Auditory Brainstem Anomalies in Human Albinos

Abstract. *Brainstem auditory evoked potentials recorded from human albinos indicate significant hemispheric asymmetry. The asymmetry is symptomatic of differences between decussated and nondecussated auditory pathways in albino and pigmented humans at approximately the level of the superior olivary nuclei. Abnormal decussation of auditory pathways in albinos probably coincides with known visual system anomalies.*

Abnormalities in the routing of retinal fibers from the eye to the brain in albino humans and animals have been described (*1*). An abnormal proportion of retinal ganglion fibers decussating at the optic chiasm results in an inadequate substrate for binocular vision. The disorganization of visual pathways is correlated with reduced retinal pigmentation; it occurs in mammals, including humans, with various mutations that cause ocular and oculocutaneous forms of albinism (*2*, *3*).

Melanin present in the inner ear of pigmented humans and animals (*4*) is positively correlated with the general pigmentation of the body (*4*) and specifically with the amount of pigmentation of the eye (*5*). Pigment is absent from the inner ear of albino humans and animals. We have found electrophysiological evidence of a significant difference in decussation of brainstem auditory pathways in human albinos and pigmented humans.

In studies of scalp-recorded visually evoked potentials in human subjects, in which hemispheric asymmetries were compared after monocular stimulation, misrouting of visual fibers in albinos was reflected by visually evoked potentials recorded in each hemisphere (*3*). Scalp-recorded auditory evoked potentials, particularly the brainstem auditory evoked potential (BAEP), provide a similar method for studying the functional anatomy of the auditory pathways. The BAEP is composed of far-field potentials generated in the brainstem and recorded from scalp electrodes (*6*). Although the precise neural generators of components of the BAEP are unknown, there is general agreement on the neural generators of vertex-positive components I to V (*7*, *8*). By analogy with the model of the albino visual system (*3*), significant alteration in decussation of auditory pathways should be reflected in the pattern, amplitude, and latency of components of the BAEP in each hemisphere after monaural stimulation.

The recording system in this study was a Nicolet CA-1000. We used click intensities of 40, 50, 60, and 70 dB sound level above each individual's auditory threshold. Stimuli were 100-μsec condensation clicks presented at a rate of 11.3 per second to avoid an integral factor of 60 Hz. Each ear was stimulated monaurally. Potentials evoked by 2000 clicks were averaged. The period of analysis was 10 msec from the onset of each click. The bandpass setting was 150 to 3000 Hz with a fixed gain of 10^4. We used electrode positions C3 and C4, referred to the ipsilateral tips of the left and right mastoid process, respectively. The common ground electrode was placed on the midline anterior to Cz. Subjects were tested in a quiet, electrically shielded, but not soundproof, room; clicks were presented through cushioned earphones (TDH-39).

All participants had normal audiograms. They were selected for the same pattern of BAEP with five distinct components (I to V) recorded in each hemisphere regardless of ear stimulated so direct comparisons could be made between hemispheres and between individuals. The control group was composed of ten females and ten males between 20 and 35 years old and having brown eyes and brown hair. The albino group was composed of 18 oculocutaneous albinos between 20 and 35; 11 were female and 7 were male. The uneven sex ratio was unavoidable in the albino group without reducing the number. Separate statistical analyses compared each sex to ensure that the unequal sex ratios were not biasing the analysis. Statistical analyses were *t*-tests for dependent scores in which individuals were their own controls. The slightly faster peak latencies of some components of BAEP's in females as a group did not significantly bias the result. Statistical analyses and Table 1 are based on BAEP's evoked by 70-dB clicks. The potentials evoked by the ear with the lower threshold were used for statistical analysis.

Auditory fibers first synapse in the cochlear nuclei and subsequently decussate at several sites in the brainstem. The decussated and nondecussated auditory fibers are first differentiated at the level of the brainstem that includes the trapezoid body, the superior olivary complex, and the beginning of the ascending lateral lemniscus (*9*). The superior olivary complex is a neural generator contributing to component III of the BAEP, and the lateral lemniscus one contributing to component IV (*7*, *8*).

