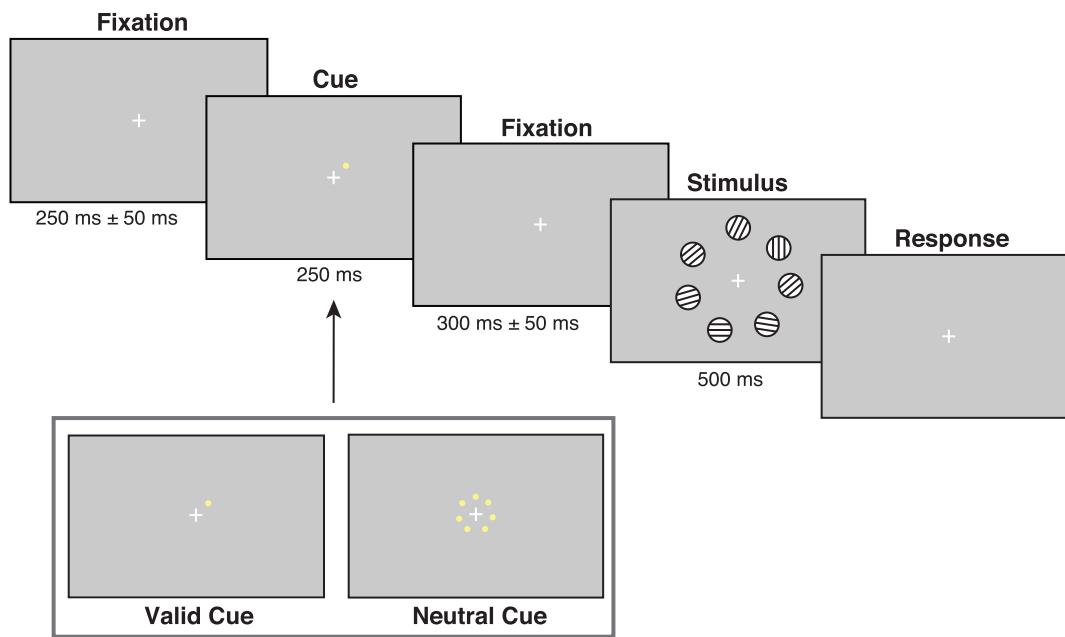


Figure 2. Trial sequence. The monkey initiated a trial by fixating the fixation cross in the center of the screen. Following a brief fixation interval, a cue was presented; the cue was either valid, with a single dot indicating the actual location in which the target would appear during the stimulus interval (lower left, inset box), or neutral, with seven dots appearing conveying no information about the location of the target (lower right, inset box). Note: The cues were in fact white dots; they are colored yellow in this schematic for clarity. A variable length interval, during which continued fixation was required, was followed by the stimulus presentation interval, after which the subject was free to make its choice. The task was to indicate—L or R—the drift direction of the vertical “target” patch. Trial sequence timing is indicated under each box.

Testing

The task was a two-alternative, forced-choice direction discrimination of one of an array of Gabor patches arranged in a circle around a central fixation cross. The procedure was modeled on the visual search task and cueing protocol used by Carrasco and McElree (2001). An array of randomly oriented, drifting Gabor patches was presented simultaneously, each at one of seven locations equidistant from fixation. The target was a vertical Gabor that could appear at any of the seven locations around the circle; the six distractor Gabors were oriented randomly but were never vertical. Each grating patch subtended 1.7° and had a spatial frequency of 2 c/deg; they each drifted at $2^\circ/\text{s}$, perpendicularly to their orientation in either direction. Subjects were required to report the direction of motion (left or right) of the vertical drifting target patch. All gratings were uniformly distributed along the 7° diameter circle. A schematic representation of the display is shown in Figure 2.

Figure 2 also illustrates the sequence of a sample trial. Subjects were trained to fixate a white cross at the center of the screen throughout the trial; accurate fixation was signaled by a continuous tone so long as the eye was in the window. Each trial began with a fixation period of 250 ms on average with a temporal

jitter of ± 50 ms to reduce predictability. A brief cue (valid or neutral, described below) then appeared on the screen for 250 ms. After the offset of the cue, the subject fixated for an interstimulus interval of 300 ± 50 ms prior to the onset of the stimulus array. The stimuli were then displayed for a limited duration of 500 ms. The subject could respond by pulling a bar at any point after stimulus array onset so long as fixation was maintained. A correct response was a bar pull that corresponded with the direction of motion (left or right) of the target: the vertical drifting grating. If the subject broke fixation before making a bar pull, the display blanked, and the trial was aborted. Feedback was provided following the subject's response: correct responses were followed by a juice reward with 100% probability; an error tone signaled an incorrect response. The total duration of each trial was 1,300 ms on average. The intertrial interval was 100 ± 50 ms, following juice delivery or error tone offset so long as the subject maintained fixation; otherwise, the monkey self-initiated the subsequent trial.

