Effects of Aging on Middle-Latency Auditory Evoked Potentials: A Cross-Sectional Study

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Background: *The results of previous studies comparing the middle-latency auditory evoked potentials (MAEPs) of young and elderly subjects have suggested that thalamic inhibitory deficits underlie age-related increases in MAEP amplitudes.*

Methods: *MAEPs were recorded from 73 healthy subjects aged between 20 and 86 years. The latencies of MAEPs recorded at Fz were subjected to two-way analyses of variance for the effects of age group and sex. Amplitude data were subjected to analyses of covariance with age group and sex as between-subjects factors, electrode position as within-subject factor, and individual perceptual thresholds as covariates. Variables exhibiting significant effects of age group were further investigated by regression analysis.*

Results: *Age correlated positively with Na, Na-Pa, and Nb-Pb amplitudes. The distribution of Na-Pa amplitude over the scalp varied with age.*

Conclusions: *The observed age-related increases in amplitude are believed to reflect diminished capacity of subcortical and related cortical systems to inhibit the response to repetitive auditory stimuli that require no attentional effort. Possible age-related changes in the cortical distribution of MAEPs are also discussed.* Biol Psychiatry 1998;43:210–219 © *1998 Society of Biological Psychiatry*

Key Words: Aging, middle-latency auditory evoked potentials, auditory processing, central inhibitory mechanisms

Introduction

Dustman and coworkers have reported that the amplitudes of flash-evoked potential waves with latencies shorter than 100 msec are significantly larger in subjects older than 50 years than in younger subjects (Dustman and Beck 1966, 1969; Dustman and Snyder 1981). Partly on this basis, and in keeping with a suggestion by Straumanis et al (1965), they hypothesized that central inhibitory capacity changes with age and is lowest among infants and the elderly (Dustman and Shearer 1987; see also Hasher et al 1991; Prinz et al 1990).

A general aging-induced decline in central inhibition of the neural centers responsible for middle-latency event-related potential waves would affect waves evoked by auditory as well as visual stimuli (Dustman et al 1993), and hence account for reports that the amplitudes of middle-latency auditory evoked potentials (MAEPs) are also greater in elderly than in young subjects (Kelly-Ballweber and Dobie 1984; Woods and Clayworth 1986). Although general agreement on the neural origins of MAEPs has not yet been reached, this hypothesis is in keeping with the most mutually consistent findings of studies of animals and human beings (see Discussion), including results on inhibition in subcortical structures and in feedback paths between subcortical and cortical structures (Kelly 1991).

The effect of aging on all evoked and event-related potentials except MAEPs has been investigated in cross-sectional experiments, which allow rapid acquisition of valid information on aging so long as care is taken to ensure that all age groups are similar as regards health status and years of education, and that the age range of interest is sampled sufficiently homogeneously and intensely (Botwinick 1981; John et al 1987; Salthouse 1991). The MAEP studies cited above (Kelly-Ballweber and Dobie 1984; Woods and Clayworth 1986) both compared two subject groups with widely different ages (elderly and young subjects). For a more precise determination of the effects of aging on MAEPs, in this work we carried out a cross-sectional study of the latencies and amplitudes of MAEPs recorded from 73 healthy subjects ranging in age from 20 to 86 years.

Methods and Materials

Subjects

One hundred and six volunteers were recruited from retirement homes, clubs for retired persons living on their own, cultural

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Table 1. Descriptive Statistics of Each Age Group (Means with Standard Deviations in Parentheses)

Group	Sex	*n*	Age (years)	Education (years)	Perceptual thresholds to clicks[a]		MEC (MMS) scores
					Right	Left	
1 (20–29 years)	Female	5	26.0 (3.8)	10.0 (4.8)	47.7	44.0	34.4 (0.5)
	Male	5	25.2 (1.4)	9.7 (4.8)	(2.9)	(4.1)	33.8 (2.1)
2 (30–39 years)	Female	5	36.6 (3.5)	8.2 (4.0)	52.6	49.8	33.8 (1.6)
	Male	5	35.6 (3.5)	10.3 (4.6)	(5.1)	(5.5)	32.4 (2.0)
3 (40–49 years)	Female	5	43.8 (3.0)	7.0 (1.8)	54.9	55.0	32.6 (1.8)
	Male	5	44.4 (3.2)	10.3 (4.6)	(3.4)	(6.1)	33.0 (1.5)
4 (50–59 years)	Female	5	56.2 (3.4)	7.2 (3.2)	53.7	50.8	32.4 (1.6)
	Male	5	56.0 (2.4)	11.7 (6.1)	(4.0)	(5.6)	33.4 (1.3)
5 (60–69 years)	Female	8	64.1 (1.6)	9.6 (4.4)	57.0	56.3	31.8 (1.4)
	Male	6	66.5 (2.5)	9.3 (5.0)	(5.6)	(5.7)	31.6 (2.3)
6 (70–86 years)	Female	11	75.8 (2.8)	8.5 (4.8)	63.2	63.0	31.2 (1.9)
	Male	8	76.8 (4.2)	8.3 (4.0)	(6.3)	(6.3)	31.1 (1.9)

[a]Decibels sound pressure level, male and female subjects.

