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Olfactory event-related potentials in normal human subjects: effects of age and gender

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Abstract

Behavioral and electrophysiological testing of olfactory function was performed in 33 normal human male and female subjects, 18–83 years of age. Acuity for odor identification and odor detection was verified by standard psychophysical tests. For evoked potential testing, a constant flow olfactometer provided odorant stimuli (amyl acetate) or air control stimuli that were presented to the right nostril by a nasal cannula at a flow rate of 5 l/min, duration of 40 msec and random interstimulus intervals of 6–30 sec. The behavioral tests revealed no significant difference between males and females, whereas increasing age was associated with a decline in performance on the odor identification test. No reproducible evoked potentials were recorded in response to the air control stimulus. Potentials to the odorant stimulus consisted of 4 components named P1, N1, P2 and N2. A significant correlation was found between P2 latency and odor identification test scores, suggesting a relationship between the generation of the P2 component and olfactory processing. P2 peak latency increased significantly with age at 2.5 msec/year. An age-related decline in N1-P2 interpeak amplitude was seen in male subjects. Topographic differences were seen in the P2 peak amplitude and the N1-P2 and P2-N2 interpeak amplitudes such that their amplitudes were greatest at Cz and Pz. On average, N1-P2 interpeak amplitudes were larger in the female subjects than in the male subjects, possibly revealing a hormonal influence on the olfactory event-related potential.

Keywords: Olfaction; Odor identification; Odor threshold; Event-related potentials; Evoked potentials; Aging; Gender; Chemosensation

1. Introduction

An age-related decline in olfactory function has been demonstrated by a number of psychophysical measures including odor detection threshold (Venstrom and Amoore, 1968; Murphy, 1983; Schiffman, 1992), magnitude estimation (Stevens and Cain, 1985; Schiffman and Warwick, 1990), odor discrimination (Schiffman, 1992), odor identification (Doty et al., 1984; Murphy and Cain, 1986; Schiffman, 1992) and odor recognition memory (Murphy et al., 1991). Anatomical changes associated with aging have been detected in both peripheral olfactory structures, e.g., olfactory epithelium (Naessen, 1971; Dodson and Bannister, 1980), and central olfactory pathways, e.g., olfactory bulb (Liss and Gomez, 1958; Hinds and McNelly, 1981), but their relative contributions to the age-related functional deficits are unknown.

Olfactory evoked potentials offer an objective and quantitative method for studying changes in olfactory function due to aging or gender in humans. A number of investigators have been able to record olfactory evoked potentials from the scalp in response to odorant stimuli in animals (Evans and Starr, 1992) and in normal human subjects (Finkenzeller, 1966; Allison and Goff, 1967; Gerull et al., 1975; Heberhold, 1975; Plattig and Kobal, 1979; Uziel, 1982; Tonoike, 1987; Lorig, 1989; Prah and Benignus, 1992; Murphy et al., 1994). The effects of age have been examined in one study (Murphy et al., 1994) which showed a decline in amplitude with increasing age. Differences due to gender were explored in another study (Becker et al., 1993) with higher amplitudes being seen in females than in males. The purpose of the current study is to further define the effects of age, gender, and their interactions on the olfactory evoked potential.

2. Methods and materials

2.1. Subjects

Olfactory evoked potentials were recorded from 11 "young" subjects (6 females, 5 males, aged 18–30 years),

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11 "middle-aged" subjects (6 females, 5 males, aged 36–57 years), and 11 "old" subjects (6 females, 5 males, aged 64–83 years). Subjects under the age of 70 were recruited from the university community. Subjects older than 70 years were recruited from the Successful Aging Program and have been observed longitudinally for at least 5 years with neuropsychological testing and neuroimaging. All subjects reported a normal sense of smell. Subjects with a history of sinus disease, smoking, head trauma or dementia were excluded. Olfactory acuity was verified by standardized psychophysical measures including the Smell Identification Test (Sensonics, Inc.) and odor detection threshold determinations for isoamyl acetate (Olfacto-Labs, Inc.). All subjects older than 60 years scored at least 28 on the Mini-Mental State examination (Folstein et al., 1975).