In pigmented individuals, the hemi-

Table 1. Latencies and amplitudes of BAEP's to monaural 70-dB clicks in albino and pigmented humans. Within groups, the hemisphere that responded significantly faster or with higher amplitude is indicated in boldface type.

Component	Pigmented (N = 20)			Albino (N = 18)		
	Ipsilateral	Contralateral	P	Ipsilateral	Contralateral	P
			Latency (msec)			
I	**P1.65** ± 0.14	P1.68 ± 0.17	< .01	**P1.61** ± 0.11	P1.64 ± 0.12	< .01
II	**P2.82** ± 0.14	P2.88 ± 0.17	< .01	**P2.75** ± 0.11	P2.83 ± 0.12	< .001
III*	P3.74 ± 0.17	P3.73 ± 0.21	.57	P3.73 ± 0.11	**P3.69** ± 0.11	< .01
IV	P4.94 ± 0.29	**P4.90** ± 0.27	.05	P4.95 ± 0.18	**P4.88** ± 0.18	< .001
V	**P5.70** ± 0.18	P5.75 ± 0.17	< .01	**P5.65** ± 0.29	P5.71 ± 0.23	< .01
VI	P7.25 ± 0.23	P7.29 ± 0.25	.35	P7.26 ± 0.27	P7.27 ± 0.30	.84
			Interpeak latency (msec)			
I-II	**1.16** ± 0.13	1.20 ± 0.15	< .01	**1.14** ± 0.10	1.23 ± 0.11	< .001
I-III*	2.08 ± 0.14	2.07 ± 0.16	.49	2.11 ± 0.09	**2.03** ± 0.08	< .03
I-IV	3.30 ± 0.25	**3.27** ± 0.24	< .04	3.34 ± 0.16	**3.27** ± 0.16	< .001
I-V	**4.04** ± 0.16	4.09 ± 0.15	< .01	**4.05** ± 0.19	4.09 ± 0.17	< .01
III-IV*	1.23 ± 0.16	1.20 ± 0.17	< .16	1.23 ± 0.12	**1.19** ± 0.12	< .03
III-V	**1.96** ± 0.13	2.01 ± 0.15	< .02	**1.94** ± 0.19	2.00 ± 0.15	< .01
IV-V	**0.76** ± 0.24	0.85 ± 0.21	< .001	**0.71** ± 0.21	0.82 ± 0.18	< .001
			Amplitude (μV)			
I-IIa	**0.18** ± 0.10	0.11 ± 0.05	< .001	**0.20** ± 0.06	0.10 ± 0.03	< .001
IIa-II	**0.20** ± 0.11	0.17 ± 0.07	< .02	0.18 ± 0.09	0.16 ± 0.08	< .07
II-IIIa*	0.13 ± 0.08	0.11 ± 0.06	.30	**0.14** ± 0.06	0.10 ± 0.06	< .002
IIIa-III	**0.19** ± 0.08	0.10 ± 0.06	< .001	**0.21** ± 0.07	0.08 ± 0.04	< .001
III-IVa	**0.21** ± 0.07	0.12 ± 0.05	< .001	**0.22** ± 0.09	0.15 ± 0.05	< .001
IVa-IV*	0.22 ± 0.09	0.20 ± 0.08	< .12	**0.24** ± 0.12	0.20 ± 0.11	< .01
IV-Va	0.11 ± 0.07	0.12 ± 0.07	.55	0.10 ± 0.09	0.10 ± 0.08	.87
Va-V	0.06 ± 0.05	**0.09** ± 0.07	< .001	0.06 ± 0.05	**0.10** ± 0.07	< .001
V-VIa	0.24 ± 0.07	0.24 ± 0.08	.58	0.27 ± 0.11	0.27 ± 0.12	.70

*Components significantly differing between pigmented and albino subjects (*t*-tests, α = .05).