During the cue interval, before stimulus onset, covert endogenous attention was manipulated by presenting a brief central signal (valid or neutral), which instructed the subject where to attend in the display. The interval between cue and stimulus onset was designed to facilitate endogenous attention (~ 550 ms; Nakayama

& Mackeben, 1989; Liu, Stevens, & Carrasco, 2007; Giordano, McElree, & Carrasco, 2009). On half of the trials—*valid cue* trials—a single white-filled circle (of 0.35° diameter) was presented at an eccentricity of 0.6° from the fixation point in alignment with the location of the upcoming target grating. Thus, the valid cue was 100% informative of the location of the upcoming target, encouraging the subjects to direct their attention toward the cued location. On the remaining half of the trials—*neutral cue* trials—seven identical white-filled circles were simultaneously presented, each at 0.6° eccentricity, each one aligned with a grating position, thus distributing the subject's attention and providing no information about the location of the upcoming target. Thus, the neutral cue was noninformative and provided a baseline against which to compare the effects of endogenous attention. Valid and neutral cue trials were randomly intermixed throughout each session.

As described above, the subjects were trained to perform a two-alternative, forced-choice discrimination of motion direction of the vertical target, which required identifying the location of the vertical target grating and then discriminating its motion direction. We measured performance as a function of contrast of the drifting gratings. Stimulus contrast was varied around the subjects' threshold (75%) with five logarithmically spaced contrast levels spanning the performance range from chance to about 90% correct. The same contrast range was used for both types of cue trials, but that range was established independently for each eye. To ensure stable performance, training continued until the animals showed no additional improvement over three consecutive sessions. Throughout one session, subjects completed 25 trials for each cue condition at each contrast level for a total of 250 trials per session. To ensure reliable estimates for reaction time, we set a criterion minimum number of correct trials for the lowest contrast condition at 200 trials for each cue condition. The total number of trials per subject and cue condition ranged from 45,000 to 83,000.

Data analysis

To quantify attention, we compared performance (d' , primary dependent variable) and reaction time (from stimulus onset to monkey's response, secondary dependent variable) as a function of contrast on valid cue versus neutral cue trials.

Accuracy

For each subject, performance was assessed across experimental sessions at each contrast level and cue

condition (valid and neutral) for each eye (fellow eye and amblyopic eye for amblyopic subjects). Performance accuracy, d' ($d' = z\text{-score hit} - z\text{-score miss}$), is a measurement that reflects whether the stimulus has been perceived and is proportional to the signal-to-noise ratio of the underlying neuronal responses (Herrmann, Montaser-Kouhsari, Carrasco, & Heeger, 2010). The performance data were fit with the Naka–Rushton function as follows:

$$d'(c) = d'_{\max}(c^n / (c^n + C_{50}^n)),$$

where $d'(c)$ represents performance as a function of contrast, d'_{\max} is the asymptotic performance at high contrast values, C_{50} is the contrast when half the asymptotic level of performance is reached, and n is an exponent that determines the slope of the psychometric function (e.g., Cameron, Tai, & Carrasco, 2002; Herrmann et al., 2010; Barbot, Landy, & Carrasco, 2011, 2012). The two parameters d'_{\max} and C_{50} were used to index response gain and contrast gain, respectively (see Figure 1). They were assessed separately for each cue condition (valid and neutral), and the exponent n (slope) was constrained to have a fixed value across conditions (Herrmann et al., 2010) for each subject's eye.

