PERGAMON

Vision Research 41 (2001) 2951–2960

Vision Research

www.elsevier.com/locate/visres

Is second-order spatial loss in amblyopia explained by the loss of first-order spatial input?

Erwin H. Wong [a,*], Dennis M. Levi [a], Paul V. McGraw [b]

[a] *University of Houston, College of Optometry, The University Eye Institute, 4901 Calhoun Blvd, Houston, TX 77204-6052, USA*
[b] *University of Bradford, Department of Optometry, Richmond Road, Bradford BD7 1DP, UK*

Received 13 July 2001

Abstract

The purpose of the study was to determine whether amblyopes show detection loss for second-order spatial information, and if present, whether the loss is explained by the loss of first-order spatial input. We psychophysically determined detection thresholds for the amblyopic and non-amblyopic eyes of five adult amblyopes and the dominant eyes of three control observers. We found that four amblyopic eyes and two non-amblyopic eyes showed second-order loss relative to the control eyes. The second-order loss was greater than the first-order loss at the carrier spatial frequency (first-order input). The extra second-order loss indicates an early amplification of cortical neural loss that we speculate is due to deficient binocular input to second-order neurons.

Keywords: Amblyopia; First-order; Second-order; Neural loss; Spatial vision

1. Introduction

Amblyopia is a developmental disorder that results in a number of spatial vision deficits. The neural basis for this disorder is not yet completely known. Amblyopes show detection loss for first-order spatial information (luminance variations across space) (Hess, Field, & Watt, 1990; Levi, 1991; Kiorpes, Kiper, O'Keefe, Cavanaugh, & Movshon, 1998). Recent work suggests there may be specialized neural mechanisms for detecting second-order spatial information (contrast modulations with the same space-averaged luminance) (Mareschal & Baker, 1998; Schofield & Georgeson, 1999). To date, it remains unknown whether amblyopes show loss in detecting second-order or non-luminance defined spatial information. However, such a deficit might be expected based on the visual mechanisms thought to underlie second-order detection.

The notion that dedicated mechanisms mediate the detection of first-order and second-order image structure is supported by evidence from human psychophysics (Sutter, Sperling, & Chubb, 1995; Langley, Fleet, & Hibbard, 1996; Lin & Wilson, 1996; McGraw, Levi, & Whitaker, 1999) and single-cell physiology in cat (Zhou & Baker, 1994; Mareschal & Baker, 1998). The first-order mechanism involves linear neurons in area V1 of the visual cortex that detect spatial luminance variations across their receptive field. The second-order mechanism involves two filtering stages: initially, the luminance information within the contrast modulation is analyzed by V1 first-order neurons and undergoes a non-linear transformation, such as rectification, and subsequently, second-order neurons in area V1 or V2 receive the rectified output for analysis.

Neurons tuned to second-order image structure have been located in both V1 and V2, but with a preponderance in V2. There is strong evidence for this from single-cell responses to amplitude modulated sinusoids in cat (Zhou & Baker, 1994; Mareschal & Baker, 1998, 1999), and to illusory contours in monkey (von der Heydt & Peterhans, 1984, 1989; Grosof, Shapley, & Hawken, 1993; Leventhal, Wang, Schmolesky, & Zhou, 1998) and cat (Redies, Crook, & Creutzfeldt, 1986; Leventhal et al., 1998). Further evidence is shown by

* Corresponding author. Tel.: +1-713-743-2024; fax: +1-713-743-1888.
E-mail address: ewong@bayou.uh.edu (E.H. Wong).

0042-6989/01/$ - see front matter
PII: S0042-6989(01)00189-4

Table 1
Visual characteristics of amblyopic subjects

Subject	Age	Type	Prescription	Acuity[a]	Fixation	Strabismus	Treatment Hx
JF	25	Aniso	R −0.50–0.25x177	20/20	Central	None	No surgery or patching
	M		L +3.50 DS	20/50	Central		Glasses age 11
RH	34	Strab	R −1.00–0.50x170	20/15	Central	Constant	No surgery or patching
	M		L −1.50–1.50xx010	20/40	Central	L.ET 2Δ	Glasses age 12
QM	20	Both	R −0.50–0.25x180	20/20	Central	Constant	Surgery age 4, patched
	M		L +1.75–2.50x180	20/50	3° nasal	L.ET 7Δ	Age 4–7, glasses age 4
DM	40	Both	R −0.50–0.25x92	20/20	Central	Constant	No surgery or patching
	F		L +2.50-1.00x160	20/80	0.5° nasal	L.XT 3Δ	glasses age 12
DS	26	Both	R +2.25 DS	20/40	2° nasal	Constant	No surgery, patching
	M		L +0.50 DS	20/20	central	R. ET 8Δ	Age 5–8, glasses age 5

[a] Snellen acuity.

brain activity to illusory contours in cat by optical imaging (Sheth, Sharma, Rao, & Sur, 1996) and in humans by PET (Ffytche & Zeki, 1996) and fMRI (Hirsch et al., 1995).

Given that second-order mechanisms receive rectified output from first-order mechanisms and that the amblyopic visual system shows a first-order processing deficit, we anticipate that amblyopes will also show a deficit in processing second-order information. Here, we ask whether, in amblyopia, the second-order loss is explained by loss of first-order input or whether there is additional second-order loss. If amblyopia involves an amplification of neural deficits, an additional second-order loss is expected.

2. Methods

2.1. Observers

Five amblyopic and three normal adults participated in the experiment. The visual characteristics of the amblyopes are given in Table 1. Amblyopes were strabismic (misalignment of the visual axes), anisometropic (significant unequal refractive error between the eyes), or both. We tested both eyes of the amblyopes and the dominant eyes of the normal observers. All observers wore refractive correction as required, and were naïve as to the purpose of the experiment, except for EW. Informed consent was obtained from all observers prior to data collection.

