Olfactory Evoked Responses in Alzheimer's Disease

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Abstract: In Alzheimer's disease, a rapid adaptation was recognized by suprathreshold odorant stimulation. This adaptation in Alzheimer's disease may be caused by dysfunction of the mechanism in adaptation of a quickly recovering central process.

Key Words: Alzheimer's disease; olfactory evoked response; rapid adaptation

Several reports have discussed olfactory evoked potentials [1–3], and our technique for olfactory stimulation synchronized with a subject's inspiration has been introduced [4–7]. As a result, reproducible and stable responses were obtained. In this article, we discuss a change of olfactory evoked response in Alzheimer's disease that is considered to show olfactory disorder at its early stage.

MATERIALS AND METHODS

An electroencephalograph was recorded as upper negative from the central midline by an active electrode using a monopolar recording. Other electrodes were attached to one ear auricle and the forehead, according to the international 10/20 system (bandpass, 1–30 Hz; impedance, 2–6 kOhm). Odorant pulses were introduced by a new odorant stimulator at a flow rate of 1 L/min (Fig. 1). Just prior to the onset of the subject's inspiration, the tip of the stimulator was inserted atraumatically 1 cm into the nostril. After introduction of the odorant, the tip was removed gently from the nostril. The odorant pulse trigger was the subject's respiration. Trigger pulses were generated by a hand switch attached at the stimulator just after the start of inspiration and were determined by visual inspection of the subject's abdominal movement at a rate of once in four slow, regular respirations. After eight responses to a given concentration of odorant had been recorded, the results were averaged by a Neuropack Four Computer (Nihon Kohden Co., Tokyo, Japan). An electrical valve was thus used to introduce odorant stimulations and was activated for 300 msec by a trigger pulse generated by the hand switch. The analysis time was 1,000 msec.

Each subject was tested using skatole by an ascending method from an undetectable level to a clearly detectable level, with eight presentations in each concentration. A much higher concentration of odorant was presented by an interval of 15 minutes. Skatole is one of the standard odorants supplied with the T & T olfactometer that has been adopted by the Japanese Society of Otorhinolaryngology (Fig. 2) [8]. The highest concentration of skatole is defined as E5 (9.75% skatole) and is diluted to a 10% solution in turn. The lowest concentration of skatole is defined as E−2 (E minus 2; 0.0975 ppm skatole).

The study involved six cases of Alzheimer's disease in Japanese male nonsmokers (64–72 years old). The highest concentration of skatole (E5) was reported as being detected clearly by all subjects. The environmental temperature of the test room was maintained between 21° and 24°C.

RESULTS

No detectable response was noted in the absence of the odor, as shown in Figure 3. When the odorous stimulation was introduced at the end of inspiration or during the expiration, the evoked response was undetectable. A typical pattern of an evoked response to E5 in a normal healthy young subject (i.e., an apparently healthy,
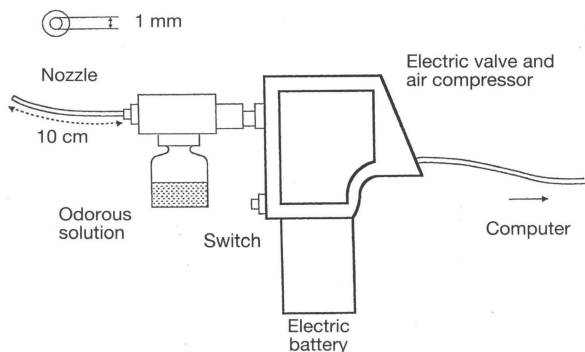
Figure 1. Schematic diagram of the stimulator. (Nozzle length, 10 cm; inside diameter, 1 mm.)

Japanese, nonsmoking man aged 26 to 38 years) before averaging is shown in Figure 4. Similar results were recognized in all of eight normal subjects. Positive responses were detectable at a certain peak latency by using the superimposition technique and, after the averaging, a positive response became obvious (Fig. 5). In this graph, the number 8 wave represents eight times the total; thus, wave 4 or 5 shows the largest amplitude, and wave 7 or 8 represents the clearest wave. E5 evoked a positive response, with a peak latency of between 68 and 84 msec in eight normal young subjects.

Figure 6 shows the evoked response to E4 in a case of Alzheimer's disease (65 years old). The detection threshold measured by the T & T olfactometer was E2 in this case. As shown here, a rapid adaptation was recognized. Figure 7 shows the evoked response to the highest concentration of skatole (E5) in the same subject. Also shown, a rapid adaptation was recognized more clearly on stimulation by the much higher concentrations of odorant. Consequently, after four to five averagings, the positive response was undetectable.

