Variation in Vernier Evoked Cortical Potential with Age

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Purpose. To investigate the effects of age on transient vernier visual evoked potential (VEP) and vernier acuity estimated by extrapolation.

Methods. Transient vernier VEPs were examined in normal subjects aged 20 to 75 years. Vernier offsets were presented for the first 350 msec of the stimulus period, and the segments were then realigned in the following 400 msec. The six vernier offsets used were 20, 40, 60, 80, 100, and 140 seconds of arc. Averaging for each offset setting produced vernier VEP waveforms, for which amplitude and latency of visual evoked response and background electroencephalographic (EEG) noise level were determined. Extrapolation of the function relating signal-to-noise ratio and log vernier offset to a ratio of 1.0 resulted in an estimate of vernier acuity.

Results. Amplitude of vernier VEP waveforms was significantly reduced in subjects more than 60 years of age, and the latency to the first negative peak was progressively prolonged with increasing age. There was no statistically significant change in electroencephalographic (EEG) noise with advancing age. VEP vernier acuity was significantly degraded in the 61- to 75-year age group. These results are parallel to recent psychophysical findings that alignment performance is worse in older persons than in younger ones.

Conclusions. The present findings provide the first electrophysiological evidence of age-related cortical degeneration associated with vernier processing. Reduced neural activity probably contributes to the loss of vernier acuity with advancing age. Also provided are the first normative data for subjects of different ages for vernier VEP and VEP vernier acuity. Moreover, the present study has demonstrated that vernier VEP is sensitive to neural changes and therefore may be applied in clinical situations to evaluate the integrity of the visual system. (*Invest Ophthalmol Vis Sci.* 2001;42:1119–1124)

We have recently shown that vernier threshold, obtained using a psychophysical method, is elevated by a factor of two in subjects more than 60 years of age.[1] Senile miosis and reduced transmittance of ocular media in the elderly decrease retinal illuminance. We have shown that, at the high stimulus luminance level used in the present work (240 candelas [cd]/m^2), reduced retinal illuminance (produced with a 3-mm artificial pupil and a neutral density filter, 0.2 log unit) has minimal effect on vernier acuity in young subjects.[1] In contrast, at low stimulus luminance levels, vernier acuity has been shown to have a square-root dependence on retinal illuminance.[2–4] The stimulus configurations used in our previous study are strongly resistant to optical degradation,[5] and vernier acuity is quite stable with respect to changes in contrast and luminance of the stimuli at suprathreshold levels.[6,7] The deterioration in alignment performance can therefore be mainly attributed to age-related neural loss.

The present experiment was conducted to investigate the age-related cortical changes in vernier processing using an electrophysiological approach. A large number of studies have shown an age effect on traditional flash[8–13] and pattern visual evoked potentials (VEPs).[12,14–29] Simultaneous recordings of electroretinogram (ERG) and VEP have also confirmed age-related effects on the neural visual system.[25,27,30] However, there have been no previous reports of variations in vernier VEP or extrapolated vernier acuity with age. There is extensive evidence from psychophysical and electrophysiological studies that vernier acuity reflects cortical processing[31–34] and is thus a good indicator of cortical integrity at any age. Amblyopic eyes have shown increased deterioration in vernier acuity relative to visual acuity.[33,35–38] Cats without a striate cortex show impaired vernier acuity while maintaining high levels of grating acuity.[39] These provide the functional correlates of vernier acuity in the visual cortex.

Cortical evoked potentials can be elicited at striate and extrastriate cortices by the presentation of vernier offset.[31,40–42] Topographic mapping has shown that the vernier stimulus evokes the greatest cortical activity in the extrastriate, and a smaller response at the striate cortex.[43,44] Extrapolation of the function relating amplitude and log vernier offset to 0 V provides an electrophysiological estimate of vernier acuity,[31,40,41] and this objective electrophysiological technique has been applied clinically to measure the vernier acuity in infants.[45,46] In the present experiment, this VEP technique was used to study the effects of age on vernier VEP and extrapolated vernier acuity.

Methods

Subjects

Forty subjects were recruited, 10 subjects in each of four age groups: 21 to 40, 41 to 50, 51 to 60, and 61 to 75 years. There were five men and five women in each group. Preliminary eye examinations were performed in the Optometry Clinic of The Hong Kong Polytechnic University. The maculae of all subjects were assessed as normal, and, specifically, had no drusen in an area of one disc diameter around the macula and no pigmentary changes. All subjects had clear ocular media (assessed by direct ophthalmoscopy) and were free of lens opacities in the dilated pupillary area. They had no known visual problems (by self-report), and no subject had strabismus or amblyopia. All subjects had log minimum angle of resolution (logMAR) acuity of 0 (20/20 Snellen) or better in both eyes.

