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Relation between Olfactory Cleft Endoscopic Findings, Olfactory Metrics, and Quality of Life

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Table of Contents **Page**

Abbreviations

AD	Alzheimer's disease
AN	Agger nasi
AR	Allergic rhinitis
BOLD effect	Blood Oxygenation Level-dependent effect
CCCRC	Connecticut Chemosensory Clinical Research Carried out Test
CCSIT	Cross-Cultural Smell Identification Test
CRS	Chronic Rhinosinusitis
CT	Computed Tomography
ESS	Endoscopic Sinus Surgery
FDP	Frontal drainage pathway
fMRI	Functional Magnetic Resonance Imaging
MALT	Mucosa-associated lymphatic tissue
MS	Multiple Sclerosis
MRI	Magnetic Resonance Imaging
MT	Middle turbinate
NC	Nasal cycle
NO	Nitric oxide

NP	Nasal polyposis
OB	Olfactory bulb
OE	Olfactory epithelium
OECs	Olfactory ensheathing cells
OERPs	Olfactory event-related Potentials
OMC	Ostiomeatal complex
OSN	Olfactory Sensory Neurons
OT	Olfactory training
PEA	phenyl ethyl alcohol
PET	Positron emission tomography
PD	Parkinson's disease
POC	Primary Olfactory Area
QOL	Quality of Life
SIT	Smell Identification Test
SNOT-20	Sino-Nasal Outcome Test
SNOT 20 GAV	Sino-Nasal Outcome Test German adapted version
TDI score	Threshold Discrimination Identification score
TUD	Technischen Universität Dresden
UP	Uncinate Process
UPSIT	University of Pennsylvania Smell Identification Test

Abstract

Olfactory disorders affect about 22% of the general population (Vennemann et al. 2008). Although most of the times neglected, many patients present a remarkable reduction in the general quality of life (QOL). This study has compared and correlated many variables in two populations based on smell complaint. First, using questionnaires, tried to evaluate its impact on the QOL. In a second stage, the olfactory function has been tested with the Sniffing Sticks Test. Finally, the nasal endoscopic evaluation has been made to address nasal anatomy with a focus in the olfactory cleft (OC). This piece discusses the relation between anatomical endoscopic findings (with focus in the OC), smell test results and its relation in the QOL.

Medical literature suggests that olfactory loss leads to a poor QOL. In this study, especially patients with parosmia confirmed to have a remarkable worse QOL.

Among other interesting relations made, it was found, with statistic relevance, that mucosal redness presented in the OC, observed during the endoscopic nasal examination, was more frequent found in subjects with smell complaint. This mucosal erythema in the OC may translate an inflammatory state that disables the normal function of the olfactory epithelium that would result in a worse smell capability. Further studies are necessary to confirm this results and in the future, mucosal redness in the OC may be considered an important and reliable nasal endoscopic sign observed in many patients with the olfactory complaint.

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1. Introduction

According to the free dictionary by Farfex (retrieve from *http://www.thefreedictionary.com/sense*) a sense can be defined as “any of the faculties by which stimuli from outside or inside the body are received and felt, as the faculties of hearing, sight, smell, touch, taste, and equilibrium”. The Meeiam-Webster dictionary (retrieve from *www.merriam-webster.com/dictionary/sense*) defines as “a specialized function or mechanism (as sight, hearing, smell, taste, or touch) by which an animal receives and responds to external or internal stimuli”. A shorter definition would be as a faculty by which outside stimuli are recognized.

The sense of smell differs in many aspects from other senses: odors can bring out emotional memories, they can be remembered after a long time, and they are usually difficult to describe (Savic 2002). Although very common, smell disorders are not completely understood and properly addressed by most physicians (Landis et al. 2009, Keller and Malaspina 2013).

Although less important compared to other senses like hearing and seeing, olfactory loss changes daily life activities and pleasures. This includes hygiene matters, safety concerns, eating issues, and changes in emotional, social and sexual behavior. It is known that about 75% of these patients visiting at specialized smell and taste clinics report difficulty noticing spoiled foods. Patients are also at risk for being unable to detect other safety hazards such as smoke, gas leaks, cleaning solution vapors, chemicals and pesticides (Miwa 2001, Keller and Malaspina 2013).

Olfactory disorders can affect between 3.8% (Schubert et al. 2012) to 22% of the population (Vennemann et al. 2008). However, when it is analyzed a population over 50 years old, about 25% have some degree of olfactory loss (Fokkens et al. 2012, Pekala et al. 2016). In persons above 80 years old, (see Murphy et al. 2002) the prevalence of smell dysfunction reaches 62.5%. For complete loss of the sense of smell, the variation ranges from 2% to 3% (Haro-Licer et al. 2008) reaching 5% in some studies (for review see Mullol et al. 2012 and Hüttenbrink et al. 2013).

However, some patients not only have quantitative smell dysorders, but also experience qualitative olfactory dysfunction or dysosmia. These disorders can be classified as parosmia (known as ‘‘troposmia’’) and phantosmia (Leopold 2002). Phantosmia (perception of an odor when none is present) is a rare symptom. Usually, phantosmia is a consequence of damage in the frontal lobe, which is known to be involved in the conscious perception of odors (Wilson et al. 2014).

Parosmia (distorted olfactory experiences in the presence of an odor) has been estimated to range from 10 to 60% among patients with olfactory dysfunction (Nordin et al. 1996, Leopold 2002, Frasnelli and Hummel 2005).

Qualitative olfactory dysfunction is typically associated with quantitative olfactory loss and it is often seen either during neuronal death or during regeneration (Leopold 2002, Frasnelli and Hummel 2005). Another relevant aspect is that many patients are not aware of their smell loss (Philpott and Boak 2014).

However, in some patients, the olfactory disfunction can bring to a significant reduction in the QOL and increase the chance of depression and anhedonia (reduced ability to experience pleasure) development (Keller and Malaspina 2013, Croy et al. 2012, Croy et al. 2014). Indeed, according to some studies,

smell loss-induced anhedonia is the least-appreciated consequence of smell loss. This happens because affected individuals are usually unaware to perceive the relation between their olfactory loss and the reduced enjoyment of previously pleasant activities (Deems et al. 1991, Temmel et al. 2002, Nordin et al 2011, Croy et al. 2012). In their paper from 2013, the authors Keller and Malaspina showed that over 40% of the individuals with smell loss reported decreased wellbeing, mood, and satisfaction with life and that 66% of the subjects felt more anxious than before the change in their sense of smell.

The quality of life has many different definitions depending on the reference used. It can be defined as a "multidimensional concept emphasizing the self-perceptions of an individual's current state of mind" (Bonomi et al. 2000) and can also often referred to as "well-being" situation (Paraskevi 2013). The World Health Organization offer one good definition: "QOL includes psychological and social functioning as well as physical functioning and incorporates positive aspects of well-being as well as negative aspects of disease or infirmity". (van Oene et al. 2007). A more specific and modern definition would include "three dimensions particularly physical function, mental status, and ability to engage in normative social interactions" (Post 2014).

In many countries, otolaryngologists are most likely to see patients with the olfactory complaint. To access and investigate the anatomy of the nose, the endoscopy is a very common and suitable approach. According to the American Rhinologic Society (retrieve from *http://care.american-rhinologic.org/nasal_endoscopy*) the nasal endoscope is a "medical device consisting of a thin, rigid tube with fiberoptic cables for bringing in light" and endoscopy is a "minimally invasive, diagnostic medical procedure".

With this important instrument, many portions of the nasal cavity are visible such as nasal septum, inferior and medium turbinate, inferior, and middle meatus and the sphenoethmoidal recess. The upper part of the nose, also feasible to be seen in this exam, holds particularly an important region named olfactory cleft (OC) (Henrot et al. 2010). There are several types of endoscopic grading systems to evaluate the noses anatomy. A largely used endoscopic scoring system is Lund-Kennedy endoscopic scoring system that attributes grades to five characteristics: polyps, mucosal edema, crusting, discharge and scaring with a maximum rating of 2 for each sign (see Lund and Kennedy 1995).

The olfactory cleft (OC), situated in the roof of the nose, is known to have a different and individual type of covering called olfactory epithelium (OE). It contains olfactory sensory neurons (OSN) that are responsible for the odor sense and hold a extraordinary and particular feature: they are able to regenerate themselves (Ekberg and St. John 2015). The OSN are organized with their dendrites into contact with the surface of the epithelium while the axons group in bundles (known as *fila*). They are surrounded by a Schwann sheath. There are approximately 20 *fila* on each OC and together they form the olfactory nerves that transverse the skull base through the many openings of the cribriform plate to enter the olfactory bulb. This special epithelium is responsible for processing volatile chemical stimuli that may finally result in the perception of smells. (Kivity et al. 2009, Pinto 2011, Leboucq et al. 2013, Joiner et al. 2015).

One study from Bushdid et al. in 2014 suggested that humans can discriminate at least one trillion olfactory stimuli. This is possible because there are about 1000 olfactory receptors and each receptor can respond to multiple stimuli.