The olfactory threshold measured by the chemosensory event–related potentials to olfactory stimulations

E5	highest concentration of E 9.75 % skatole
E4	0.975 % skatole
E0	9.75 ppm skatole
E–1	0.975 ppm skatole
E–2	lowest concentration of E, 0.0975 ppm skatole

Figure 2. T & T olfactometer [7]. Odorant E is skatole, which is one of the standard odorants adopted by the Japanese Society of Otorhinolaryngology.
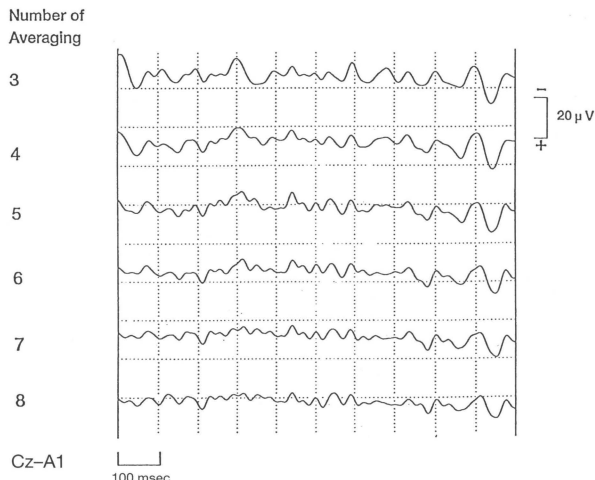

Figure 3. Responses to unscented air. Unscented air produced no positive response.

in eight apparently healthy, Japanese male nonsmokers (68–88 years old) was E–1 in two subjects (with a peak latency at 73–119 msec); E0 in four subjects (with a peak latency at 79–106 msec); or E1 in two subjects (with a peak latency at 74–102 msec). (In young healthy subjects, the lowest concentration of skatole was E–2, with a peak latency at 82–116 msec, or E–1, with a peak latency at 71–108 msec [7].)

DISCUSSION

The positive waves were distinguishable as an evoked response by using the superimposition technique before
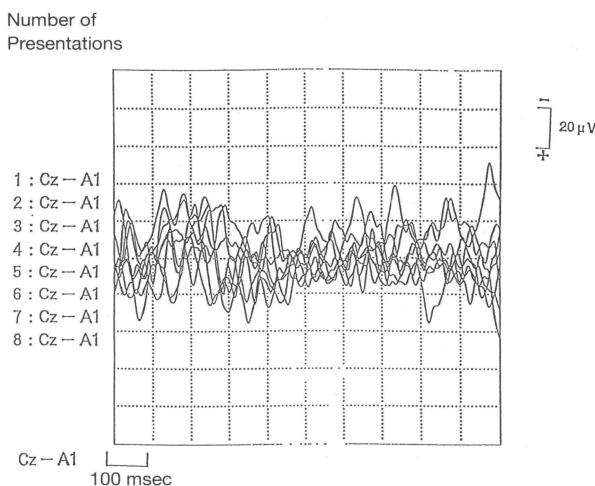

Figure 4. Evoked response to E5 (9.75% skatole, the highest concentration of skatole) in a normal young subject. Positive responses were rendered distinguishable by using superimposition technique before averaging.
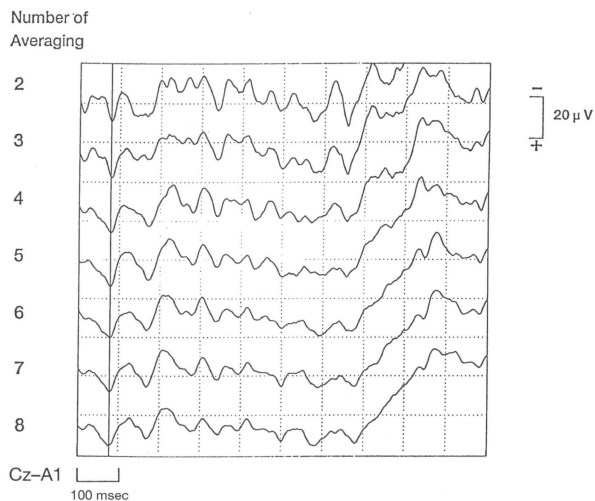
Figure 5. The averaged evoked responses to E5. The positive responses became obvious after averaging. Wave 8 represents eight times the total; thus, wave 4 to 5 showed the largest amplitude and wave 7 or 8 represented the clearest wave. The highest concentration of skatole (E5) evoked a positive response, with a peak latency of between 68 and 84 msec in eight normal young subjects.

averaging, and the positive response became obvious after averaging [4–7]. A saturation of responses was found after four to five averagings. Also, stimulating olfaction at a precise time is essential for discussing olfactory evoked response. Therefore, we decided to deliver the aerosolized odorant by pressurized air synchronized with a subject's inspiration.