0036-8075/80/0912-1253$00.50/0

spheres did not differ statistically in amplitude of components IIIa or IV or latency of component III (Table 1). In albinos, however, there was asymmetry in (i) amplitude of both components IIIa [$t(17) = 3.67$, $P < .002$] and IV [$t(17) = 2.74$, $P < .01$], (ii) peak latency of component III [$t(17) = 2.5$, $P < .01$], and (iii) interpeak latencies (*10*) of I to III and III to IV [t's$(17) = 2.4$, $P < .03$].

We use the criterion of greater than 50 percent attenuation as a significant alteration of a component of either an auditory or a visual evoked potential. There was more than 50 percent attenuation of component III in the contralateral BAEP of 13 of 18 albinos whereas only 7 of 20 pigmented individuals showed similar attenuation of the contralateral component III (Fig. 1) [$\chi^2(1) = 5.28$, $P = .03$].

The attenuation of components IIIa to IV of contralateral BAEP's in albinos must be examined as a group phenomenon requiring analysis of larger numbers of subjects. On an individual basis, seven of the pigmented subjects appear to have alteration of the hemispheric distribution of brainstem auditory pathways. Among the albinos five did not have obvious asymmetries. Variation such as this has been reported in anatomical studies of the visual system. An occasional pigmented animal will have lateral geniculate nuclei resembling an albino, and some albinos have normal lateral geniculate nuclei (*11*). The decussation of auditory and visual pathways probably varies considerably between individuals as it does in the pyramidal tracts.

Component III was associated with the most dramatic differences between BAEP's of albino and pigmented humans. Analysis of component III requires the dissection and individual assessment of the principal lateralized superior olivary nuclei: the medial superior olive (MSO) and the lateral superior olive (LSO). The relative size of these nuclei reflects the predominant mode of binaural analysis for a species (*9*, *12*). Humans, apes, and diurnal monkeys are characterized by a large MSO and a small LSO (*9*). Most studies of the neural genesis of components of the BAEP have identified the MSO as the most probable primary generator of component III (*13*, *14*).

If such is the case, our data indicate a significant difference between the decussated and nondecussated innervation of the MSO in albino and pigmented humans. In pigmented humans, ipsilateral and contralateral primary generators of component III seem to be nearly equally innervated. In albino humans, innervation seems to be significantly lateralized. If we accept the premise that the MSO is the primary generator of component III, there is a logical connection with visual anomalies.

The key to the interrelationship of visual and auditory anomalies of decussation lies in the finding in many species of a strong correlation between the size of the MSO and the size of the nucleus of the abducens nerve that innervates the lateral rectus muscle of the eye (*9*, *15*, *16*). Irving and Harrison regarded the MSO "as a visual auditory system, having evolved as an adjunct to vision" (*16*, p. 85). They observed that the slope of the regression line relating the size of the MSO to the size of the abducens nucleus varied markedly between animals with predominantly rod or cone foveae. Instead of differentiating on the basis of rod or cone foveae, we suggest that there are differences in the sizes of the MSO and the abducens nucleus between mammals with panoramic vision and less-developed temporal retinae versus those with well-developed binocular vision, temporal retinae, and lateral rectus muscles of the eye.