Additionally, each odor can activate several types of receptors (Elterman et al. 2014).

To access the sense of olfaction, there are many different and trustful psychophysiological tests. They may evaluate three aspects regarding olfaction: odor sensitivity, identification, and discrimination (Attems et al. 2015). Unfortunately, the evaluation of the olfaction ability is not yet habitually applied by clinicians in the process of diagnosis and treatment (Kivity et al. 2009).

Among the tests, we can quote: University of Pennsylvania Smell Identification Test (UPSIT) (Doty et al. 1984, Livack et al. 2009), Cross-Cultural Smell Identification Test (CCSIT) (Doty et al. 1996, Hummel and Welge-Lüssen 2008), Connecticut Chemosensory Clinical Research Carried out Test (CCCRC) (Cain et al. 1988), Sniffing Sticks Test (Kobal et al. 1996, Hummel et al. 1997), T & T-test (Takagi and Toyota 1975) and others.

Apart from ageing (Mullol et al. 2012, Keller and Malaspina 2013, Sinding et al. 2014), being male (Hummel et al. 2007, Oliveira- Pinto et al. 2014, Wilson et al. 2014) and smoking habits (Katotomichelakis et al. 2007, Vennemann et al. 2008) are also risk factors related to worse olfactory performance.

There are several causes of olfactory impairement. A person may have smell loss because there is a blockage to the passage of the odorant, before arriving the olfactory cleft. May also happens when there is a damage in the olfactory epithelium or a central dysfunction related to central nervous system disease (Pinto 2011). Among several specific causes of olfactory disorders, there are - apart from ageing - four with great relevance: chronic rhinosinusitis (CRS), upper airway infections, head trauma and idiopathic cases (Pinto 2011, Chen et al 2013, Hüttenbrink et al. 2013, Doty and Kamath 2014, Philpott and Boak 2014).

Unfortunately, the molecular mechanisms of olfactory dysfunction is not completely understood and has occasioned limited treatment options (Pekala et al. 2016).

1.1 Objectives

1.1.1 General Objective

- To determine if subjects with olfactory complaint had any specific olfactory cleft endoscopic finding.

1.1.2 Specific Objectives

- To associate poor smell test scores with smoking habits.
- To associate poor smell test scores with age and gender.
- To verify which subgroup of subjects with smell complaint presented lower smell test results.
- To establish which subgroup had more parosmia.
- To verify if parosmia was a relevant olfactory indication, related to low quality of life.

Having this answers may provide a better understanding of the olfactory disorders and will add valuable information to improve the approach with which otolaryngologists evaluate their patients with olfactory complaint.

2. Literature review

2.1 General Nasal Anatomy

The nasal cavity is a very complex and anatomic varied chamber covered mainly by the respiratory epithelium. Understanding nasal anatomy tridimensional can be extremely challenging and occasionally even frustrating because there are innumerous anatomical variations between humans (see Morre et al. 1998, Adeel et al. 2013, Saccucci et al. 2015).

The nasal septum is an important structure that separates the nasal cavity in two, has the major support mechanism for the nasal dorsum and projects anteriorly to form part of the dorsal nasal profile. It is formed by one cartilage; quadrilateral cartilage and two bones; vomer and perpendicular plate of ethmoid bone (Stucker et al. 2009). The anterior part defines the columella and the postero-superior angle has contact with the sphenoid bone. The nasal septum lays in the crista nasalis of the bony palate (Watelet and Van Cauwenberge 2007). Importantly, the upper part of the septum, especially the medium third, contains the olfactory epithelium (OE) (Pinto 2011).

The vestibule stands in the nasal entrance and is covered by skin (squamous epithelium). Anteriorly lies the nasal valve that is formed by the lower border of the upper lateral cartilage, the septum, and the anterior portion of the inferior turbinate. This cross-sectional is a very important region and correspond to the narrowest portion of the nostril. The nasal valve has the highest airflow resistance of the respiratory tract and divides nasal vestibule from the nasal cavity (Janfaza 2011, Pinto 2011).

Thinking of the nasal cavity tridimensional, we would have the floor as being the hard palate, the hoof as the anterior skull base, the medium aspect simply the nasal septum and the lateral boundary as the lateral wall. Anteriorly we find the nasal vestibule and posteriorly the nasopharynx. The cribriform plate (ethmoid bone), which contains the OE, is situated in the middle third of the roof (Rajagopal and Paul 2005). Within this space there are many intricate anatomic relationships that influence the nasal physiological functioning and, in some cases, can lead to malfunction of the nose.

The lateral wall is probably the most difficult and tricky anatomical area of the nasal cavity (Kopp et al. 1988) . It contains usually three and rarely four projecting shelves of bone known as turbinates or conchae. These are paired scroll-shaped bones covered in nasal mucosa, which project into the nasal cavity. They greatly increase the surface area of the nasal cavity and function to direct airflow through the nose. They are also very important serving as landmarks for sinus surgery (Stucker et al. 2009, Sahin-Yilmaz and Naclerio 2011). The three turbinates converge posteriorly toward the nasopharyngeal meatus (Stucker et al. 2009).

The medial surfaces of the middle and the inferior turbinates are covered by an especially thick mucosa that contains a vast vessel venous plexus that functions as an erectile tissue that warms and humidifies the inspired air (Janfaza 2011).

The inferior turbinate is considered the largest of the three paired turbinates, and runs along the entire length of the lateral nasal wall, following the nasal floor. It has the most important role in the air conditional action of the nose (Sahin-Yilmaz and Naclerio 2011, Janfaza 2011).

The middle turbinate (MT) has a complex, boomerang shape and lies above the inferior turbinate (Janfaza 2011). It is considered, for most authors, an important landmark in endoscopic sinus surgery. The MT can be anatomically divided into three portions. It has a special interest in this paper because its anterior third is attached to the cribriform plate, which holds the OE. In addition, the middle third is fixed to the lamina papyracea by the ground lamella and finally, its posterior third is fixed to the perpendicular plate of the palatine bone, and/or to the lamina papyracea (Morre et al. 1998, Kountakis and Önerci 2007). It is important to understand the MT anatomy because it has also a relevant complementary function in olfaction capability, deflecting the inspired air toward the OE (Blaugrund 1989).

The superior turbinate belongs to the ethmoid bone, medially limiting the superior meatus. The sphenoethmoid recess lies between the tail of the superior turbinate and the posterior-superior septum, just above the choana. This recess drains the sphenoid sinus and the posterior ethmoids via the superior meatus. (Kountakis and Önerci 2007).

Although being a rare anatomical variation, a fourth small, supreme turbinate may be present in some individuals. The supreme turbinate is also known as the “forgotten turbinate” as it is difficult to identify through nasal endoscopy (Clerico 1996).

The openings of the sinus ostia into the middle meatus are close together and form the ostiomeatal complex (OMC) which serves as the final drainage pathway for the maxillary, anterior ethmoidal, and frontal sinuses to the middle meatus. OMC is considered a key area in the nose and the most common region of inflammatory disease (Hoang et al. 2010). Pathology in this region can interfere

with ventilation and mucociliary clearance of the sinuses and may lead on to chronic rhinosinusitis (CRN)– an important cause of olfactory loss (Rajagopal and Paul 2005).

The superior part of the nasal cavity can be divided into the olfactory cleft (OC) anteriorly and the sphenoethmoid recess posteriorly. The OC can be defined as a site located under the olfactory fossa between the insertion of the middle turbinate and the nasal septum (Pinto 2011). This specific and more detailed anatomy will be addressed and carefully described in the next chapter.

The air-filled spaces within the bones of the facial skeleton are known as “sinuses” or “antrum” (Mavrodi and Paraskevas 2013). There are four sinuses each side as follows: maxillary, ethmoidal, sphenoidal and frontal sinus. All the sinus are lined by respiratory epithelium and communicate with the nose via small ostia (passages) with no more than a few millimeters in diameter. There is enormous variation in nasal sinus anatomy regarding size and symmetry. (Saccucci et al. 2015).

The ethmoid sinus is referred to as the ethmoid labyrinth because of the complexity of its anatomy and due to the honeycomb-like appearance. Located lateral to the OC, the ethmoid sinus is the most compartmentalized paranasal sinus. It is divided in anterior and posterior by the middle turbinate attachment also called basal lamella of the middle turbinate or third ethmoidal lamella. The frontal bone in its posterior extension covers the roof of the ethmoid sinus, forming the *foveolae ethmoidales*. The width of the ethmoid increases from anterior to posterior because of the conelike structure of the orbit (Kountakis and Önerci 2007).

2.1.1 Specific Olfactory Cleft Anatomy

The upper nose also called roof of the nose can be divided into three regions. The anterior part corresponds to the inferior edge of the nasal spine of the frontal bone. The middle or ethmoidal part is the cribriform plate and the posterior part correlates to the ethmoidal process of the sphenoid (Henrot et al. 2010).