centers, faculties of the University of Santiago de Compostela, and employment agencies. From this initial sample, 27 subjects were excluded because they had cardiovascular diseases and/or hypertension (9), cataracts and/or glaucoma (4), pulmonary problems (3), audiological problems (7), or MEC scores lower than 28 (4) [MEC = Mini Examen Cognoscitivo (Lobo et al 1979), the Spanish version of the Mini Mental State Examination (Folstein et al 1975)]; 3 were excluded because of cranioencephalic traumatism in childhood; 2 because of alcohol abuse; and 1 because he was currently taking antidepressive drugs. The final sample was composed of 73 healthy subjects (39 female, 34 male), whose distribution in six age groups is shown in Table 1. All subjects had subjective auditory thresholds that were normal for their age (see Stimuli and Table 1), and there was no statistically significant difference in auditory threshold between the sexes [$F(1,61) = 0.60$, $p \leq .44$], but there were differences among age groups [$F(5,61) = 19.81$, $p \leq .0001$], the group aged 70–86 years having higher thresholds than the others (Scheffé test, $p = .05$). There were no significant differences in number of years of formal education either among age groups [$F(5,61) = 1.33$, $p \leq .26$] or between sexes [$F(1,61) = 2.27$, $p \leq .13$]; see Table 1.

Stimuli

Rarefaction clicks of 0.1 msec duration were presented binaurally through earphones (Telephonics TDH-39-P) at a rate of 1.1/sec and an intensity of 60 dB sound level (60 dB above individual perceptual threshold; individual perceptual thresholds were estimated using the method of ascending and descending limits with increment and decrement intervals of 0.75 dB sound pressure level). A total of 800 clicks were presented to each subject, 400 in each of two consecutive runs.

Data Acquisition and Recording

Recordings were made with subjects comfortably seated in an armchair in a semidarkened room with constant illumination intensity. A butterfly pillow was placed at the back of the subject's neck to minimize the activity of neck muscles. Subjects were instructed to direct their gaze to a spot 2 cm in diameter located at 1.5 m in front of their eyes and to ignore the click stimuli.

Electroencephalogram (EEG) was recorded via an Electrocap (Electrocap International Inc.) with 20 active electrodes positioned according to the International 10/20 system (Fz, Cz, Pz, Oz, Fp1, Fp2, F3, F4, C3, C4, P3, P4, O1, O2, F7, F8, T3, T4, T5, and T6). The electrodes were referred to linked earlobes with Fpz as ground. In this paper we report data from Fz, Cz, and Pz. Vertical and horizontal electro-oculogram (EOG) activities were recorded bipolarly from above and below the left eye and from the outer canthi of both eyes. Stimulation, acquisition, amplification, filtering, EOG artifact correction, and averaging were performed using the Stim and Scan modules of a Neuro Scan system connected to a Grass Model 12 Neurodata Acquisition System. The continuous EEG signal was amplified (50 K), filtered (band-pass 1–300 Hz), and digitized at a 1500-Hz rate. For each electrode, an epoch consisting of 110 msec of signal was used (165 digitized points), of which the first 10 msec preceded the stimulus and was used as a baseline. For each subject, the 400 epochs in each of the two runs (see Stimuli) were averaged off-line, and because the two averages proved to be similar they were in turn averaged to yield MAEPs based on 800 epochs. Subsequent analyses of wave latencies and amplitudes were based on these 800-epoch MAEPs.

The peak latencies and amplitudes of the Na, Pa, Nb, and Pb waves were automatically measured from baseline using latency windows of 15–25, 25–40, 40–50, and 50–80 msec respectively. The peak-to-peak amplitudes Na-Pa, Pa-Nb, and Nb-Pb were also measured, as the differences between the maximum positive or maximum negative voltages in the appropriate latency windows. The Po wave varied greatly among subjects, and investigation of its dependence on age or sex was not pursued.

Design and Data Analysis

To determine the influence of age and sex on MAEP latencies, latency values at Fz were subjected to analyses of variance in

accordance with a 6 × 2 (age group × sex) design. MAEP amplitudes were subjected to analyses of variance (ANOVAs) with age group and sex as between-subjects factors and electrode position (Fz, Cz, or Pz) as the within-subject factor. Greenhouse–Geisser epsilon values and the corresponding corrections were calculated when appropriate.

Fast activity was observed between 0 and 12 msec in almost all the waveforms of subjects older than 60 years (Figure 1). Because stimulus intensities were adjusted with respect to the subjects' thresholds, the clicks that elderly subjects heard will have been both objectively and subjectively more intense than those presented to younger subjects. To check the possible effects of setting stimulus intensity with respect to individual sensation levels to compensate for the normal hearing loss associated with aging, all the analyses were repeated with individual perceptual thresholds included as covariates.

MAEP parameters exhibiting significant effects of age group after adjustment for perceptual threshold were further investigated by regression analysis using linear, quadratic, and cubic models for the effect of subject age on the dependent variable (a MAEP latency or amplitude) at each electrode (Fz, Cz, or Pz). The fit of each model was assessed by means of ANOVA F values.

All data analyses were performed using SPSS for Windows (SPSS Inc. 1993).

Results

Effects of Age Group and Sex on Latencies

MAEP latencies at Fz are presented in Table 2. Age group had no significant effect on the latencies of Na [$F(5,57) = 2.04, p \leq .08$], Pa [$F(5,58) = 1.96, p \leq .23$], Nb [$F(5,57) = 0.69, p \leq .62$], or Pb [$F(5,57) = 1.68, p \leq .15$], and analyses were likewise negative when perceptual threshold was included as covariate [Na, $F(5,56) = 1.51, p \leq .20$; Pa, $F(5,56) = 1.61, p \leq .17$; Nb, $F(5,56) = 0.59, p \leq .70$; Pb, $F(5,56) = 1.90, p \leq .10$].

