Olfactory Function Assessment

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Key Points

- Subjective smell tests allow the qualitative and quantitative assessment of olfactory disorders.
- Smell tests use substances at standardized fixed concentrations identifiable by healthy people, or at different concentrations to determine olfactory threshold.
- There exist rapid, reliable, and low-cost screening tests suitable for differentiating normosmia from smell impairment to be used in daily clinical practice.

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25.1 Introduction

The sense of smell is one of the oldest and most important for living organisms. It is responsible for detecting and processing odors, providing critical information about the environment to all species [1]. Assessment of olfactory function is a common problem in otolaryngology and other medical specialties such as neurology. There are diseases of great prevalence in the population that produce smell impairment such as rhinitis, nasal polyposis, Alzheimer's disease, major depression, diabetes mellitus, Parkinson Disease, etc. [2–4].

The olfactory process is initiated when odor particles in the airflow reach the olfactory epithelium and interact with odorant binding proteins (OBP). Perception is completed with cortical processing. Odorants mainly use two different routes to reach the olfactory epithelium: orthonasal and retronasal. Along the orthonasal route, volatile chemical compounds pass through the nostrils via the turbinates and eventually reach the olfactory epithelium. Conversely, the retrona-

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sal route requires a retrograde direction starting from the oral cavity, continuing through the nasopharynx and choana, ending at the olfactory mucosa [5]. As the orthonasal route serves as the primary source of olfaction, the retronasal route plays an important role in taste perception.

Olfactometry is a test that allows assessing the olfactory status of subjects in a normal or pathological situation, as well as quantifying the results and interpreting them. In clinical practice, smell tests together with an exhaustive physical examination can be useful to determine the presence and intensity of hyposmia, to identify a potentially treatable cause and to monitor its evolution over time. Likewise, it may allow us to establish the severity of the smell loss for legal purposes.

The examination of olfaction consists of electrophysiological and psychophysical tests and measurements. Electrophysiological tests assess cortical neural responses to an odor stimulus. Psychophysical tests, conversely, provide qualitative information about olfaction rather than the objective results obtained from electrophysiological recordings and thus are only employed for clinical symptom assessment [6].

Subjective olfactometry has considerable advantages over conventional methods based on the principles of analytical chemistry, since it allows measuring smell in terms of human perception instead of relying on incomplete assumptions about how odors behave and are perceived.

25.2 Subjective Smell Tests

The active collaboration of the patient is required in subjective smell tests. The subject must remain seated in a noise isolated room in optimal conditions of temperature and humidity. Neither the examiner nor the patient is allowed to use perfumes, lotions, or creams on the day of the test. The patient is given samples of substances to smell that give off different types of odors at different concentrations. The odorant samples are placed approximately at one to three centimeters from the nostrils and the subject is asked to breathe normally and might be asked to recognize certain characteristics of the odor such as: whether the subject identifies the odor and its intensity or perceives it as pleasant or irritating. Several substances are usually used at standardized fixed and identifiable concentrations by healthy people, or at different concentrations to determine the olfactory threshold. These tests have the advantage of using simple and transportable materials, which make them more practical in daily clinical practice. Most olfactometric techniques belong to this group.

25.2.1 Screening Tests

Screening tests for the sense of smell are designed to detect whether a patient has or not an impaired sense of smell. These tests should be fast, reliable, and cheap. A commonly known example is a series of bottles that contain certain odors such as coffee, chocolate, or perfume.

In recent years more sophisticated tests have been developed that are both reliable and easy to use [7]. Some examples are:

- *12-item Cross-Cultural Smell Identification Test* (CC-SIT) [8]: uses 12 selected odorants from the University of Pennsylvania Smell Identification Test (UPSIT). It is a self-administered olfactometry that evaluates the olfactory function in less than 5 min.
- *Japanese Odor Stick Identification Test* [9]: it consists of 13 odorants familiar to the Japanese population, quite different from those used in the other tests marketed. The odors used are described as: condensed milk, curry, hinoki (Japanese cypress wood), Indian ink, Japanese orange, menthol, perfume, rotten smell, toasted garlic, rose, sweaty clothes/natto (fermented soybeans), and wood.
- *Scandinavian Odor Identification Test* (SOIT) [10]: consists of 16 smells with four alternatives for forced-choice identification.
- *The Pocket Smell Test* [11]: very fast test, also derived from the UPSIT, administered in a disposable paper that releases three aromas through the scratch-and-sniff method.