2.2. Apparatus

Stimuli were generated using the macro capabilities of NIH Image™ 1.62f (available from http://rsb.info.nih.gov/nih-image/). The host computer was Apple Power Macintosh G3, and stimuli were presented on a 15 inch (38 cm) Sony Multiscan 200PS monitor at a frame rate of 75 Hz, and a mean background luminance of 10 cd/m^2. The non-linear response output of the monitor was corrected using standard photometric procedures (Minolta LS-110 digital luminance meter). Contrast resolution of up to 12-bit accuracy was obtained by combining the red, green and blue outputs of the video board using a video summation device (Pelli & Zhang, 1991).

2.3. Stimuli: First-order

We used stationary windowed sinusoids as first-order spatial stimuli (Fig. 1). Stimuli were constructed by multiplying a 1-D sinusoid by a 2-D gaussian window and are mathematically described by:

$$L_{\text{mean}}\left[1 + C\sin(2\pi Fx + \phi) * \exp\left(\frac{-(x^2 + y^2)}{2\sigma^2}\right)\right] \quad (1)$$

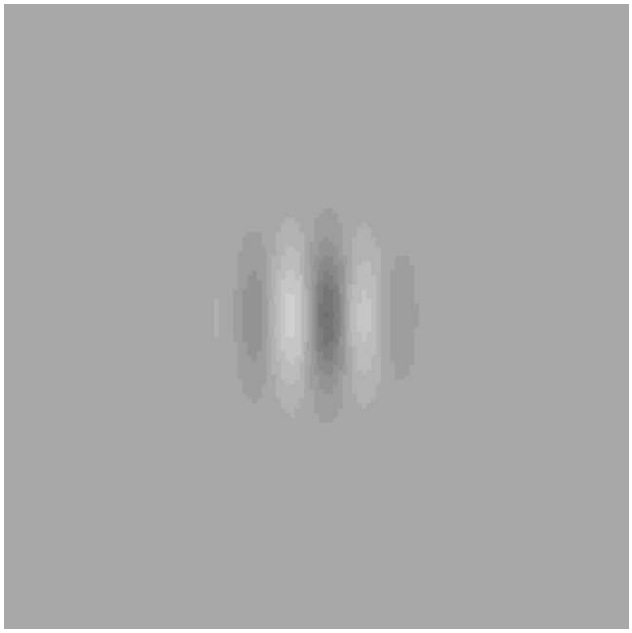

Fig. 1. Example of our first-order stimuli: windowed sinusoid. We measured threshold contrast for six spatial frequencies: 0.27, 0.54, 1.1, 2.2, 4.4, and 8.7 c/deg.

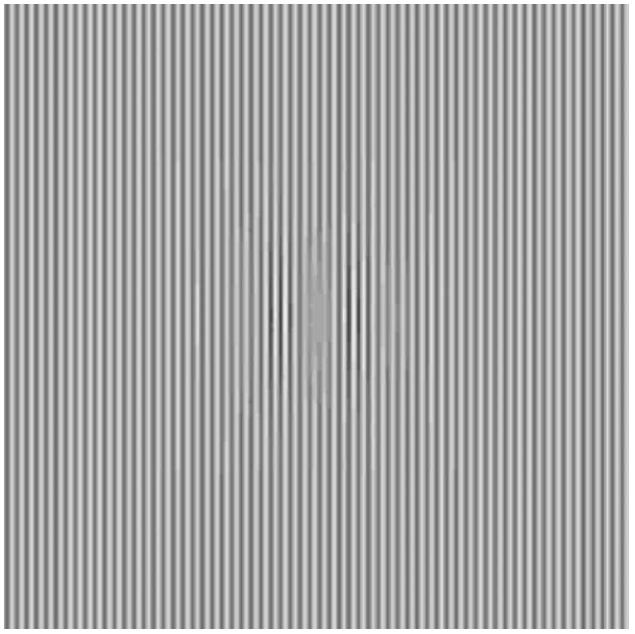

Fig. 2. Example of our second-order stimuli: amplitude modulated sinusoid. We measured threshold contrast for three carrier/envelope spatial frequencies (2.2/0.27, 4.4/0.54, 8.7/1.1 c/deg) at a number of carrier contrasts.

where L_{mean} is the mean luminance of the background, C is the contrast, F is the spatial frequency of the carrier grating, ϕ is the spatial phase, x and y are the horizontal and vertical distances from the peak of the contrast envelope, and σ is the standard deviation of the Gaussian envelope (which was 1.3°). Viewing distances were 33.5, 67 or 134 cm, depending on the spatial frequency tested (0.27, 0.54, 1.1, 2.2, 4.4, 8.7 c/deg), and σ varied in inverse proportion to the spatial frequency.

2.4. Stimuli: Second-order

We used stationary amplitude modulated (AM) sinusoids as second-order spatial stimuli (Fig. 2). An AM sinusoid consists of a high spatial frequency sinusoid (carrier) whose contrast is modulated sinusoidally by a low spatial frequency sinusoid (envelope). The Fourier spectrum of an AM sinusoid contains energy at the spatial frequency of the carrier but not the envelope. That is, the envelope has no change in mean luminance across space and thus represents second-order information. Stimuli were constructed by multiplying a 1-D carrier sinusoid (first-order component) by a windowed 2-D envelope sinusoid (second-order component), the envelope spatial frequency was one eighth of the carrier frequency (i.e. carrier to envelope spatial frequencies ratio of 8:1), defined by:

$$L_{mean} + \left[L_{mean} + C\sin(2\pi F_c x) * \left(1 + C\sin(2\pi F_e x + \phi) * \exp\left(\frac{-(x^2+y^2)}{2\sigma^2} \right) \right) \right] \quad (2)$$

where F_c is the carrier spatial frequency, F_e is the envelope spatial frequency, and L_{mean}, C, x, y, ϕ, and σ are as defined above. The AM stimuli had carrier-to-envelope spatial frequency ratios of 2.2/0.27, 4.4/0.54 and 8.7/1.1 c/deg. We separated the spatial frequencies in each stimulus by 3-octaves so that side-bands (luminance artifacts at the spatial frequency difference between the carrier and envelope sinusoids) (Henning, Hertz, & Broadbent, 1975) fell within the pass-band of the carrier sinusoid, thereby not confounding detection of the envelope sinusoid.