Based on models of attention (Pestilli, Ling, & Carrasco, 2009; Reynolds & Heeger, 2009; Herrmann et al., 2010), change in response gain of the underlying neuronal responses yielded a scaling of the psychometric function (change in d'_{\max}) whereas change in contrast gain of the underlying neuronal responses yielded a horizontal shift along the log contrast axis of the psychometric function (change in C_{50}). A bootstrap procedure was used to determine confidence intervals for the fitted response gain (d'_{\max}) and contrast gain (C_{50}) parameters and to establish whether changes in response and/or contrast gain were statistically significant. Specifically, we randomly resampled individual psychophysical trials with replacement to generate a resampled data set that was then refit. This resampling and refitting procedure was repeated 10,000 times to generate bootstrap distributions of the psychometric data and of the fitted parameters. Confidence intervals were extracted for each parameter estimate from these bootstrap distributions. We compiled the bootstrap distribution of the differences between the conditions (i.e., valid vs. neutral trials) and determined the percentage of the values in the tail of the distribution of differences greater than zero for response gain changes (d'_{\max}) or less than zero for contrast gain changes (C_{50}). The use of these one-tailed statistical tests was based on previous studies, which reported a benefit for valid and a cost for invalid, relative to neutral, cues (e.g., Carrasco, Penpeci-Talgar, & Eckstein, 2000; Ling & Carrasco, 2006; Giordano et al., 2009; Herrmann et al., 2010; Barbot et al., 2012).

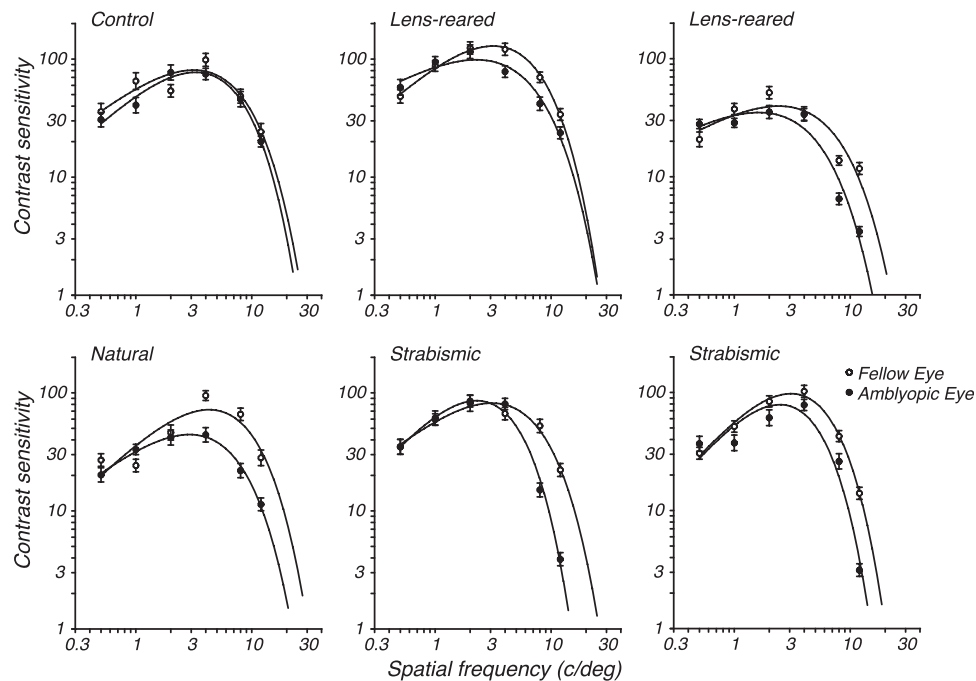


Figure 3. Contrast sensitivity for the subjects in the study. Contrast sensitivity is plotted as a function of spatial frequency for each of the six macaques included in the study. The monocular contrast sensitivity data were collected using standard methods for the lab (see Kiorpes et al., 1993; Kiorpes et al., 2006).

Reaction time

For each subject, reaction time was assessed across experimental sessions at each contrast level and cue condition (valid and neutral) for each subject's eye (fellow eye and amblyopic eye for amblyopic subjects). Reaction time, $RT(s) = \text{stimulus onset time} - \text{response time}$, was used as a secondary metric to rule out speed–accuracy trade-offs. We assessed the effect of cue condition on reaction time separately for correct trials at high and low contrast because the valid cue is expected to have a greater effect at low contrast.

Results

Prior to inclusion in this study, all animals were evaluated to establish the presence of amblyopia. In Figure 3, we plot full-contrast sensitivity functions for each eye of the six macaques included in the study.

Our goal was to establish whether or not there would be a difference in the effect of attention for the amblyopic versus the fellow eye among amblyopes and whether their response to endogenous attentional cueing was similar to control, nonamblyopic macaques. Few studies have manipulated and measured spatial attentional cueing effects in macaques, but none has done so for psychophysical contrast response functions. To assay the ability of amblyopes to allocate attentional resources, we measured performance (d') in a

motion discrimination task as a function of contrast for each eye under neutral and valid cue conditions.