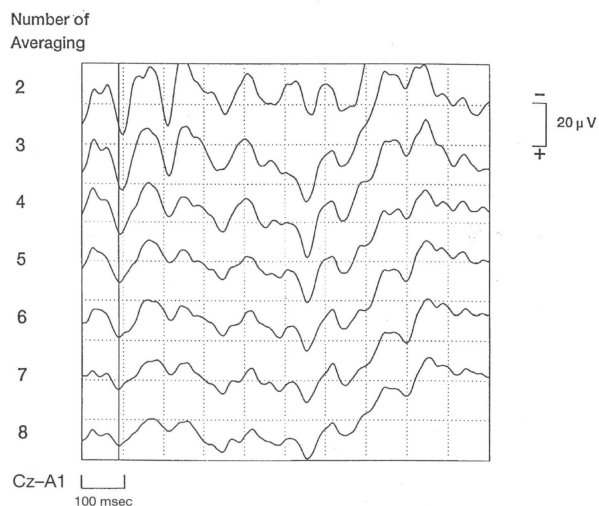A reproducible and stable response as recorded by our technique is obtained by a slow respiration with a

Figure 6. The evoked response to skatole (E4) in a 65-year-old man with Alzheimer's disease. As shown here, skatole evoked a rapid adaptation.
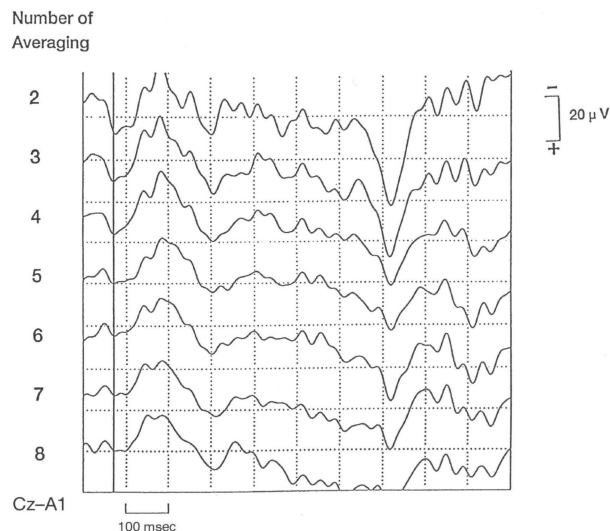

Figure 7. The evoked response to the highest concentration of skatole (E5) in same subject as in Figure 6. As shown here, a rapid adaptation was recognized more clearly on stimulation by the much higher concentrations of odorant.

constant rhythm. Introduction of an odorant stimulation at the end of inspiration or during expiration did not result in any detectable positive response. If slow and regular respiration is achieved, respiration will be repeated at a constant speed; consequently, the odorant air will be delivered to the olfactory fissure at a certain time in the same subject. No detectable response in the absence of the odor was noted, and glacial acetic acid, which is thought to be a trigeminal nerve–sensitive substance, evoked a negative response without detection of odor in anosmic patients [4–7]. Accordingly, the evoked response to skatole reported in this study was thought to be elicited mainly by odorant stimulation to the olfactory nerve.

Kobal and Hummel [2] reported that a change of peak latency depends on the odorant concentration presented. In their study, the shortening of peak latency was recorded by the much higher concentrated odorant stimulation.

In healthy aged subjects tested, saturation was recorded after four to five averagings, as it was in young normal subjects [4,6,7]. According to our results in healthy aged subjects, after eight averagings, the clear positive response was detectable. The olfactory threshold measured by chemosensory event–related potentials to olfactory stimulations were E−1, E0, or E1 (in young healthy subjects [7], E−1 or E−2). Most studies report an accelerating decline in the ability to smell after the age of 60 [8] but, in our results, the age-related change in the olfactory threshold by the evoked response technique was small. Age-related changes in the

olfactory threshold are considered to be affected by the alteration in respiration, with a decrease of lung capacity caused by aging. Hence, the age-related change in olfactory threshold was not very remarkable using our method of pressurized air delivering aerosolized odorant synchronized with a subject's inspiration.

Age-related changes occur in one's ability to perceive odors at both threshold and suprathreshold levels. Such changes are robust and include deficits in an absolute olfactory sensitivity, odor identification or recognition, suprathreshold odor discrimination, the perception of odor pleasantness, and odor memory [9]. Furthermore, aging is associated with a greater susceptibility to olfactory adaptation and a slower rate of recovery from such adaptation [9].

Recently, the alterations in smell function associated with age-related disease, such as Alzheimer's disease, became a current medical topic [9]. Now, a relatively large body of literature addresses changes within the higher sectors of the olfactory system of persons with Alzheimer's disease. The saturation phenomenon was related to the amplitude of the evoked potentials for repeated pulse stimuli and was found to be related to olfactory fatigue. At least two mechanisms are involved in adaptation: a quickly recovering central process and a slowly recovering peripheral process. The extent of adaptation appears to depend on both the strength and the duration of the preceding stimulation, and adaptation has a degree of specificity so as not to block the influx of new information. Adaptation is believed to be an important functional mechanism preventing overflow in the central parts of the system by neural activity resulting from stimuli that are either too strong or of long duration [10]. Rapid adaptation recognized in Alzheimer's disease may be caused by the dysfunction of the mechanism in adaptation of a quickly recovering central process.

In the future, the assessment of olfactory function with chemosensory event–related potentials to olfactory stimulations should be applied to the discussion of aging in olfaction and for the early diagnosis of Alzheimer's disease.

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