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The Current Status of Evaluation Technologies for the Function of Human Olfaction

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The sense of smell is one of the essential tools for all living things to survive. With recent increase in diseases associated with olfactory dysfunction, the evaluation of olfactory function aims to shed light on the understanding and assessment of the human olfactory system. The methods for assessing the olfactory function are largely divided into electrophysiological and psychophysical methods. The psychophysical inspections such as University of Pennsylvania Smell Identification Test (UPSIT), The Sniffin' Stick, and T & T Olfactometer are methods mostly based on questionnaires or simple apparatus. Those have been generally used in clinical and research field due to their relatively short examination time and low cost. The electrophysiological tests evaluate olfactory function based on objective measurements like biosignals and medical imaging. Compared to the psychophysical methods, they comparably have higher reliability and are possible to assess more specific diagnosis. However, the system configuration seems to be more complicated. In this paper, we review the overall evaluation methods of olfactory functions and suggest complementary points to improve conventional technologies.

Key Words: Olfactometry; Smell; Olfaction Disorders

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INTRODUCTION

The sense of smell is one of the essential tools for all living things to survive. For example, it enables them to escape from danger in advance or find food to sustain life [1,2]. For human beings, it also has been crucial function for better quality of life.

There has been a recent increase in diseases associated with olfactory dysfunction as shown in Fig. 1 [3]. Moreover, because many patients with olfactory dysfunction have often complained of their olfactory functions as well as reported of chronic pain, olfactory dysfunction must not be neglected anymore [4]. In addition, the olfactory function has been considered to be one of the biological markers associated with various diseases, such as Alzheimer's disease [5], Parkinson disease [6], multiple sclerosis [7], and brain tumor. Thus, the evaluation of olfactory function will shed some light to understand the function of the human olfactory system as well as assess the olfaction value in day-to-day life [2].

The methods for assessing the olfactory function are largely divided into electrophysiological and psychophysical methods. The psychophysical inspections such as University of Pennsylvania Smell Identification Test (UPSIT), The Sniffin' Stick, and T & T Olfactometer [7-9], are methods mostly based on questionnaires or simple apparatus. Normally, the evaluator presents a fragrance and then evaluates subjectively the subject's awareness of smelling, whereas the electrophysiological tests evaluate olfactory function based on objective measurement such as biosignals and medical imaging. In this paper, we review the overall evaluation methods of olfactory functions and suggest complementary points to improve conventional technologies.

METHODS FOR ASSESSING THE OLFACTORY FUNCTION

1. Psychophysical inspections

Psychophysical inspections are methods for evaluating the function of the sense of smell through the questionnaires and simple apparatus. Sniffin' Stick, the UPSIT and the Connecticut Chemosensory Clinical Research Center Test (CCCRC) have been gener-

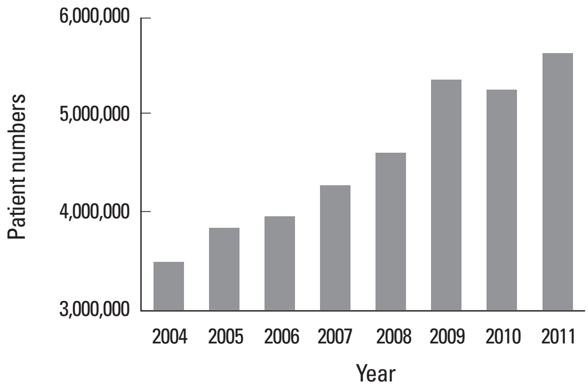

Fig. 1. Patient trends with olfactory disorders by year.

ally used in clinical and research field due to their relatively short examination time and low cost. However, the results aren't consistent and difficult to diagnose which olfactory disorder it is with such low reliability and the dependence on subjective response.

1) Sniffin' Sticks

Sniffin' sticks is a typical psychophysical method. It uses the tip of a pen (with 1.3 cm diameter and 14 cm in length) to present a specific scent. Using the stick, the scent is presented less than 2 cm in front of the nose and the olfactory stimulation within 3 seconds. The experiment must be done in a well-ventilated area and subjects are required to not ingest anything 15 minutes prior to the experiment. Three tests can be performed with Sniffin's sticks: olfactory threshold, identification and discrimination test. Between these tests, a break is required (3-5 minutes). Olfactory threshold test mainly uses butanol or phenylethylalcohol scent. Three sticks were presented to each subject in a randomized order, two contained the solvent and the other contained the odorant of a particular dilution. The task of the subject was to indicate the stick with the odorant. The three sticks were presented to a subject every 20 seconds, until they had correctly discerned the odorant. To help desensitization, experiment should have an interval (30-40 seconds) between each stimuli [10]. Olfactory discrimination test is performed by means of triplets of odorants. This test's evaluation method is similar to threshold test. Subjects are required to find a different odor in three odors. In olfactory identification test, odor stimulus is present. Then subjects identify the stimulus among the four presented. The successful identification of individual odorants from a list of four descriptors should be $>75\%$ in healthy subjects. In Korea, KVSS test (Korean Version of Sniffin' Sticks test), a modified type of Sniffin' stick was recently developed to reliably test Koreans [11,12]. In this test, all the odors in this test set have been changed to ones familiar to Koreans.