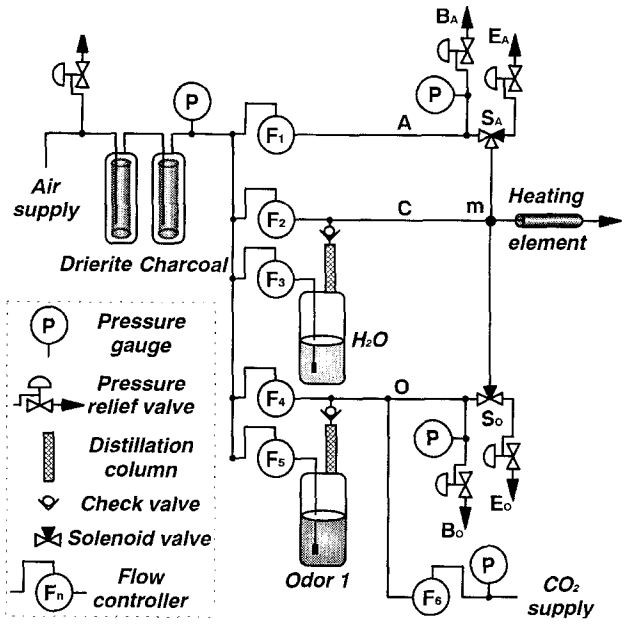

Fig. 1. Scheme of the constant flow olfactometer used to deliver odorant stimuli. The air supply to the olfactometer was passed through a coalescing filter to remove oil, water and solid particles (> 0.1 μm), dehumidified by drierite and passed through a 5 Å molecular sieve to remove trace impurities, a 40 μm stainless steel frit to remove dust and filter particles, and a charcoal filter to remove contaminating odors. The inlet pressure to the flow meters was maintained at a pressure of 15 pounds/in.^{2}. The flow dilution system allowed the concentration of odorant or the humidity of the carrier stream to be changed by diluting vapor-saturated air with clean, dry air. Air was bubbled through fritted cylinders into 1 l flasks containing either distilled/deionized water or pure odorant solution and the resulting vapor-saturated air was deatomized by a Wheaton-Vigreaux distillation column (100 cm in length). A check valve prevented backflow into the column and flask. The output of each distillation column was connected to a flow-regulated stream of clean, dry air. The ratio of volume flow rates of vapor-saturated air to clean air determined the odor concentration and humidity. The odorant stimulus was produced by activating the pair of solenoid valves simultaneously. This opened the normally closed port of the "odor" solenoid valve ("SO"), diverting a continuous flow of odorous air ("O") into the mixing point ("m"). Activation of the "air" solenoid valve ("SA") diverted the continuous flow of clean, dry air (A) to the "air" exhaust valve (EA). In the resting state, i.e., when the solenoid valves were *not* activated, clean air (A) flowed continuously to the mixing point through SA and odorous air (O) passed through SO to the "odorant" exhaust valve (EO). In order to reduce changes in volume flow rate at the output of the olfactometer due to solenoid activation, pressures at the inlet port of SA and SO were equalized by pressure relief "bypass" valves (BA, BO). Metering "exhaust" valves (EA, EO) were used to equilibrate flow through each "exhaust" port to the corresponding "outlet" ports connected to the mixing point.

2.2. Olfactometer design and calibration

A constant flow olfactometer delivered the odorant stimuli. A schematic diagram and description of its operation are provided in Fig. 1. The olfactometer features: (1) tandem, 3-way electromagnetic solenoid valves which switch between continuous streams of odorous and clean air; (2) pressure regulators and relief valves at the input and exhaust ports of the solenoid valves to reduce fluctuation in pressure and volume flow rate with solenoid activation; (3) a "carrier" flow of humidified air into which the odorant stimulus is injected to further reduce fluctuation in volume flow rate with solenoid activation; and (4) a flow dilution system to control stimulus concentration and humidity.

Before recording, a mass flow sensor verified the total volume flow rate at the output of the olfactometer. Pressure fluctuations during solenoid activation were minimized to within one tenth of an inch of water by using an electronic low pressure sensor at the mixing point ("m") to make final adjustments in the bypass and exhaust valve settings. Stimulus rise time was estimated by measuring a CO_2 stimulus at the outlet of the nasal cannula (4.75 mm, internal diameter) using both a thermocouple and a hot wire anemometer (TSI Model 10-50). Fig. 2 shows the response of the anemometer. Stimulus transit time was defined as the time from the onset of solenoid activation to the onset of the anemometer response. Stimulus rise time was defined as the time from onset of the thermistor or anemometer response to two thirds maximum voltage. Results obtained with the two techniques were similar, yielding a stimulus rise time of < 50 msec and a transit time of 370 msec (air velocity of 5 m/sec). The time delay between stimulus onset at the nostril and the onset of the olfactory receptor potentials, i.e., the electro-olfactogram (Ottoson, 1956; Osterhammel et al., 1969) was not measured in the current study.

2.3. Stimulus parameters

The relative humidity of the total volume output was maintained at 35% and the air temperature was heated to 93 ± 2°F. Stimuli consisted of 50% amyl acetate (banana oil) and an air control, 40 msec in duration, 5 l/min volume flow rate presented at random interstimulus intervals of 6–30 sec. Three sets of 10 air control stimuli each were presented first with 10 min rest periods between sets. Three sets of 10 odor stimuli were then presented, also

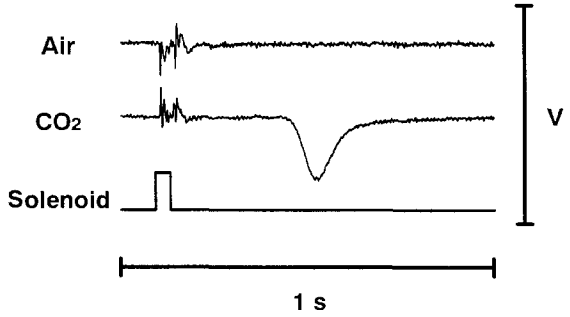

Fig. 2. Anemometer response to a CO_2 stimulus (middle trace) and an air control stimulus (top). A stimulus artifact was seen in both the air and CO_2 recordings at 14 msec latency due to transient fluctuations in pressure (< 0.1 in. H_2O) associated with solenoid valve activation (bottom trace). A negative voltage was seen several hundred milliseconds later in the CO_2 condition only, reflecting the difference in thermal conductivity between CO_2 and air as the stimulus arrived at the output of the olfactometer. The onset latency of the anemometer response to CO_2 defined the transit time of the odorant stimulus from solenoid valve to nostril and enabled direct calculation of the air velocity of the odorant stimulus entering the nose.

with 10 min rest periods intervening between sets. During stimulation no behavioral response was required. The subjects were instructed to breathe through the mouth, to focus on an object and to refrain from blinking. Velopharyngeal closure (a technique of reducing air flow through the nasopharynx by elevating the soft palate) was not performed. The sound of solenoid activation transmitted through the nasal cannula was masked by a 65 dB SPL white noise presented through speakers in the chamber.