All these tests are validated and well documented in the literature and, therefore, are currently used for the initial approach to an olfactory

disorder or to assess the olfactory function before nasal surgery. However, with screening tests you can only distinguish between normal or abnormal olfactory function. For a more detailed evaluation of an olfactory dysfunction, smell identification and threshold tests are required (Table 25.1).

Subjective determination of smell loss can also be quickly obtained by a psychometric scale such as the Likert scale (0–3) or the *Visual Analogue Scale* (VAS, 0–10 cm). VAS has been widely used in studies evaluating the effect of different olfactory disorders such as nasal polyposis

Table 25.1 Subjective smell tests validated for adult populations

Smell test	Author, year (country)	Supraliminar method	Threshold	Test duration (minutes)	Scoring
University of Pennsylvania Smell Identification Test (UPSIT)	Doty et al. [12] (USA)	40 encapsulated odors. Scratch and sniff. 4AFC	–	15	Reference values according to age and gender
Connecticut Olfactory Test (CCCRC)	Cain et al. [13] (USA)	10 odors, in jars. Forced- choice among 20 descriptors Separate nostrils	*n*-butanol. 2AFC. 4-correct-in-a-row	35	0–7 points scale: <2 anosmia 2–5 hyposmia 6–7 normosmia
Smell Diskettes	Briner et al. [14] (Switzerland)	8 diskettes that must be opened to release the odor. 3AFC	–	5	0–8 points scale: 0–6 hyposmia 7–8 normosmia
Sniffin' Sticks	Kobal et al. [15] (Germany)	Identification: 16 odors in felt-tip pens. 4AFC Discrimination: 16 odors in 3AFC. Identify the pen having the different smell	N-butanol in 3AFC. Single staircase method	25	Normosmia if >75% forced-choice identification Updated normative values according to age and gender in Oleszkiewicz A et al. [16]
Barcelona Smell Test (BAST-24)	Cardesin et al. [17] 2006 (Spain)	24 odors (semisolid gel) in glass jars. Evaluates detection, identification, and 4AFC identification	–	20	Reference values according to age, gender and smoking habit
European Test of Olfactory Capabilities (ETOC)	Thomas-Danguin et al. [18] (France, Sweden, The Netherlands)	16 odors in liquid flasks. Evaluates detection and 4AFC identification	–	20	Linear discriminant analysis using both detection and identification for estimating individual probabilities of being anosmic, hyposmic or normosmic [19]
Pocket Smell Test (PST)	Solomon et al. [11] (USA)	Based on UPSIT. Three encapsulated odors, scratch and sniff	–	<5	Normosmia if 2 or 3 correct identifications, hyposmia if 0 or 1 discriminates Alzheimer's dementia from major depression
Odor Stick Identification Test (OSIT-J)	Saito et al. [20] (Japan)	13 odors, solid cream applied in a paraffin paper. Four-plus alternative method and two-step identification method	–	8	0–13 points scale Normative values not available

(continued)

Table 25.1 (continued)

Smell test	Author, year (country)	Supraliminar method	Threshold	Test duration (minutes)	Scoring
Scandinavian Odor Identification Test (SOIT)	Nordin et al. [10] (Sweden)	16 odors in bottles. 4AFC	–	15	0–16 points scale Reference values according to age and gender
Combined olfactory test	Robson et al. [21] (United Kingdom)	Based on CCCRC Nine odors in opaque jars. 4AFC	*n*-butanol in plastic containers. 2AFC	–	0–9 points scale Normative values not available

AFC alternative forced choice paradigm

[22, 23], allergic rhinitis [24], or traumatic brain injury [25].