The weakest and most vulnerable area of the anterior cranial fossa is the lateral lamella of the lamina cribosa, where the anterior ethmoid artery passes through the ethmoidal sulcus. The deeper the olfactory fossa is, the thinner and therefore the more vulnerable and exposed to injury is its lateral wall (Hoang et al. 2010, Janfaza 2011). Keros, in 1965, reported three types of the olfactory fossa, depending on how low the level of the cribriform plate is with relation to the roof of the ethmoids. The Keros classification is defined as follow: Type 1 corresponds to an olfactory fossa 1-3 mm deep in relationship to the roof of the ethmoids. Type 2 is 4-7 mm deep and type 3 indicates a depth of 8 mm or more (Kountakis and Önerci 2007).

As already said, the OC is based beneath the olfactory fossa between the insertion of the middle turbinate and the nasal septum. It lies just inferior to the cribriform plate. Other definition would be that the OC corresponds to the olfactory region, covered by the olfactory mucosa or olfactory epithelium, featuring the cribriform plate and 1 cm^2 on each side, on the lateral nasal wall and on the septal wall. Also, the airflow passes for preference along the floor of the nose and the inferior meatus during quiet respiration. The nasal cavity can be separated into two physiologically different zones. A wide zone conducting the high-speed

airflow and another, a narrow zone conducting a low-speed airflow toward the olfactory region - the OC. Adopting this concept, the inferior limit of the OC corresponds to the inferior end of the middle turbinate. (Henrot et al. 2010).

OC pathological findings and its relations with olfactory capability have been intensively studied in various late researchers. In 2011, Kim et al. published a CT study that concluded that opacification of the anterior portion of the OC had a statistically significant association with the postoperative olfactory tests results. Another example, that also shows the practical importance of a proper evaluation of the OC, comes from Chang et al. Their study with 210 patients with CRS indicated that opacification of the OC region had a negative correlation with the olfactory function scores (see Chang et al. 2009). Finally, a study from Nguyen et al. in 2013 suggested that surgery to polyps removal in the OC may improve the sense of smell and does not worsen olfaction.

The olfactory epithelium is a very particular and specific nasal cover and contains support cells, Bowman´s Glands and olfactory sensory neurons (OSN). Bowman's glands produce a particular olfactory mucus capable in maintaining the ion balance and pH regulation. These OSN are well known as being bipolar. The single dendrite encounters the surface of the epithelium and terminates in a knob (olfactory knob) (Pinto 2011). About 10–25 no motile sensory cilia, about 5 µm long (longer than the microvilli of respiratory cells), extend from each knob. Their proximal diameter is the diameter of the microvilli of respiratory cells (about 0.3 µm) and their distal segment is about half of it. These sensory cilia have receptors to bind with odor molecules. (Menco 1980, Pinto 2011, Lapid and Hummel 2013). The OSN axons, on the other hand, a group in groups called fila and pass through the cribriform plate to reach the olfactory bulb (see fig.1). It is

important to emphasize that only these bundle of axons (fila), and not each OSN axon, are myelinate. These axon groups arises about 20 branches, each side of the nasal cavity (Pinto, 2011, Joiner et al. 2015).

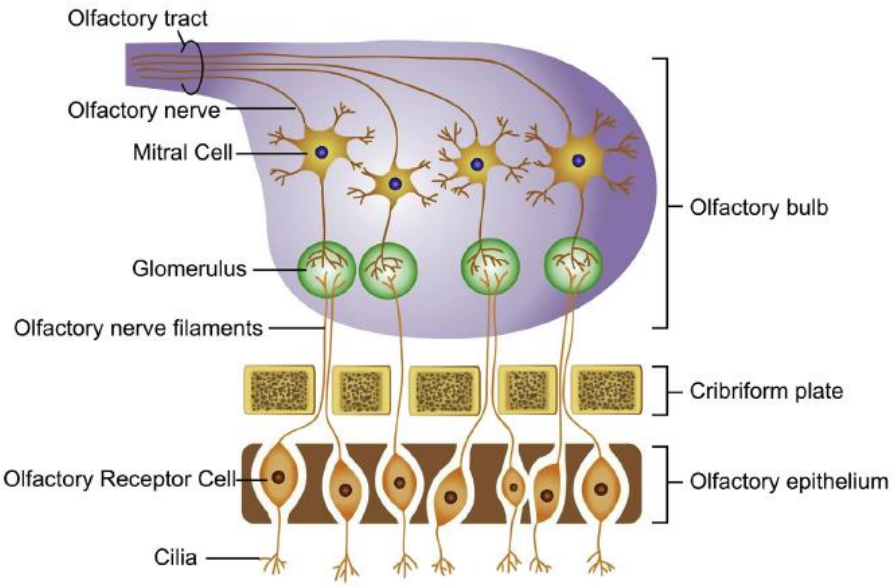


Fig. 1. From Fan et al. 2015.

Remarkably, the adult OE is a region for ongoing, permanent and constantly regeneration through the entire life (Zhang et al. 2012, Ekberg and St John 2015). The OSN are responsible for detecting odors but they are also exposed to many pathogens and toxic substances that are inhaled into the nasal cavity. Consequently, OSN frequently dies off and are replaced by stem cells located at the base of the OE. Similar to stem cells, the OE has two main roles: to participate in the maintenance and regeneration of a tissue and to be a reserve cell. In this scenario, two cells deserve great attention. Globose basal cells can originate all the differentiated cells found in the normal tissue and horizontal basal cells that

constitute reserve stem cells and may be activated by tissue damage (Ekberg and St John 2015).

The olfactory ensheathing cells (OECs) are the glia of the peripheral olfactory nerve and provide all support to the OSN. Within the outer layer of the olfactory bulb, OECs interact with astrocytes from the central nervous system (Ekberg and St John 2015) and have this incredible ability to exhibit characteristics of both astrocytes and Schwann cells. OECs can express various growth factors, molecules related to cell adhesion and several neurotrophic factors to provide a good environment for nerve regeneration. Consequently, they act modulating the growth of newly generated axons, into the olfactory bulb and making connections with the second order neurons. (Zhang et al. 2012, Schnittke et al. 2015). In addition, OECs not only stimulate the growth of the axon, but they are also the main phagocytic cells of the olfactory nerve. OECs can remove debris that arises from the degenerated axons and is able to phagocyte bacteria (Ekberg and St John 2015). Also, important, the extension of the meningeal layers from the brain to the nasal cavity make it possible the transmission of an infection to the intracranial cavity, passing through the subarachnoid space (Henrot et al. 2010).

The ability of OECs to promote axon growth has made them a remarkable candidate for cell transplantation therapy to repair the injured spinal cord (Zhang et al. 2012, Ekberg and St John 2015). In a systematic review and meta-analysis from 2016, including 49 studies, from Watzlawick et al, the author revealed that the gathered data clearly justify OECs as a “cellular substrate to promote, develop and optimize safe cellular transplantation procedures to repair lesioned spinal cord”.

2.2 General Nasal Physiology

The superior airway has several important functions such as protection of the lower airway, production of nitric oxide, humidify and warm the breathed air. Finally, the nose is considered a chemosensory organ responsible for smelling. (Watelet and Van Cauwenberge 1999).

There are two distinct types of epithelia within the nose: olfactory and respiratory. The OE lies in the superior portion of the nasal cavity, is a non-ciliated epithelium and contains the bipolar olfactory cells. Trauma to the cribriform plate may shear the OSN resulting in loss of smell (Pinto 2011).

The respiratory epithelium lines the rest of the nasal cavity and is known to be the same that lines the trachea, bronchi, and eustachian tube. Goblet cells and mucous glands are distributed throughout the submucosa (Rajagopal and Paul 2005). The respiratory mucosa shows a thickness of 0.3-5 mm and all cells are attached to the basal membrane. Basal cells lie on the membrane and show non-contact with the epithelial surface. Their specific morphologic features are desmosomes for cell adhesion (Beule 2010). Columnar cells may represent up to 70% of the epithelium and have 300-400 microvilli on their surface. The main purpose of microvilli is the increase in surface area to retain moisture and to prevent drying of the surface. Another 20–50% of epithelial cells are ciliated cell possessing 200-300 cilia on their surface, which are the morphological substrate of the mucociliary clearance. Cilia are 5 to 10 μm long and 250 nm thick and consists of microtubules arranged in more or less fixed patterns. The cilia movement can be compared to a “wheat field swaying in a windy day so that all the cilia do not move at once” (Beule 2010). Ciliated cells have multiple sensors

that give the cell the capability to respond to locally produced mediators. In this context, changes in mucus thickness and mucus loads make their cilia increase the speed at which they beat (Beule 2010).

Nasal mucus contains 90% water and glycoproteins as well as ions. It is produced by submucosal and seromucous glands, goblet cells, transudation of blood plasma, mucosal tissue fluid, and tear fluid. Due to transudate, most serum proteins may also be found in nasal secretions (Beule 2010).