2.4. Recording parameters

All recordings were made in a sound-attenuated, electrically shielded chamber. The evoked potentials were recorded from scalp electrodes placed at Fz, Cz, Pz, C3, C4, and referenced to A1. An eye channel (supraorbital referenced to infraorbital) registered the electro-oculogram (EOG) allowing offline rejection of single trials contaminated by eye movements or blinking. Electrode impedances were < 5 kΩ. The electroencephalogram was amplified 20,000 times, bandpass filtered at 0.1–100 Hz and notch filtered at 60 Hz using a Grass® Model 12 Neurodata Acquisition System™. The filtered electroencephalogram was digitized at a rate of 125 Hz using a Microstar Laboratories™ 2400 Data Acquisition Processor™. For each single trial, 500 data points/channel were saved in individual data files on a 80486-25 MHz platform using a computer program written in ASYST™ Version 4.0 by one of the authors (W.J.E.). The computer program also controlled the olfactometer via digital to analog channels of the Data Acquisition Processor™, activating the electromagnetic solenoid valves 1 sec after beginning data acquisition. This resulted in an evoked potential timebase of 4 sec including a prestimulus period of 1 sec for determination of the baseline voltage. A 50 μV square wave pulse was recorded following each session for purposes of calibration. Prior to data analysis, additional low-pass digital filtering to 15 Hz was performed offline to satisfy the sampling theorem and to enhance the primary components of the evoked potential. The low-pass digital filter program used a function in ASYST™ which employed an inverse Fourier transform of the Blackman window for the convolution weights (Ackroyd, 1973).

2.5. Data analysis

Single trials in which EOG artifacts were identified in the eye channel were excluded from the evoked potential averages. Up to 25% of the trials for any given subject were rejected for this reason. Peak latencies of the evoked potential components were calculated from the time of stimulus onset at the nostril to the point of maximum voltage or to a point extrapolated from the intersection of the ascending and descending limbs of a wave form. Peak amplitudes were defined as the difference between the maximum voltage of a component and the average voltage of the prestimulus baseline. Interpeak amplitudes were calculated as the difference between the peak amplitudes of 2 successive components.

Analysis of variance (ANOVA) procedures for repeated measures were used to evaluate the evoked potential measures. Separate ANOVAs for each component (P1, N1, P2, N2) were computed to analyze the amplitude and latency measures for 2 grouping factors (age group $\times$ gender) and 1 repeated measure (electrode). Results reaching $P < 0.05$ or better after Geisser-Greenhouse correction to adjust for violations of sphericity (Greenhouse and Geisser, 1959; Vasey and Thayer, 1987) were considered significant. Post hoc comparisons of the means at each electrode position were evaluated by single factor ANOVA and Fisher's LSD test. Psychophysical measures (odor identification and odor detection threshold) were also evaluated using similar ANOVA procedures. The relationships among olfactory evoked potential measures, psychophysical test scores and subject age were explored by regression analysis. For significant correlations, the adequacy of the linear model was verified by analysis of residuals.

3. Results

Performance on the Smell Identification Test differed significantly between age groups ($P < 0.01$) with a mean raw score of 38 ± 1 for the "young" group, 38 ± 1 for the "middle-aged" group, and 33 ± 4 for the "old" group. There was a significant negative correlation between age and Smell Identification Test scores, both linearly ($r = -0.59$, $P < 0.001$) and exponentially, using the square of the Smell Identification Test score ($r = -0.60$, $P < 0.001$). The quadratic function is plotted in Fig. 3. Isoamyl acetate detection thresholds did not differ between the 3

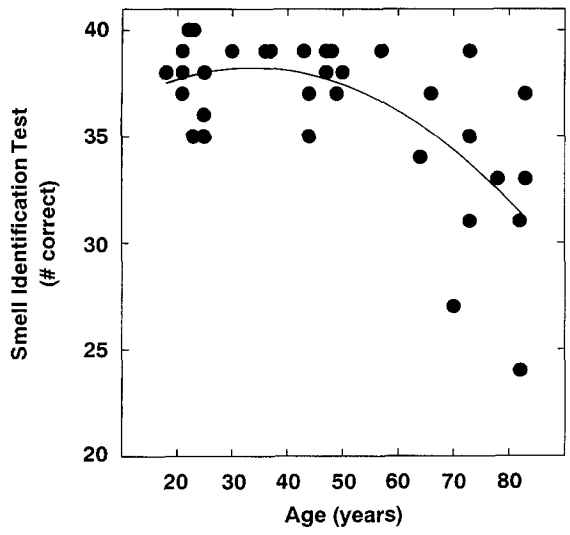

Fig. 3. Smell Identification Test scores as a function of age. Both the raw Smell Identification Test scores and the square of the scores correlated with age ($r = -0.6$, $P < 0.001$). The best fit quadratic curve is represented by the solid line and is defined by the function $f(x) = -0.003x^2 + 0.2x + 35$, where x = age.

age groups. Neither odor identification nor odor threshold test scores differed between male and female subjects.

The evoked potential averages for each subject and the grand averages at Cz for the "young" group are shown in Fig. 4 in response to both the amyl acetate and the air control. Fig. 5 shows the grand averages at the 5 electrode positions and the EOG for each age group. The evoked potential to amyl acetate consisted primarily of 2 positive components (P1 and P2) and 2 negative components (N1 and N2) as designated by a NIH sponsored work group on olfactory evoked potentials (Evans et al., 1993). The peak latencies and amplitudes at each electrode position are listed in Table 1. No reproducible potentials were elicited by the air control stimulus.