Example data from one control animal and one amblyope are shown in Figure 4. It is clear that the valid cue resulted in significant enhancement of performance in both eyes of both subjects. In all cases, the psychometric functions obtained under the valid cue condition (filled circles) were shifted toward lower contrasts compared with the neutral cue (open circles), resulting in substantial contrast gain effects. For the control subject, performance at high contrasts was comparable under neutral and valid cue conditions (Figure 4a and b). The fellow eye of the example amblyope (Figure 4c) showed the same pattern as the control eyes. On the other hand, with the amblyopic eye there was a substantial boost in performance as a result of the valid cue even at high contrast (Figure 4d): an increase in d'_{max} indicative of response gain.

To directly compare performance differences between neutral and valid cue conditions, we plotted C_{50} and d'_{max} in Figure 5 for all subjects. Figure 5a shows the effect of the valid cue on contrast gain. Overall, there was greater benefit of the cue for amblyopes (circles) compared to controls (triangles); all subjects showed better sensitivity (lower threshold) under the valid cue condition. The data for the example amblyopic animal, shown in Figure 4d, are representative of the amblyopic group in that they also reflect an improvement in response gain with the amblyopic eye viewing. Comparison of d'_{max} across neutral and

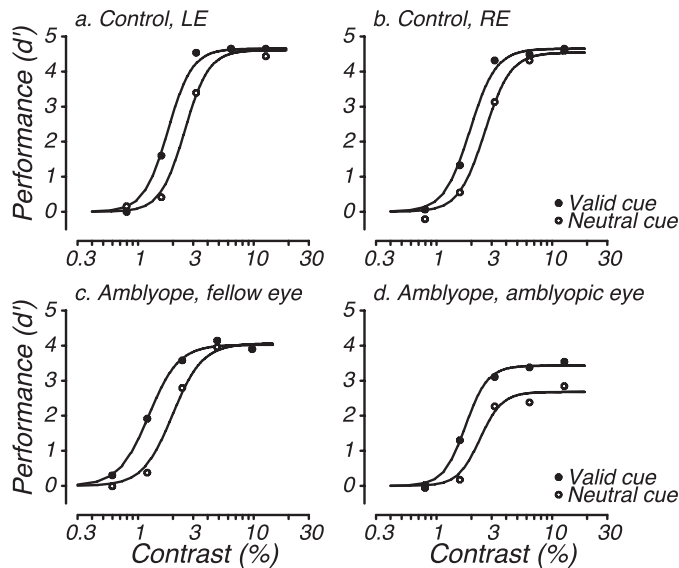


Figure 4. Psychometric functions for valid and neutral cue conditions. Performance is plotted as a function of contrast for each eye of one control (top) and one amblyope (bottom). Data collected under neutral cue conditions are represented by the open symbols and, with the valid cue, filled symbols. The valid cue enhanced contrast discrimination (C_{50}) for control and fellow eyes (a–c), shifting the psychometric function to the left. For amblyopic eyes (d), there was an additional improvement in asymptotic level (d' max).

valid cue conditions is shown in Figure 5b for all subjects. Enhancement of response gain was large for all but one amblyopic subject when viewing with the amblyopic eye and largely absent for fellow and control eyes. To assess the effect of the cue on C_{50} and d' max

quantitatively, we computed the log difference between the valid and neutral cue conditions for each eye of each amblyopic subject. These effects on contrast and response gain are plotted in Figure 6a and b. The plots show that there is a similar or larger effect on C_{50} for the amblyopic eyes compared with the fellow eyes for all but one monkey and a substantially larger effect on d' max of the valid cue for amblyopic eyes (except for one subject). Results of a bootstrap analysis showed a significant effect on C_{50} for all eyes ($p < 0.001$) but a significant effect on d' max only for amblyopic eyes ($p < 0.001$; fellow eyes, $p = 0.137$; control, $p = 0.122$). This analysis is summarized in Figure 7 for control eyes (Figure 7a), fellow eyes (Figure 7b), and amblyopic eyes (Figure 7c). In the psychometric functions, contrast threshold and d' at asymptote for each function are indicated by the isolated symbols near the abscissa (C_{50}) and top right (d' max) of each panel. The amblyopic eye function shows enhanced response gain as well as contrast gain.