25.2.2 Smell Identification Tests

Qualitative olfactory tests allow the detection of alterations in perception and are used to evaluate a wide range of olfactory stimuli. The ability to recognize certain odors can be assessed by identification tests, while discrimination tests assess the ability to distinguish between different odors. Subjective smell tests can be performed on one or two nostrils. Some of the most used smell tests are shown in Tables 25.1 and 25.2, and described in detail below:

- *University of Pennsylvania Smell Identification Test* (UPSIT) [12] (Fig. 25.1). The model created by the University of Pennsylvania (USA) is a method that uses strips of paper covered by a layer of resin microspheres that contain the odoriferous substance (scratch-and-sniff method). It explores only the first cranial nerve and does not distinguish between the right or left nostril. It only values the correct knowledge of the smell. It is presented in cases of 40 odors along with response curves, depending on age and sex. The UPSIT has the advantages of not requiring trained personnel to do it, so the patient can perform the test at home, and that it is very easy to handle because of its small size. In addition, there are normative values curves and the containers are sealed, reducing the problem of volatility and the progressive reduction of the concentration of odors.
- *Smell Diskettes* [14] (Fig. 25.2). The Swiss model is simpler. It consists of 8 odorants housed in a disk-shaped case. The concentration of the odor is uniform and unilateral nasal examinations can be carried out. As in the UPSIT model, it only considers the "correct answer" as the sole value of the olfactory function.
- *Sniffin' Sticks* [15] (Fig. 25.3). This test developed in Germany is widely spread for its simplicity and reliability. It uses pen-shaped containers with odorants in different concentrations, which allows to assessing the detection threshold (*n*-butanol) and the discrimination olfactory capacity (forced-choice for 16 pairs of odorants) in addition to the identification and olfactory memory (16 odorants for forced identification from four options). Normative values based on a sample of more than 3000 subjects were defined [35]. Additionally, it has been validated for use in the pediatric population [36].

Recently, an update on the Sniffin' Sticks normative data has been published [16]. Data were obtained from 9139 healthy subjects (aged 5–96 years) and hyposmia was established at a TDI (threshold, discrimination, and identification) score of less than 30.7. Age-related changes were found in each domain, more pronounced for thresholds. Individuals aged 20–30 years performed best, whereas children below the age of 10 years and adults above the age of 71 years

Table 25.2 Subjective smell tests validated for children population

Test name	Author, year (country)	Odorants and methods	Age range (year)	Scoring system	Performance in pre-school children
Pediatric Odorant Identification Task (POIT)	Richman et al. [26] (USA)	Five microencapsulated "scratch and sniff" cards. 5AFC	4–17	Percentage of correct responses is transformed to a logit	The 5 odors were correctly identified by 80% of children as young as 5 years of age
Candy Smell Test (CST)	Renner et al. [27] (Germany)	Retronasal smell. Twenty-three hard candies, containing sorbitol and one unique aroma. 4AFC	4–85	0–23 points scale: Reference values according to age and gender Score < 13 for detecting anosmia in all age groups	Significant lower scores were obtained in children aged 4–6 years These children more often declared items to be unfamiliar
National Institutes of Health (NIH) Toolbox	Dalton et al. [28] (USA)	Six microencapsulated "scratch and sniff" odors. Picture recognition. 4AFC	3–17	0–6 points scale Normative data not available	Time for testing was longer in children <5 years of age Percent of correct identification in 3-4yo children was below 63% for all odorants [29]
Smell Wheel	Cameron et al. [30] (USA)	Cardboard wheel or disk that rotates with 11 scratch and sniff odorants. 4AFC	4–19	0–11 points scale (percentage)	Mean correct identification score was lower than 70% for 4–6 yo children
Sniffin' Kids	Schriever et al. [31] (Germany)	14 odors in felt-tip pens. 4AFC. Descriptors presented in writing and in pictures	6–17	0–14 points scale Normosmia: 6–8 yo >7 9–14 yo >8 15–17 yo >10	Not included
Universal Sniff Test (U-Sniff)	Schriever et al. [32] (multinational)	12 odors in felt-tip pens. 4AFC. Descriptors presented in writing and in pictures	6–17	0–12 points scale Normative data reported for each country	(multicenter study involving 19 countries)
Pediatric Barcelona Olfactory Test (pBOT-6)	Mariño-Sánchez et al. [33] (Spain)	• Identification task: 6 odorants (semisolid gel) in glass jars. • Threshold test: 6 sniff bottles with dilutions of PEA in a geometric series.	6–17	0–6 points scale. Normosmia (IS): 6–11yo >4 12–17yo >5 Normosmia (TS): <2	Not included

