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Smell dysfunction from symptoms to diagnosis – recent methods of olfactory function assessment

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Abstract
Sense of smell poses an incredibly significant aspect of our life, it has been present from the beginning of our existence and its role in maintaining the well-being of our organism is non-sustainable. Olfactory system dysfunctions have a negative influence on general health status, psychological condition and quality of life. Smell detection disturbances can not only lead to loss of pleasant feelings or basic defence mechanism deficiency, but also may be symptoms of serious ongoing or commencing diseases.
The authors aimed to present in this article the most important information on physiology of olfaction system, most recent methods of examination and possible causes of smell dysfunction.

A systematic review of the literature concerning smell examination was conducted including both previous review articles and original papers.
Smell assessment remains an enigmatic branch of medicine, qualified personnel and special equipment which would enable to fully and reliably evaluate the condition of olfactory function is still not widely available. It seems that serious consideration of patients' complaints on odour perception, directed and complete investigation of reported dysfunctions, and adequately adjusted multidisciplinar treatment would be effective according to both, quality and length of patients' life.

Introduction and purpose of work

Sense of smell in one of the least investigated senses in human body and surely the most mysterious one. It's basic role is to identify odours. However, the significance of olfaction function for our psychical and psychological well-being remains underestimated. What is more, disturbances in smell detection are commonly ignored by both, patients and physicians. Dysfunction of this ancient sense exacerbates quality of life and sometimes may be the first symptom of neurological diseases such as brain tumours or neurodegeneration [1].
The authors aimed to present in this article the most important information on physiology of olfaction system, most recent methods of examination and possible causes of smell dysfunction.

Description of knowledge

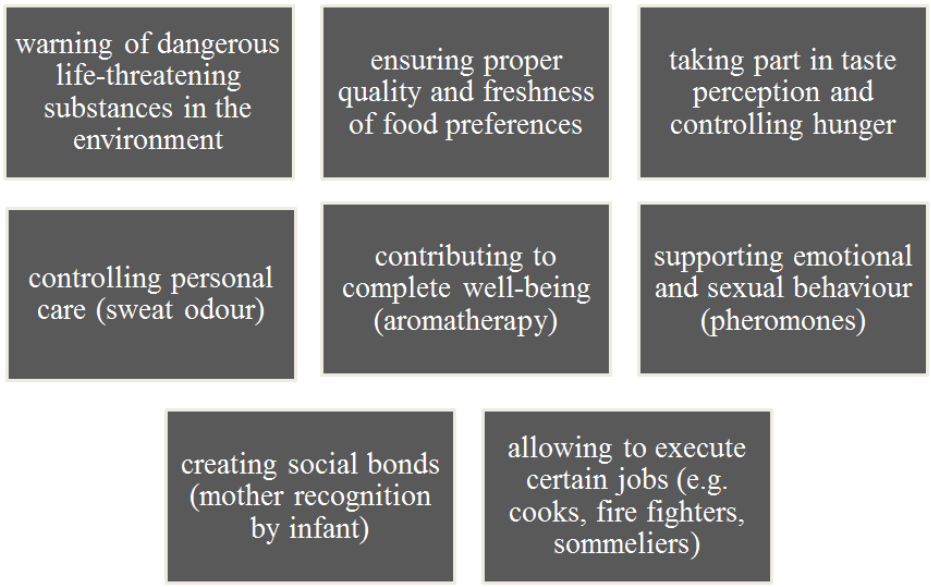
Relevance and functions of olfactory system

Odour reception system is phylogenetically considered as one of the first senses in human body, while cortical areas responsible for smell stimuli analysis are located in the oldest regions of the brain. Despite general misconception the ability to receive odorant information encourages us from the beginning of our life – it enables newborns to recognise their mother and takes part in sucking reaction initiation [2]. Not only we are able to notice odours in the environment, but also the olfactory system is involved in countless processes: taste perception, saliva and gastric acid secretion; it warns the organism of dangerous substances in our surroundings, facilitates hygienic condition supervision, supports the reception of aesthetic sensations and desirability perception (Table 1., Figure 1.).