The carrier was twice the size of the windowed envelope and both sinusoids were vertically oriented. The windowed envelope sinusoid had a standard deviation (σ) of 1.3° from a viewing distance of 67 cm, making it equal in size to the first-order stimuli. We tested a large range of carrier contrasts to a maximum of 84%.

High-contrast information is more likely to undergo transformations early in the visual pathway (MacLeod, Williams, & Makous, 1992). For an AM sinusoid, such transformations could produce luminance distortions at the envelope frequency or local luminance artifacts. Theoretically, these first-order cues could confound measures of second-order (envelope) detection. However, psychophysical research has shown that such first-order cues are of little or no use in envelope detection (Derrington & Badcock, 1985; Badcock & Derrington, 1989; Cropper, 1998; Willis, Smallman, & Harris, 2000).

2.5. Experiment

We measured threshold contrast for detection of first-order and second-order stimuli. Measurements were done in parallel. The observer sat in a dimly lit room, head positioned on a chin rest, and one eye patched. The observer fixated the center of the screen where the stimuli were presented. We used a two-alternative forced-choice paradigm with the method of constant stimuli. Each trial presented the stimulus at one of nine contrast levels. The nine levels (in 0.05 log unit steps) were chosen to span the psychometric function, i.e. to give responses from chance to near perfect performance. Each run consisted of 145 trials. To allow for task adaptation, the first 10 trials were discarded. Each trial consisted of two 200 ms presentations, separated by 500 ms, respectively, signaled by simultaneous single or dual tones. The computer randomized the nine contrast levels, and each was presented 15 times (for a total of 135 trials). Each run tested one spatial frequency at a set of contrasts chosen by the experimenter. For each

spatial frequency, we collected at least six consecutive runs (on at least three different days) that produced good psychometric functions (giving approximately 810 trials in the cumulative psychometric function).

For all eyes, we measured second-order thresholds using a number of carrier contrast levels in order to equate carrier visibility. Levels were specified in carrier contrast threshold units (CCTU), i.e. multiples of carrier contrast threshold when acting as first-order stimuli. We reasoned that because the contrast response function for first-order information is generally unaffected in low to moderate amblyopia (see Section 4), equating carrier visibility would essentially compensate for any amblyopic eye (AE) or non-amblyopic eye (NAE) first-order deficit. By equating first-order input, any residual second-order loss in the AE or NAE is likely to be due to specific deficits in the second-order mechanism.

2.6. Analysis

For each condition, the data from at least six consecutive runs were pooled and fitted with a Weibull function to obtain the threshold contrast (75% correct response) and standard errors. Threshold contrast is the minimum detectable contrast for the windowed sinusoid stimulus, or envelope sinusoid of the AM stimulus. We compared the AE to control eyes (CE, weighted averages) as our results suggest that the NAE may not be 'normal', and thus does not serve as an optimum control for the AE. Consequently, a visual loss is indicated by a higher threshold contrast for the AE than the CE or higher for the NAE than the CE.

We plotted second-order threshold as a function of CCTU for the AE, NAE and CE. An exponential curve was fit to each eye's data for qualitative comparisons. We then determined second-order loss by calculating the ratios AE/CE and NAE/CE for a common CCTU level, i.e. loss when first-order input is equal. This loss was compared to the loss when carrier contrast was at maximum (84%), i.e. loss when first-order input was not equal.

We further attempted to characterize the second-order loss by comparing the Weibull function exponent (slope indicator) for the AE, NAE and CE first-order and second-order experiments. We did this by calculating weighted average exponents and testing the differences for significance with a two-sample t-test. Finally, we made qualitative associations of first-order and second-order loss to amblyopia type, degree of acuity loss, and age of initial treatment.

3. Results

For first-order spatial stimuli, four of five AEs showed detection loss that increased with spatial frequency relative to the fellow NAE (Fig. 3a) or the CE (Fig. 3b). The exception was DS, who showed no loss at the highest spatial frequency relative to the NAE, and slight loss at only one frequency relative to the CE. Detection loss for first-order spatial structure is a fundamental property of amblyopia (Levi, 1991), so our findings were generally expected.

We compared the NAEs to the CE and found that three NAEs showed first-order loss: DM at all spatial frequencies, RH at the lowest four frequencies and QM at only the highest frequency (Fig. 3c). Only DS and JF showed detection contrast that was equal to, or better than, the CE at all frequencies.

We determined threshold contrast for second-order spatial stimuli and found that two of five NAEs (RH and DM) had second-order loss relative to the CE (Fig. 4c and f), again suggesting that the NAE may not serve as an appropriate control for the fellow AE. This is shown by the NAE (open symbols) having a higher threshold contrast than the CE (gray line) for all CCTU. This finding prompted us to compare the AE and NAE to the CE in our remaining analyses.

We found that four of five AEs showed second-order loss relative to the CE (Fig. 4). This is readily seen by the curve fitted to the filled symbols (AE) being higher than the gray curve (CE). The amount of AE second-order loss ranged from a factor of 1.58 (DS) to 6.03 (DM) when assessed at carrier maximum physical contrast (Table 2 and Fig. 5). The fitted exponential curves (AE, NAE, and CE) were generally proportional to each other, which enabled second-order threshold comparisons at many CCTU values. At 12 CCTU (a common data point), second-order loss ranged from a factor of 1.96 (DS) to 2.29 (RH) (Table 2 and Fig. 5). DM could detect only one second-order stimulus, and only at 26 CCTU (which was equivalent to the maximum contrast) (Fig. 4f). Comparison of this threshold to the CE at 28 CCTU yielded a loss factor of 3.72. QM had limited study participation, so his data are sparse. However, QM showed no AE or NAE second-order loss with the stimuli tested (Fig. 4b). JF had poor first-order contrast sensitivity, which resulted in a 66 CCTU limit (Fig. 4e).

Interestingly, the AE of DS showed second-order loss (Fig. 4d) but essentially no first-order loss relative to the CE (Fig. 3b). This unexpected finding is plausible if second-order neurons in normal visual cortex are substantially binocular (see Section 4).