Surprising, about 12.000 liters of airflow pass through the adult nose and are heated, hydrated, and filtered by a complex and efficient nasal system (Beule 2010). Particles over 4 mm can be trapped by the nasal vibrissae and removed in the mucus. (Rajagopal and Paul 2005). It is one of the initial defenses of the airway. Actually, the nasal passage may filter about 95% of particles with a diameter of more than 15 µm. The sneeze reflex occurred in some situations, provoked by foreigner bodies in the anterior portion of the nose and has a simple objective, removal of particles from the nose (Beule 2010). The defensive mucus layer within the nose is habitually transported in the posterior direction back towards the throat in about 20 minutes, at around 3-25 mm/min (White et al. 2010). The mucus blanket has two layers: a gel and sol phase. The top gel layer (gel phase) is structured by embedded mucin and is moved by the ciliary beat. The lower liquid layer is covered by the more viscous gel phase.

The immune defense in the nose is very active and has a great importance. Nasal secretions also contain many substances as immunoglobulins(Ig), IgA, IgM and IgG, lysozymes, interferon, and complement factors against unwanted pathogens (bacteria and viruses) (Rajagopal and Paul 2005). Neutrophil granulocytes, monocytes, and macrophages are cellular components of the host defense using

phagocytosis in the subepithelial tissue. Immigrated natural killer cells destroy infected cells. The specific immune system in nasal respiratory mucosa is in fact, part of the lymphatic system (mucosa-associated lymphatic tissue or MALT). These are just some good examples to give a glance of how important is the nose to protect the entire airway against dreadful substances and pathogens.

Nitric oxide (NO), produced by the paranasal sinuses, has a potent vasodilating, and antimicrobial activity and can be measured noninvasively in a nasally exhaled breath. In the sinuses, the role of NO is likely to enhance local host defense mechanisms via direct inhibition of pathogen growth and stimulation of mucociliary activity (Lefevere et al. 2000, Lundberg 2008). A study in 2007, Elsherif et al. suggested that, although nasal NO has evident anti-inflammatory activity, seemed not to have directly influence the olfactory function.

The sinonasal cavity also functional as a resonating chamber for certain consonants in a speech during exhalation. This is quite evident during phonation of M, N, and NG, as sound passes upwards through the nasopharynx and is emitted through the nose. These findings suggest that the sinuses may act as a relevant resonator for the voice (Acar et al. 2014).

Inspired air enters the nostrils with a 60-degree angulation and splits into different airflows following the different meatus and the space under the turbinates. It is known that only turbulent airflow enters to the sinus ostia. The speed at the entrance of the nasal cavity is between 2 and 3 m/s. But this is not constant, for example, at the narrowest part of the nasal cavity, the nasal valve, the speed may reach 12-18 m/s. In the region of the turbinates, the speed diminishes again to 2-

3 m/s. Regarding olfaction, during sniffing, the airflow deviates towards the superior turbinate and the OC (Watelet and Van Cauwenberge 1999).

The nasal airway is the primary pathway for normal breathing. Surprisingly, during quiet breathing, the resistance through the nasal passage represents more than 50% of the total respiratory resistance. This is more than twice the resistance during mouth breathing. (Rajagopal and Paul 2005). As described by Poiseuille's Law, airflow resistance is proportional to the length and is inversely proportion to the radius to the fourth power. Because the radius is such an important variable, subtle changes, such as a 10% increase in the cross-sectional area of the nasal cavity airway, can imply in a 21% increase in airflow (Powell et al. 2001). Nevertheless, there are important variations in nasal airflow patterns and properties within the healthy population, and it is difficult to determine a universal arrangement for a standard nasal airflow (Zhao and Jiang 2014).

The nose also plays an important function of the air heating and air humidification. It has a large surface area and a remarkable rich blood supply, which is close to the surface of the nose. The mucus layer that covers the nasal mucosal and the blood passing through nose vessels are usually enough, to heat and moist, the cool and dry air. (Rajagopal and Paul 2005).

Apart from the olfaction function, the other major chemosensory component of the nose is the trigeminal system. The first and the second branches (V1 and V2) of the fifth cranial nerve innervate the mucosa of the nose and sinuses and are considered the airway’s first defense against harmful inhalants (Pinto 2011). V1 and V2 afferent axons synapse in the trigeminal nucleus, which transmits signals to the ventral posterior medial nucleus located in the Thalamus. Finally, the signal arrives cortical areas that process facial irritation and pain. Therefore, nociceptive

neurons of the fifth cranial nerve are activated by chemicals classified as irritants, including air pollutants, ammonia, ethanol and other alcohols, acetic acid, carbon dioxide, menthol, capsaicin, and others (Rajagopal and Paul 2005).

Sympathetic fibers from the first five thoracic segments of the spinal cord ascend and synapse in the superior cervical ganglion, located opposite the second and third cervical vertebra. Then postganglionic fibers follow with the blood vessels to the nose. When there is an increase in sympathetic stimulus, vasoconstriction and diminish secretion is expected to occur.

On the other hand, the parasympathetic supply to the nose comes from the lacrimal nucleus with the fibers leaving the brain stem in the intermedius nerve (also known as the nerve of Wrisberg), actually part of the facial nerve (cranial nerve VII). They relay in the pterygopalatine ganglion before entering the nasal cavity. Swelling and greater secretion from the nasal mucosa are expected with an increase of the parasympathetic tone. For this reason, the pterygopalatine ganglion is also known as the “hay fever ganglion” (Rajagopal and Paul 2005).

A very interesting and important phenomenon regulated by the hypothalamus, where is the observed growth of venous sinusoids that alters between the left and right nasal passages are called nasal cycle (NC). It is defined as the natural and reciprocal modification of nasal congestion, usually ignored since the total nasal airflow resistance remains unchanged (White et al. 2015).

Finally, the nose is also responsible for the sense of olfaction considered one of the oldest senses and developed at a very early stage of the evolution of our species. This topic will be addressed in the next chapter.

2.3 Physiology of Smell

Distinct brain regions initially process smell, sight, and sound, yet responding neural pathways can join on similar control centers to, for example, accomplishing a common behavior like fear. Other sensory stimuli such as the smells of mates, food, or offspring, will induce different behaviors related to reproduction, feeding, or parental care. Therefore, within a sensory system, neural pathways that are anatomically quite similar can diverge centrally for execution of specific responses (Li and Liberles 2015). Odor preferences result from a learning process. Positive or negative emotions frequently originated by smells are molded by prior experience and are supposed to increase the appropriate behavioral response (Lapid et al. 2011, Croy et al. 2014).

Chemosensation in the nose is mediated by two cranial nerves: the olfactory nerve (cranial nerve I) and trigeminal nerve (cranial nerve V). The olfactory epithelium (OE) is characterized by the presence of olfactory neurons whose axons project across the cribriform plate at the roof of the nasal cavity. The distribution of OE occurs along the cribriform plate, medial to the superior turbinate and along this turbinate itself. Recent studies have shown a more extensive distribution of OE that may reach farther down the nose in the anterolateral middle turbinate and also posterior and middle nasal septum (Pinto 2011). The location of the OE is variable among humans and may change with time (age process), from environmental insult (toxins, volatile chemicals, tobacco smoke, industrial or occupational or airborne pollutants) and pathophysiologic processes such as infection or inflammation (Beule 2010).

In the adult nervous system, neural stem cells can be found, in the OE, subventricular zone of the lateral ventricle, and the subgranular zone of the hippocampus (Joiner et al. 2015). In order to guarantee tissue repair and neuroplasticity, some mechanisms that regulate cell proliferation, migration, differentiation, and survival during development can be active in the adult nervous system. Unlike most sensory systems, the OE is able to reconstitute neuronal and non-neuronal populations after injury and neuronal death. The OE is composed of supporting sustentacular cells, Bowman's gland duct cells and two groups of basally located stems cells, globose basal cells and horizontal basal cells. These cells are considered to be progenitor or stem cells of the OE and are capable of promoting regeneration and neurogenesis both for tissue homeostasis and in response to injury (Joiner et al. 2015). When damaged, the olfactory epithelium can be reconstituted from these cells, although age-related processes influence the success of such regeneration (Doty and Kamath 2014).

In order to the odorant properly achieve the olfactory mucosa, sniffing is a crucial phenomenon. It consists in a strong contraction of the diaphragm leading to rapid nasal airflow, often above 18 l/min in humans (Lapid and Hummel 2013). Sniffing plays a major part in the formation of the olfactory percept by facilitating odorant detection, odor discrimination and by increasing olfactory attention (Frasnelli et al. 2009). Once the odorant reaches the nasal cavity, it is absorbed into the mucus covering of the olfactory epithelium. Different from the mucus within the nasal cavity proper, this mucus is largely derived from specialized Bowman’s glands. Among its secretions, there are odorant-binding proteins that lead odorants to the olfactory receptors, growth factors associated with mitosis and numerous immune factors. (Doty and Kamath 2014).