Vernier Stimulus

Vernier stimuli were presented to the subjects (Fig. 1). The stimulus configuration consisted of bright white rectangular patches of light (1 × 8 minutes of arc) on the dark screen of a computer monitor. All the segments were aligned initially. The vernier offsets were introduced by displacing the test line segments either to the left or right at random, while the reference line segments remained stationary. Vernier offsets appeared for the first 350 msec of the stimulus period, and the segments were then realigned in the following 400 msec. The whole pattern subtended 2° × 2° at 2.5 m. The flat 15-in. screen was

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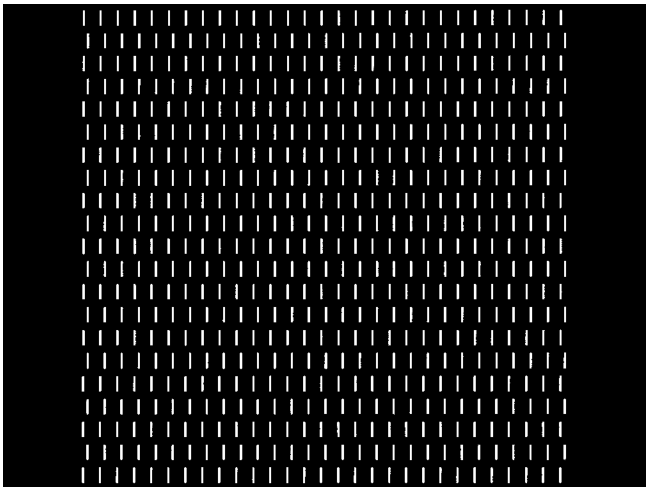

FIGURE 1. Vernier stimuli used in VEP measurement.

viewed monocularly at a distance of 2.5 m. The monitor resolution was 1024 × 768 pixels, and the smallest interpixel visual angle was 20 seconds of arc. The vertical screen refresh rate was 85 Hz. The laboratory was kept completely dark, the only light source being the stimulus itself. The luminances of the target and the dark background were 240 cd/m^2 and 0.6 cd/m^2, respectively. The vernier segments were separated by 8 minutes of arc laterally and 4 minutes of arc vertically.

Subject Preparation

The evoked voltages were recorded with silver disc electrodes applied to the scalp. The abrasive preparation paste (Omni Prep; DO Weaver, Aurora, CO) was applied to the electrode sites on the scalp and was rubbed into the skin lightly with a cotton swab. The conductive electrode gel (Medi-Trace EEG Sol; Graphic Controls, Buffalo, NY) was applied over the preparation paste. In this way, the impedance between any pair of electrodes was reduced to approximately 5 kΩ. A bipolar arrangement of electrodes was adopted. Four electrodes were used: Two active electrodes were placed 6 cm to either side of the reference electrode, which was placed 2 cm above the inion. The right and center electrodes were connected to one channel, and the left and center electrodes were connected to the second channel. The ground electrode was placed on the right ear lobe.

Vernier VEP Measurement

The electrical activity elicited at the scalp by the vernier offsets was amplified 10^5 times by means of two physiological preamplifiers (P511(K); Grass, Quincy, MA), with band-pass frequencies of 1 to 30 Hz in combination with a 50-Hz filter. The amplified analog electrical responses were then digitized by a 12-bit analog-to-digital converter (NB-MIO-16; National Instruments, Austin, TX) at 1000 Hz. Each epoch length was 700 msec. The data acquisition was handled and the data were analyzed by computer (using LabView, ver. 2.2.1; National Instruments). The data acquisition was synchronized with stimulus reversals. Artifacts of unusually high or low electrical voltages were rejected by the software program's subroutine. The six vernier offsets used were 20, 40, 60, 80, 100, and 140 seconds of arc, and the sequence of presentation of offset size was randomized. Averaging of 150 epochs for each offset setting produced reliable and robust VEP waveforms.

For VEP measurement, the subject was seated 2.5 m from the monitor. The stimulus was viewed monocularly with the subject wearing refractive correction appropriate for the working distance. The subject was asked to look steadily at the center of the stimulus, keep the stimulus in focus, avoid blinking, avoid tracking the stimuli, and avoid any mental activity, such as counting or thinking. Each group of trials lasted for 5 seconds. The measurements were self-paced; subjects were asked to click a mouse button to initiate the procedure. Breaks were allowed on request, and on average, the VEP measurements took approximately 45 minutes.

Estimating Electrophysiological Vernier Acuity

Electrical potentials at the extrastriate cortex are positive relative to those at the inion. The amplitude of vernier VEP was defined as the average of the differences in potential between the first prominent negative and positive peaks in the vernier waveforms recorded in two channels, and the latency was taken as the shorter time to the first negative peak recorded in two channels. An ideal digital high-pass filter with cutoff frequency at 10 Hz was implemented, using discrete Fourier transform, to extract the background EEG noise from an averaged VEP waveform for all vernier settings. The SD of the extracted background was calculated as an estimate of EEG noise level. The signal-to-noise ratio was defined as the ratio of VEP amplitude to the background EEG noise level. Extrapolation of the function relating signal-to-noise ratio and log vernier offset to a ratio of 1.0 resulted in an estimate of vernier acuity. An EEG noise estimation was used similar to that used in previous studies.[47]

Procedures

Subjects were carefully refracted, and their refractive errors were fully corrected for the working distance of 2.5 m for electrophysiological measurement, the endpoint criterion being minimum minus power for best visual acuity. In electrophysiological procedures, only the dominant eye was tested, and the other eye was occluded. One drop of 1% tropicamide was used to dilate the pupil of the eye being tested. Another drop was instilled 10 minutes after the first one, if the dilated pupil size was less than 6 mm. Vernier VEPs were measured monocularly with a 5 mm artificial pupil 10 mm from the cornea. The whole experiment took approximately 1.5 hours. The research followed the tenets of the Declaration of Helsinki. Only subjects who gave informed consent participated in the experiment. This research was approved by institutional review.