For the NAEs, it can be readily seen that RH & DM showed second-order loss relative to the CE (Fig. 4c and f). The amount of NAE second-order loss when calculated at either maximum carrier contrast or 12

CCTU was roughly the same for RH (2.09 and 1.95, respectively) and DM (1.95 and 2.17, respectively) (Table 2 and Fig. 5). This consistent loss (roughly a factor of 2) is reflected in the proportional nature of the fitted curves. The slight differences in loss are most easily attributable to carrier visibility differences at the two disparate contrasts. It should be noted that the amount of loss shown by three AEs at 12 CCTU was also roughly a factor of 2 (Table 2 and Fig. 5). The finding of NAE loss and the similarity of this loss to

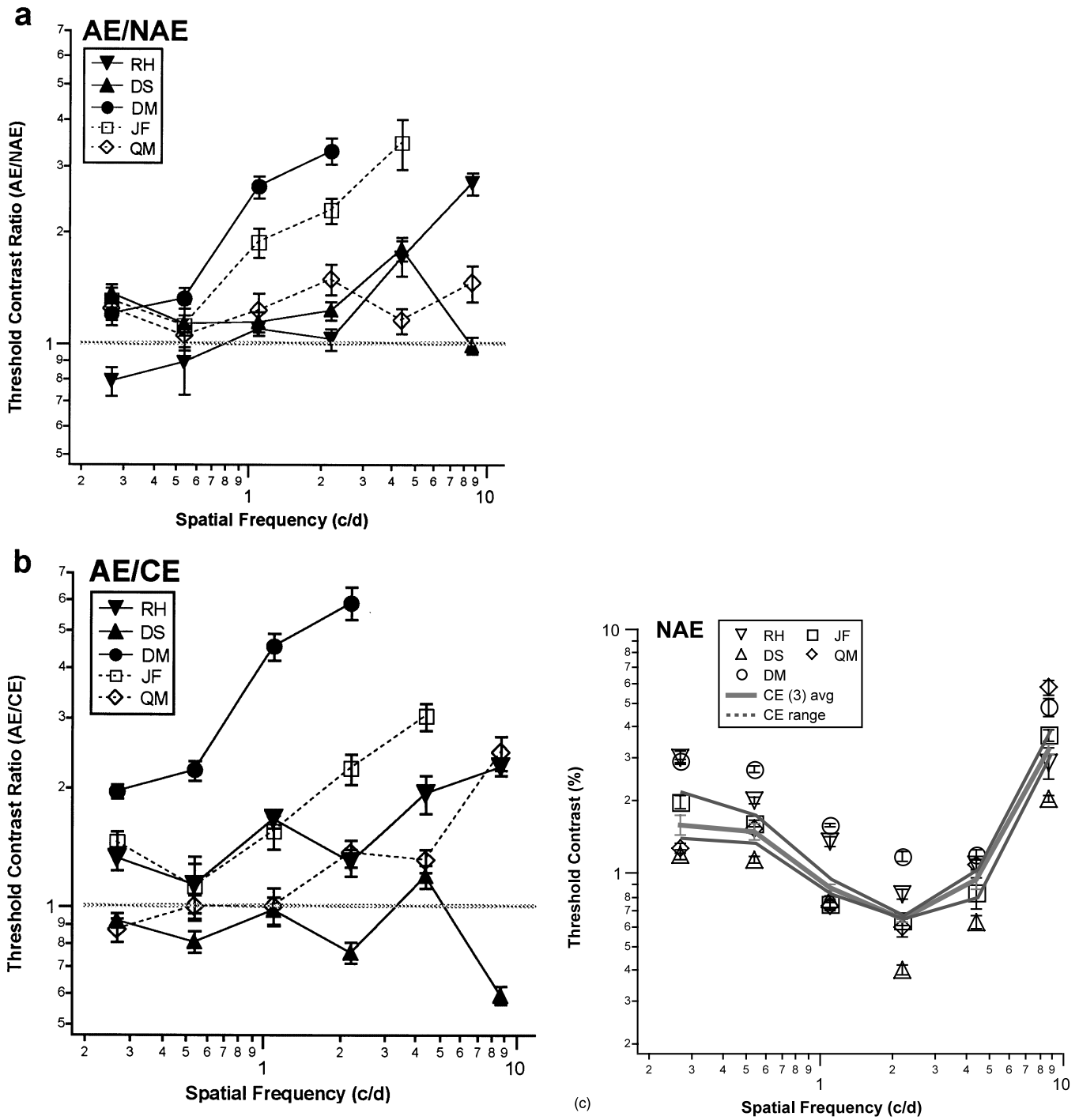

Fig. 3. (a, b) Visuograms showing the ratio of first-order threshold contrast (i.e. first-order loss) for the AE relative to the NAE (a) and the CE (b), as a function of spatial frequency. Each symbol represents an amblyope, and error bars are ± 1 combined fractional S.E. The six spatial frequencies tested also represent the carrier and envelope frequencies of our second-order stimuli. DM AE could not detect the 4.4 and 8.7 c/deg stimuli, and JF AE could not detect the 8.7 c/deg stimulus. (c) Threshold contrast as a function of spatial frequency for the NAEs and CE. Shown are the CE weighted average (gray line) and range (dotted line).