Finally, to assess whether the effect of the valid cue was sufficient to normalize the performance of the amblyopic eye to that of the fellow eye, we plotted C_{50} and d' max for the amblyopic eye under valid cue conditions versus the fellow eye C_{50} and d' max under neutral cue conditions (Figure 8a and b). With the aid of the valid cue, contrast threshold of the amblyopic eye was similar to that of the fellow eye under the neutral condition, suggesting that attentional enhancement could potentially negate deficits in amblyopic contrast sensitivity. With respect to response gain, d' max of the cued amblyopic eye was similar or substantially better than the fellow eye performance with the neutral cue for all but one subject.

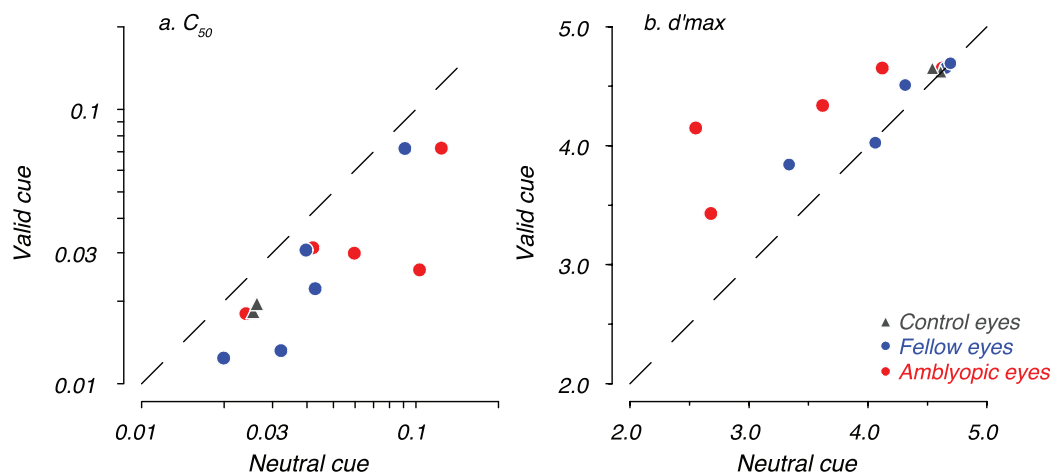


Figure 5. Effect of the valid cue on performance. Comparison of C_{50} (a) and d' max (b) under valid and neutral cue conditions for each eye of each subject. Fellow eye data are represented in blue, amblyopic eye data in red, and the control data are gray triangles. Note that the cluster of points at the top right of panel b are arbitrarily offset slightly for clarity; in fact, they overlap nearly completely. Most amblyopic eyes, and some fellow eyes, show substantially greater performance benefit from the valid cue compared with the control.

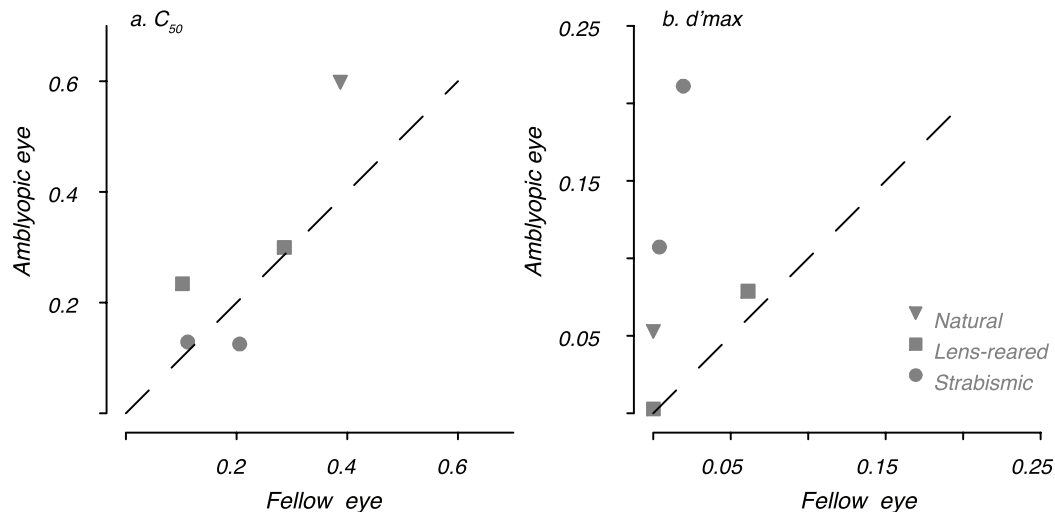


Figure 6. Comparison of valid cue performance enhancement for individual amblyopic subjects. The interocular difference (log difference) in C_{50} (a) and d'_{\max} (b) between performance with the valid and neutral cue conditions is plotted for each amblyopic monkey. There is a similar or larger effect on C_{50} for the amblyopic eye compared with the fellow eye for all but one subject and a substantially larger effect on d'_{\max} of the valid cue for amblyopic eyes for all but one subject. Different symbols identify the animals with different types of amblyopia (see legend).