Table 1. Functions of olfactory system

Basic	odour perception
	odour concentration measurement
	odour identification
	odour classification (pleasant/unpleasant)
Superior	odour differentiation
	odour memorization
	odour integration

Figure 1. Significance of olfactory system



Olfactory system

Since the nervous route of olfactory system consists only of three nerves, the sense of smell is the fastest one to be driven [2]. The olfactory neurons originate in the olfactory epithelium, which is located in the superior aspect of nasal cavities. Human olfactory cleft measures up to 9 cm^2. These bipolar neurons are responsible for odorant reception – each equipped with 8 to 20 fibres which extend out to the nasal cavity airspace – and stimuli transmitting via axons through the holes in the cribriform plate of the ethmoid bone (olfactory nerve fascicles). Olfactory neurons synapse with dendrites of second-order neurons (mitral cells) – creating olfactory glomeruli – within olfactory bulbs. Mitral cells axons leave the olfactory bulb in the lateral olfactory tract and lead directly to the olfactory tubercle and anterior perforated substance. The last neuron of olfactory system is located in rhinencephalon – anterior olfactory nucleus, the amygdala, the piriform cortex, and the entorhinal cortex [3,4].

Evaluation of olfactory function

Nowadays, olfactory function can be examined by several methods, not always available for any practitioner. For the purpose of this article we divided them into two groups: subjective and objective (Table 2.).

Table 2. Methods of olfactory system evaluation

Subjective	NHANES Pocket Smell Test
	UPSIT (University of Pennsylvania Smell Identification Test)
	BSIT (Brief Smell Identification Test)/ CC-SIT (Cross-Cultural Smell Identification Test)
	CCCRC (Connecticut Chemosensory Clinical Research Center Test)
	Sniffn' Sticks Test
	Blow olfactometry by Elsberg-Levy modified by Pruszewicz
Objective	OERPs (Olfactory Event-Related Potentials)
	EOGs (Electroolfactography)
	medical imaging techniques e.g. MRI, PET

MRI – Magnetic resonance imaging PET – Positron emission tomography

Subjective methods

These methods are based on psychophysical olfactometry. The basic rule of all test is simple – the odours are presented to the patient and then their presence shall be signalized. Some of commercially available tests are based on choosing the name of detected smell from a list of possible answers. There are also methods that allow to estimate the detection threshold, identification threshold or discrimination threshold. The smell identification threshold depends on variety of factors, e.g. odour memory, associating processes in the central nervous system or general intelligence. Therefore, smell detection threshold is believed to be more reliable [5]. The most popular subjective methods of smell examination are: the family of UPSIT tests (University of Pennsylvania Smell Identification Test), Sniffin' Sticks method and blow olfactometry.

NHANES Pocket Smell Test seems to be a useful screening method – it is cheap, quick, easy and safe for the patient; the test consists of two books each containing four scented spots (chocolate, strawberry, smoke, leather, soap, grape, onion and gas) [6]. The patient has to identify the smell by choosing one of four presented answers. The impairment of smell should be suspected when six or more substances are not named correctly; that cases should be followed by more precise diagnostics including other methods of subjective assessment (authors of this method suggest UPSIT) or objective tests.

UPSIT, the longest-standing test, performed mostly in USA, consists of forty microencapsulated odour samples, including smells of specific plants, foods or household cleaning products [7]. That method can be prosecuted at the hospital, clinic, as well as at patient's home. Naming correctly at least thirty-four presented samples can be clinically interpreted as normal olfactory function; score between six and eighteen suggests anosmia, while identifying less than six smell could imply patient malingering [8]. Nowadays, due to large amount of presented samples, UPSIT became less popular. There are many authors all over the world who try to modify and decrease number of substances used in smell investigation; some of them created tests specific for particular populations, adjusted geographically and culturally.

BSIT (Brief Smell Identification Test) or CC-SIT (Cross-Cultural Smell Identification Test) is one of the mostly performed UPSIT modifications [9]. This test gained its popularity due to reduction of samples to twelve odours (six foods and six non-foods), which are widely recognisable for almost every population; on that grounds this method is faster to perform and could be useful in studies of wider range.