A significant effect of age, but not gender, was seen on ANOVA for P2 latency at all electrode sites ($P < 0.01$). Post hoc analysis showed that this was primarily due to longer latencies in the "old" group than in the "young" subject group (Fig. 6). ANOVA also showed an effect of age on N2 latency ($P < 0.05$) due to differences between the "young" and "old" groups. The P1 and N1 peak latencies and the interpeak latencies (P1-N1, P1-P2, P1-N2, N1-P2, N1-N2 and P2-N2) did not differ significantly among age and gender groups. Peak and interpeak latency measures did not differ significantly from one electrode site to another.

Regression analysis revealed significant correlations between age and P2 peak latency at all electrode sites ($r = 0.49$–0.61, $P < 0.001$). A scatter plot of the individual P2 latency values at Cz is shown in Fig. 7. Significant correlations between age and N2 latency were also seen at Fz, Cz and Pz ($r = 0.43$–0.47, $P < 0.01$). Regression analysis showed a significant negative correlation between P2 latency at Fz with Smell Identification Test scores ($r = -0.36$, $P < 0.05$). Multiple regression analysis revealed that 3 variables (the Smell Identification Test scores, the square of the Smell Identification Test scores and age) accounted for almost 50% of the variability in P2 latency at Fz ($r^2 = 0.46$, $P < 0.001$). Evoked potential amplitudes did not correlate significantly with Smell Identification Scores. No significant correlations were observed among isoamyl acetate threshold scores and evoked potential component latencies or amplitudes.

ANOVA revealed significant differences between males and females for N1-P2 interpeak amplitude ($P < 0.05$). Evoked potential amplitudes for the female subjects were usually 60–90% larger than those for male subjects. Moreover, a significant interaction between the factors "age" and "gender" was also observed for the N1-P2 interpeak amplitude ($P < 0.05$). Post hoc analysis revealed that significantly larger N1-P2 interpeak amplitudes in female

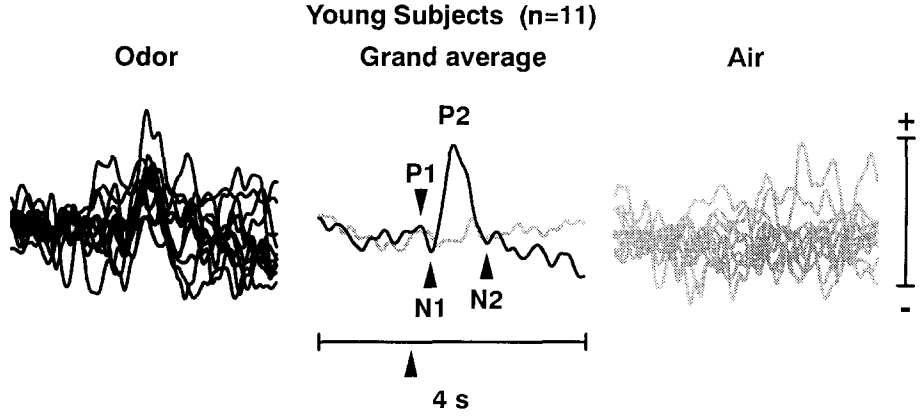

Fig. 4. Olfactory evoked potentials from 11 "young" subjects in response to amyl acetate (solid lines, left panel) and the air control stimulus (hatched lines, right panel). The grand averages of the 11 "young" subjects are shown in the middle panel. The horizontal scale represents the 4 sec timebase with the arrow indicating the approximate time of stimulus onset at the nostril. The vertical scale represents a 20 μV deflection for the superimposed averages (right and left panels) and 10 μV for the grand averages (middle panel). Polarity is plotted with positivity up.

Table 1
Olfactory evoked potentials: latency and amplitude at Cz as a function of gender and age (mean ± S.D.)

		Young		Middle-aged		Old	
		Male (n = 5)	Female (n = 6)	Male (n = 5)	Female (n = 6)	Male (n = 5)	Female (n = 6)
Latency (msec)	P1	128 ± 86	126 ± 115	201 ± 111	167 ± 180	176 ± 152	155 ± 62
	N1	358 ± 62	321 ± 95	473 ± 107	353 ± 168	393 ± 107	405 ± 107
	P2 [a]	668 ± 147	681 ± 36	752 ± 133	727 ± 103	819 ± 166	861 ± 84
	N2 [b]	1139 ± 234	1183 ± 114	1035 ± 284	1297 ± 206	1377 ± 203	1342 ± 129
	N1-P2	310 ± 138	360 ± 77	278 ± 110	375 ± 168	426 ± 165	456 ± 68
Amplitude (μV)	P1	2.4 ± 4.7	1.9 ± 4.1	0.7 ± 2.8	2.1 ± 3.1	1.2 ± 2.2	0.3 ± 1.7
	N1	−0.9 ± 5.1	−1.8 ± 3.9	−3.6 ± 1.8	−0.7 ± 2.7	−1.1 ± 3.8	−4.0 ± 1.9
	P2	5.5 ± 2.7	8.3 ± 3.9	2.3 ± 2.3	5.0 ± 3.5	3.6 ± 3.4	7.3 ± 7.3
	N2	−1.8 ± 2.5	−2.7 ± 5.8	−1.8 ± 1.9	−1.1 ± 4.1	−2.5 ± 2.1	−2.5 ± 7.3
	N1-P2 [c,d]	6.5 ± 2.8	10.2 ± 2.5	5.9 ± 1.0	4.3 ± 0.8	4.7 ± 2.2	11.3 ± 7.5

[a] ANOVA main effect of "age" ($P = 0.01$): young < old.
[b] ANOVA main effect of "age" ($P = 0.04$): young < old.
[c] ANOVA main effect of "gender" ($P = 0.02$): female > male.
[d] ANOVA "age" × "gender" interaction ($P = 0.03$): young and old females > young, middle-aged and old males, middle-aged females.

