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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; Schifffman, 1992), magnitude estimation (Stevens and Cain, 1985; Schifffman and Warwick, 1990), odor discrimination (Schifffman, 1992), odor identification (Doty et al., 1984; Murphy and Cain, 1986; Schifffman, 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),
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).

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 CO₂ 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...
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 × gender) and a 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 32 ± 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

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**Fig. 2. Anemometer response to a CO₂ stimulus (middle trace) and an air control stimulus (top). A stimulus artifact was seen in both the air and CO₂ recordings at 14 msec latency due to transient fluctuations in pressure (<0.1 in. H₂O) associated with solenoid valve activation (bottom trace). A negative voltage was seen several hundred milliseconds later in the CO₂ condition only, reflecting the difference in thermal conductivity between CO₂ and air as the stimulus arrived at the output of the olfactometer. The onset latency of the anemometer response to CO₂ was verified by analysis of residuals.**
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 \((P1-N1, P1-P2, P1-N2, N1-P2, N1-N2 \text{ and } P2-N2)\) 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 subjects.
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  | Female           | Male        | Female           | Male| Female           |
|                | (n = 5)| (n = 6)          | (n = 5)     | (n = 6)          | (n = 5)| (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        |
| N2             | 668 ± 147 | 681 ± 36    | 752 ± 133  | 727 ± 103        | 819 ± 166 | 861 ± 84         |
| N1-P2          | 1139 ± 234 | 1183 ± 114  | 1035 ± 284 | 1297 ± 206       | 1377 ± 203 | 1342 ± 129       |
| 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       |
| N2             | 5.5 ± 3.7 | 8.3 ± 3.9    | 2.3 ± 2.3  | 5.0 ± 3.5        | 3.6 ± 3.4 | 7.3 ± 7.3        |
| N1-P2          | -1.8 ± 2.5 | -2.7 ± 5.8   | -1.8 ± 1.9 | -1.4 ± 4.1       | -2.5 ± 2.1 | -2.5 ± 7.3       |
| P1             | 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.
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.

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 (Coles 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

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 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; Koelga 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; Maïr 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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