Results

Vernier VEP

Adult transient vernier VEP was characterized by a prominent negative wave with a peak at 200 to 220 msec after the appearance of vernier misalignment, and this was followed by a prominent positive wave that peaked at approximately 270 msec (Fig. 2). The VEP amplitude gradually decreased as the magnitude of vernier offset decreased. The evoked potentials elicited in a younger subject (IL, 23 years of age) and an older subject (CK, 63 years of age) by vernier offsets of 140, 100, 80, 60, 40, and 20 seconds of arc at the right extrastriate cortex are shown in Figures 2A through 2F. The latency of the first negative peak was inversely proportional to the magnitude of vernier offset. Latency was prolonged in waveforms elicited by smaller vernier offsets. Because it was occasionally difficult to extract accurate responses from the background electrical activity in some subjects, the variations in amplitude and latency of VEP generated by a vernier offset of 20 seconds of arc were not included in the analysis.

VEP Amplitude as a Function of Age

VEP amplitude gradually decreased with increasing age for all vernier settings. Mean amplitudes for different vernier settings for different age groups are shown in Figure 3A. The VEP amplitude was compared between age groups using two-way analysis of variance (ANOVA). There was a statistically significant reduction in mean amplitude elicited by vernier offsets with increasing age ($df = 3$; F = 22.54; $P < 0.001$), and there

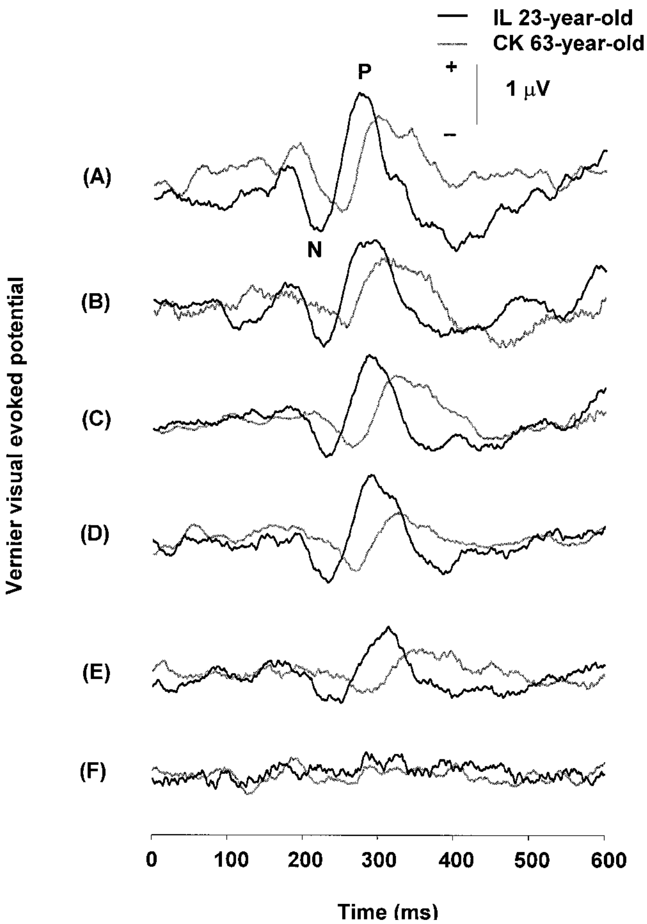

FIGURE 2. VEPs elicited by vernier offsets of (**A**) 140, (**B**) 100, (**C**) 80, (**D**) 60, (**E**) 40, and (**F**) 20 seconds of arc at the right extrastriate cortex. The upward deflection represents the changes of electrical potentials in the extrastriate area in a positive direction, and the downward deflection represents changes in a negative direction.

was a statistically significant increase in mean amplitude with increasing offset magnitude ($df = 4$; $F = 26.20$; $P < 0.001$). There was no statistically significant interaction between age group and offset ($P = 0.98$). Post hoc testing using the Tukey test revealed that the 21- to 40-year-old group had significantly larger mean amplitude than the 41- to 50-year-old group ($P < 0.05$), the 51- to 60-year-old group ($P < 0.05$) and the 61- to 75-year-old group ($P < 0.05$). The 41- to 50-year-old group had a significantly larger mean amplitude than the 61- to 75-year-old group ($P < 0.05$). There were no significant differences between the other age groups ($P > 0.05$ in all cases).