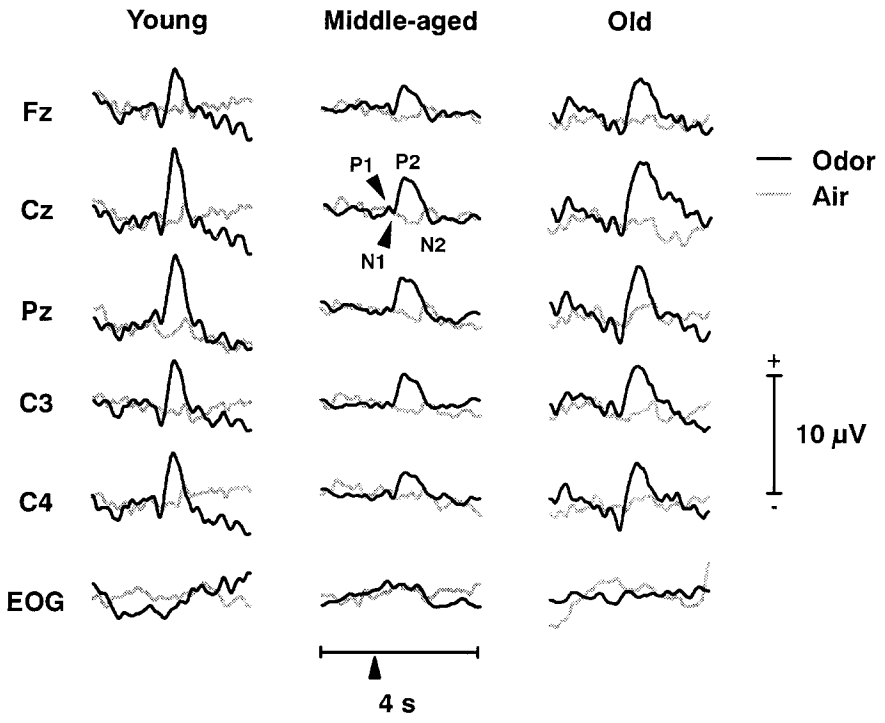

Fig. 5. Grand averages to amyl acetate (solid lines) and the air control stimulus (hatched lines) at 5 electrode positions (referenced to A1) and the electro-oculogram (EOG).

subjects were found only in the "young" and "old" groups, not in the "middle-aged" group (see Fig. 8). Furthermore, "middle-aged" female subjects exhibited lower mean N1-P2 interpeak amplitudes than "young" and "old" females, whereas in male subjects, the lowest mean N1-P2 interpeak amplitudes were seen in the "old" age group.

Topographic differences between electrodes were seen on ANOVA for P2 peak amplitude ($P < 0.05$), N1-P2 interpeak amplitude ($P < 0.01$), and P2-N2 interpeak amplitude ($P < 0.01$). The effect was consistent across electrodes for each of these measures such that amplitudes were greater at Pz and Cz than at Fz, C3 and C4 (see Fig. 5).

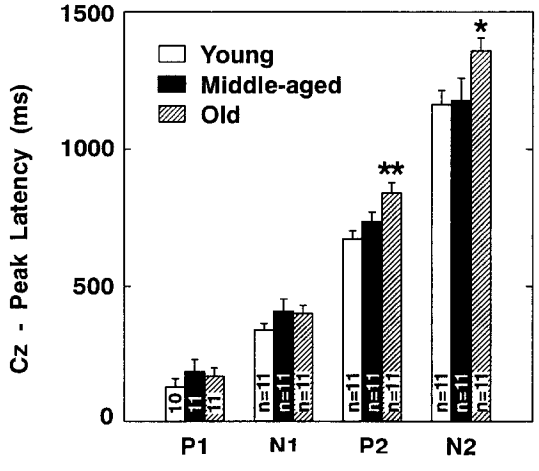

Fig. 6. Mean peak latencies (+S.E.) of the olfactory evoked potential components at Cz by age group. The number of data points analyzed is indicated by n at the base of each bar. Significant differences from the "young" group are denoted by ** ($P < 0.01$) and * ($P < 0.05$).

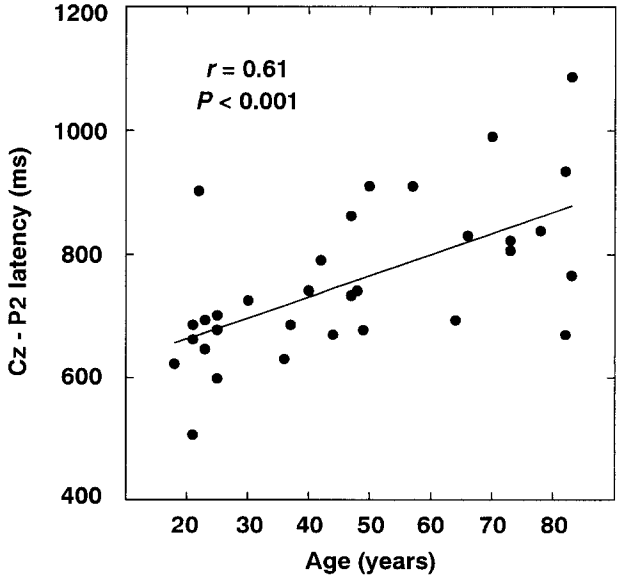

Fig. 7. Scatter plot of P2 peak latencies at Cz as a function of age. The linear regression function is plotted as the solid line.