The second method of perception of odorants comes posteriorly through the nose via retronasal olfaction. In this situation, the odorant molecules arise from the oropharyngeal cavity into the nose during consumption of food and liquids (Kent et al. 1996, Hummel 2008, Beule 2010, Hummel et al. 2011, Ni et al. 2015). Consequently, while the orthonasal smell is used to sense fragrances in the ambient air, the retronasal smell is used to sense the volatiles released from the back of the mouth during eating and drinking. Many studies confirm that retronasal olfaction plays an important key role in the sensation of flavor (Beule 2010, Elterman et al. 2014, Ni et al. 2015). According to Ni et al, 2015, the ability to recognize the subtle differences in food flavors depends mainly on retronasal smell. Many experiments suggest differences in the processing in ortho e retronasal information. This is possible because the direction of the airflow changes the pattern of olfactory mucosal activation, and consequently, the perception of the same odor in relation to the route of presentation (Kent et al. 1996, Hummel 2008).

The olfactory receptor genes account for approximately 1% of all expressed genes in the human genome. This makes it the largest known vertebrate gene family. The work leading to the discovery of the olfactory receptor genes resulted in the 2004 Nobel Prize in Physiology or Medicine (Linda Buck and Richard Axel). There are approximately 1000 olfactory receptors and each receptor can respond to multiple stimuli. Additionally, each odor can activate several types of receptors, resulting in the possibility for billions of combinations (Elterman et al. 2014). In fact, in a recent study (see Bushdid et al. 2014) the authors calculated that humans can discriminate at least one trillion olfactory stimuli. This is significantly more than previous estimates of distinguishable olfactory stimuli. It demonstrates

that the human olfactory system, with its hundreds of different olfactory receptors, far exceed the other senses in the number of physically different stimuli it can discriminate (Bushdid et al. 2014). When the odorant's concentration increases, more types of receptors are recruited. Olfactory receptors neurons (ORN) that express the same receptor target their axons to one or two ovoid structures called glomeruli at the surface of the olfactory bulb (OB) (Doucette and Restrepo 2008).

The OB is the first relay station in the brain where significant incoming odors information is processed (D´Souza and Vijayaraghavan 2014). The activity at the glomerular layer of the OB contains enough information to differentiate between odors and undergo variations in time that may contribute to the information conveyed to the brain. However, the use of this information poses a challenging dilemma for the brain because of a large number of glomeruli activated by each odor, and the high degree of overlap in the glomerular activity patterns of closely related odors (Doucette and Restrepo 2008). Moreover, in the central nervous system, the key transmitter invoked in olfactory tasks involves the cholinergic projections from the basal forebrain, long thought to be involved in attention, arousal, learning, and memory. In a large study in 2006, conducted by Rombaux et al revealed that the OB volume varies with regard to olfactory function and decreases with duration of olfactory loss. Furthermore, patients with parosmia had smaller OB volumes compared with patients without smell complaint, although their overall olfactory ability was not significantly different from each other. In 2008, it has been showed that olfactory bulb volume changes with the degree of olfactory dysfunction (Haehner et al. 2008). The same author demonstrated, for the first time, that the human OB is a highly plastic structure able to react to individual changes in olfactory status. In fact, the plasticity of our

olfactory system can be verified by temporal changes in OB volumetric measurements (Rombaux et al. 2009b). Moreover, that it decreases with the duration of the smell loss and that patients with parosmia have smaller olfactory bulbs than patients without parosmia (Rombaux et al. 2009a). Measurement of OB volume may provide useful information for patients with olfactory impairment. (Rombaux et al. 2009a). In a study from 2010, Rombaux et al. concluded that patients with idiopathic olfactory loss have decreased olfactory function and decreased OB volume when compared with controls. In a 2014 publication by Zhang et al., the author demonstrated that the OB volume is correlated with olfactory capability, while the depth of olfactory sulcus has no correlation with olfactory function.

The other major chemosensory component of the nose is the trigeminal system. As already commented, branches of the trigeminal nerve (cranial nerve V) innervate the mucosa in order to protect the airways from harm. A stimulus such as burning, pungency, stinging, temperature, or pain is felt because of the trigeminal innervation (Hüttenbrink et al. 2013). Intranasal trigeminal stimulation evokes neuronal activation of pain processing areas, like the anterior cingulate cortex, the insula, or the primary somatosensory cortex as well as chemosensory processing regions, such as the orbitofrontal cortex (Kollndorfer et al. 2015). Studies suggest that trigeminal activation is quite specific and based on the interaction of a ligand with a receptor. For instance, the trigeminal receptor TRPA1 is highly activated by cinnamaldehyde, the active ingredient of cinnamon, creating a warmth sensation. This receptor is not activated by eucalyptol, the active ingredient of eucalyptus, which, however, activates the TRPM8 receptor and by this evokes a sensation of freshness (Filiou et al. 2015). An important

study from Hummel et al, 2003, showed that patients with olfactory dysfunction have lower trigeminal sensitivity compared with normosmic controls. This finding seemed to be independent of the etiology of the olfactory loss. Additionally, the deficit appeared to improve with duration of the olfactory impairment, probably suggesting adaptive mechanisms.

Some fragrances have a strong active trigeminal component, while others need to be in considerably higher concentration to produce a trigeminal activation (Frasnelli et al. 2011). It is well known that menthol can activate olfactory receptors (minty smell) and trigeminal receptors (cooling and pain effect), however not in the same threshold. Lower concentrations stimulate olfactory receptors and at medium concentrations originate a cooling sensation in addition to the smell, and at higher concentrations evoke a pain sensation in addition to the smell and cooling. (Renner and Schreiber 2012). It follows that thresholds for trigeminal sensations, such as burning, cooling, stinging, and fullness, are generally higher than thresholds for olfactory sensations (Frasnelli et al. 2011). It is also remarkable that strong trigeminal activity commonly results in secretory activity and congestion of the mucosa (Lapid and Hummel 2013).

The ability to localize an odorant is also an important issue. It depends if the odor can activate olfactory receptors or mixed olfactory and trigeminal receptors, as well as, the degree of trigeminal stimulation. The greater this stimulation higher is the accuracy of odor localization (Frasnelli et al. 2011). PEA has long been used as a chemical stimulating predominantly the olfactory nerve, where only 1 in 15 anosmic subjects could detect it. It also understood that almost all chemicals

can produce a trigeminal activation (Doty et al. 1978), at least from a certain concentration (Negoias et al. 2013).

The physiology of the cerebral processing of odor impressions is not completely understood. The olfactory system is unique among the senses as it projects initially to cortical regions, instead than thalamic nuclei (Good and Sullivan 2015). Among some brain areas that are activated during normal olfactory stimuli are: entorhinal cortex, amygdala, insula, putamen, and visual cortex (see fig. 2 and 3). The cortical areas activated are those that have been implicated in the integration of olfactory stimuli, including some regions of the limbic system (Toledano et al. 2012). It is known that the orbitofrontal cortex plays a major role in the conscious perception of odors (Hüttenbrink et al. 2013) and that the temporal lobe pole plays an important role in the central processing of olfactory information (Lotsch et al. 2016). The so-called POC - primary olfactory area, include five brain regions: the anterior olfactory nucleus, amygdala, olfactory tubercle, piriform and periamygdaloid cortex and, finally, the rostral entorhinal cortex (fig. 2). Actually, from the OB the olfactory signals project predominantly through the lateral olfactory tract to the POC. Collaterals from these axons project to the anterior olfactory nucleus. A minority of fibers project via the medial olfactory tract to the contralateral olfactory bulb. It is important to notice, however, that the clear majority of olfactory projections are ipsilateral (Good and Sullivan 2015).

It is known for a long time, that Entorhinal cortex and amygdala are the most commonly activated areas during olfactory processing (fig. 3) (see Carpenter 1985). The amygdala is in the anterior temporal lobe being a heterogeneous structure with numerous nuclei. One of these nuclei is the corticomedial nuclear

group, which appears to relate to parts of the hypothalamus, involved in regulating food intake, as well as in regulating some reproductive behaviors (Hadley et al. 2004). Moreover, the entorhinal cortex, located in the parahippocampal gyrus, is important in allowing certain fragrances to evoke memories (fig 2). This cortex projects towards the hippocampal formation (especially the hippocampus and the thalamus), an essential area that converts short-term memories into long-term memories (Hadley et al. 2004, Toledano et al. 2012). The amygdala is closely connected to the hippocampus and enthorhinal cortex, which leads to an emotional enhancement of odor memories and their unique long-term preservation (Savic 2005) and partly explains the emotional character of odors and the role of odors in the recalling of (typically children's) memory records. (Savic 2005, Hummel et al. 2011, Arshamian et al. 2013).

When is presented a mixture of odors many brain regions such as the cingulate and the insula can be activated. This situation is true even if subjects are not able to distinguish the mixture with and without the odor. Consequently, the addition of a certain compound to a mixture of odors may not be detected on a cognitive level; however, this additional fragrance may significantly change the brain processing of this mixture (Hummel et al. 2013). So, the processing of odors has revealed that odorant mixtures are treated differently than individual odorants. Odorant mixtures not only recruit more brain areas than individual odorants but also activate high-order olfactory regions that are specialized in mixture processing (Filiou et al. 2015).

Primary Olfactory Area (POC)
• anterior olfactory nucleus • amygdala • olfactory tubercle • piriform and periamygdaloid cortex • rostral entorhinal cortex

Fig. 2 From Good and Sullivan 2015.