We also evaluated the effect of the endogenous spatial cue on reaction time. We expected the valid cue to speed reaction time primarily with low contrast stimuli, for which the discrimination is most challenging. We plotted reaction time under valid versus neutral cue conditions for both high and low contrast. As expected, the greatest speeding of response time was at low contrast (Figure 9, filled symbols), but the response time effect was also present for the high-contrast stimuli (Figure 9, open symbols). Interestingly, the effect was similar for amblyopic and fellow eyes although the control subject showed especially long reaction times at low contrast. It is clear that there is no evidence of any speed–accuracy trade-off. It is worth noting that the effect on d'_{\max} for the amblyopic eye

not only manifested in accuracy but also via correspondingly faster reaction times.

Discussion

In this study, we show that endogenous attention is intact in all monkeys tested: amblyopic and control. Endogenous attention significantly improved performance for the amblyopic eyes. The benefit from the valid cue was at least as pronounced as—and in many cases larger than—the benefits afforded to the fellow eyes of the amblyopes and both eyes of the control monkey. Moreover, there was a difference in the nature of the effect for the amblyopic eye: The benefit was not

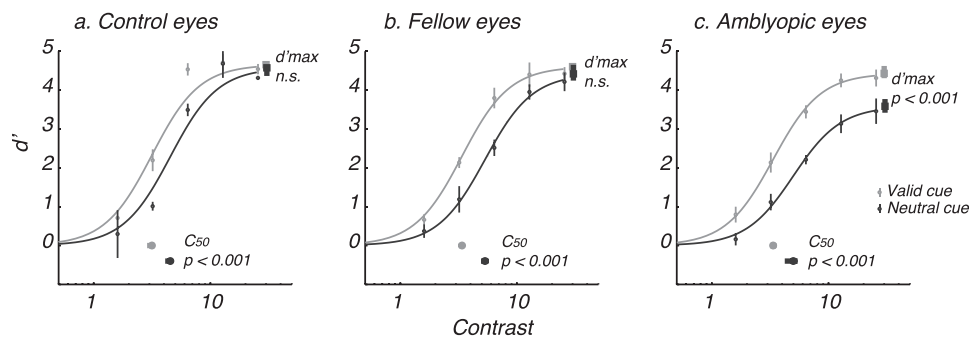


Figure 7. Results of a bootstrap analysis of valid cue effects. Psychometric functions summarizing the outcome for control eyes (a), fellow eyes (b), and amblyopic eyes (c) are plotted. Black indicates neutral cue conditions; gray indicates valid cue conditions. Contrast threshold and d' at asymptote for each function are indicated by the isolated symbols near the abscissa (C_{50}) and top right (d'_{\max}) of each panel. All eyes' functions show significant contrast gain shifts, and only the amblyopic eye function shows significant enhancement of response gain.