Sex only had a significant effect on Pa latency [$F(1,57) = 5.8, p \leq .01$], which was longer in male than in female subjects.

Effects of Age Group and Sex on Amplitudes

Analyses of variance showed that age group had statistically significant effects on the peak amplitudes of Na [$F(5,61) = 10.66, p \leq .0001$], Pa [$F(5,61) = 3.9, p \leq .004$], and Pb [$F(5,52) = 3.17, p \leq .014$], and on the peak-to-peak amplitudes Na-Pa [$F(5,61) = 11.53, p \leq .0001$], Pa-Nb [$F(5,61) = 4.69, p \leq .001$], and Nb-Pb [$F(5,52) = 3.24, p \leq .013$]. In general, amplitudes tended to be larger in groups older than 50 years (see Table 3 and Figure 1). When individual perceptual threshold was included as covariate, the effect of age group was significant for the peak amplitudes of Na [$F(5,59) = 5.26, p \leq .0001$] and Pb [$F(5,50) = 2.98, p \leq .016$], and the peak-to-peak amplitudes Na-Pa [$F(5,59) = 4.46, p \leq .002$] and Nb-Pb [$F(5,50) = 3.1, p \leq .02$].

When perceptual threshold was included as covariate, no effect of age group on the Pa and Pa-Nb amplitudes

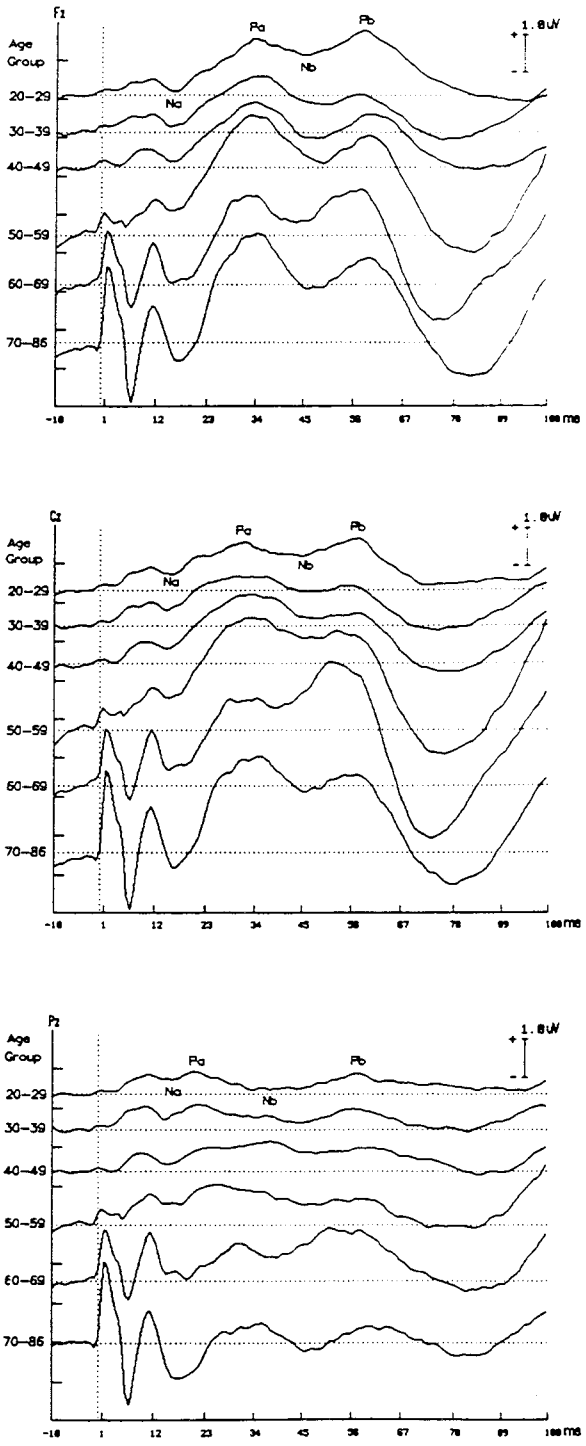

Figure 1. Grand average MAEP waveforms of each age group at Fz (top), Cz (middle), and Pz (bottom).

Table 2. Mean MAEP Latencies at Fz, in Milliseconds, in Each Age Group (Standard Deviations in Parentheses)