VEP Latency as a Function of Age

In general, the latency gradually increased with increasing age and with decreasing magnitude of vernier offset. Mean latencies for different vernier settings for four age groups are shown in Figure 3B. The mean latencies for all vernier settings were approximately 30 msec longer in the 61- to 75- than in the 21- to 40-year age group. Two-way ANOVA revealed that the differences in latency were statistically significant with increasing age ($df = 3$; $F = 14.32$; $P < 0.001$), and there was a statistically significant increase in mean latency with decreasing offset magnitude ($df = 4$; $F = 10.00$; $P < 0.001$). There was no statistically significant interaction between age group and offset ($P = 0.98$). Post hoc testing using the Tukey test revealed that the 61- to 75-year group had significantly increased latency compared with the 21- to 40-year group ($P < 0.05$) and the 41- to 50-year group ($P < 0.05$). The 51- to 60-year group had significantly increased latency compared with the 21- to 40-year group ($P < 0.05$) and the 41- to 50-year-old group ($P < 0.05$).

EEG Noise as a Function of Age

Mean background EEG noise levels for different vernier settings for different age groups are shown in Figure 3C. Two-way ANOVA revealed that there was no statistically significant difference in background EEG noise with age ($df = 3$; $F = 1.67$; $P = 0.18$) or with vernier offset ($df = 4$; $F = 0.13$; $P = 0.97$) and no statistically significant interaction between vernier offset and age ($df = 12$; $F = 0.74$; $P = 0.71$).

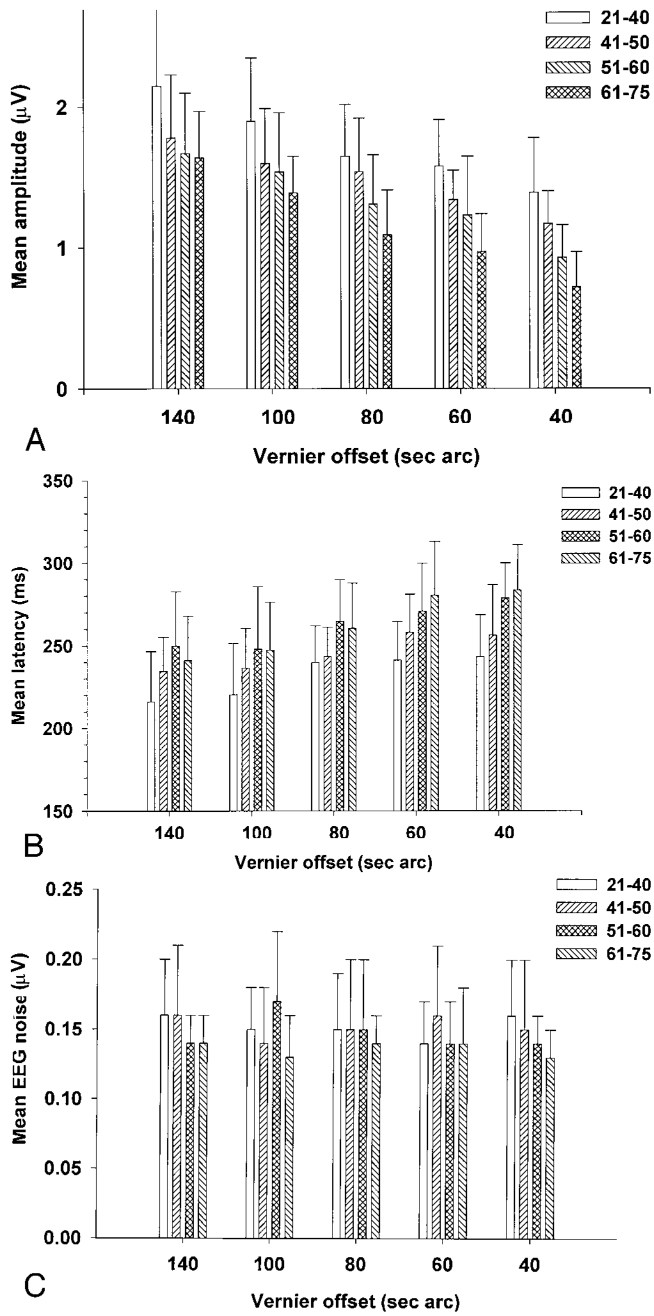

FIGURE 3. Mean amplitudes (**A**), latencies (**B**), and EEG noise (**C**) in the four age groups. Bars are SE.

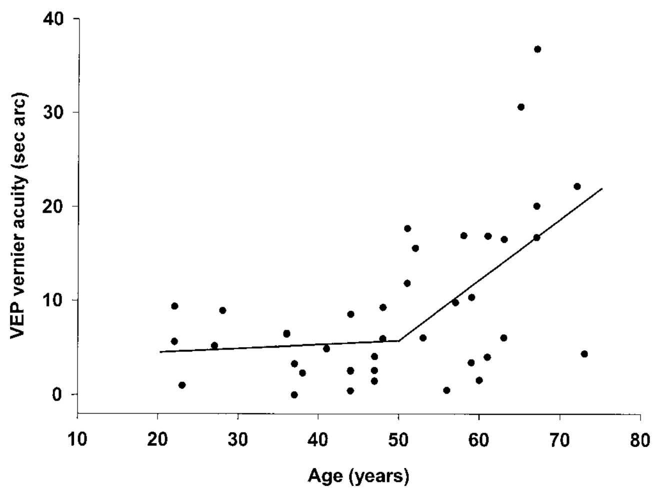

FIGURE 4. VEP vernier acuity as a function of age.