The olfactory system is extraordinarily plastic, due to mechanisms that have been the subject of extensive investigation (Wilson et al. 2004, Li et al. 2006, Haehner et al. 2008). Olfactory information can be routed by modulating the response of neurons throughout the circuit, and new neurons can be recruited to the circuit during odor learning (Li and Liberles 2015). Compared to other senses, the anatomical organization of the olfactory network is much more dispersed (see Lundström et al. 2011). According to Gottfried, there are 40 cerebral areas reportedly involved in the human central nervous processing of smell (see Gottfried, 2006). Secondary and tertiary areas of olfactory processing involve parts of the limbic system and are thus closely linked to memory and emotional states (Arshamian et al. 2013). Moreover, the olfactory system holds the unique ability to be activated by the sensorimotor act of sniffing, without the presentation of a fragrance (Sobel et al. 1998). In addition, olfactory impairment may induce effects in the whole brain. This includes compensatory mechanisms from other sensory systems due to the close interconnectivity of the olfactory system with other functional networks (Kollndorfer et al. 2015b).

Commonly activated areas during olfactory processing	Location	Function
Entorhinal cortex	parahippocampal gyrus	certain fragrances can evoke past memories
Amygdala	anterior temporal lobe	involved in regulating food intake and some reproductive behaviors

Fig.3. From Hadley et al 2004 and Toledano et al. 2012.

2.4 Olfactory Disorders

2.4.1 Importance of olfactory dysfunction

The sense of olfaction has a profound significance in human's daily life. It gives the possibility to feel pleasant odors like many kinds of food, and the lack of this sense consequently diminish the richness of food perception (Stevenson 2010, Croy et al. 2014). Olfaction input plays a major role in food intake (Keller and Malaspina 2013) and contributes up to 80% of the flavor of our food (Patel et al. 2015). Food-related issues are not limited to eating; also, the food preparation can be quite challenging for many patients with olfactory impairments (Croy et al.

2014). Regardless of geographic location or socioeconomic status, food and drink occupy a relevant part of human culture. The sense of smell helps also for food localization and indicate the food's edibility (Stevenson 2010). These patients, with smell dysfunction, typically complain about a lack of appetite and low interest in eating (Temmel et al. 2002). Some patients report losing weight after losing their sense of smell (Mattes et al. 1990), however, high body max index appears to be associated with olfactory dysfunction (Patel et al. 2015).

In a recent study (see Pastor et al. 2016), 161 females were separated into five groups of body mass index subcategories, ranging from underweight to morbidly obese and then analyzed. It was found that obese subjects have a lower olfactory capacity than non-obese ones. Both, loss and gain of the total weight, appears to be a consequence of food being less enjoyable in the absence of olfactory input (Mattes et al. 1990, Nordin et al. 2011,). Another interesting finding is that spicy food becomes more attractive because taste and mechanosensation should compensate for the lost olfactory input (Mattes et al. 1990). Many patients with smell disorders who visit special clinics also complain of a loss of taste. Only about 10% of the patients complain of an isolated loss of taste. But, in fact, less than 5% of these patients have only a measurable loss of taste (Deems et al. 1991).

The simple experience of feeling odorants like perfumes fragrances; sea shore, flowers and grass odors and many others, are diminished, abolished or distorted in the olfactory disorders, bringing many bad consequences to the QOL. Most patients seem to manage well olfaction restrictions; however, a smaller proportion has a remarkable reduction in general QOL and enhanced depression (Gelstein 2011, Kohli et al. 2016). Putting in numbers, according to Miwa et al., in a study

from 2011, about 17 to 30% of patients with olfactory disorders report decreased QOL, including symptoms of depression. In a recent study (Kohli et al. 2016), patients with depression have reduced olfactory performance when compared with the healthy controls and that the symptoms of depression were worse with the severity of smell loss. Although the mechanism is unknown, there is clearly a correlation between smell loss, depressive symptoms, and mood changes (Keller and Malaspina 2013). The problem is even worse when there is parosmia (distorted odor perception). According to Croy et al. 2014, 35% of the patients with parosmia or phantosmia, exhibited high depression scores. In others studies, more than 50% of the patients with this complaint described that their condition severely affected their QOL (Bonfils et al. 2005, Keller and Malaspina 2013). The loss of quality of life is most severely noticed by younger patients with poor smell sense (Shu et al. 2011).

Odors have also been reported to have a relevant impact on reproductive behavior, including inbreeding avoidance, mate selection and emotional contagion (Stevenson 2010). In a study, female tears were demonstrated to contain chemical signals that decrease sexual excitement and testosterone levels in men (Gelstein et al. 2011). Another recent study (from Croy et al. 2013) said that men born without a sense of smell (congenital anosmia) described a reduced number of sexual relationships. Furthermore, patients with olfactory impairment report daily life problems associated with social situations (Frasnelli and Hummel 2005) and concerns about their body odor (Miwa et al. 2001).

Proper olfaction is also very important to alert us from dangerous situations. Patients with olfactory dysfunctions have an increased risk for hazardous events (Santos et al.k 2004) such as contact with microbial threats, spoiled food,

and poisonous fumes. In a study from Miwa et al 2001, it was reported a common problem about “failure to detect fire, gas or smoke”, in 61% of the patients. The failure to detect fire or smoke was described as the main risk associated with olfactory disorders in 45% of the patients (Nordin et al. 2011). Indeed, a large number of the elderly die in accident gas poisonings each year. (Doty and Kamath 2014). Additionally, when there is a large divergence between the perceived flavor (the combined experience of retronasal olfaction, taste, and somatosensation) and the expectation formed prior to ingestion, can result in the rejection without further consumption, avoiding microbial contamination (spoiled food) or poison (Stevenson 2010).

Olfactory dysfunction is a very common condition with a reported prevalence estimated to be 22% (25–75 years; Vennemann et al. 2008), 24% (≥53 years; Murphy et al. 2002) and 19% (≥20 years; Bramerson et al. 2004), with highest prevalence in older men (Murphy et al. 2002). Olfactory dysfunction is present in 7% of the general population of the USA (Wysocki and Gilbert 1989). But, between 65 and 80 years of age, about 50% of the USA population has smell loss and, over the age of 80, about 75% experience such impairment (Doty and Kamath 2014). Based in many studies, it can also be stated, that women have better results compared with men in different aspects of olfactory sensitivity, irrespective of their age (Hummel et al. 2007, Oliveira- Pinto et al. 2014). One study with 496 respondents with smell disorders, has demonstrated high rates of depression (43%) and anxiety (45%), impairment of eating experience (92%), isolation (57%), and relationship difficulties (54%) (fig 4). Relating to olfactory loss, women seems to show notably more issues compared to men in terms of social and domestic dysfunction (Philpott and Boak 2014).

As many other studies have said, olfactory loss unawareness is also very frequent (Murphy et al. 2002; Shu et al. 2011, Keller and Malaspina 2013, Croy et al. 2014) maybe due to the fact that olfactory information is processed unconsciously to a relatively large level. Consequently, the prevalence of self-reported smell loss ranges between 1.4% and 15% (Murphy et al. 2002, Croy et al. 2014). Often, physicians do not give the proper attention and counseling to this group of patients. According to a study (see Landis et al. 2009), 60 % of the patients with olfactory complaint described that they had received by the doctor either no or unclear or unsatisfactory information about their diagnosis, 30% had received no instruction about their prognosis, 25 % felt they had not been managed well and 6% noticed that their smell disability had been trivialized.

Fig. 4 Adapted from Croy et al. 2014.

2.4.2 Quantitative and Qualitative Olfactory Disorders

The previously reported importance that olfaction plays in the quality of life, including having correlations with many conditions and pathologies, makes the

measurement of this sense extremely relevant. For identification of olfactory dysfunction, the references have pointed to two evaluative dimensions: quantitative and qualitative olfactory disorders.

2.4.2.1 Quantitative smelling disorders

Smell loss can be partial, a condition called hyposmia, or total, a condition called anosmia (Keller and Malaspina, 2013). The most often diagnosed is hyposmia, defined as the decreased ability to smell, however, anosmia is also quite frequent (Ricco et al. 2016). Quantitative olfactory disorders are usually acquired dysfunction of the olfactory system with several causes (Murphy et al. 2003, Upadhyay and Holbrook 2004). The term “functional anosmia” is defined as a TDI score, in the Sniffing Stick Test, of less than 16.5 (Kobal et al. 2000, Hummel et al. 2007). In this situation, subjects does not have olfactory ability or have some function left, but not valuable in daily life (Hummel et al. 2007). According to Lötsch and Hummel 2006, patients with functional anosmia can exhibit olfactory event-related potentials because functional anosmia also reflects people with some olfactory information left. Specific anosmias also have been described for a series of different odors and are considered a physiological phenomenon. The occurrence of these specific anosmias indicates that specific receptors are necessary for perceiving a specific odor (Hummel et al. 2011). Furthermore anosmia is considered an early finding, that frequently occurs before the motor impairment in Parkinson’s disease (Leboucq et al. 2013).