	Age group (years)					
Latency	20–29	30–39	40–49	50–59	60–69	70–86
Na	16.1 (1.6)	15.5 (1.0)	16.6 (2.8)	15.4 (1.5)	15.8 (2.1)	17.4 (2.0)
Pa	34.0 (4.0)	32.3 (5.1)	34.3 (2.9)	33.6 (5.5)	31.7 (2.7)	34.6 (4.5)
Nb	46.3 (2.3)	46.9 (4.5)	46.8 (7.2)	46.7 (4.5)	45.5 (7.0)	48.2 (3.9)
Pb	58.0 (1.1)	58.4 (2.8)	58.9 (3.1)	58.7 (2.6)	56.6 (6.3)	59.8 (3.1)

was detected. Following Woods and Clayworth (1986), as a further control, we excluded from the original sample the 11 subjects with the highest perceptual thresholds (all from the two oldest groups). Grand mean waveforms of the remaining 22 elderly subjects in these groups are presented in Figure 2. The effects of age group on the MAEP amplitudes of the new sample (62 subjects) were investigated by mixed model ANOVAs with age group and sex as between-subjects factors and electrode position as within-subject factor. The results agreed with those obtained from the analyses of covariance (ANCOVAs) of the data from the 73-member sample, showing effects of age group on the peak amplitudes of Na [$F(5,50) = 7.09$, $p \leq .0001$] and Pb [$F(5,43) = 2.45$, $p \leq .05$], and on the peak-to-peak amplitudes Na-Pa [$F(5,50) = 9.44$, $p \leq .0001$] and Nb-Pb [$F(5,43) = 2.47$, $p \leq .047$].

ANCOVA showed no statistically significant effects of sex on MAEP amplitudes, and no significant interactions between age group and sex.

Effects of Electrode Position

ANCOVA showed significant effects of electrode position on the peak amplitudes of Pa [$F(1.69,103.18) = 37.22$, $p \leq .0001$, $\epsilon = .84572$], Nb [$F(1.93,117.46) = 20.71$, $p \leq .0001$, $\epsilon = .96278$], and Pb [$F(1.88,97.56) = 25.01$, $p \leq .0001$, $\epsilon = .93769$], and significant interaction between age group and electrode for Na-Pa amplitude [$F(9.19,112.06) = 3.2$, $p \leq .002$, $\epsilon = .91856$]. Repeated-measures ANOVAs carried out for each peak separately with electrode as within-subject factor showed that Pa had maximum amplitudes at Fz and Cz [$F(1,72) = 66.61$, $p \leq .0001$], Nb at Pz [$F(1,72) = 52.58$, $p \leq .0001$], and Pb at Fz and Cz [$F(1,63) = 46.15$, $p \leq .0001$]; and similar analyses for Na-Pa amplitude carried out on each age group separately showed that Na-Pa amplitude was smaller at Pz than at the other electrodes in the 50–59-year-old group, largest at Cz in the oldest group, and largest at Fz in subjects aged < 50 years (Figure 3).

Table 3. Mean MAEP Amplitudes, in Microvolts, in Each Age Group (Standard Deviations in Parentheses)

		Age group (years)					
Electrode	Amplitude	20–29	30–39	40–49	50–59	60–69	70–86
Fz	Na	0.03 (0.2)	−0.007 (0.5)	−0.15 (0.6)	0.35 (0.8)	−0.21 (0.8)	−1.75 (1.9)
	Na-Pa	1.55 (0.7)	1.84 (1.0)	2.22 (1.1)	3.23 (1.9)	2.95 (1.1)	5.16 (2.4)
	Pa	1.56 (0.8)	1.82 (1.2)	2.04 (1.0)	3.59 (1.7)	2.73 (0.7)	3.35 (1.4)
	Pa-Nb	0.68 (0.5)	1.36 (1.0)	1.38 (0.8)	1.82 (1.1)	1.54 (1.0)	2.08 (1.4)
	Nb	0.94 (0.8)	0.27 (1.2)	0.67 (1.0)	1.48 (1.7)	1.18 (1.0)	1.28 (1.8)
	Nb-Pb	0.98 (0.6)	0.94 (0.5)	1.08 (0.7)	1.61 (1.2)	2.22 (1.9)	1.25 (1.0)
	Pb	1.91 (0.7)	1.12 (0.8)	1.75 (1.1)	3.09 (1.8)	3.32 (1.8)	2.48 (1.6)
Cz	Na	0.34 (0.3)	0.24 (0.6)	0.06 (0.6)	0.52 (0.9)	0.11 (0.6)	−1.65 (1.8)
	Na-Pa	1.10 (0.6)	1.47 (0.7)	2.05 (1.1)	3.04 (2.2)	2.62 (1.5)	6.37 (3.7)
	Pa	1.43 (0.8)	1.74 (0.8)	2.11 (1.1)	3.56 (2.1)	2.75 (1.4)	4.47 (3.3)
	Pa-Nb	0.79 (0.6)	1.17 (0.8)	1.35 (1.0)	2.60 (1.8)	1.35 (0.9)	4.09 (4.2)
	Nb	0.70 (1.0)	0.66 (0.6)	0.75 (0.9)	1.60 (3.1)	1.38 (1.8)	0.65 (1.3)
	Nb-Pb	0.87 (0.6)	0.56 (0.3)	1.07 (0.7)	1.21 (1.0)	2.61 (2.2)	1.48 (1.4)
	Pb	1.61 (0.8)	1.20 (0.5)	1.81 (0.6)	2.81 (3.2)	4.00 (2.5)	2.13 (1.2)
Pz	Na	0.26 (0.2)	0.05 (0.7)	−0.20 (0.5)	0.26 (0.8)	−0.22 (0.7)	−2.18 (1.5)
	Na-Pa	0.57 (0.3)	1.00 (0.6)	1.20 (0.8)	1.10 (0.6)	1.45 (1.2)	4.15 (2.6)
	Pa	0.79 (0.6)	1.10 (0.4)	0.94 (1.0)	1.33 (1.0)	1.15 (1.5)	1.64 (1.3)
	Pa-Nb	0.93 (0.5)	0.76 (0.3)	0.96 (0.5)	1.60 (1.2)	1.17 (0.9)	1.74 (1.0)
	Nb	0.05 (0.6)	0.33 (0.3)	0.02 (0.7)	−0.27 (1.0)	−0.02 (1.0)	−0.09 (1.0)
	Nb-Pb	0.89 (0.4)	0.69 (0.5)	1.04 (0.6)	1.83 (1.0)	1.80 (1.0)	1.21 (0.7)
	Pb	0.78 (0.4)	1.02 (0.6)	1.06 (0.5)	1.15 (2.0)	1.78 (1.0)	1.10 (0.6)