AFC alternative forced choice paradigm, *yo* years old, *IS* identification score, *TS* threshold score, *PEA* phenylethyl alcohol

Fig. 25.1 University of Pennsylvania Smell Identification Test (UPSIT) [12]. The picture on the right shows the release of the microencapsulated odorant from the surface of strips by means of a pencil and the four-multiple forced-choice list

Fig. 25.2 Smell Diskettes test [14]. The eight odorants are presented in a disk-shaped case, when opening it releases the odor. The test includes sheets with pictures and names of the three forced-choice options

scored only half as well. Sex-related differences were also found with women outperforming men.

- *Connecticut Chemosensory Clinical Research Center* (CCCRC) [13]. This American model comprises two parts: the threshold test (with *n*-butanol) and the supraliminar test consisting of eight opaque jars. Subjects then choose from a printed list containing the correct items as well as an equal number of distractor items. It is easy to manufacture and cheap. However, it needs a lot of time to be performed and must be carried out by qualified personnel.
- *Barcelona Smell Test-24* (BAST-24) [17] (Fig. 25.4). It is a model developed in Barcelona (Catalonia, Spain) that consists of 24 semisolid

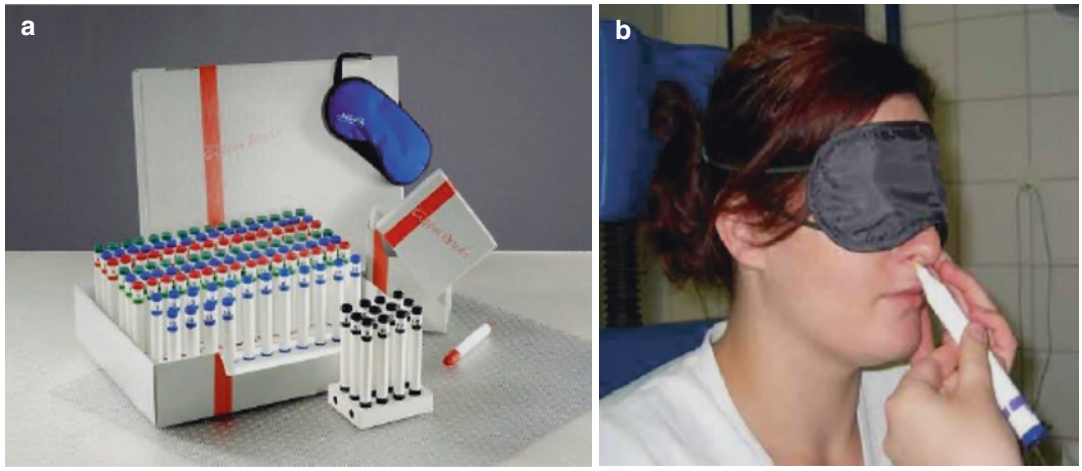

Fig. 25.3 Sniffin' Sticks [15]. Reproduced from Welge-Lüssen et al. [34]. (**a**) Pen-shaped containers with odorants in different concentrations. (**b**) During the threshold test the subject is blind folded to prevent visual identification of the odorants