VEP Vernier Acuity as a Function of Age

VEP vernier acuity was significantly reduced after the age of 60 years. Electrophysiological vernier acuities for individuals are shown in Figure 4 with the data fitted by a bilinear function ($r^2 = 0.33$):

$$y = 0.04(x - 50) + 5.74 \quad \text{(before age of 50 years)}$$

$$y = 0.65(x - 50) + 5.74 \quad \text{(after age of 50 years)}$$

Age had a significant influence on VEP vernier acuity (ANOVA: $F_{3,36} = 8.41$, $P = 0.0002$). Mean VEP vernier acuities were 4.86, 4.24, 9.38, and 17.44 seconds of arc for the 21- to 40-, 41- to 50-, 51- to 60-, and 61- to 75-year age groups, respectively. The corresponding SDs were 3.16, 2.93, 6.30, and 10.85 seconds of arc. Post hoc testing with the Tukey–Kramer test revealed that there were statistically significant differences between the age groups 21 to 40 and 61 to 75 years ($P < 0.001$), between the age groups 41 to 50 and 61 to 75 years ($P < 0.001$), and between the age groups 51 to 60 and 61 to 75 years ($P < 0.05$), but no statistically significant difference between other age groups.

DISCUSSION

The vernier VEP waveform was consistent across the life span but with decreased amplitude and increased latency as age increased. In general agreement with previous vernier VEP studies,[31,40,41,44] the vernier VEP in young adults comprised a late negative wave with a peak at approximately 200 to 220 msec, which was then followed by a prominent positive wave. The reduction in amplitude was approximately 25% to 50% for the different vernier offsets in the oldest age group, but there was no significant change in EEG noise. Older subjects showed prolonged latency to the first negative peak, although the differences were not statistically significant for some vernier settings. These findings were not unexpected, because the literature supports the notion that age has a significant influence on flash and pattern evoked cortical potential.[8–30] In addition, VEP vernier acuity was found to be reduced significantly in subjects more than 60 years of age, supporting our previous psychophysical findings.[1] The fact that all subjects in this study had good visual acuity indicates that a disproportional reduction in vernier acuity occurs with increasing age. We suggest that this is because vernier acuity reflects cortical processing to a greater extent than does visual acuity.

It has been reported that the decrease in retinal illumination resulting from senile miosis[48,49] and increased media absorption[50,51] causes delayed and reduced electrophysiological response.[15,52–54] All the subjects in the present experiments had the same effective pupil size, achieved by placing an artificial pupil in front of the dilated pupil, and they had clear ocular media. Moreover, the vernier stimulus configurations used are markedly resistant to the optical scattering[5] that occurs in elderly eyes. Thus, optical factors had minimal impact on the changes in vernier VEP, and the loss of vernier acuity was essentially neural in origin. The lowered amplitudes of response probably reflect weakened neural activity and reduced signal for vernier tasks.

The vernier stimulus used in the present experiment is similar to those used in previous transient and steady state vernier VEP studies,[31,40,42–44,46] which reported steep dependences of vernier VEP and VEP vernier acuity on gap size, eccentricity, and spatial interference as psychophysical tasks. VEP vernier acuity is comparable with its psychophysical measurement. Moreover, we recently reported similar age-related trends in psychophysical vernier acuity.[1] Two-dimensional Fourier analysis of the two stimulus states (i.e., with and without vernier offsets) shows that there are differences in the distribution of their spatial frequency components. Apart from the vertical modulations that provided the offset cues, some horizontal modulations were also introduced by the offset stimulus, and we recognize that these may also stimulate cortical responses.

The vertical separation between vernier elements chosen has been shown to result in near optimum vernier acuity in young adults[5,55]; however, the ideal vertical separation may be different in older subjects. In this experiment, the vernier stimuli presented to both younger and older subjects had the same vertical separation. Further psychophysical and electrophysiological studies are necessary to investigate the variation in gap size that produces optimum vernier acuity with age. We adopted the extrapolation method used in previous studies[31,40,41,56] of VEP vernier acuity. The regression analysis in the present experiment was based on five vernier offsets (40, 60, 80, 100, and 140 seconds of arc), and more data points would provide a more precise estimate of vernier acuity.