4. Discussion

The results of this study show that both gender and age are significant factors affecting the amplitude and latency of olfactory evoked potentials to amyl acetate. Increasing age was associated with a prolongation of the P2 peak latency at about 2.5 msec for each year of life between 18 and 83 years. A similar, but less significant trend was seen for N2 peak latency. Systematic age-related changes in evoked potential amplitudes were seen only in males with a reduction in N1-P2 interpeak amplitude occurring in the "old" group. In "old" females, the N1-P2 interpeak amplitude was highly variable with the mean amplitude for this group being significantly greater than for "middle-aged" females.

One other study has examined the effect of age on the olfactory event-related potential. Murphy et al. (1994) recorded evoked potentials to amyl acetate presented at a volume flow rate of 7.4 l/min in 7 young subjects (20–35 years) and 7 old subjects (53–84 years) including approximately equal numbers of males and females. Although these investigators did not find age-related differences in component latencies as in the current study, they did find a significant decline in N1 peak amplitude and N1-P2 interpeak amplitude at Cz with increasing age. They also observed a significant correlation between P2 peak amplitude and odor threshold. In the current study, the lack of differences in odor detection thresholds between age groups may account for the lack of significant correlations between odor thresholds and the evoked potential measures. Furthermore, the results in the current study are similar to those of Schiffman (1992) who found that odor discrimination and odor identification abilities declined in the eighth decade of life without significant change in odor detection thresholds.

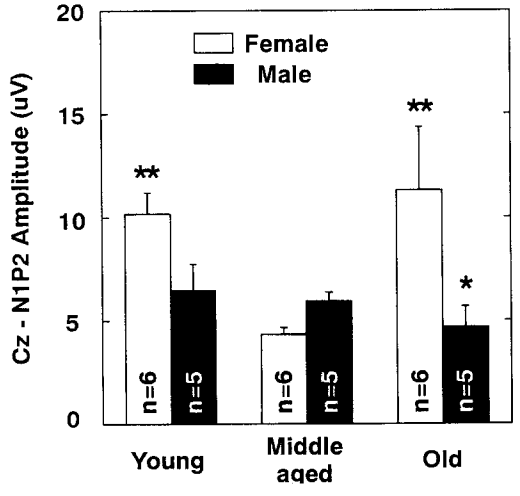

Fig. 8. Mean N1-P2 interpeak amplitudes (+S.E.) by function and age group. The number of data points in each group is represented by n at the base of each bar. Significant differences from "young" males are indicated by * ($P < 0.05$) and ** ($P < 0.01$).

Evoked potential studies on aging in other sensory modalities (Allison et al., 1984; also see review by Evans and Starr, 1994) reveal that the absolute peak latencies of most sensory evoked potential components increase with age. However, when the effects of age-associated diseases on the receptor organs are eliminated, aging effects become less pronounced, particularly when interpeak latencies are considered, since these latter measures bypass receptor function. Age-related effects also differ depending on the stimulus parameters and sensory channels being analyzed. For instance, visual evoked potential latencies increase with age when using stimuli at high spatial frequencies but not when using low spatial frequencies (Celesia et al., 1987) suggesting a differential effect of aging on the magnocellular and the parvocellular systems. In the auditory system, wave I of the auditory brain-stem evoked potential is known to be more dependent on the high frequency portions of the cochlea than wave V. Thus, high frequency hearing loss associated with aging results in prolongation of wave I but not wave V (Don and Eggermont, 1978). In contrast, latencies of the cognitively evoked potentials, for example P300, typically increase with age. Thus, the effect of age on sensory evoked potentials is not uniform and depends on stimulus parameters, sensory channels and task paradigms being tested, as well as criterion used to define the "normal" population under study.

Since the generators of the olfactory event-related potential are unknown, it is not clear whether the age-related changes observed in the current study are due to alterations peripherally at the receptor or more centrally in the brain. The correlation of P2 latency with odor identification scores suggests an intimate relationship between the generation of P2 and olfactory processing. Since increasing age was associated with prolongation in latency of the later components (P2 and N2) and not the earlier components (P1 and N1), it is possible that age-related alterations in central olfactory structures contribute disproportionately to the decline in olfaction typically seen in the elderly. It is also possible that the selection of a particular group of elderly subjects carefully determined to be free from disease biased the results in this study by eliminating subjects with conditions causing olfactory receptor damage.

In the current study, N1-P2 interpeak amplitude was found to be significantly larger in females than in males, particularly at Cz and Pz. Gender differences in evoked potentials have been reported in other sensory modalities. Visual (Bulayeva et al., 1993; Emmerson-Hanover et al., 1994) and somatosensory (Kakigi and Shibasaki, 1992) evoked potential amplitudes are larger in females than in males. For auditory brain-stem evoked potentials not only are the amplitudes larger in female subjects, but the latencies are shorter than in males. Don et al. (1993) have provided reasonable evidence that this is due, at least in part, to gender-related anatomical differences in the cochlea. Hormonal influences may also contribute to the