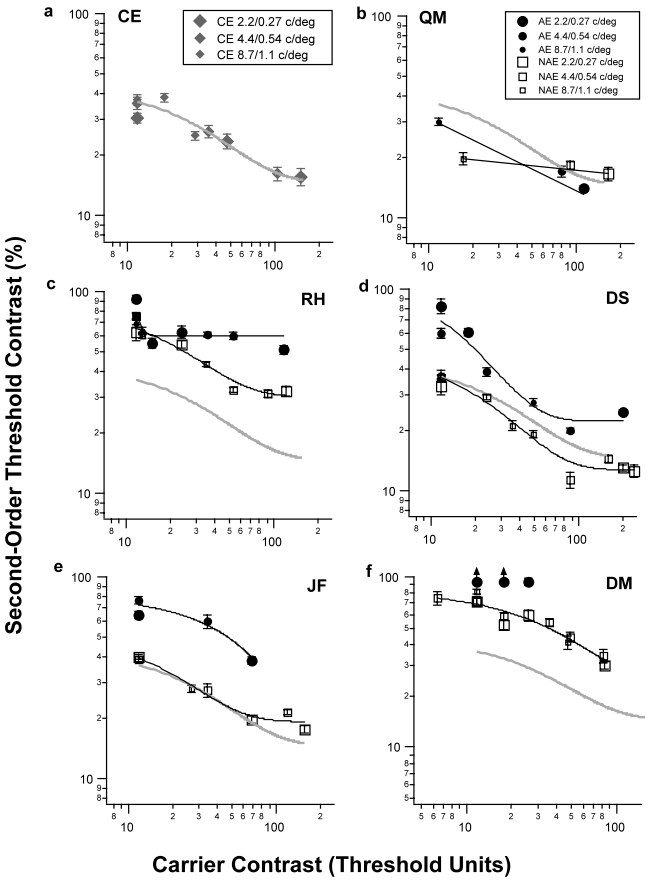

Fig. 4. Second-order threshold contrast as a function of carrier contrast threshold units (multiples of carrier threshold contrast). Panel (a) represents the average data from the three control eyes (CE), and panels (b)–(f) represent each amblyopic observer's AE and NAE, with the CE (gray curve) as reference. Filled symbols are AE, open symbols are NAE, and the largest to smallest symbols represent 2.2/0.27, 4.4/0.54 and 8.7/1.1 c/deg stimuli. Each eye's data are fit with an exponential curve, except for QM (b), who is fit with a line due to limited data, and error bars are ± 1 S.E. DM AE (f) could only detect one stimulus at 26 CCTU (we also tested at $12\times$ and $18\times$), and 26 CCTU represented maximum contrast. At equal CCTU, first-order input is essentially equated, so an AE or NAE threshold that is higher than the CE would indicate a second-order loss that is more likely specific to the second filter stage.

that of the AEs might be taken to indicate involvement of a common binocular mechanism (see Section 4).

To further investigate the nature of the second-order loss, we compared the Weibull function exponents (slope indicator) for first-order and second-order experiments. From Fig. 6, the CE average second-order slope was flatter than the average first-order slope (exponent 1.95 vs. 2.21). However, the opposite trend was found for the AE and NAE: the average second-order slope was steeper than the average first-order slope (AE exponent 2.48 vs. 2.30; NAE exponent 2.30 vs. 2.17). Independent analysis of first-order and second-order average exponents best characterized the second-order loss.

The average first-order slopes were not significantly different for the CE (2.21), AE (2.30) and NAE (2.17) (Fig. 6). However, the average second-order slopes for the AE and NAE were steeper than the CE (exponents 2.48, 2.30, 1.95, respectively), which implicates the second-order mechanism as the primary site of deficit. We found significant differences between the average exponent of the CE versus both the AE and NAE, but no significant difference between the AE and NAE (Fig. 6). This AE and NAE functional deficit, when compared with the CE, implies the presence of a binocular component to the second-order mechanism deficit, consistent with our other findings.

For our small group of amblyopes, qualitative analysis revealed that both the presence and severity of second-order loss shown by AEs and NAEs might be associated with the age of amblyopia treatment. No strong association was found between second-order loss and either amblyopia type or level of acuity loss. The three mixed amblyopes best demonstrate these findings. Loss was absent for QM (extensive early age treatment, 20/50), present for DS (later and less extensive treatment, 20/40), and greatest for DM (no early treatment, 20/80) (Table 1 and Fig. 5).

4. Discussion

4.1. Second-order spatial loss is greater than the loss of first-order spatial input

In this study, we provide evidence that some amblyopes show detection loss for second-order spatial information, and that this loss is greater than the loss of first-order spatial input. This latter finding suggests a deficit specific to the second-order mechanism and is also taken as evidence of an early cortical amplification of neural loss in amblyopia, over and above the first-order loss known to occur in V1.

We base our inference on three findings. First, both AEs and NAEs showed second-order loss when the carrier was equated for visibility. Second, relative to the CE, the AE of DS showed second-order loss but no first-order loss to the carrier spatial frequencies. Third, both the pooled AE and NAE psychometric slopes for second-order detection were significantly steeper than that for the CE, whereas the slopes for first-order detection were not significantly different between groups.

Our inference from the first and second findings is based on the assumption that equated carrier contrast and an intact contrast response function would predict equal information available to all eyes prior to the rectification and second filter stage. Second-order loss would therefore implicate the second filter stage, as was strongly suggested by the AE of DS (second-order loss

Table 2
AE and NAE second-order loss at maximum carrier contrast (84%) and 12 carrier contrast threshold units (CCTU)

Observer	Second-order threshold contrast:		Second-order loss (AE/CE, NAE/CE):	
	@ 84% carrier contrast	@ 12 CCTU	@ 84% carrier contrast	@ 12 CCTU
Control eyes (CE)	15.45 ± 1.49	34.49 ± 2.82	–	–
Amblyopic eye				
DM	93.13 ± 4.54	93.13 ± 4.54[a]	6.03 ± 0.65	3.72 ± 0.26[a]
RH	51.66 ± 2.55	78.99 ± 2.96	3.34 ± 0.36	2.29 ± 0.21
JF	38.47 ± 1.75	71.11 ± 4.87	2.49 ± 0.27	2.06 ± 0.22
DS	24.41 ± 0.68	67.61 ± 4.53	1.58 ± 0.16	1.96 ± 0.21
QM	14.03 ± 0.34	30.01 ± 1.43	0.91 ± 0.09	0.87 ± 0.08
Non-amblyopic eye				
DM	30.14 ± 1.68	75.00 ± 3.60	1.95 ± 0.22	2.17 ± 0.21
RH	32.28 ± 1.63	67.14 ± 3.06	2.09 ± 0.23	1.95 ± 0.18
JF	17.57 ± 0.81	39.73 ± 1.44	1.14 ± 0.12	1.15 ± 0.10
DS	12.51 ± 0.91	35.72 ± 2.04	0.81 ± 0.10	1.04 ± 0.10
QM	17.57 ± 0.81	19.59 ± 1.41[b]	1.14 ± 0.12	0.51 ± 0.04[b]

[a] DMAE value @ 26 CCTU (see Fig. 4f) and loss calculated from CE @ 28 CCTU (25.05 ± 1.26).
[b] QMNAE value @ 17 CCTU (see Fig. 4b) and loss calculated from CE @ 17 CCTU (38.31 ± 1.88).

in the absence of first-order loss). Our assumption is also supported by previous psychophysical research showing that the AE contrast response function for first-order information is essentially equal to, or higher than, the NAE (Hess & Bradley, 1980; Loshin & Levi, 1983; Bradley & Ohzawa, 1986; Levi, Klein, & Wang, 1994).