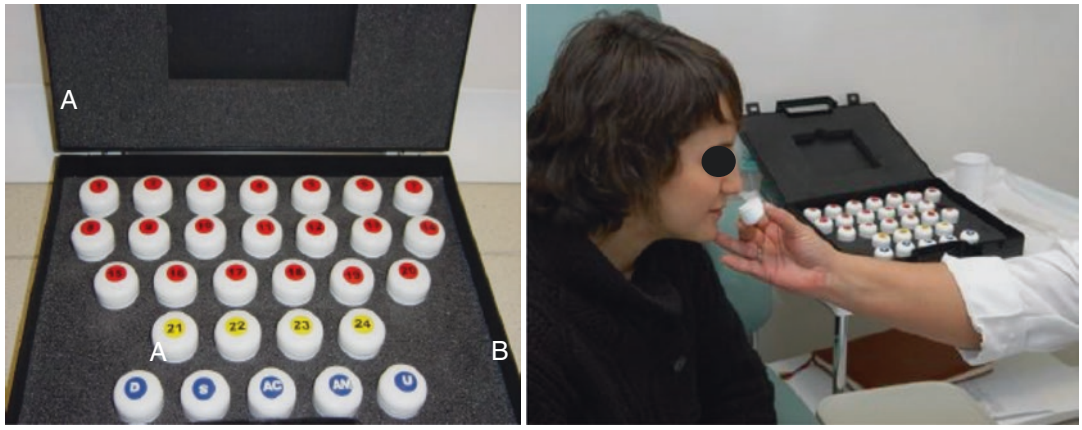

Fig. 25.4 Barcelona Smell Test-24 (BAST-24) [17]. (**a**) BAST-24 briefcase with the 24 odorants (the last 4 predominantly stimulate the trigeminal nerve) and the gustometry (sweet, salty, sour, bitter, and umami). (**b**) Performing the olfactometry, note that the container is a few centimeters apart from the nose of the subject

odorants contained in hermetic glass jars, and 5 additional substances to assess taste. From the 24 odorants, 20 predominantly stimulate the first cranial nerve and the other 4 predominantly stimulate the fifth cranial nerve. The test includes questions for the evaluation of different sensorial aspects of olfaction such as detection, memory, and forced-choice identification among four options (also sensitivity such as odor intensity, irritability, freshness, pleasantness). It differs from American and other European models by its ability to analyze different olfactory characteristics such as quantitative detection, smell memory area, spontaneous recognition, and the correct identification of odors. Any smell assessment should be complemented with a taste examination. BAST-24 includes a chemical gustometry using five substances: sweet, salty, bitter, acid, and umami (glutamate).

25.2.3 Smell Tests in Children

Most of the above-mentioned tests have been used in children despite they are not well suited

Fig. 25.5 Smell Wheel [30]. This olfactory test specially designed for children has a game-like presentation, the patient has to scratch and sniff the odor and choose between four options

for them due to the lengths of the test and unfamiliarity of some of the odors. To date there are a few odor identification tests, which have been especially developed for children (Table 25.2).

- The "*Sniffin' kids*" [31] and the *Smell Wheel* [30] are two of the most used smell tests in children (Fig. 25.5). The "*Sniffin' kids*" is a 14-item test that includes selected odors from the original Sniffin' Sticks 16-item odor identification test. It has been validated for children aged 6–17 years and normative data for three age groups is available. The *Smell Wheel* is a game-like test presented as a cardboard disk that rotates within an outer jacket, showing one microencapsulated "scratch and sniff" odorant. Both pictures and words are provided in the four-alternative forced choice task to reduce cognitive/linguistic load and potentially to improve performance. Normative values are not available.
- The *U-Sniff* test [32] is a new international odor identification test for children that contains 12 odor items presented as pen-like sniffin' sticks. This test does not include a threshold test. The U-Sniff is administered in a four answer forced choice model using image and name of odors. It has been recently validated across 19 different countries.
- The *pediatric Barcelona Olfactory Test (pBOT-6)* [33] is a smell test recently validated in 6- to 17-year-old Spanish children. It consists of a set of six odorants for a forced-choice identification test and six dilutions phenylethyl alcohol geometric series for the threshold test. It is a fast screening method that distinguishes, with high sensitivity and specificity, between normosmia and smell dysfunction.