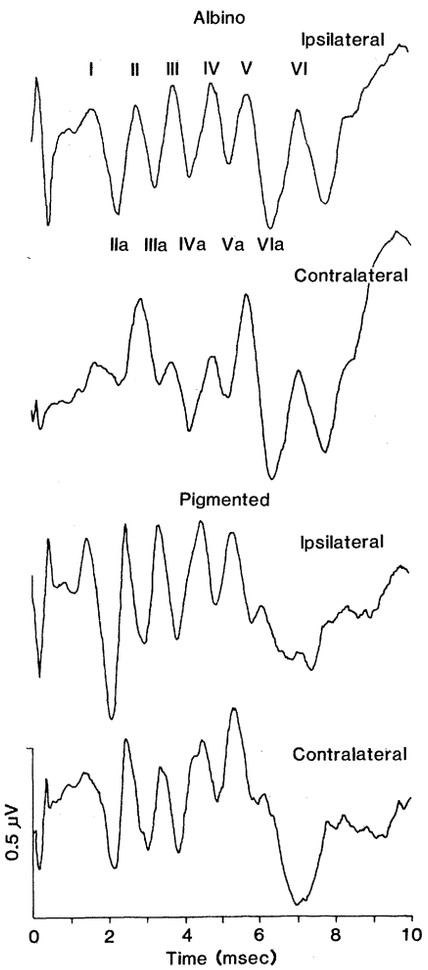

Fig. 1. Representative BAEP recorded from a male albino and a female pigmented human. BAEP's recorded from the hemisphere ipsilateral and contralateral to the stimulated ear may be compared. Electrode-positive locations were C3 and C4 with reference to the ipsilateral mastoid. Ground was anterior to Cz. Click intensity was 70 dB. Positive is up.

Mammals with well-developed binocular vision and temporal retinae have a significant proportion of nondecussated visual fibers and good motor control of the eye by the lateral rectus muscle. Albino mutants of these mammals have poor binocular vision and poor motor control of the eye, because the misrouting of nondecussated visual fibers disrupts innervation of the visual cortex and of the midbrain nuclei affecting eye movement (*1*, *3*). We suggest that the development of the abducens nucleus may be anomalous in albino mammals.

A correlative functional development of the MSO and the development of the abducens nucleus has been proposed (*9*, *15*, *16*). As an extension, we propose that the functional development of temporal retinae, binocular vision, abducens nuclei, and MSO are correlated, along with the appropriate distribution of decussated and nondecussated visual fibers and brainstem auditory pathways. Conversely, we hypothesize that a significant anomaly of decussation in visual projections, which affects binocular vision, may also coincide with anomalous decussation of brainstem auditory pathways innervating the superior olivary nuclei subserving auditory localization.

DONNELL CREEL*

Veterans Administration Medical Center, 151A, Salt Lake City, Utah 84148, and *Departments of Psychology* and *Ophthalmology, University of Utah, Salt Lake City 84112*

SHARON R. GARBER
RICHARD A. KING
CARL J. WITKOP, JR.

Department of Oral Pathology and Genetics, School of Dentistry, University of Minnesota, Minneapolis 55455

References and Notes

1. D. Creel, *Nature (London)* **231**, 465 (1971); R. W. Guillery *Sci. Am.* **230**, 44 (May 1974); _____ and J. H. Kaas, *J. Comp. Neurol.* **143**, 73 (1971); R. W. Guillery, A. N. Okoro, C. J. Witkop, Jr., *Brain Res.* **96**, 373 (1975); D. H. Hubel and T. N. Wiesel, *J. Physiol. (London)* **218**, 33 (1971); R. E. Kalil, S. R. Jhaveri, W. Richards, *Science* **174**, 302 (1971); R. D. Lund, *ibid.* **149**, 1506 (1965).
2. D. Creel and R. A. Giolli, *J. Comp. Neurol.* **166**, 445 (1976); R. W. Guillery, M. D. Oberdorfer, E. H. Murphy, *ibid.* **185**, 623 (1979); J. H. LaVail, R. A. Nixon, R. L. Sidman, *ibid.* **182**, 399 (1978).
3. J. Coleman, C. F. Sydnor, M. L. Wolbarsht, M. Bessler, *Exp. Neurol.* **65**, 667 (1979); D. Creel, F. E. O'Donnell, Jr., C. J. Witkop, Jr., *Science* **201**, 931 (1978); D. Creel, C. J. Witkop, Jr., R. A. King, *Invest. Ophthalmol.* **13**, 430 (1974).
4. A. Corti, *Z. Wiss. Zool.* **3**, 109 (1851); W. Kolmer, in *Haut- und Sinnesorgane, Handbuch der Mikroskopischen Anatomie des Menschen*, W. Möllendorff, Ed. (Springer, Berlin, 1936), vol. 3; K. LaFerriere, I. Arenberg, H. Hawkins, L.