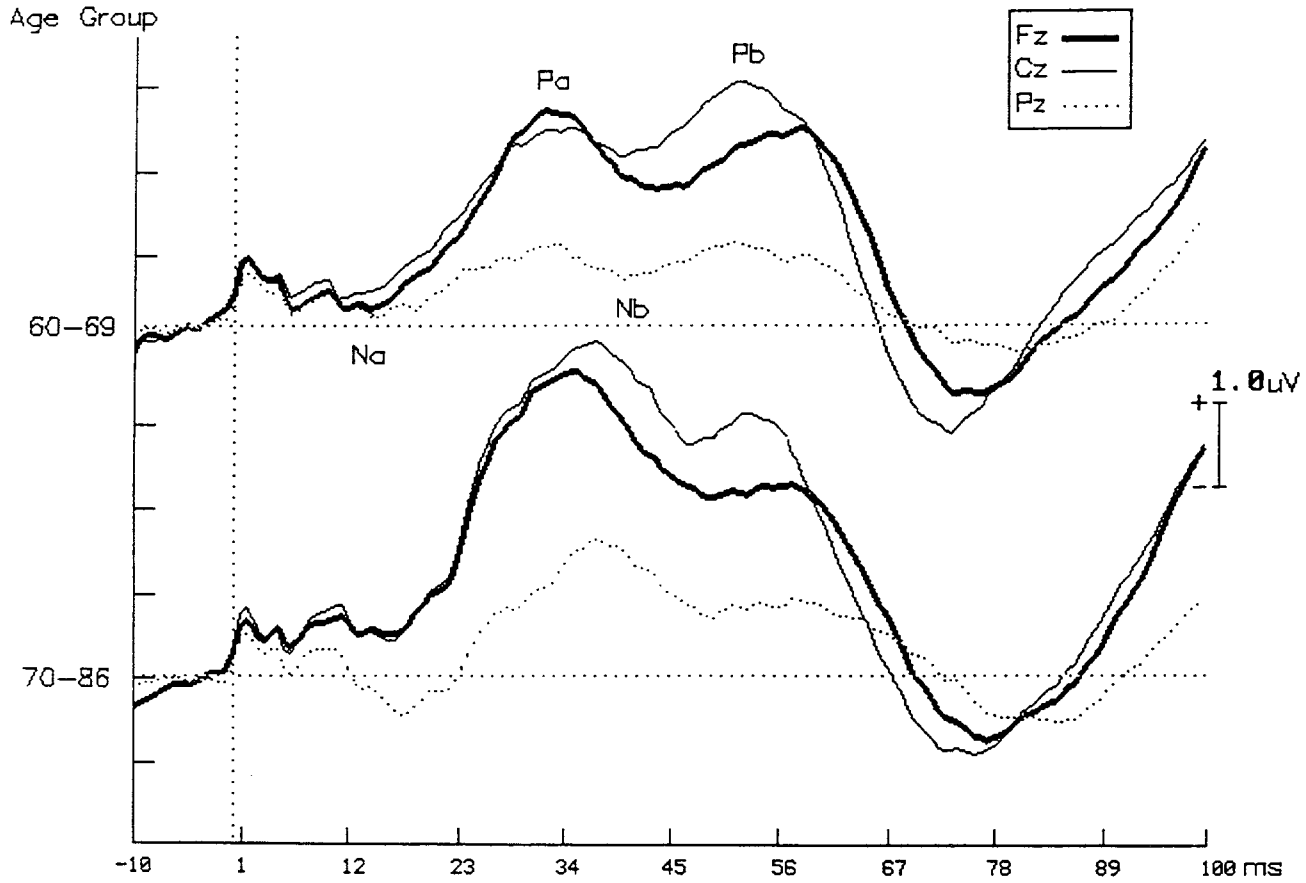

Figure 2. Grand average MAEP waveforms of elderly subjects with the lowest perceptual thresholds.

In keeping with this, a one-way ANOVA was carried out for Na-Pa amplitude ratios between Fz and Cz with age group as between-subjects factor. This analysis showed a significant effect of age group on the ratio between the Na-Pa amplitudes at Fz and Cz [$F(5,72) = 2.68$, $p \leq .029$].

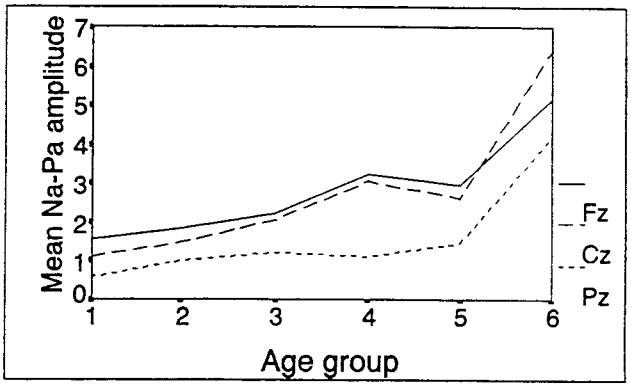

Figure 3. Distribution of mean Na-Pa amplitudes at Fz, Cz, and Pz across age groups. Y axis represents microvolts.