Our inference from the third finding is based on the assumption that steeper psychometric slopes for contrast detection may be associated with large degrees of intrinsic (observer) uncertainty (Pelli, 1985). In this case, intrinsic uncertainty could be attributed to decreased pooled signal strength from second-order neurons. This hypothesis is supported by fMRI findings showing that greater average neural activity in early visual cortex is consistent with simultaneous psychophysical detection of contrast increments (Boynton, Demb, Glover, & Heeger, 1999). Contrast discrimination was essentially the task in our second-order experiment, i.e. we effectively measured contrast increment thresholds with equated first-order input. From this, our finding of similar first-order psychometric slopes for all eyes is taken to reflect roughly equal neuronal activity, whereas the steeper second-order slopes shown by the amblyopes suggest reduced neuronal activity. Whilst this analysis cannot reveal the exact nature of the neural deficit, the data do interestingly suggest a deficit specific to the second stage filter that warrants further investigation.

4.2. Second-order neurons appear to be substantially binocular

We speculate that second-order neurons are substantially binocular, i.e. driven by both eyes equally well, based on three findings. First, losses shown by AEs and NAEs were very similar (roughly a factor of 2). Second, the AE of DS showed second-order loss but essentially no first-order loss (relative to the CE). Third, later treatment age appeared to be associated with a greater second-order loss, whereas amblyopia type or level of acuity loss did not.

In our small group of amblyopes, NAE loss was shown by the amblyopes who received late treatment (DM and RH), and the only amblyope without loss was treated earliest (QM). Further, the degree of AE second-order loss appeared to increase with later treatment age (Fig. 5). These findings are consistent with first-order deficits that develop when there is an imbal-

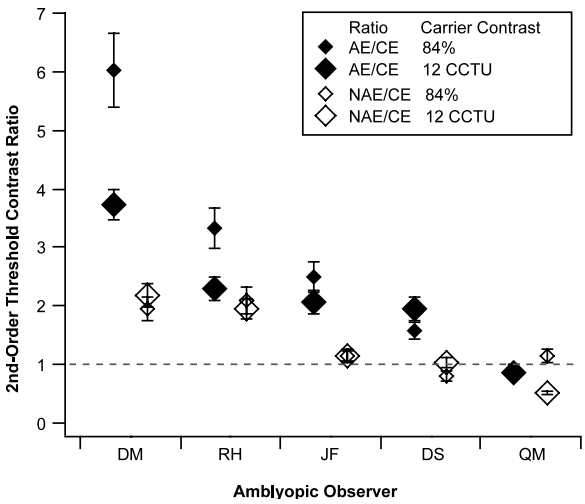

Fig. 5. Second-order loss (threshold contrast ratios AE/CE and NAE/CE) of each amblyopic observer taken at two data points: maximum carrier contrast (small diamond symbols) and 12 CCTU (large diamond symbols). See text for data details of DM and QM.

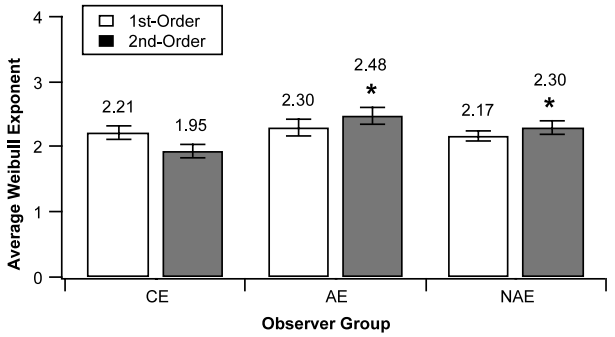

Fig. 6. Comparison of CE, AE and NAE average Weibull function exponent (slope indicator) for first-order (white bars) and second-order (gray bars) experiments. Values are pooled data from all stimuli tested, and error bars are +1 S.E. The second-order average exponent is smaller than the first-order average exponent for the CE but larger for the AE and NAE. For the first-order experiment, no significant difference was found between the CE, AE and NAE (two-sample, two-tailed t-tests, $df = 17$, $P < 0.50$ for all three comparisons). However, for the second-order experiment, the same t-test showed a significant difference (asterisk) between the average exponents of the CE versus the AE ($df = 19$, $P < 0.005$) and the CE versus the NAE ($df = 19$, $P < 0.02$). The AE versus the NAE was not statistically significant ($df = 24$, $P < .30$).

ance in the sensory input from the two eyes during a critical period (Harwerth, Smith, Crawford, & von Noorden, 1983, 1990; Kiorpes, Kiper, & Movshon, 1983; Kiorpes, Kiper, & Movshon, 1990; Kiorpes, Kiper, & Movshon, 1993; Kiorpes et al., 1998). More importantly, these findings point out the importance of unimpeded binocular development.

Our speculation that second-order neurons are substantially binocular is strongly supported by adaptation experiments comparing interocular transfer of subjective versus real contours (Paradiso, Shimojo, & Nakayama, 1989), flicker versus real motion after-effects (Nishida, Ashida, & Sato, 1994), and contrast versus luminance modulated spatial stimuli (Whitaker, McGraw, & Levi, 1997). Each study found the interocular transfer of second-order information to be both substantial and greater than that for first-order information. Complete interocular transfer of a monocular signal is taken to indicate both higher-order cortical processing and significant binocular integration, i.e. can only be carried out by neurons that receive a strong sensory input from each eye.