2) The University of Pennsylvania Smell Identification Test

UPSIT consists of 4 different 10 page booklets, with a total of 40 questions. On each page, there is a different "scratch and sniff" strip which is embedded with a microencapsulated odorant. The fragrances are released using a pencil or small knife. After each fragrance is released, the subject smells and selects one from the four choices [7].

Although there is no smell detected, it is still required that a subject chooses a response. There is an answer on the back of the test booklet, and the test is scored out of 40 items. The score is compared to scores in a normative database from 4,000 normal subjects. This tells the olfactory function level of absolute smell function. The score also indicates how the subject does in accordance to their age group and gender [13].

This test is occasionally judged to have an American cultural bias. There have British, Chinese, French, German, Italian, Korean and Spanish UPSIT versions made. There are called the Brief (Cross-Cultural) Smell Identification Test. It evaluates olfactory functions uses 12 odor capsules that are familiar with people from other cultures [14].

3) The Connecticut Chemosensory Clinical Research Center Test

Finally, the CCCRC exams threshold and identification [15]. The threshold test present three bottles composed of one diluted solution and the others of water. Then subjects identify the one with the diluted solution. If the subject fails to identify the correct bottle, a higher concentrated solution is presented. The identification test which uses 8 familiar odors is a method where subjects correctly identify one among the others. Then, the right answers were counted and scored to evaluate olfactory functions. T & T, which is used a lot in Japan, is an evaluation method that was derived from CCCRC. It uses five odors that are familiar to Japanese and each odor is divided by the concentration of eight odors.

2. Electrophysiological inspections

Electrophysiological inspection is one of the representative methods evaluating olfactory function based on biosignal measurement systems such as Magnetic Resonance Imaging (MRI), Magneto Encephalography (MEG), and Electro Encephalography (EEG). Compared to the psychophysical methods, it comparably has higher reliability and is possible to assess more specific diagnosis. However, the system configuration seems to be more complicated rather than psychophysical methods due to the need of additional systems such as the olfactometer, control unit and biosignal measurement system shown in Fig. 2.

1) Olfactometer

In order to measure precise physiological responses to stimuli, electrophysiological methods essentially require an olfactometer to provide quantitative odorant stimulation. Usually, it is companied by a control system (computer hardware and control software) to manipulate the switching valve used to supply odorants to subjects. Commercially available olfactometers are listed in Table 1.

These commercialized olfactometers have their own unique features such as MRI compatibility and pumplessness depending on the applicable fields such as aromatherapy as well as electrophysiological olfactory function test. However, those are generally very expensive and have limited functions. Thus, in order to overcome cost and functional problems, few researches suggested a new type of olfactometers. Washington and Lee University in 1999 has developed the MR compatible olfactometer [16]. It has various functions such as a computer-controlled injection, low production costs and the system construction with non-ferrous metals, which enables MRI based olfactory studies. Also, it is composed of commercially available products on the market. In 2004, University of Regensburg developed an olfactometer equipped with continuous positive airway pressure (CPAP) to be used on apnea patients during sleep. It is possible to provide odor stimulations in accordance with the breathing patterns. It can separate continuous air and odor air and maintain a constant temperature and humidity using a CPAP. In 2012, University Hospital Mannheim has developed an olfactometer which has been reduced in size. This results in an increase in portability and storability. In addition, using non-ferrous metals is MR compatible. Using a gas washing bottle, the apparatus has a function to generate an odor by maximizing the area of odor contact with air. Despite all these efforts to develop olfactometers, the associated research and development are still needed.

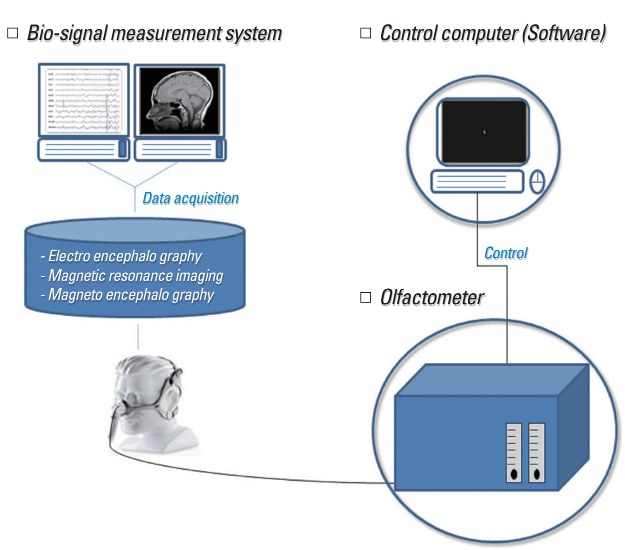

Fig. 2. System configuration of olfactory functional testing using biosignal.