Regression Functions

The best-fitting models for the dependence of MAEP parameters on age were all linear except for the amplitude of Pb at Fz and Cz, for which a cubic equation fitted best (see Table 4 and Figure 4).

The Nb-Pb amplitude at Fz and the Pb peak amplitude at Pz failed to show significant trends with age. This absence of age dependence was corroborated by one-way analyses of variance, post hoc comparisons (Scheffé test, $p = .05$) showing that there were no significant differences among age groups.

Finally, regression analysis showed that the age dependence of the ratio between the Na-Pa amplitude at Fz and Cz was fitted by a linear model (Table 4 and Figure 5).

Discussion

Effects of Age on Latencies

In this study, age did not affect MAEP latencies. Longer latencies among elderly subjects were reported for Pa and Nb by Kelly-Ballweber and Dobie (1984), and for Pa, Nb,

Table 4. Regression of MAEP Parameters on Age and Levels of Significance

Electrode	Parameter	F(df), p	Regression function
Fz	Na amplitude	$F(1,71) = 16.67$, $p \leq .0001$	$Y = 1.31 - 0.03x$
	Na-Pa amplitude	$F(1,71) = 38.12$, $p \leq .0001$	$Y = -0.57 + 0.06x$
	Pb amplitude	$F(3,66) = 5.58$, $p \leq .002$	$Y = 10.67 - 0.68x + 0.01x^2 - 0.0001x^3$
Cz	Na amplitude	$F(1,71) = 5.67$, $p \leq .0001$	$Y = -0.46 - 0.03x$
	Na-Pa amplitude	$F(1,71) = 39.85$, $p \leq .0001$	$Y = -2.08 + 0.09x$
	Nb-Pb amplitude	$F(1,66) = 5.57$, $p \leq .02$	$Y = 0.15 + 0.02x$
	Pb amplitude	$F(3,64) = 5.99$, $p \leq .001$	$Y = 12.93 - 0.87x + 0.02x^2 - 0.0001x^3$
Pz	Na amplitude	$F(1,71) = 33.31$, $p \leq .0001$	$Y = 1.75 - 0.04x$
	Na-Pa amplitude	$F(1,71) = 31.16$, $p \leq .0001$	$Y = -1.47 + 0.06x$
	Nb-Pb amplitude	$F(1,66) = 5.67$, $p \leq .02$	$Y = 0.53 + 0.01x$
Fz-Cz	Na-Pa amplitude ratio	$F(1,71) = 8.37$, $p \leq .005$	$Y = 1.68 - 0.008x$

and Pb by Woods and Clayworth (1986). The reason for these discrepancies may lie in these authors having recorded MAEPs at Cz, whereas in this study we analyzed MAEP latencies only for Fz, the electrode with maximum amplitudes in our younger subjects. MAEP amplitudes have also been reported to be maximum at frontal electrodes by Deiber et al (1988), and this finding is consistent with the hypothesis of Scherg and Von Cramon (1986) as to the orientation of the electrical sources of MAEPs.

Effects of Age on Amplitudes

Kelly-Ballweber and Dobie (1984) and Woods and Clayworth (1986) reported that elderly subjects exhibited greater Pa amplitudes than young subjects at Cz. The fact that in our study the apparent effect of age on Pa amplitude disappeared both when hearing threshold was included as covariate and when the deafest subjects were excluded suggests that this "effect" may have been caused, at least in part, by the higher intensities used to stimulate elderly subjects. This suggestion is supported by the activity observed between 0 and 12 msec in the traces of elderly subjects, since the first few milliseconds of MAEP waveforms have been reported to be affected by stimulus intensity (Erwin and Buchwald 1986).

In an attempt to disentangle the effects of aging and other variables of interest from the effects of mere hearing loss, it has been common, in studies of MAEPs, to fix stimulus intensity with respect to the perceptual threshold of the individual (Cacace et al 1990; Gott and Hughes 1989; Kileny et al 1987; Liégeois-Chauvel et al 1994; Woods and Clayworth 1985, 1986; Yokoyama et al 1987). The problem with this procedure is that it only guarantees uniform input at the threshold itself; a sound intensity 60 dB above perceptual threshold may be subjectively louder for an elderly person with a high hearing threshold than for a young person with a normal hearing threshold. It is therefore advisable, in analyzing the results, to include hearing threshold as a covariate so as to filter out the effect of this subjective experience.