evoked potential differences between males and females. Elkind-Hirsch et al. (1994) found that auditory brain-stem evoked potentials correspond to levels of estrogen or testosterone. In olfaction, Becker et al. (1993) also reported evoked potential amplitudes to be larger in females than in males. The larger olfactory evoked potential amplitudes in females defined in both the Becker and the current studies might be related to the superior performance of females usually seen in olfactory tests (LeMagnen, 1952; Koelega and Koster, 1974; Doty et al., 1981; Cain, 1982). The causes of such gender-related differences in olfactory function are not known, but may be related to hormonal effects on neurons or other cells involved in olfaction. Estradiol-binding proteins have been found in the cytoplasm of olfactory epithelial cells from female rats in diestrus (Balboni and Vannelli, 1982) suggesting that the olfactory epithelium is a target organ for estrogens. Hormonal influences on the olfactory epithelium may be mediated by direct effects on primary olfactory receptor neurons which contain estrogen metabolizing enzymes in rats (Shinoda et al., 1989). Hormonal effects on olfactory epithelium may also be mediated via autonomic control of vascular and secretory processes affecting patency of the nasal passages and composition of mucus (Schneider and Wolf, 1960; Mair et al., 1978). Gender-related differences in olfaction may result from hormonal modulation of more central olfactory structures, e.g., mitral and tufted cells, secondary olfactory neurons which are also capable of metabolizing estrogens (Shinoda et al., 1990).

Olfactory event-related potentials may prove helpful in characterizing olfactory impairment in disease states. Current olfactory psychophysical techniques are limited in differentiating between olfactory deficits due to peripheral (intranasal) disorders such as chronic sinusitis, and central nervous system disorders such as Parkinson's disease or fronto-temporal contusion. The variability of peak latencies in normal subjects described in both the current study and other studies (Kobal and Hummel, 1991) limits clinical applications of this technique. The results of the present study emphasize the importance of subject parameters (i.e., age and gender) as a source of variability in the olfactory event-related measures. The role of stimulus parameters (e.g., volume flow rate, velocity, concentration, respiratory cycle) may be sources of variability that can also be controlled.

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References

Ackroyd, M.H. (1973) Computers in Medicine Series. Digital Filters. Butterworth, London.

Allison, T. and Goff, W.R. (1967) Human cerebral evoked responses to odorous stimuli. Electroenceph. clin. Neurophysiol., 23: 558–560.

Allison, T., Hume, A.L., Wood, C.C. and Goff, W.R. (1984) Developmental and aging changes in somatosensory, auditory and visual evoked potentials. Electroenceph. clin. Neurophysiol., 58: 14–24.

Balboni, G.C. and Vannelli, G.B. (1982) Morphological features of the olfactory epithelium in prepubertal and postpubertal rats. In: W. Breipohl (Ed.), Olfaction and Endocrine Regulation. IRL, London, pp. 285–297.

Becker, E., Hummel, T., Piel, E., Pauli, E., Kobal, G. and Hautzinger, M. (1993) Olfactory event-related potentials in psychosis prone subjects. Int. J. Psychophysiol., 15: 51–58.

Bulayeva, K.B., Pavlova, T.A. and Guseynov, G.G. (1993) Visual evoked potentials: phenotypic and genotypic variability. Behav. Genet., 23: 443–447.

Cain, W.S. (1982) Odor identification by males and females: prediction vs. performance. Chem. Senses, 7: 129–142.

Celesia, G.G., Kaufman, D. and Cone, S. (1987) Effects of age and sex on pattern electroretinograms and visual evoked potentials. Electroenceph. clin. Neurophysiol., 68: 161–171.

Dodson, H.C. and Bannister, L.H. (1980) Structural aspects of ageing in the olfactory and vomeronasal epithelia in mice. In: H. Van der Starre (Ed.), Olfaction and Taste VII. IRL, London, pp. 151–154.

Don, M. and Eggermont, J.J. (1978) Analysis of click-evoked brainstem potentials in man using high-pass noise masking. J. Acoust. Soc. Am., 63: 1084–1092.

Don, M., Ponton, C.W., Eggermont, J.J. and Masuda, A. (1993) Gender differences in cochlear response time: an explanation for gender amplitude differences in the unmasked auditory brain-stem response. J. Acoust. Soc. Am., 94: 2135–2148.

Doty, R.L., Snyder, P.J., Huggins, G.R. and Lowry, L.D. (1981) Endocrine, cardiovascular, and psychological correlates of olfactory sensitivity changes during the human menstrual cycle. J. Comp. Physiol. Psychol., 95: 45–60.

Doty, R.L., Shaman, P., Appelbaum, S.L., Giberson, R., Sikorsky, L. and Rosenberg, L. (1984) Smell identification ability: changes with age. Science, 226: 1441–1443.

Elkind-Hirsch, K.E., Wallace, E., Malinak, L.R. and Jerger, J.J. (1994) Sex hormones regulate ABR latency. Otol. Head Neck Surg., 110: 46–52.

Emmerson-Hanover, R., Shearer, D.E., Creel, D.J. and Dustman, R.E. (1994) Pattern reversal evoked potentials: gender differences and age-related changes in amplitude and latency. Electroenceph. clin. Neurophysiol., 92: 93–101.

Evans, W.J. and Starr, A. (1992) Stimulus parameters and temporal evolution of the olfactory evoked potential in rats. Chem. Senses, 17: 61–77.

Evans, W.J. and Starr, A. (1994) Electroencephalography and evoked potentials in the elderly. In: M. Albert and J. Knoefel (Eds.), Clinical Neurology of Aging. Oxford University Press, New York, pp. 235–273.

Evans, W.J., Kobal, G., Lorig, T. and Prah, J. (1993) Suggestions for collection and reporting of chemosensory event-related potentials. Chem. Senses, 18: 751–756.

Finkenzeller, P. (1966) Gemittelte EEG-Potentiale bei olfactorischer Reizung. Pflügers Arch., 292: 76–80.

Folstein, M.F., Folstein, S.E. and McHugh, P.R. (1975) "Mini-Mental State": a practical method of grading the cognitive state of patients for the clinician. J. Psychiat. Res., 12: 189–198.