Our hypothesis of binocularity is supported by physiological evidence from monkey that shows the overwhelming majority of neurons in V2 to be binocularly driven (Zeki, 1978; Burkhalter & Van Essen, 1986; Hubel & Livingstone, 1987). Further, in alert behaving monkeys, von der Heydt, Zhou, and Friedman (2000) found neurons in V2 that signal features produced by random-dot stereograms (whereas none were found in V1), and Bakin, Nakayama, and Gilbert (2000) found more neurons in V2 than V1 that were sensitive to global depth cues. Therefore, to the extent that the second filter stage is predominantly located in V2 (see Section 1), the strong possibility of binocular neuron involvement should also be acknowledged.

Currently, there is an almost complete absence of studies examining second-order neuron population, ocular dominance or contrast gain, so our hypothesis of deficient binocular input underlying second-order loss is speculative. However, this hypothesis has a sound anatomical basis in that most neurons are binocularly driven beyond monocular input layer 4C. Early-onset monocular deprivation is thought to produce competitive imbalance for synaptic sites, which in turn results in a reduced proportion of functionally binocular neurons (Blakemore, Garey, & Vital-Durand, 1978; Movshon et al., 1987; Smith et al., 1997). Further, binocular suppression of the NAE by the AE has been shown in cat (Chino, Smith, Yoshida, Cheng, & Hamamoto, 1994; Sengpiel, Blakemore, Kind, & Harrad, 1994), monkey (Smith et al., 1997) and in humans (Levi, Harwerth, & Smith, 1979). In light of these facts, it follows that late treatment could result in more severe amblyopic deficits along with additional NAE deficits.

In summary, we report a novel spatial loss shown by some amblyopes and also that an amplification of neural deficits occurs in amblyopia. These results, when considered in light of contemporary neurophysiological findings, suggest that amplification occurs at very early levels in the extrastriate cortex (V2). As this information outputs to higher-order mechanisms there may invariably be further amplification of the neural deficit at higher levels (Sharma, Levi, & Klein, 2000). Further, we speculate that second-order neurons are substantially binocular, therefore requiring normal binocular input during development. Supporting this, we show that if amblyopia treatment is late, the non-amblyopic eye may also develop second-order spatial loss.

Acknowledgements

Supported by grants RO1EY01728 and P30EY07551 from the National Eye Institute, NIH, Bethesda, MD, and P.V.M. is supported by a Research Career Development Fellowship from the Wellcome Trust, UK.

References

Badcock, D. R., & Derrington, A. M. (1989). Detecting the displacements of spatial beats: no role for distortion products. *Vision Research*, *29*, 731–739.

Bakin, J. S., Nakayama, K., & Gilbert, C. G. (2000). Visual responses in monkey areas V1 and V2 to three-dimensional surface configurations. *Journal of Neuroscience*, *20*, 8188–8198.

Blakemore, C., Garey, L. J., & Vital-Durand, F. (1978). The physiological effects of monocular deprivation and their reversal in the monkey's visual cortex. *Journal of Physiology*, *283*, 223–262.

Boynton, G. M., Demb, J. B., Glover, G. H., & Heeger, D. J. (1999). Neuronal basis of contrast discrimination. *Vision Research*, *39*, 257–269.

Bradley, A., & Ohzawa, I. (1986). A comparison of contrast detection and discrimination. *Vision Research*, *26*, 991–997.

Burkhalter, A., & Van Essen, D. C. (1986). Processing of color, form and disparity information in visual areas VP and V2 of ventral extrastriate cortex in the macaque monkey. *Journal of Neuroscience*, *6*, 2327–2351.

Chino, Y. M., Smith, E. L. III, Yoshida, K., Cheng, H., & Hamamoto, J. (1994). Binocular interactions in striate cortical neurons of cats reared with discordant visual inputs. *Journal of Neuroscience*, *14*, 5050–5067.

Cropper, S. J. (1998). Detection of chromatic and luminance contrast modulation by the visual system. *Journal of the Optical of America A*, *8*, 1969–1986.

Derrington, A. M., & Badcock, D. R. (1985). Detection of spatial beats: non-linearity or contrast increment detection? *Vision Research*, *26*, 343–348.

Ffytche, D. H., & Zeki, S. (1996). Brain activity related to the perception of illusory contours. *Neuroimage*, *3*, 104–108.

Grosof, D. H., Shapley, R. H., & Hawken, M. J. (1993). Macaque V1 neurons can signal 'illusory' contours. *Nature*, *365*, 550–552.

Harwerth, R. S., Smith, E. L. III, Boltz, R. L., Crawford, M. L. J., & von Noorden, G. K. (1983). Behavioral studies on the effect of abnormal early visual experience: spatial modulation sensitivity. *Vision Research*, *4*, 1501–1510.

Harwerth, R. S., Smith, E. L. III, Crawford, M. L. J., & von Noorden, G. K. (1990). Behavioral studies of the sensitive periods of development of visual functions in monkeys. *Behavioral Brain Research*, *41*, 179–198.

Henning, G. B., Hertz, B. G., & Broadbent, D. E. (1975). Some experiments bearing on the hypothesis that the visual system analyses spatial frequency patterns in independent bands of spatial frequency. *Vision Research*, *15*, 887–899.

Hess, R. F., & Bradley, A. (1980). Contrast perception above threshold is only minimally impaired in human amblyopia. *Nature*, *287*, 463–464.

Hess, R. F., Field, D., & Watt, R. J. (1990). The puzzle of amblyopia. In C. Blakemore, *Vision*: *coding and efficiency* (pp. 267–280). London: Cambridge University Press.

Hirsch, J., DeLaPaz, R. L., Relkin, N. R., Victor, J., Kim, K., Li, T., Borden, P., Rubin, N., & Shapley, R. (1995). Illusory contours activate specific regions in human visual cortex: evidence from functional magnetic resonance imaging. *Proceedings of the National Academy of Sciences USA*, *92*, 6469–6473.

Hubel, D. H., & Livingstone, M. S. (1987). Segregation of form, color, and stereopsis in primate area 18. *Journal of Neuroscience*, *7*, 3378–3415.