Johnson, *Ann. Otol.* **83**, 685 (1974); D. Wolff, *Arch. Otolaryngol.* **14**, 195 (1931).
5. P. Bonaccorsi, *Ann. Laringol. Otol. Rinol. Faringol.* **64**, 725 (1965).
6. D. L. Jewett, M. N. Romano, J. S. Williston, *Science* **167**, 1517 (1970); D. L. Jewett and J. S. Williston, *Brain* **94**, 681(1971).
7. J. J. Stockard and V. S. Rossiter, *Neurology* **27**, 316 (1977); J. J. Stockard, J. E. Stockard, F. W. Sharbrough, *Am. J. EEG Technol.* **18**, 177 (1978); J. E. Stockard, J. J. Stockard, B. F. Westmoreland, J. L. Corfits, *Arch. Neurol.* **36**, 823 (1979).
8. A. R. Allen and A. Starr, *Electroencephalogr. Clin. Neurophysiol.* **45**, 53 (1978); A. Starr and A. E. Hamilton, *ibid.* **41**, 595 (1976).
9. J. M. Harrison and M. E. Howe, in *Handbook of Sensory Physiology*, vol. 5, *Auditory System. Anatomy, Physiology (Ear)*, W. Keidel and W. Neff, Eds. (Springer-Verlag, New York, 1974), pp. 284–336.
10. For measurement of interpeak latencies, the ipsilateral component I was used in both groups because several individuals in both groups did not have a discernible contralateral component I.
11. D. Creel and R. A. Giolli, *J. Comp. Neurol.* **166**, 445 (1976); R. A. Giolli and D. Creel, *Brain Res.* **55**, 25 (1973).
12. R. B. Masterson, *Fed. Proc. Fed. Am. Soc. Exp. Biol.* **33**, 1904 (1974).
13. J. S. Buchwald and C.-M. Huang, *Science* **189**, 382 (1975).
14. J. L. Martin and A. C. Coates, *Brain Res.* **60**, 496 (1973).
15. J. M. Harrison, *Fed. Proc. Fed. Am. Soc. Exp. Biol.* **33**, 1901 (1974); _____ and R. Irving, *Science* **154**, 738 (1966).
16. R. Irving and J. M. Harrison, *J. Comp. Neurol.* **130**, 77 (1967).
17. This work was supported by the Medical Research Service of the Veterans Administration, by grants GM-22167 and GM-24558 from the Public Health Service, and by grant RR-400 from the General Clinical Research Centers. We thank T. N. Parks and J. F. Peters for their suggestions.
* Send reprint requests to D.C. at Veterans Administration Medical Center, Salt Lake City, Utah 84148.

10 June 1980

Human Aging and Spatial Vision

Abstract. *The ability to see spatial structures of a wide range of sizes was measured for two groups of observers (mean ages, 18 and 73 years). All observers had good visual acuity. Although older and younger observers did not differ in ability to see targets with fine structure (high spatial frequencies), older observers were only one-third as sensitive to targets with coarse structure (low spatial frequencies) as were younger observers. This difference cannot be attributed to ocular pathology in the older observers or to changes in criterion. Older observers were also less able than younger observers to see moving targets. The reduced sensitivity of the older observers may adversely affect routine perceptual activities, such as face recognition and visually guided postural behavior, that depend upon low spatial frequencies.*

Eye charts quantify visual acuity in terms of the smallest letter that can be seen, but some visual disorders cannot be detected by testing visual acuity (*1*). A comprehensive assessment of spatial vision requires measuring sensitivity to targets over a wide range of sizes (*2*). Since processes associated with aging could selectively affect visual mechanisms that process targets in a particular size range, we compared the vision of two groups differing by more than 50 years in average age. Our older observers displayed a previously unsuspected visual handicap: diminished ability to see large and intermediate-size targets.