In this study, the Na and Na-Pa amplitudes increased linearly with age. The midline Na wave appears to originate subcortically, in either the inferior colliculi (Caird and Kinkle 1987; Fischer et al 1995; Hashimoto 1982; Littman et al 1992; McGee et al 1991) or the medial geniculate nuclei of the thalamus (Deiber 1993; Deiber et al 1988; Fischer et al 1995; Ibáñez et al 1989), although the possibility of modulation by the temporal cortex has not been ruled out (Jacobson et al 1990; Liégeois-Chauvel et al 1994). The midline Pa wave is generally thought to originate in the primary auditory cortex (Buchwald 1991; Deiber 1993; Deiber et al 1988; Erwin and Buchwald 1986, 1987; Kileny et al 1987; Liégeois-Chauvel et al 1994; Scherg and Von Cramon 1986), although an origin in the thalamic medial geniculate nuclei or in the thalamocortical radiations has been suggested by studies of lesions in human patients (Ibáñez et al 1989; Jacobson et al 1990; Kraus et al 1982; Özdamar and Kraus 1983; Woods et al 1987; Yokoyama et al 1987), by inactivation and selective lesion experiments on the primary and secondary auditory pathways of guinea pigs (Kraus et al 1988; Littman et al 1992; McGee et al 1991; Smith and Kraus 1988), and by human cortical mapping studies (Cacace et al 1990).

In view of the putative generators of Na and Pa, the age dependence of the Na and Na-Pa amplitudes may perhaps be attributed to either or both of two possible causes. The first is a possible reduction in inhibitory feedback connections from layer VI of the auditory cortex to the inferior colliculi or from layer V to the medial geniculate body, which have been suggested to play a role in the control of attention to auditory input by reducing the activity of these midbrain and diencephalic structures in response to irrelevant stimuli (Kelly 1991). Jacobson et al (1990) attributed increased Na-Pa amplitude in epileptic patients from whom the anterior temporal lobe had been extirpated to loss of cortical modulation of the subcortical source of the Na wave. It is well established that the elderly exhibit loss of projecting neurons in neocortical areas, including the temporal region (Creasey and Rapoport 1985; Horvath and

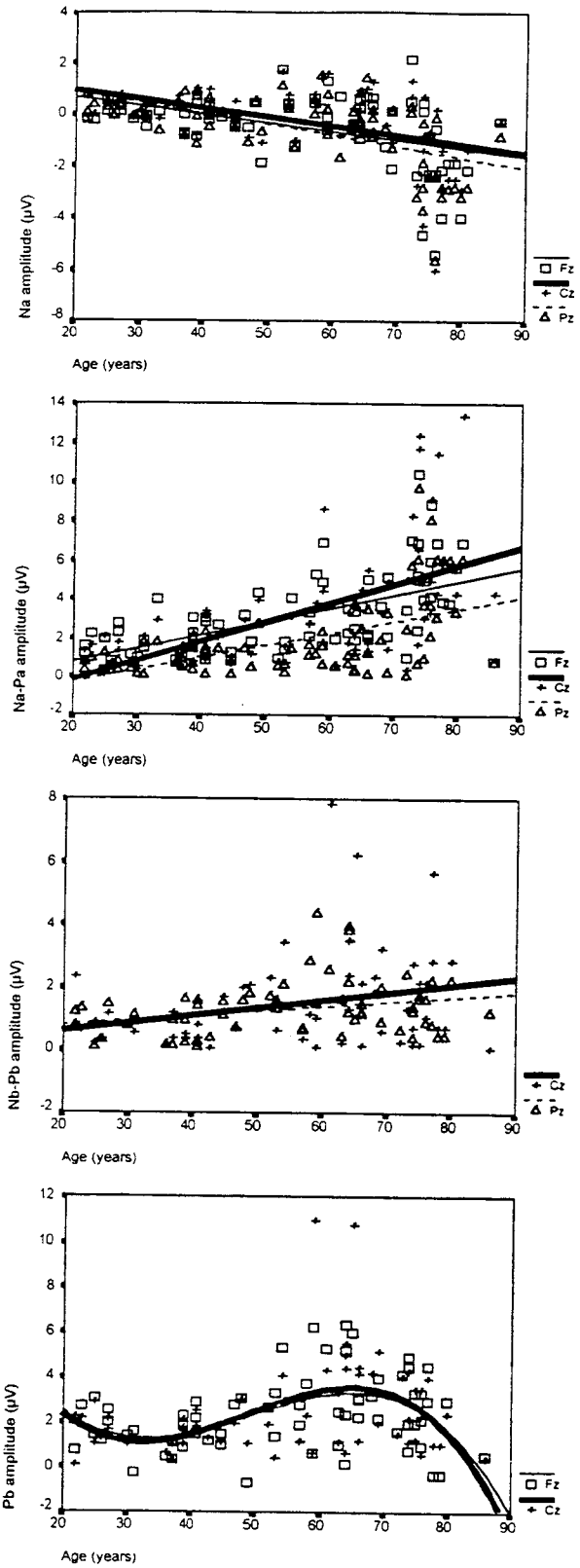

Figure 4. MAEP parameters plotted against age, and the fitted regression functions.

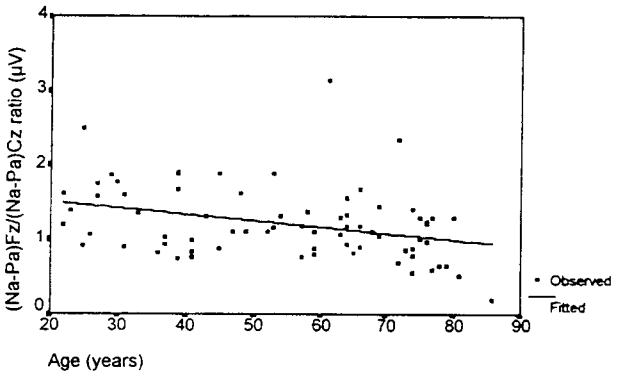

Figure 5. Fz-Cz ratio for Na-Pa amplitude plotted against age, and the fitted regression function.