Kiorpes, L., Kiper, D. C., & Movshon, J. A. (1993). Contrast sensitivity and vernier acuity in amblyopic monkeys. *Vision Research*, *33*, 2301–2311.

Kiorpes, L., Kiper, D. C., O'Keefe, L. P., Cavanaugh, J. R., & Movshon, J. A. (1998). Neuronal correlates of amblyopia in the visual cortex of macaque monkeys with experimental strabismus and anisometropia. *Journal of Neuroscience*, *18*, 6411–6424.

Langley, K., Fleet, D. J., & Hibbard, P. B. (1996). Linear filtering precedes nonlinear processing in early vision. *Current Biology*, *6*, 891–896.

Leventhal, A. G., Wang, Y., Schmolesky, M. T., & Zhou, Y. (1998). Neural correlates of boundary perception. *Visual Neuroscience*, *15*, 1107–1118.

Levi, D. M., Harwerth, R. S., & Smith, E. L. III (1979). Humans deprived of normal binocular vision have binocular interactions tuned to size and orientation. *Science*, *206*, 852–854.

Levi, D. M. (1991). Spatial vision in amblyopia. In J. Cronly-Dillon, *Vision and visual dysfunction*, vol. 10B (pp. 212–238). New York: Macmillan Press.

Levi, D. M., Klein, S. A., & Wang, H. (1994). Discrimination of position and contrast in amblyopic and peripheral vision. *Vision Research*, *34*, 3293–3313.

Lin, L., & Wilson, H. R. (1996). Fourier and non-fourier pattern discrimination compared. *Vision Research*, *36*, 1907–1918.

Loshin, D. S., & Levi, D. M. (1983). Suprathreshold contrast perception in functional amblyopia. *Documenta Ophthalmologica*, *55*, 213–236.

MacLeod, D. I. A., Williams, D. R., & Makous, W. (1992). A visual non-linearity fed by single cones. *Vision Research*, *32*, 347–363.

McGraw, P. V., Levi, D. M., & Whitaker, D. (1999). Spatial characteristics of the second-order visual pathway revealed by positional adaptation. *Nature Neuroscience*, *2*, 479–484.

Mareschal, I., & Baker, C. L. Jr. (1998). Temporal and spatial response to second-order stimuli in cat area 18. *Journal of Neurophysiology*, *80*, 2811–2823.

Mareschal, I., & Baker, C. L. Jr. (1999). Cortical processing of second-order motion. *Visual Neuroscience*, *16*, 527–540.

Movshon, J. A., Eggers, H. M., Gizzi, M. S., Hendrickson, A. E., Kiorpes, L., & Boothe, R. G. (1987). Effects of early unilateral blur on the macaque's visual system. III. Physiological observations. *Journal of Neuroscience*, *7*, 1340–1351.

Nishida, S., Ashida, H., & Sato, T. (1994). Complete interocular transfer of motion aftereffect with flickering test. *Vision Research*, *34*, 2707–2716.

Paradiso, M. A., Shimojo, S., & Nakayama, K. (1989). Subjective contours, tilt aftereffects, and visual cortical organization. *Vision Research*, *29*, 1205–1213.

Pelli, D. G. (1985). Uncertainty explains many aspects of visual contrast detection and discrimination. *Journal of the Optical Society of America A*, *2*, 1508–1531.

Pelli, D. G., & Zhang, L. (1991). Accurate control of contrast on microcomputer displays. *Vision Research*, *31*, 1337–1350.

Redies, C., Crook, J. M., & Creutzfeldt, O. D. (1986). Neuronal responses to borders with and without luminance gradients in cat visual cortex and dorsal lateral geniculate nucleus. *Experimental Brain Research*, *61*, 469–481.

Schofield, A. J., & Georgeson, M. A. (1999). Sensitivity to modulations of luminance and contrast in visual white noise: separate mechanisms with similar behavior. *Vision Research*, *39*, 2697–2716.

Sengpiel, F., Blakemore, C., Kind, P. C., & Harrad, R. (1994). Interocular suppression in the visual cortex of strabismic cats. *Journal of Neuroscience*, *14*, 6871–6885.

Sharma, V., Levi, D. M., & Klein, S. A. (2000). Undercounting features and missing features: evidence for a high-level deficit in strabismic amblyopia. *Nature Neuroscience*, *3*, 496–501.

Sheth, B. R., Sharma, J., Rao, S. C., & Sur, M. (1996). Orientation maps of subjective contours in visual cortex. *Science*, *274*, 2110–2115.

Smith, E. L. III, Chino, Y. M., Ni, J., Cheng, H., Crawford, M. L. J., & Harwerth, R. S. (1997). Residual binocular interactions in the striate cortex of monkeys reared with abnormal binocular vision. *Journal of Neurophysiology*, *78*, 1353–1362.

Sutter, A., Sperling, G., & Chubb, C. (1995). Measuring the spatial frequency selectivity of second-order texture mechanisms. *Vision Research*, *35*, 915–924.

von der Heydt, R., & Peterhans, E. (1984). Illusory contours and cortical neuron responses. *Science*, *224*, 1260–1262.

von der Heydt, R., & Peterhans, E. (1989). Mechanisms of contour perception in monkey visual cortex. I. Lines of pattern discontinuity. *Journal of Neuroscience*, *9*, 1731–1748.

von der Heydt, R., Zhou, H., & Friedman, H. S. (2000). Representation of stereoscopic edges in monkey visual cortex. *Vision Research*, *40*, 1955–1967.

Whitaker, D., McGraw, P. V., & Levi, D. M. (1997). The influence of adaptation on perceived visual location. *Vision Research*, *37*, 2207–2216.

Willis, A., Smallman, H. S., & Harris, J. M. (2000). Comparing contrast-modulated and luminance modulated masking: effects of spatial frequency and phase. *Perception*, *29*, 81–100.

Zeki, S. M. (1978). Uniformity and diversity of structure and function in rhesus monkey prestriate visual cortex. *Journal of Physiology*, *277*, 273–290.

Zhou, Y. X., & Baker, C. L. Jr. (1994). Envelope-responsive neurons in areas 17 and 18 of cat. *Journal of Neurophysiology*, *72*, 2134–2150.