Neuroanatomy and biochemistry findings give support to the notion that age-related changes occur in the visual pathway. The reduction in vernier VEP amplitude may be due to loss of neurons and to functional changes within the visual system. It has been suggested that there is a random loss of neurons throughout the visual system with advancing age.[57,58] Approximately 50% of retinal ganglion cells are lost over a 70-year life span, and approximately half of those are responsible for macular function.[59] A reduction in amplitude of the ERG reflects neural changes at the receptor level.[60,61] At the cortical level, there is a loss of neurons in the striate cortex with increasing age.[62,63] Axonal dystrophy of the central nervous system begins at the age of 20 years and is more severe from the age of 50 years.[64] The number of dendritic spines decreases in aging cortical cells.[65]

It is known that the conduction velocity of peripheral nerves progressively decreases with advancing age.[66,67] The prolongation of nerve impulse transmission along the visual pathways can result from segmental demyelination, defective myelin regeneration,[68] and axonal dystrophy.[69,70] There is further prominent loss of ganglion cell axons in the optic nerve beginning at approximately the age of 70 years, and the large diameter nerve fibers are selectively lost with increasing age.[71] Functional changes in neurotransmitters[72] and increased synaptic delay[73] may also contribute to increased latency in the aged visual system.

The present study provides the first electrophysiological evidence of age-related reduced neural activity associated with vernier processing, and our findings provide additional evidence to support our recent psychophysical data. It is reasonable that the reduced neural activities cause degraded performance in spatial localization. We provide the first normative data for subjects of different ages for amplitude and latency of vernier VEP and for VEP vernier acuity, and it is clear that consideration of the effects of age are necessary when measuring vernier VEP in clinical situations.

Hyperacuity tasks have been applied in psychophysical clinical tests to detect neural deficits in a range of ophthalmic disorders.[33,74–80] We have shown that vernier VEP is sensitive to neural changes and may therefore be used in objective clinical tests designed to examine the integrity of vernier processing pathways and spatial vision anomalies in both clinical and research situations. Although vernier VEP has not been widely used as a clinical test, the availability of age norms should provide the basis for further development of this specialized tool for clinical assessment.

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References

1. Li RWH, Edwards MH, Brown B. Variation in vernier acuity with age. *Vision Res*. 2000;40:3775–3781.
2. Hadani I, Meiri AZ, Guri M. The effects of exposure duration and luminance on the 3-dot hyperacuity task. *Vision Res*. 1984;24:871–874.
3. Waugh SJ, Levi DM. Visibility, luminance and vernier acuity for separated targets. *Vision Res*. 1993;33:527–538.
4. Waugh SJ, Levi DM. Visibility, luminance and vernier acuity. *Vision Res*. 1993;33:505–526.
5. Williams RA, Enoch JM, Essock EA. The resistance of selected hyperacuity configurations to retinal image degradation. *Invest Ophthalmol Vis Sci*. 1984;25:389–399.
6. Leibowitz H. Some factors influencing the variability of vernier adjustments. *Am J Psychol*. 1955;68:266–273.
7. Wehrhahn C, Westheimer G. How vernier acuity depends on contrast. *Exp Brain Res*. 1990;80:616–618.
8. Kooi KA, Bagchi BK. Visual evoked responses in man: normative data. *Ann N Y Acad Sci*. 1964;112:254–269.
9. Copenhaver RM, Perry NW. Factors affecting visually evoked cortical potentials such as impaired vision of varying etiology. *Invest Ophthalmol*. 1964;3:665–673.
10. Buchsbaum MS, Henkin RI, Christiansen RL. Age and sex differences in averaged evoked responses in a normal population, with observations on patients with gonadal dysgenesis. *Electroencephalogr Clin Neurophysiol*. 1974;37:137–144.
11. Celesia GG, Daly RF. Effects of aging on visual evoked responses. *Arch Neurol*. 1977;34:403–407.
12. La Marche JA, Dobson WR, Cohn NB, Dustman RE. Amplitudes of visually evoked potentials to patterned stimuli: age and sex comparisons. *Electroencephalogr Clin Neurophysiol*. 1986;65:81–85.