The younger observers were 25 undergraduate volunteers (mean age ± standard deviation = 18.5 ± 0.7 years); older observers were ten healthy, active volunteers from a senior citizens' recreation program (73.2 ± 3.8 years). All observers wore a distance correction prescribed within the previous 12 months. Ophthalmological examinations revealed that nine of the older observers were free of ocular pathology that might affect performance in our measurements; the remaining observer, a 74-year-old man, suffered from senile macular degeneration. We measured conventional visual acuity with an Orthorater (Bausch & Lomb); subsequent tests were made with the eye having better acuity. The corrected visual acuity of the younger observers averaged 0.99 (Snellen equivalent, 20/20). Excluding the maculopathic observer, the corrected acuity of the older observers averaged 0.83 (20/24). With his better eye, our maculopathic observer's acuity was 0.4 (20/50).

Stimuli were vertical gratings whose contrast varied as a sinusoidal function of distance along the horizontal axis of a cathode-ray tube. The contrast (*3*) and spatial frequency (cycles per degree) of the gratings were controlled by a small computer. At the viewing distance of 114 cm, the gratings subtended 4.5 by 5.5 deg. Gratings had a mean luminance of 55 cd/m^2 and were surrounded by a large region of the same luminance. With the head steadied by a chin rest and forehead support, each observer fixated a small black dot in the center of the screen.

Contrast thresholds were measured by a method of adjustment for each of several different spatial frequencies: 0.5, 1, 2, 4, 8, and 16 cycle/deg. Gratings flickered in counterphase at either 0.3 or 6 Hz. Threshold for each spatial frequency was defined as the mean of the contrasts at which gratings changed from visible to invisible and vice versa (*4*). Sensitivity was defined as the reciprocal of this threshold value.

For each rate of flicker, the effects of spatial frequency and age were significant, as was the interaction between these two variables (all $P < .01$) (Fig. 1). The difference between the two age groups varied with spatial frequency, with older observers showing diminished sensitivity to low and intermediate spatial frequencies. At the lowest spatial frequencies, the older observers needed three times as much contrast to see the gratings as did the younger observers.

Although the older, maculopathic ob-

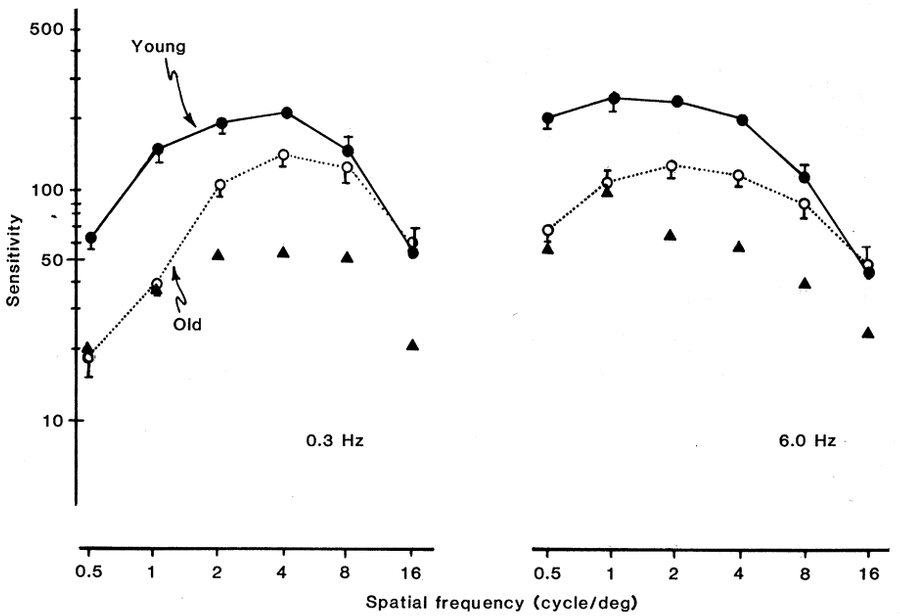

Fig. 1. Contrast sensitivity functions (± standard errors of the mean) of young and old observers for 0.3-Hz flicker and 6.0-Hz flicker. The triangles are for the older, maculopathic observer.

0036-8075/80/0912-1255$00.50/0