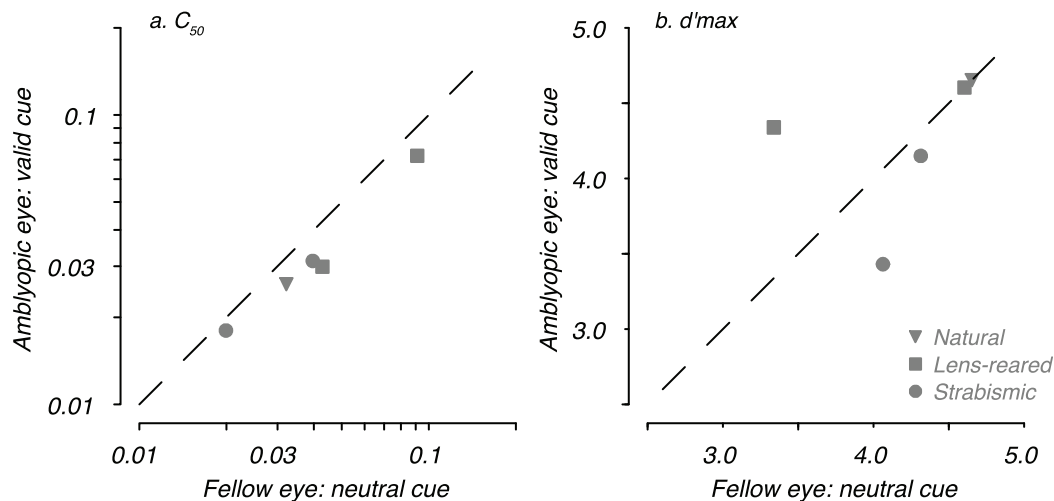


Figure 8. Attention normalizes amblyopic eye performance. C_{50} (a) and $d'max$ (b) for the amblyopic eye under valid cue conditions is plotted as a function of the fellow eye C_{50} and $d'max$ under neutral cue conditions for each amblyope. With the aid of the valid cue, contrast threshold of the amblyopic eye was similar to that of the fellow eye under the neutral condition; $d'max$ was similar or substantially higher than fellow eye performance with the neutral cue for all but one subject. Different symbols identify the animals with different types of amblyopia (see legend).

only manifest as a contrast gain shift, as was the case for the control monkey and the fellow eyes, but also as a response gain shift. Contrast gain changes are typical effects of endogenous attention (e.g., Ling & Carrasco, 2006; Pestilli et al., 2009; Barbot et al., 2012); response gain changes are not. Changes in response gain have been reported in typical observers when the attention field size is small in relation to the stimulus size (Herrmann et al., 2010).

Several studies have reported potential attentional deficits in amblyopes using different tasks. For example, deficiencies have been noted with multiple object tracking with large numbers of objects (Ho et al., 2006; Tripathy & Levi, 2008), attentional blink (Poppel & Levi, 2008), and numerosity estimation (Sharma et al., 2000). However, in most studies, the authors have attributed the differences in performance to a deficit in visual attention, inferring its contribution to their tasks without manipulating it directly. In fact, only three studies have used attentional cues to investigate voluntary attention in human amblyopes. One study that assessed its effects on numerosity estimation (Sharma et al., 2000) is often cited as providing evidence for an attention deficit in amblyopia, notwithstanding the fact that their findings indicate an effect of endogenous attention (valid–invalid cue) on performance of amblyopes that was similar to the visually normal observers. A second study sought to explore the underlying neural correlates of deficient attention using fMRI-informed EEG source imaging as strabismic observers were cued to voluntarily attend to one hemifield at a time during a contrast change detection task (Hou et al., 2016). They reported

decreased attentional modulation in V1 with the amblyopic eye viewing, which was correlated with the depth of amblyopia. The third study investigated the effects of both endogenous and exogenous attention on an orientation discrimination task mediated by contrast sensitivity. For each type of attention, the magnitude of the benefit did not differ between the group of amblyopes and the age- and gender-matched control group (Roberts et al., 2016). Roberts et al. (2016) acknowledged that several observers had a mild degree

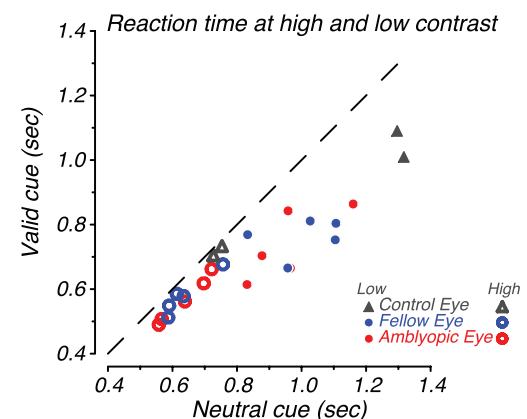


Figure 9. Effect of the valid cue on response speed. Comparison of reaction time under valid and neutral cue conditions for each eye of each subject. The comparison is shown for two contrast levels: low (just below threshold, filled symbols) and high (the highest contrast tested, open symbols). The color code is the same as in Figure 5. The effect of a valid cue on response speed was similar across individuals and viewing eye at both low and high contrast levels.

of amblyopia and showed that the magnitude of their attentional effect was similar to those with a moderate or pronounced severity. Our findings are consistent with the Roberts et al. human study in that we found that amblyopic macaques were able to deploy attentional resources similarly to visually normal controls. In that study, the authors obtained for each individual the stimulus contrast yielding 80% accuracy in the neutral condition and then evaluated the benefits of covert attention at that performance level. No prior study has investigated the effect of endogenous spatial cues on psychophysical contrast response functions in amblyopia.