13. Fokin VF, Ponomareva NV. Interdependence of the level of the steady potential of the brain and visual evoked potentials in human aging: the norm and Alzheimer's disease. *Neurosci Behav Physiol*. 1995;25:136–141.
14. Asselman P, Chadwick DW, Marsden CD. Visual evoked responses in the diagnosis and management of patients suspected of multiple sclerosis. *Brain*. 1975;98:261–282.
15. Stockard JJ, Hughes JF, Sharborough FW. Visually evoked potentials to electronic pattern reversal: latency variations with gender, age and technical factors. *Am J EEG Technol*. 1979;19:171–204.
16. Shearer DE, Dustman RE. The pattern reversal evoked potential: the need for laboratory norms. *Am J EEG Technol*. 1980;20:185–200.
17. Shaw NA, Cant BR. Age-dependent changes in the latency of the pattern visual evoked potential. *Electroencephalogr Clin Neurophysiol*. 1980;48:237–241.
18. Shaw NA, Cant BR. Age-dependent changes in the amplitude of the pattern visual evoked potential. *Electroencephalogr Clin Neurophysiol*. 1981;51:671–673.
19. Synder EW, Dustman RE, Shearer PE. Pattern reversal evoked potential amplitude: life span changes. *Electroencephalogr Clin Neurophysiol*. 1981;52:429–434.
20. Sokol S, Moskowitz A, Towle VL. Age-related changes in the latency of the visual evoked potential: influence of check size. *Electroencephalogr Clin Neurophysiol.*1981;51:559–562.
21. Allison T, Hume AL, Wood CC, Goff WR. Developmental and aging changes in somatosensory, auditory and visual evoked potentials. *Electroencephalogr Clin Neurophysiol*. 1984;58:14–24.
22. Pitt MC, Daldry SJ. The use of weighted quadratic regression for the study of latencies of the P100 component of the visual evoked potential. *Electroencephalogr Clin Neurophysiol*. 1988;71:150–152.
23. Bobak P, Bodis–Wollner I, Guillory S, Anderson R. Aging differentially delays visual evoked potentials to checks and gratings. *Clin Vision Sci*. 1989;4:269–274.
24. Tobimatsu S. Aging and pattern visual evoked potentials. *Optom Vis Sci*. 1995;72:192–197.
25. Wright CE, Williams DE, Drasdo N, Harding GFA. The influence of age on the electroretinogram and visual evoked potential. *Doc Ophthalmol*. 1985;59:365–384.
26. Tobimatsu S, Kurita–Tashima S, Nakayama–Hiromatsu M, Akazawa K, Kato M. Age-related changes in pattern visual evoked potentials: differential effects of luminance, contrast and check size. *Electroencephalogr Clin Neurophysiol*. 1993;88:12–19.
27. Celesia GG, Kaufman D, Cone S. Effects of age and sex on pattern electroretinograms and visual evoked potentials. *Electroencephalogr Clin Neurophysiol*. 1987;68:161–171.
28. Morrison JD, Reilly J. The pattern visual evoked cortical response in human ageing. *Q J Exp Physiol*. 1989;74:311–328.
29. Tomoda H, Celesia GG, Cone Toleikis SC. Effects of spatial frequency on simultaneous recorded steady-state pattern electroretinograms and visual evoked potentials. *Electroencephalogr Clin Neurophysiol*. 1991;80:81–88.
30. Tomoda H, Celesia GG, Brigell MG, Toleikis S. The effects of age on steady-state pattern electroretinograms and visual evoked potentials. *Doc Ophthalmol*. 1991;77:201–211.
31. Levi DM, Manny RE, Klein SA, Steinman SB. Electrophysiological correlates of hyperacuity in the human visual cortex. *Nature*. 1983;306:468–473.
32. Wilson HR. Responses of spatial mechanisms can explain hyperacuity. *Vision Res*. 1986;26:453–469.
33. Levi DM, Klein SA. Vernier acuity, crowding and amblyopia. *Vision Res*. 1985;25:979–991.
34. Klein SA, Levi DM. Hyperacuity thresholds of 1 sec: theoretical predictions and empirical validation. *J Opt Soc Am A*. 1985;2:1170–1190.
35. Levi DM, Klein S. Differences in vernier discrimination for gratings between strabismic and anisometropic amblyopes. *Invest Ophthalmol Vis Sci*. 1982;23:398–407.
36. Levi DM, Klein SA. Hyperacuity and amblyopia. *Nature*. 1982;298:268–270.
37. Wilson HR. Model of peripheral and amblyopic hyperacuity. *Vision Res*. 1991;31:967–982.
38. Murphy KM, Mitchell DE. Vernier acuity of normal and visually deprived cats. *Vision Res*. 1991;31:253–266.
39. Berkley MA, Sprague JM. Striate cortex and visual acuity functions in the cat. *J Comp Neurol*. 1979;187:679–702.
40. Steinman SB, Levi DM, Klein SA, Manny RE. Selectivity of the evoked potential for vernier offset. *Vision Res*. 1985;25:951–961.