Gerull, G., Giesen, D. and Mrownski, D. (1975) Registrierung olfaktorisch evozierter Potentiale für die klinische Diagnostik. Z. EEG-EMG, 6: 37–40.

Greenhouse, S.W. and Geisser, S. (1959) On methods in the analysis of profile data. Psychometrica, 24: 95–112.

Heberhold, C. (1975) Funktionsprüfungen und Störungen des Geruchssinnes. Arch. Otorhinolaryngol., 210: 67–164.

Hinds, J.W. and McNelly, N.A. (1981) Aging in the rat olfactory system: correlations of changes in the olfactory epithelium and olfactory bulb. J. Comp. Neurol., 203: 441–453.

Kakigi, R. and Shibasaki, H. (1992) Effects of age, gender and stimulus side on the scalp topography of somatosensory evoked potentials following posterior tibial nerve stimulation. J. Clin. Neurophysiol., 9: 431–440.

Kobal, G. and Hummel, T. (1991) Olfactory evoked potentials in humans. In: T.V. Getchell, R.L. Doty, L.M. Bartoshuk and J.B. Snow (Eds.), Smell and Taste in Health and Disease. Raven Press, New York, pp. 255–275.

Koelega, H.S. and Koster, E.P. (1974) Some experiments on sex differences in odor perception. Ann. NY Acad. Sci., 237: 234–246.

LeMagnen, J. (1952) Les phénomènes olfacto-sexuels chez l'homme. Arch. Sci. Physiol., 6: 125–160.

Liss, L. and Gomez, F. (1958) The nature of senile changes of the human olfactory bulb and tract. Arch. Otolaryngol., 67: 167–171.

Lorig, T. (1989) Human EEG and odor response. Prog. Neurobiol., 33: 387–398.

Mair, R.G., Bouffard, J.A., Engen, T. and Morton, T.H. (1978) Olfactory sensitivity during the menstrual cycle. Sens. Proc., 2: 90–98.

Murphy, C. (1983) Age-related effects on the threshold, psychophysical function, and pleasantness of menthol. J. Gerontol., 38: 217–222.

Murphy, C. and Cain, W.S. (1986) Odor identification: the blind are better. Physiol. Behav., 37: 177–180.

Murphy, C., Cain, W.S., Gilmore, M.M. and Skinner, R.B. (1991) Sensory and semantic factors in recognition memory for odors and graphic stimuli: elderly versus young persons. Am. J. Psychol., 104: 161–192.

Murphy, C., Nordin, S., De Wijk, R., Cain, W. and Polich, J. (1994) Olfactory evoked potentials: assessment of young and elderly, and comparison to psychophysical threshold. Chem. Senses, 19: 47–56.

Naessen, R. (1971) An inquiry on the morphological characteristics and possible changes with age in the olfactory region of man. Acta Otolaryngol., 71: 49–62.

Osterhammel, P., Terkildsen, K. and Zilstorff, K. (1969) Electro-olfactograms in man. J. Laryngol. Otol., 83: 731–733.

Ottoson, D. (1956) Analysis of the electrical activity of the olfactory epithelium. Acta Physiol. Scand., 35, Suppl. 122: 1–83.

Plattig, K.H. and Kobal, G. (1979) Spatial and temporal distribution of olfactory evoked potentials and techniques involved in their measurement. In: D. Lehmann and E. Callaway (Eds.), Human Evoked Potentials: Application and Problems. Plenum Press, New York, pp. 285–301.

Prah, J.D. and Benignus, V.A. (1992) Olfactory evoked responses to odorous stimuli of different intensities. Chem. Senses, 17: 417–425.

Schiffman, S.S. (1992) Olfaction in aging and medical disorders. In: M.J. Serby and K.L. Chobor (Eds.), Science of Olfaction. Springer, New York, pp. 500–525.

Schiffman, S.S. and Warwick, Z.S. (1990) Changes in taste and smell over the life span: effects on appetite and nutrition in the elderly. In: M.I. Friedman, M.E. Tordoff and M.R. Kare (Eds.), Chemical Senses. Vol. 4. Appetite and Nutrition. Marcel Dekker, New York, pp. 341–365.

Schneider, R. and Wolf, S. (1960) Relation of olfactory acuity to nasal membrane function. J. Appl. Physiol., 15: 914–920.

Shinoda, K., Shiotani, Y. and Osawa, Y. (1989) "Necklace olfactory glomeruli" form unique components of the rat primary olfactory system. J. Comp. Neurol., 284: 362–373.

Shinoda, K., Yagi, H., Osawa, Y. and Shiotani, Y. (1990) Involvement of specific placental antigen X-P2 in rat olfaction: an immunohistochemical study in the olfactory bulb. J. Comp. Neurol., 294: 340–344.

Stevens, J.C. and Cain, W.S. (1985) Age-related deficiency in the perceived strength of six odorants. Chem. Senses, 10: 517–529.

Tonoike, M. (1987) Response characteristics of olfactory evoked potentials using time-varying filtering. Ann. NY Acad. Sci., 510: 658–661.

Uziel, A. (1982) Present status of olfactometry. In: L. Surjan and Gy. Bodo (Eds.), Borderline Problems in Otorhinolaryngology. Excerpta Medica, Amsterdam, pp. 19–24.

Vasey, M.W. and Thayer, J.F. (1987) The continuing problem of false positives in repeated measures ANOVA in psychophysiology: a multivariate solution. Psychophysiology, 24: 479–486.

Venstrom, D. and Amoore, J. (1968) Olfactory threshold in relation to age, sex or smoking. J. Food Sci., 33: 264–265.