In the current study, we evaluated performance across the full psychometric function. Amblyopic and fellow eyes both showed typical contrast gain benefits. Moreover, these benefits were generally larger for amblyopic eyes, effectively equating their contrast sensitivity on the motion direction discrimination task to that of the corresponding fellow eyes with the neutral cue. Remarkably, this was also the case with regard to d' max; attention restored contrast sensitivity at high contrast levels. Indeed, all but one of the amblyopic eyes showed response gain whereas only one fellow eye showed response gain, and in that case, the effect was less pronounced than that of the corresponding amblyopic eye.

These findings suggest that subjects were able to compensate for the relatively poor performance of the amblyopic eye under the neutral condition by adjusting the size of the attention field as a function of stimulus contrast; a larger field for low contrast and smaller for high contrast (Reynolds & Heeger, 2009; Herrmann et al., 2010). The high-contrast distractors may have impaired target discrimination more for the amblyopic eye (lower d' max than for the fellow and control eyes). Thus, it is possible that to ameliorate the detrimental effect of the distractors the size of the attention window was tightened around the target location, resulting in response gain. Also consonant with this finding is a reduction in spatial uncertainty in the presence of the valid cue. Amblyopic vision has long been associated with increased spatial positional uncertainty (e.g., H. Wang, Levi, & Klein, 1998; Fronius, Sireteanu, & Zubcov, 2004; Niechwiej-Szwedo, Goltz, Chandrakumar, & Wong, 2012). Herrmann et al. (2010) found that attentional fields were larger under conditions of spatial uncertainty. Therefore, it is possible that the valid cue served to improve attentional focus by reducing spatial uncertainty. However, given that the overall maximum d' with the amblyopic eye viewing was quite poor compared with most fellow eyes in the neutral cue condition, whether due to the proximity of the distractors or greater spatial uncertainty, there was effectively greater room for improvement at high contrast for the amblyopic eyes than for the fellow eyes.

Numerous groups have evaluated the neural mechanisms underlying covert endogenous attention, but there are no such data for amblyopes. A number of neural correlates of voluntary attention have been identified, including increased firing rates, narrowing of neural tuning functions, increased signal-to-noise ratios, and changes in interneuronal response correlation (both increased and decreased) with different effects depending on stimuli and tasks (for reviews, see Reynolds & Chelazzi, 2004; Carrasco, 2011; Anton-Erxleben & Carrasco, 2013; Buschman & Kastner, 2015; Maunsell, 2015) and on the relative size of the attention window (Reynolds & Heeger, 2009; Herrmann et al., 2010). A recent unifying analysis demonstrates that normalization processes can account for many of the phenomena that accompany attentional engagement (Verhoef & Maunsell, 2017); see also Rabinowitz, Goris, Cohen, and Simoncelli (2015) and Kanashiro, Ocker, Cohen, and Doiron (2017) for additional comprehensive models. In the context of their normalization model, Verhoef and Maunsell (2017) show that attention changes the balance of excitation and suppression in local circuits and modifies spike-count correlations via normalization. Interestingly, the balance of excitation and suppression within amblyopic eye receptive fields is altered with suppression dominant and excitation reduced compared with fellow eye receptive fields in early visual cortex (Hallum et al., 2017). Binocular interactions are also predominantly suppressive in amblyopic cortex (Bi et al., 2011; Hallum et al., 2017). In addition, measuring the correlation structure among pairs of neurons in V1 of amblyopic monkeys revealed that spike-count correlation is higher and evoked activity is lower with amblyopic eye viewing than with the fellow eye viewing (Clemens, Kiorpes, Movshon, & Smith, 2016). Given that attention affects both of these aspects of cortical activity, we can speculate that the somewhat greater effect of attention on amblyopic sensitivity may be mediated by these imbalanced excitatory and inhibitory mechanisms.

Conclusions

In this study, we evaluated the nature of the effect of endogenous spatial attention on psychophysical performance in amblyopic macaques. We found that spatial cues benefit macaque amblyopes as they benefit human amblyopes (Roberts et al., 2016). In particular, we found that amblyopic eye sensitivity benefits to a somewhat greater degree than the fellow eye. Importantly, this study reveals that the effect of a valid spatial cue on the psychometric function is qualitatively different between the two eyes of amblyopic subjects

and is different from controls. Amblyopic eye performance shows both contrast gain and response gain whereas fellow and control eyes show only contrast gain. Future development of treatments for amblyopia may be able to leverage attentional manipulations to improve outcomes.

Keywords: *amblyopia, contrast sensitivity, contrast response function, endogenous attention, macaque monkey, motion discrimination*

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