Davis 1990; Ivy et al 1992; Kemper 1984; Riederer and Kruzik 1987), and loss of more than half the neurons of the superior temporal gyrus has also been reported (Hayes and Jerger 1984). These losses may significantly reduce communication between the auditory cortex and subcortical auditory structures, and therefore reduce capacity for inhibition of activity generated in these structures in response to repetitive stimuli requiring no attention.

The second possible cause of the age-related increase in Na and Na-Pa amplitudes is the decrease in thalamic gamma-aminobutyric acid (GABA) levels with age (Selkoe and Kosik 1984), a process to which Woods and Clayworth (1986) attributed the differences they observed between the Pa amplitudes of their young and elderly subjects. Since the thalamic reticular nucleus is one of the main sources of GABAergic projections inhibiting the medial geniculate nuclei and other thalamic relay nuclei (Kelly and Dodd 1991), GABA deficiency must tend to reduce inhibition of waves originating in these nuclei. The finding that abstinent chronic alcoholics have greater Na-Pa amplitudes than healthy controls has similarly been attributed to reduced thalamic GABA levels (Díaz et al 1990).

The age-related increases in MAEP amplitudes observed in the present study may also be influenced by the known loss of white matter from prefrontal areas in the elderly (Creasey and Rapoport 1985; Lim et al 1992; Riederer and Kruzik 1987). These areas are involved in inhibiting the activation of cortical regions receiving signals produced by sensory stimuli that fail to evoke an orienting response (Van Zomeren and Brouwer 1994). Since prefrontal cortical lesions have been reported to cause a significant increase in Pa amplitude (Knight et al 1989), it seems likely that in this study age-related increases in the response to repetitive unattended stimuli may have been partly due to the proven degeneration of this region in elderly subjects.

In this work it was possible to investigate the Pb wave because we recorded MAEPs with low stimulation rates (Buchwald et al 1991; Erwin and Buchwald 1986, 1987); the previous studies of the effects of aging on MAEPs (Kelly-Balweber and Dobie 1984; Woods and Clayworth 1986) employed stimulation rates at which Pb is highly variable.

The complex age dependence of Pb amplitude observed in this work is not easy to explain. Buchwald and coworkers (Buchwald et al 1991; Erwin and Buchwald 1986, 1987) have suggested that this wave is an indicator of arousal that arises in the projections from the mesencephalic reticular formation to the thalamic intralaminar nuclei and depends on cholinergic pathways. This hypothesis has received support from Cacace et al (1990) and Smith and Kraus (1988), but Liégeois-Chauvel et al (1994) and Reite et al (1988) hold that Pb is essentially generated in the auditory cortex.

On the basis of the hypothesis of Buchwald and coworkers, our findings would suggest that reticular activity in response to repetitive unattended stimuli decreases between the ages of 20 and 40 years, increases between the ages of 40 and 65 years, and declines thereafter; however, if we consider the existing neurochemical data from studies in humans that inform that certain brain structures lose cholinergic markers during aging (Coté and Kremzner 1984; Morgan and May 1990; Rinne 1987), and if the reticular formation is among them, then the Buchwald hypothesis suggests a monotonic decrease in Pb amplitude with increasing age; and in this case our results on the effects of aging on Pb amplitude appear to contradict the Buchwald hypothesis. This does not mean, however, that our Pb data can be regarded as supporting the hypothesis of Liégeois-Chauvel and Reite, since any attempt to explain our findings on the basis of this latter hypothesis would, in the absence of further relevant data, be mere speculation.

Effects of Electrode Position

The effects of electrode position on MAEP amplitudes in this study agree with previous reports that these waves are largest in frontal areas (Deiber et al 1988). The observed interaction between age and electrode for Na-Pa amplitude, and the significant age-induced decrease in the ratio between the Na-Pa amplitude at Fz and Cz show a change in the topographical distribution of Na and Pa. Cortical folding changes with age, and this, along with some degree of cortical atrophy (Creasey and Rapoport 1985; Horvath and Davis 1990; Ivy et al 1992; Kemper 1984; Riederer and Kruzik 1987), may change the orientation of cortical sources, giving rise to changes in scalp potentials. The sources of MAEPs in humans have been reported to lie partly in the supratemporal plane, tangentially oriented to frontal areas (Scherg and Von Cramon 1986); small changes in orientation may thus cause changes in scalp distribution.

As a conclusion, except for the Pb results, our findings in this study are in keeping with the hypothesis that central inhibition is deficient in the elderly (Dustman and Shearer 1987; Dustman et al 1993; Hasher et al 1991; Prinz et al 1990). This hypothesis was originally put forward on the basis of similar results for visual evoked potentials in the middle-latency range, i.e., as an explanation of the greater excitability of certain areas of the cortex in elderly people. Our results on auditory evoked potentials suggest that inhibitory deficits in the elderly also include loss of thalamic inhibition and inhibitory feedback from the auditory cortex to subcortical auditory structures. With increasing age, these structures appear to become increasingly less efficient in their inhibition of activity induced by repeated unattended auditory stimuli. Changes in the MAEP amplitudes observed at any particular electrode location may also be partly due to age-related changes in the orientation of MAEP sources.

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