On the other hand, the increased ability to smell is called hyperosmia. It is the rare pathological situation and usually is linked with the exposure to toxic vapors or neurologic disorders such as migraine (Henkin 1990, Upadhyay and Holbrook 2004).

2.4.2.2 Qualitative smell disorders

Some patients not only suffer from quantitative olfactory impairment but also experience qualitative olfactory dysfunction (Leopold 2002) classified under terms such as dysosmia or olfactory distortion. Patients with partial smell loss often also suffer from distorted olfactory perception that can be subdivided into parosmia, also called ‘‘troposmia’’, (distorted olfactory experiences in the presence of an odor) and “phantosmia” (perception of an odor when none is present) (Leopold 2002, Pinto 2011, Cheng et al. 2013).

Interestingly, parosmia requires both intact and damaged brain regions. So, either the medial or lateral orbitofrontal cortices must be damaged, however, not at the same time. In addition, undamaged areas such as the lateral orbitofrontal cortex or the temporal lobe pole are also essential (Lötsch et al. 2016). Typically, the great majority of patients with parosmia describes these experiences as unpleasant (Leopold 2002). Phantosmia and parosmia often coexist, although, parosmia is much more common than phantosmia (Keller and Malaspina 2013, Hüttenbrink et al. 2013). Indeed, while phantosmia appears to be a relatively rare symptom and it is usually a consequence of damage in the frontal lobe (Wilson et al. 2014).

Parosmia seems to be a frequent finding in patients with olfactory impairment. Its frequency has been estimated, by many studies, from 10 to 60% among patients with olfactory dysfunction (Deems et al. 1991, Nordin et al. 1996, Frasnelli and Hummel 2005). Parosmia can generally occur after viral infections of the upper respiratory tract or after skull-brain traumas, in other words, seems to occur either during neuronal death or during regeneration. Parosmia can be caused by sinusitis, by odors that come from the infected paranasal sinuses, although this is considered rare (Leopold 2002, Frasnelli and Hummel 2005).

As suggested by Hummel et al., in 2011, it is possible to make a simple classification of qualitative smell disorders based on 3 criteria: daily/not daily (1 or 0 points respectively); intense/not intense (1 or 0 points respectively); social or other notable consequences (for example: weight increase/loss)/no social or other consequences (1 or 0 points respectively). The sum of the points provides the degree of parosmia or phantosmia (0 to 3rd degree). As already said, parosmia is associated with higher rates of depression than hyposmia and should point to different counseling by the clinician (Frasnelli and Hummel 2005, Landis et al. 2009). Additionally, it should be of diagnostic value in terms of the prognosis (Steinbach et al. 2008). Fortunately, the routine assessment of parosmia appears to be possible by using instruments based on questionnaires regarding daily life problems (Frasnelli and Hummel 2005).

2.4.3 Etiologies and Therapies

Impairment of smell may occur after injury to any portion of the olfactory tract, from nasal cavity to brain. Because of this, there are innumerous causes of smell dysfunction. In fact, it is well documented that more than 200 diseases can contribute to olfactory dysfunction (Murphy et al. 2003). An extensive understanding of the anatomy and pathophysiology together with detailed obtained medical history, physical exam, nasal endoscopy, olfactory testing, and neuroimaging may be valuable to identify the mechanism and the degree of dysfunction. (Costanzo and Miwa 2006, Coelho and Costanzo 2016). Olfactory sensory neurons (OSNs) are unique and have a particular behavior. They have directly contacted both the external environment and the brain and while this direct contact makes it possible OSNs to detect fragrances, it also exposes the olfactory mucosal to insults from toxins, bacteria, and viruses leading to cell damage and death. (Jointer et al. 2015).

Unfortunately, most olfactory deficits are neuronal mediated and consequently unable to be corrected (Coelho and Costanzo 2016) and, also, much of the molecular mechanisms of olfactory impairment are not well understood, leading to limited treatment options (Pekala et al. 2016).

For pedagogical purposes, olfactory impairments can be classified into three large categories regarding etiology:

1. Conductive losses due to obstruction of the nasal passages.

2. Sensorineural causes from damage to the olfactory neuroepithelium.

3. Central dysfunction related to central nervous system disease.

These categories are not mutually exclusive (Pinto 2011) and include many etiologies including nasal polyps, chronic rhinosinusitis (CRS), upper respiratory infections (Damm et al. 2004), traumatic injury (Philpott and Boak 2014), and neurodegenerative diseases such as Parkinson disease or Alzheimer dementia (Pinto 2011, Hüttenbrink et al. 2013, Cheng et al. 2013, Doty and Kamath 2014). Other known causes include toxic exposure, endocrine or hormonal abnormalities, iatrogenic loss, tumors, age-related loss, and many others. In a large percentage of patients, it is not possible to identify an etiology. (Patel et al. 2015). About 0.5 to 5% of all olfactory dysfunction are suspected to be linked with work-related exposure situations. Probably, this occurrence is underestimated and ignored by the patient, especially among persons having chronic long-term and low-level exposure. These professional exposures may bring a slow and gradual decrease in the olfactory function. It is also possible that a considerable part of the “idiopathic” olfactory impairment may be work-related (Vennemann et al. 2008, Riccó et al. 2016).

Among many tests to evaluate smell performance, smell tests can contribute to the localization of the underlying pathology. If only the ability to discriminate between odors is affected, central nervous impairment can be suspected. However isolated shifting of the olfactory threshold tends to indicate peripheral damage. (Hummel et al. 2011).

Apart from ageing (Pinto 2011, Mullol et al. 2012), the three most common causes, that account for up to two-thirds of patients with olfactory complaints are sinonasal disease, upper respiratory infection, and head trauma (Murphy et al. 2003, Upadhyay and Holbrook 2004, Keller and Malaspina 2013, Hüttenbrink et al. 2013).

By definition, chronic rhinosinusitis (CRS) is an inflammation of the nose and paranasal sinuses lasting more than 12 weeks (Fokkens et al. 2012). CRS is a common cause of olfactory impairment, with 28–84% of patients experiencing a reduction in the olfaction (Thompson et al. 2015, Croy et al. 2014). Care must be taken when non-otolaryngologist diagnoses the CRS because, in this situation, most patients do not have the condition. A recent study from the USA showed that in a sample of 114 patients with newly diagnosed CRS, only one patient met the diagnostic criteria (Novis et al. 2016). Even so, CRS with or without polyps is considered the most common cause of olfactory dysfunction and accounts for 14-30% of cases (Holbrook and Leopold 2006, Litvack et al. 2008, Keller and Malaspina 2013). The prevalence CRS in Europe is as high as 10.9 % (Hastan 2011, Luukkainen et al. 2012) and it is considered the most common chronic medical condition in the United States of America (Wallace et al. 2008). In addition, more than half of CRS patients have an olfactory impairment (Litvack et al. 2008). According to the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS 2012), loss of smell is one of the four signs and symptoms used to diagnose rhinosinusitis, along with nasal congestion, nasal discharge and facial pain/ pressure (Fokkens et al. 2012). Regarding the etiology of nasal polyposis, it is defined as a chronic inflammatory process, often edematous, with hyperplastic sinonasal involvement, not completely elucidated (De Haro et al. 2010). One study showed that as many as 83% of patients with nasal polyposis had smell loss, reported by self- assessed methods (Delank and Stoll 1998).

The pathogenesis of olfactory dysfunction in CRS is likely to be multifactorial and not yet completely understood (Turner et al. 2010, Soler et al. 2015). In this context, it is believed that two independent mechanisms may cause smell loss:

conductive and sensorineural (Mott and Leopold, 1991, Raviv and Kern 2004, Litvack et al. 2008, Lane 2010, Katotomichelakis 2013). The conductive olfactory dysfunction is caused by mechanical obstruction (due to mucosal edema, polyps, crusting and discharge), that occurs due to decreased airflow to the olfactory cleft (Jafek et al. 1987, Pinto 2011, Leboucq et al. 2013). Because inflammation is the most easily treatable cause of olfactory loss, detecting other symptoms, such as sneezing, rhinorrhea, facial pain, nasal obstruction, and epistaxis is very useful (Pinto 2011).

Some clinical treatments for sinonasal disease concerning olfactory function have been described: antihistamines nasally and systemically administered corticosteroids, and surgery (Keller and Malaspina 2013). The endoscopic sinus surgery (ESS) is widely valued, and usually is an effective treatment for CRS symptoms (Szaleniec et al. 2015). Regarding the sense of smell, many (but not all) studies confirm postoperative improvement in most patients (Doty and Mishra 2001, Minovi et al. 2008, Nguyen et al. 2013, Gupta et al. 2015, Minovi et al. 2015, Szaleniec et al. 2015); including in patients with nasal polyposis (NP) (Rudmik and Smith 2012, Nguyen et al. 2015). However, the ESS in the OC is frequently avoided because of the risk of a cerebrospinal fluid leak and the fear of iatrogenic hypo-anosmia (Nguyen et al. 2013). Smell loss may also have a role in the detection of CRS with NP recurrence. In fact, following the ESS, a decrease in the olfactory ability is considered the most sensitive symptom for the early detection of recurrence of NP (Bakhshaee et al. 2016).