41. Zak R, Berkley MA. Evoked potentials elicited by brief vernier offsets: estimating vernier thresholds and properties of the neural substrate. *Vision Res*. 1986;26:439–451.
42. Norcia AM, Wesemann W, Manny RE. Electrophysiological correlates of vernier and relative motion mechanisms in human visual cortex. *Vis Neurosci*. 1999;16:1123–1131.
43. Srebro R, Osetinsky MV. The localization of cortical activity evoked by vernier offset. *Vision Res*. 1987;27:1387–1390.
44. Steinman SB, Levi DM. Topography of the evoked potential to spatial localization cues. *Vis Neurosci*. 1992;8:281–294.
45. Manny RE. The visually evoked potential in response to vernier offsets in infants. *Hum Neurobiol*. 1988;6:273–279.
46. Skoczenski AM, Norcia AM. Development of VEP vernier acuity and grating acuity in human infants. *Invest Ophthalmol Vis Sci*. 1999;40:2411–2417.
47. Oliveira PGD, Queiroz C, Silva FLD. Spike detection based on a pattern recognition approach using a microcomputer. *Electroencephalogr Clin Neurophysiol*. 1983;56:97–103.
48. Kornzweig AL. Physiological effects of age on the visual process. *Sight Sav Rev*. 1954;24:130–138.
49. Weale RA. Retinal illumination and age. *Trans Soc Ill Eng*. 1961; 26:95–100.
50. Boettner EA, Wolter JR. Transmission of the ocular media. *Invest Ophthalmol*. 1962;1:776–780.
51. Lerman S. An experimental and clinical evaluation of lens transparency and aging. *J Gerontol*. 1983;38:293–301.
52. Halliday AM, McDonald WI, Mushin J. Delayed pattern evoked responses in optic neuritis in relation to visual acuity. *Trans Ophthalmol Soc UK*. 1973;93:315–324.
53. Tobimatsu S, Celesia GG, Cone SB. Effects of pupil diameter and luminance changes on pattern electroretinograms and visual evoked potentials. *Clin Vision Sci*. 1988;2:293–302.
54. Hawkes CH, Stow B. Pupil size and the pattern evoked visual response. *J Neurol Neurosurg Psychiatry*. 1981;44:90–91.
55. Berkley MA. Integration regions for vernier acuity in the cat: comparative aspects of cortical scaling. *Vis Neurosci*. 1989;2:473–482.
56. Zemon V, Hartmann EE, Gordon J, Prunte-Glowazki A. An electrophysiological technique for assessment of the development of spatial vision. *Optom Vis Sci*. 1997;74:708–716.
57. Weale RA. Senile changes in visual acuity. *Trans Ophthalmol Soc UK*. 1975;95:36–38.
58. Weale RA. *A Biography of the Eye*. London: HK Lewis; 1982.
59. Marshall J. The ageing retina: physiology or pathology. *Eye*. 1987; 1:282–295.
60. Weleber RC. The effect of age on human cone and rod ganzfeld electroretinograms. *Invest Ophthalmol Vis Sci*. 1981;20:392–399.
61. Bagolini B, Porciatti V, Falsini B, Scalia G, Neroni M, Moretti G. Macular electroretinogram as a function of age of subjects. *Doc Ophthalmol*. 1988;70:37–43.
62. Brody H. Organization of cerebral cortex, III: a study of aging in the human cerebral cortex. *J Comp Neurol*. 1955;102:511–566.
63. Devaney KO, Johnson HA. Neuron loss in the aging visual cortex of man. *J Gerontol*. 1980;35:836–841.
64. Sung JH. Neuroaxonal dystrophy in mucoviscidosis. *J Neuropathol Exp Neurol*. 1958;23:567–583.
65. Scheibel ME, Lindsay RD, Tomisayu U, Scheibel AB. Progressive dendritic changes in aging human cortex. *Exp Neurol*. 1975;47: 392–403.
66. Downie AW, Newell DJ. Sensory nerve conduction in patients with diabetes mellitus and controls. *Neurology*. 1961;11:876–882.
67. Dorfman LJ, Bosley TM. Age-related changes in peripheral and central nerve conduction in man. *Neurology*. 1979;29:38–44.
68. Wisniewski HM, Terry RD. Neuropathology of the aging brain. In: Terry RD, Gershon S, eds. *Neurobiology of Aging*. Vol. 3. New York: Raven Press; 1976:717–724.
69. Dolman CL, McCormick AQ, Drance SM. Aging of the optic nerve. *Arch Ophthalmol*. 1980;98:2053–2058.
70. Balazsi AG, Rootman J, Drance SM, Schulzer M, Douglas GR. The effect of age on the nerve fiber population of the human optic nerve. *Am J Ophthalmol*. 1984;97:760–766.
71. Repka MX, Quigley HA. The effect of age on normal human optic nerve fiber number and diameter. *Ophthalmology*. 1989;96:26–32.
72. Samorajski T. Central neurotransmitter substances and aging: a review. *J Am Geriatr Soc*. 1977;25:337–348.
73. Wayner MJ, Emmers R. Spinal synaptic delay in young and aged rats. *Am J Physiol*. 1958;194:403–405.
74. Essock EA, Williams RA, Enoch JM, Raphael S. The effect of image degradation by cataract on vernier acuity. *Invest Ophthalmol Vis Sci*. 1984;25:1043–1050.
75. Enoch JM, Williams RA, Essock EA, Fendick M. Hyperacuity: a promising means of evaluating vision through cataract. *Prog Retinal Res*. 1985;4:67–88.
76. Enoch JM, Baraldi P, Lakshminarayanan V, Savage GL, Fendick M. Measurement of metamorphopsia in the presence of ocular media opacities. *Am J Optom Physiol Opt*. 1988;65:349–353.
77. Lakshminarayanan V, Aziz S, Enoch JM. Quantification of metamorphopsia using hyperacuity techniques. *Optom Vis Sci*. 1991;68: 942–945.
78. Alexander KR, Derlacki DJ, Fishman GA, Szlyk JP. Grating, vernier, and letter acuity in retinitis pigmentosa. *Invest Ophthalmol Vis Sci*. 1992;33:3400–3406.
79. Enoch JM. Hyperacuity, a technique for assessment of results of refractive surgery. *Contact Lens Assoc Ophthalmol J*. 1992;18:64–71.
80. Singh S, Aravind S, Hirose H, Enoch JM, Azen SP. Hyperacuity test to evaluate vision through dense cataracts; research preliminary to a clinical study, IV: data on patients with macular degeneration and minimal media disorders obtained with and without a pseudonuclear cataract 6/60 (20/200) at the Aravind Eye Hospital, Madurai, India. *Optom Vis Sci*. 1996;73:125–126.