2) The biosignals used for evaluating olfactory dysfunction

Evaluation methods of olfactory function on the basis of biosignals broadly consist of ElectroOlfactoGram (EOG), Olfactory Event-Related Potentials (OERP), and Magnetic Resonance Imaging (fMRI). EOG is an electrical potential changes in olfactory epithelium [17]. To begin with, the electrode is inserted to olfactory epithelium using endoscope. Then quantitative odor stimuli injected through nasal cavity induce action potential of olfactory cells. It could be measured via the electrodes in the epithelium. In general, it has been widely used to study animal's olfactory functions than human because of discomfort. Nevertheless, this method is known as the most objective inspection to evaluate the degree of the olfactory function and the central olfactory tract damage.

OERP is also one the objective methods to test olfactory function. It measures brain wave from the scalp, so called electroencephalography, when presenting olfactory stimulus to the nasal

Table 1. Commercialized olfactometers and their characteristics

Company	Product description
Cole-Palmer	- To identify the odors - Dividing single component type of odor
PHENOSYS	- Computer based flow control - Maximum 16 odors - Teflon tubing - Well mixing odors
ETT	- MR compatible - Maximum 6 odors - Tubing for noise reduction - 15 psi air pump - Ventilation systems
St. Croix Sensory, Inc.	- No need pump, available direct connection - Computer based valve control
Burghart	- Digital flow control - Humidity, temperature control - Computer based valve control

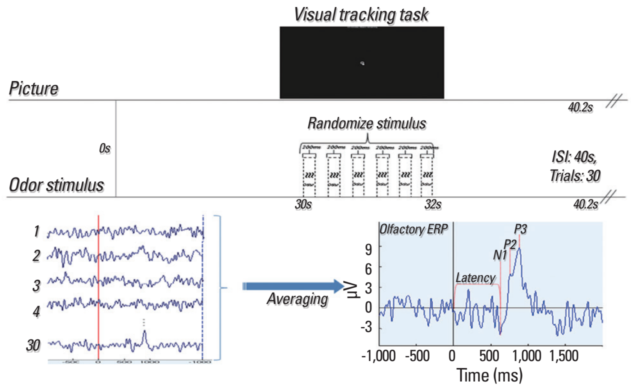

Fig. 3. The Olfactory Event-Related Potentials (OERP) Measurement paradigm.

cavity [18]. To acquire OERP signals, we record ten trial's EEG signal in minimum, then these signals are averaged due to the influence by physiological and environment noise as shown in Fig. 3. The other factor to be considered is breath in OERP. Nose breathing with irregular air inflow could lead to unreliable OERP response. Thus, breathing technique called velopharyngeal closure was suggested in OERP experiment [19], which is a method for breathing close the soft plate which divides the boundaries of the nose and mouth. The inflow of irregular air could be blocked by preventing the flow of air coming up from the oral cavity. The OERP has excellent time resolution that helps the continuous process research in olfactory information, and can be observed separately in an individual ERP propensity [20].

Lastly, MRI has been used for evaluation of olfactory function [21-23]. Because it gives three dimensional brain responses to olfactory stimuli, it is possible to investigate brain circuit related to the olfactory function. However, it was usually used in the research field rather than clinical field due to cost.

CONCLUSION

Psychophysical and electrophysiological inspections have their own pros and cons. The psychophysical test is easy to evaluate the olfactory functions in comparatively short time. But it has relatively low reliability than electrophysiological inspections because it mainly relies on an interview using questionnaires and do not present odor stimulus quantitatively, whereas the electrophysiological inspection is more objective and reliable because it is based on a biological response. However, in the clinical field, electrophysiological monitoring has not been utilized generally due to long inspection time and high cost.

There are some technical points to be addressed in electrophysiological monitoring in order for it to be widely used in the clinical field. First, the inter-stimulus interval (ISI) is a very significant determinant of the amplitude of electrophysiological inspections. At ISIs below 10seconds, the responses are much reduced in amplitude. This reduction may be related to the habituation or adaptation process. Maximal amplitudes are recorded at ISIs ranging 40-50 seconds or olfactory dysfunction [24]. In the case OERP, trials are performed 15 times at 40s ISIs, the examination duration would be 10 min, which is relatively long as a single examination at a clinic [25]. Second point to be considered is trigeminal responses in electrophysiological experiment. Depending on the type of odorants, not only olfactory nerve but the trigeminal nerve selection of odorant could be stimulated. Although ammonia, CO_2 can be classified as substances that stimulate the trigeminal nerve, some other odorants could also affect both olfactory and trigeminal nerves. Thus odor for the experiments must be chosen after careful consideration. However, trigeminal function can be additional clinical information towards the diagnosis of olfactory dysfunction because the two interact at multiple levels [26]. Thus, it would be better to get two ERP responses for olfactory and trigeminal function with a single OERP paradigm. For example, alternative simulation with two odorants (one for olfactory and the other for trigeminal) would be a good paradigm to reduce examination time and get more clinical information. Thirdly, and most importantly, the system for electrophysiological inspections should be compact and inexpensive for it to be easily available in the clinical field.

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