25.2.4 Threshold Tests

The quantitative tests measure the threshold levels of smell with certain odorants in order to quantify the olfactory loss. In general, these tests require more time than the smell identification tests, and they are useful to complement the evaluation of the degree of olfactory loss (anosmia, hyposmia, or normosmia).

Nowadays, there are many olfactory threshold tests available; most of them use *n*-butanol as an odorant, although phenylethyl alcohol (rose odor) has also been used. One study [37] compared both substances for threshold tests obtaining similar and reproducible results.

The objective is to find the lowest concentration of an odorant that the patient is able to detect, starting from the weakest dilution. The threshold testing does not require recognition of the smell [38]. Some examples of this type of widely spread tests are the Connecticut Test—CCCRC threshold test [13], which consists of 8 dilutions of *n*-butanol; the Sniffin' Sticks [15], which has 16 dilutions of n-butanol and the Smell Threshold Test that measures the threshold of phenylethyl alcohol in 17 half-log concentration steps [18].

Another instrument to measure olfactory thresholds are the olfactometers. These machines are designed to release odorants at very precise concentrations. Currently olfactory threshold olfactometers are mainly used experimentally [39].

One example of the latter is the T & T Olfactometer [40]. It was developed in Japan and

Fig. 25.6 T&T olfactometer [40]. The T&T olfactometer evaluates the detection and recognition thresholds for each of the five odorants. Reproduced from Miwa et al. [41]

consists of five odorants: β-phenylethyl alcohol, methyl cyclopentenolone, isovaleric acid, γ-undecalactone, and scatol and evaluates the detection and recognition thresholds for each stimulus. The detection threshold is defined as the lowest odorant concentration detected by a subject, whereas the recognition threshold is defined as the lowest concentration at which the odor could be identified (Fig. 25.6).

In general terms, these tests measure the olfactory performance and allow us to separate the anosmic and normosmic patients to evaluate in more detail the hyposmic patients. However, the olfactory tests have their limitations, especially when evaluating children, people with cognitive impairment or people from different cultural backgrounds. The complexity of some tests, the cost of the olfactory threshold kits, and the time required to perform the tests have prevented many physicians from adequately evaluating this specific group of patients and, therefore, these tend to be concentrated in specialized centers.

25.2.5 Objective Smell Tests

The objective evaluation of the sense of smell is complex and is based on the detection of changes in the central nervous system caused by olfactory stimulants. In patients who are not able to collaborate or simulators, objective tests are the only way to study for certain sense of smell.

Objective tests do not require the active collaboration of the patient since they register a brain response from an odor stimulus. A single substance is usually used at a very low concentration. They have the advantage of not depending on the active participation of the patient and the inconvenience of needing very complex devices, a lot of time and space, which delays the examination.

- A well-established test is the *Olfactory Event-Related Potentials (OERPs)* [42], which consist of the collection of the electrical activity (olfactory bulb and/or frontal cortex) by means of external electrodes while presenting the patient with odors. Normative data according to age is available [43].
- Another research tool to study smell is the *Olfactory Electrogram* which consists of recording the magnitude of the electrical activity of the nasal olfactory epithelium by applying intranasal electrodes. When an odorant activates the cellular receptor, a negative potential is generated, followed by a recovery potential, and this can be measured using electrodes placed on or near the surface of the olfactory epithelium. There has been little clinical application of olfactory electrogram, due to the low tolerance to intranasal electrodes, and the difficulty of placing them. In addition, reliable responses in the EOG are maintained for very short period of time [24].

New functional imaging techniques include olfactory functional magnetic resonance imaging (fMRI) and functional positron emission tomography that allow direct visualization of central changes caused by olfactory stimuli.