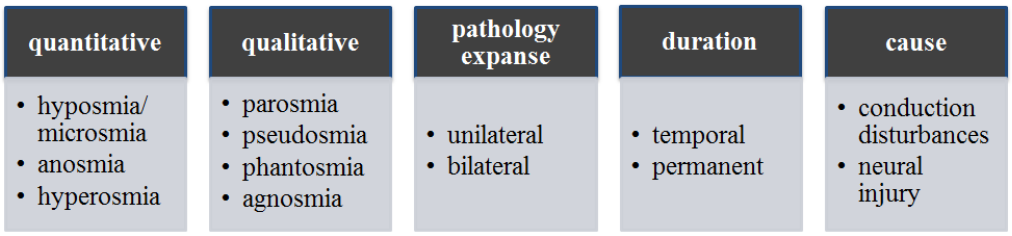
CCCRC (Connecticut Chemosensory Clinical Research Center Test) is another subjective method, which allows evaluating ability of odour detection and recognition [10]. The test consists of two parts; firstly, the patient is presented with two bottles – one containing water and one containing dilute concentration of butanol - and has to choose the bottle filled with butanol. The trials are repeated with gradually augmented concentrations until the patient correctly identifies the non-water bottle. The next step requires identification of presented smell from the list of 20 possible answers. At least ten samples have to be tested to make that step reliable. Moreover, the analyzed odours stimulate either olfactory nerve or trigeminal nerve. The score is then compared to control group results.
Sniffin Test is performed with use of special pens moistened with odour substance [11]. The end of the stick is placed approximately 2 cm under the nostrils; in order to completely evaluate one's olfactory function three trials need to be performed. To define the detection threshold the patient is presented with three samples and has to choose one with smell substance (other two contain dissolvent). In this part different substances could be used – butanol or phenylethanol – and commonly consists of sixteen trials with gradually augmented concentrations of above mentioned substances. The second part of Sniffin Test is performed in order to assess the discrimination threshold and the patient is presented with three samples from which he has to choose one that is different from two others. Also that part consists of sixteen trials. The last part is the identification test – the patient is presented with sixteen commonly recognized scents and has to name it choosing from a list of four possible answers. Sniffin Test seems to be a valuable method, which provides detailed information on patient's olfactory function. Some modifications of that test require fewer trials in each part, which significantly reduce the time of procedure [12].
Blow olfactometry by Elsberg-Levy modified by Pruszewicz involves passing specific portions of air containing a known amount of odour molecules into nasal cavity [13]. This method allows to estimate the detection and identification threshold of different substances including peppermint oil, lemon oil, vanilla oil and freshly ground coffee. Threshold concentrations are presented as grams of substance per litre or amount of molecules per 1 cm^2. According to high prices of the equipment as well as complicated and long investigation procedure, this method is less popular compared to other subjective methods of olfactory function assessment.

Objective methods
The most common procedures performed to assess the olfactory function are recording the olfactory event-related potentials (OERPs) and electroolfactography (EOG).
Olfacory event-related potentials (OERPs) are a response to chemical stimulation of nasal oflactory mucosa [14]. During this procedure the changes in bioelectric activity of the brain after olfactory system stimulation are recorded; the potentials are measured by electrodes placed on the patient's scalp over temporal and insular cortex. Scents most commonly used include vanilla, phenylethanol and hydrogen sulphide. In order to evaluate smell function odour stimuli of specific concentration, time of exposure and known influence on either olfactory or trigeminal nerve are presented. Due to above mentioned conditions and need of multiple trials, gathering reliable results is elaborate. However, this procedure allows to differentiate between anosmia, hyposmia and normosmia.
Electroolfactography (EOG) is a procedure that enables to investigate nasal mucosa function – changes in olfactory region potentials as answer to odour stimulation are recorded [15]. The results are collected with use of electrode placed – during endoscopic procedure performed in general anaesthesia– into smell epithelium; the control electrode is located on the nasal root. This method can reliably confirm/deny the neural cause of olfactory dysfunction.
Many authors investigate functional magnetic resonance imaging (fMRI) or positron emission tomography (PET) usefulness in olfactory function evaluation. These methods show alterations of blood flow and cellular metabolism changes within olfactory bulb, which indirectly indicates reception of smell stimuli [8].