- The olfactory fMRI (Fig. 25.7) allows to study the brain activity in a noninvasive way, while the subject performs a certain task, thanks to the detection of small changes in the signal depending on the level of oxygen in the hemoglobin. The olfactory fMRI identifies the cortical areas that are activated in different areas of the brain in the presence of an olfactory stimuli: entorhinal cortex, tonsil, insula, puta-

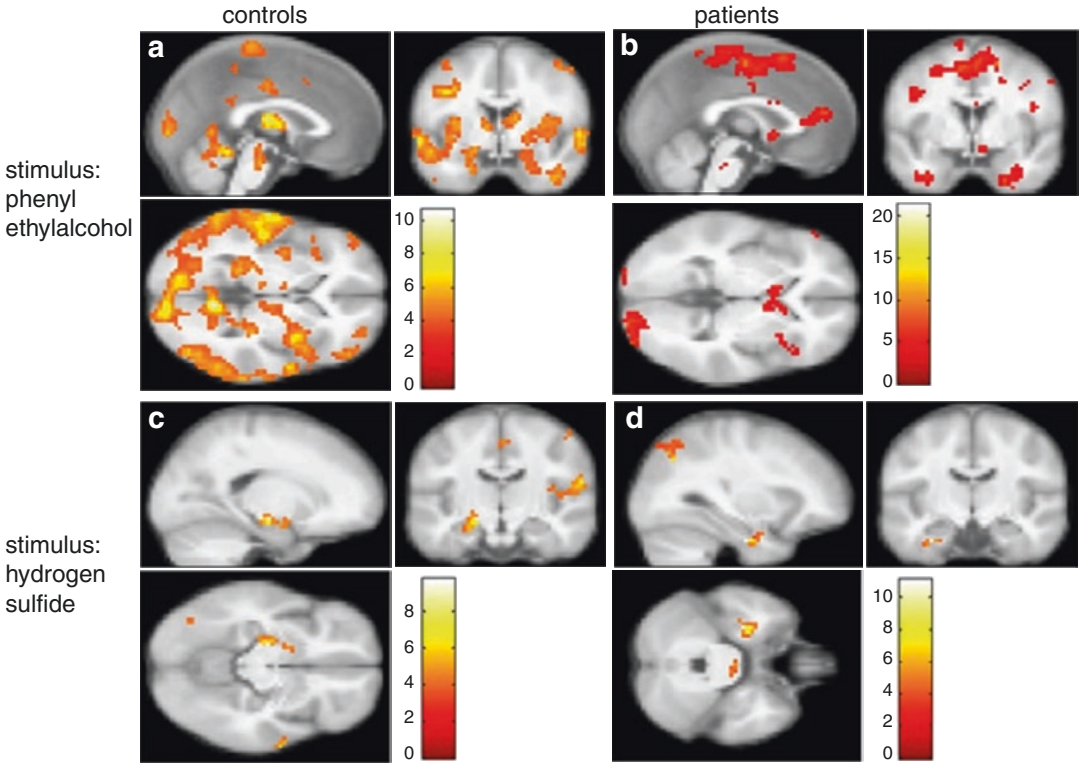

Fig. 25.7 Olfactory fMRI showing brain activation found in controls and in Parkinson Disease after presented of rose odor (phenylethyl alcohol) (**a** and **b**) or the unpleasant odor of rotten (hydrogen sulfide) (**c** and **d**). Reproduced from Hummel et al. [44]

men, and visual cortex [45]. The fMRI has been used very little in the clinical evaluation of olfactory alterations, largely due to the practicality, cost, and the fact that olfactory alterations are easier to detect and quantify through less expensive means [44].

25.3 Translation into Future Daily Practice

- Advances in technology and the proliferation of simple tests to measure olfactory function have improved knowledge of the sense of smell in humans, in both health and disease. To date, multiple smell identification tests have been developed for clinical use, in both adults and children, and validated in different countries.
- All the subjective olfactometries mentioned in this chapter are validated and well documented in the literature and are used today for the first evaluation of olfactory disorders, in clinical trials, or to assess smell function before and after medical or surgical treatment. Globally, olfactometries allow the physician to establish the diagnosis of an olfactory disorder and provide insights into the quantity and diversity of smells that can be detected, recognized, discriminated, or identified by a subject.

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