Smell dysfunction

The most commonly odour reception disturbances are result of upper respiratory tract infections and diseases of nasal lining or sinuses; however, there are countless other causes of olfactory function insufficiency [3, 16, 17]. There are many classifications of smell dysfunctions depending on specific criteria (Fig. 2). The authors of the paper decided to elaborate smell dysfunction classification considering possible causes of these symptoms.

Figure 2. Olfactory dysfunction



Disorders of conduction result from hindered interaction between smell substances and olfactory epithelium; usually caused by restricted nasal passage. Diseases that could be responsible for this mechanism include: congenital and post-surgery abnormalities, nasal polyps, deviated septum, turbinate swelling, allergic rhinitis, asthma, sinusitis, neoplasm blocking olfactory cleft.

Neural injuries could affect olfactory tract – direct injury of olfactory epithelium, olfactory fascicles disruption or olfactory bulb damage – or rhinencephalon. Those mentioned in the first place can be caused by numerous pathological processes, e.g. acute viral infections, chronic atrophic rhinitis, toxic injury (medications – aminoglycosides, corticoseroids, smoke, particulates), cocaine usage, head injuries including base of skull fractures, tumours located in frontal lobe or anterior cranial base, esthesioneuroblastoma and iatrogenic injuries after rhinosurgery.

Olfactory dysfunction resulting from changes located in central nervous system could be cause by vascular disorders, demyelinising processes (e.g. multiple sclerosis) or brain tumours; smell misperception is one of basic symptoms of Kallmann syndrome and Kartagener syndrome (primary ciliary dyskinesia). Hyposmia and anosmia may be first symptoms of neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, Huntington's disease [18]. Metabolic abnormalities, like diabetes, can gradually lead to smell loss due to macroangiopathy manifested as ischemia localized in olfactory cortex [19]. When searching for possible conditions associated with olfactory dysfunction, we can't forget about epilepsy or migraine.

Conclusion

Olfactory system allows to maintain psychical and physical well-being; if it is undisturbed it provides high quality and safety of life. Any disturbances concerning smell sense should not be ignored.

First step towards correct evaluation of olfactory dysfunction must entail complete and detailed medical history and thorough physical examination; some of the cases require neurologic or laryngological examination followed by reliable smell assessment. Further research may require performing laboratory tests for reversible causes of presented symptoms (malnutrition and mineral deficiency, metabolic abnormalities, endocrinologic diseases, intoxication). Medical imaging also may be helpful – MRI, and more appropriate computed tomography when sinusitis is suspected.

Overall, profound analysis of patient's afflictions, brief and complete diagnostic path and multidisciplinary care facilitate full comprehension of smell dysfunction aetiology and choice of proper therapy.

Summary
Introduction: Sense of smell poses an incredibly significant aspect of our life, it has been present from the beginning of our existence and its role in maintaining the well-being of our organism is non-sustainable. Olfactory system dysfunctions have a negative influence on general health status, psychological condition and quality of life. Smell detection disturbances can not only lead to loss of pleasant feelings or basic defence mechanism deficiency, but also may be symptoms of serious ongoing or commencing diseases.
Purpose of work: The authors aimed to present in this article the most important information on physiology of olfaction system, most recent methods of examination and possible causes of smell dysfunction.
Brief description of the state of the art: A systematic review of the literature concerning smell examination was conducted including both previous review articles and original papers.
Conclusions: Smell assessment remains an enigmatic branch of medicine, qualified personnel and special equipment which would enable to fully and reliably evaluate the condition of olfactory function is still not widely available. It seems that serious consideration of patients' complaints on odour perception, directed and complete investigation of reported dysfunctions, and adequately adjusted multidisciplinar treatment would be effective according to both, quality and length of patients' life.

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