Unfortunately, according to Hummel and collaborators, the olfactory function improvement with the endoscopic sinus surgery occurs, but usually only for a short term (Hummel et al. 2011). Therefore, ESS is often used if medical

treatment fails to improve the symptoms. In a recent study, a total of 40 patients diagnosed with CRS without NP, 70% had symptoms of hyposmia or anosmia before surgery, which dropped to 22.5% at 1 month after surgery and to 10% at 3 months after surgery (Gupta et al. 2015). However, not all studies confirm that ESS may significantly improve olfactory loss. Jiang et al, in 2008 and also in 2009, demonstrated that ESS had little or no impact on olfactory improvement in patients with medically refractory CRS. This is a contrast to most studies involving this matter. Another fine example confirming the benefits of ESS in CRS patients with olfactory loss is a large prospective study by Pade and Hummel, in 2008, that evaluated 206 patients with an olfactory impairment who elected ESS for CRS. The authors demonstrated that 23% of patients experianced improvement, 68% had no change, and 9% got worse after the surgery. Also in the same study, they suggested that the presence of NP and eosinophilia predicted olfactory improvement. In 2010, Katotomichelakis et al. concluded in their study with 116 patients with CRS and NP that a significant improvement of olfaction, for at least 6 months was observed after ESS. However, most researchers agree that the restoration of smell cannot be expected in every patient (Doty and Mishra 2001, Szaleniec et al. 2015). Nguyen et al. in 2015 concluded that patient with a history of previous ESS are at an increased risk of having no recovery of their olfactory function after surgery.

Data concerning the role of allergy in CRS is particularly conflicting. In a study by Cowart and colleagues, allergy patients had significantly higher detection thresholds than did the controls (Cowart et al. 1993). The olfactory function in allergic subjects is likely to be fluctuating (Seiden and Duncan 2009) and, after allergen challenge, the sense of smell is often worse (Doty and Mishra 2001).

However, in many studies, allergy did not prove to be an important predictor of olfactory ability in CRS subjects either before (Litvack et al. 2008) or after ESS (Szaleniec et al. 2015).

However, many studies agree that allergic rhinitis (AR) alone can diminish olfactory performance. In this context, it is long known that sensorineural smell dysfunction is induced by inflammation and damage to the olfactory neuroepithelium (Mott and Leopold 1991, Kern 2000) and in fact, is a key symptom in patients with AR (Stuck and Hummel 2015). In addition, there is enough evidence demonstrating that, even without mucosal hypertrophy, allergic inflammatory infiltrate may itself disturb the smell sense (Guss et al. 2009 and Turner et al. 2010). Sivam et al. in 2010 suggested that the presence of eosinophils in the olfactory area in AR may indicate a direct, deleterious effect of inflammation on olfactory epithelium leading to an olfactory dysfunction. According to Guss et al., in a 2009 study, a significant number of patients with AR will exhibit hyposmia, mostly to a mild or moderate degree. In 2009, Guilemany et al., have suggested that persistent AR induces a moderate loss of the sense of smell usually in the moderate-to-severe disease. One study from de Haro et al., in 2008, showed that people with AR have a clear impairment in olfactory levels and that subjects with pollen-related AR had greater olfactory loss compared to those allergic to mites. Stuck and Hummel, in 2015, reviewed 36 articles considered relevant in this matter. Data collected indicated that the frequency of olfactory dysfunction increases with the duration of the disorder and that most studies report a frequency in the range of 20% to 40%.

The use of systemic and topical corticosteroid in the treatment of hyposmia in CRS with NP has demonstrated statistically important improvement in several

randomized controlled trials (Hastan 2011). The histology and clinical response to systemic corticosteroids support a sensorineural component to the disorder. (Kern 2000; Stevens 2001). It is also remarkable that olfactory dysfunction caused by CRS usually fluctuates over time and can be modulated, for example, by physical exercise and hot showers (Keller an Malaspina 2013).

There are many papers in the medical literature that suggest the olfactory capability improvement with the use of corticoid. In a large patient population study, 425 patients with olfactory dysfunction were treated with systemic corticosteroids for 14 days. The olfactory performance was measured using the “Sniffing Sticks” test before and after the treatment. The results showed that treatment was more effective in patients with CRS (especially in subjects with NP) than in patients with idiopathic olfactory dysfunction (Schriever et al. 2012). Alobid et al., in 2014, also suggested that the use of 2-week oral prednisone plus intranasal budesonide for 12 weeks could improve smell capability, possibly due better passageway of odorants to the olfactory mucosal. Other study demonstrated that 20% of patients with CRS showed a relevant increase of their smell test score, with the use of oral corticosteroids, regardless of sex, age or duration of disease (Fleiner 2010). In their 2009 study, Hellings and Rombaux demonstrated that both, nasal and systemic corticosteroids, have a beneficial effect on olfactory dysfunction, with systemic treatment being the most effective. On the other hand, another study (see Heilmann et al. 2004b) used local application of corticosteroids - mometasone nasal spray, administered for 1-3 months. Their conclusion was that little or no positive effect on olfactory function was observed. In the same study, in contrast, after administration of

systemic corticosteroids, improvement of the smell ability was seen overall diagnostic categories.

Attention to the fact that there are three main ways to use topical nasal corticoid: nasal drops applied with a pipette, nasal spray irrigation and using a squirting device (like a syringe). Scheib et al., in 2008, showed that squirt devices (in this particularly study, it was used a syringe with a needle) reached the olfactory area in 73% of cases. This percentage dropped to 6.6% when it was applied with a spray and to 0% when it was administered as drops. This data also coincides with results from Lam et al. in 2013 that concluded that nasal irrigations are a more effective method of delivering topical agents to the posterior and superior aspects of the nasal cavity. On the other hand, Rudman et al., in their study about the radiographic distribution of drops and sprays in the nose, concluded that neither spray nor drops were detected in superior nasal spaces (Rudman et al. 2011). However, there is a specific position described by Mori et al. that assist the nasal drops to achieve the OC region called “Kaiteki” maneuver. This study showed that using this maneuver, nasal drops reached the OC in 96 % of the decongested cases and 75 % of the cases who had not been decongested (Mori et al. 2016).

The second most common cause of smell dysfunction is upper respiratory tract infections. In this situation, the damage of olfactory epithelium, by the virus infection, leads to an olfactory loss, that may persist long after the infection (Watelet and Van Cauwenberge 1999). Upper respiratory tract viral infections are common and can be caused by numerous viruses. In fact, there are about 20 billion virus upper airway infections per year in the world. Airway infections are an important cause of disability, days lost from school or work, hospitalization, and mortality (Denny 1995, Monto 2004). Acute respiratory infections are more

common in the pediatric population and have specific seasonal occurrences. There are several risk factors linked to an increased incidence or severity of respiratory infections such as: an occurrence in the very young or the elderly; crowding; being male; inhaled pollutants; anatomic, metabolic, genetic or immunologic disorders; and malnutrition, including vitamin or micronutrient deficiency (Denny 1995). Influenza is the virus most frequently associated with respiratory infection resulting in medical consultation and virus-related lethality (Monto 2004). The viruses frequently involved in upper airway infection are rhinovirus (cold virus), influenza viruses (flu virus), parainfluenza viruses and respiratory syncytial viruses (mainly among patients aged <1 year). However, exactly which viruses may cause a postviral olfactory loss is unknown, as well as who is more susceptible to olfactory damage after the common cold.

As commented before, the onset is abrupt and the complaint, many times, originates an important loss of QOL (Temmel et al. 2002). Patients with postviral olfactory loss generally retain some smell capacity and presence of olfactory distortion (parosmia) is very frequent in these patients (Temmel et al. 2002, Reden et al. 2007, Bonfils et al. 2005, Harris et al. 2006, Haro-Licer et al. 2008). Therefore, the olfactory disorder is not clearly understood, making treatment for the condition difficult. Although there are some controversies (see Yee and Rawson 2000), a study from 2012, pointed that the systemic application of vitamin A at a dose of 10.000 IU per day for 3 months was not useful in the treatment of postinfectious or posttraumatic olfactory loss (Reden et al. 2012). It is known that this subgroup of smell loss can have spontaneous recovery. A study showed that olfactory loss was subjectively improved in 85.7% of the patients and the recovery rate to subjective normosmia was 31.7% (Lee et al. 2014).

The third most frequent cause of smell dysfunction is head trauma (Doty et al. 1997). The mechanisms of this olfactory dysfunction comprise direct injury to the OE, shearing effect on olfactory fibers at the cribriform plate, or brain contusion or intraparenchymal hemorrhage (Reiter et al. 2004). Posttraumatic anosmia or posttraumatic olfactory dysfunction is frequent but surprisingly under-evaluated (Schofield et al. 2014, Proskynitopoulos et al. 2016). It is estimated that 5% of all head injuries may provoke olfactory loss that usually is severe (Hüttenbrink et al. 2013), with sudden onset (Harris et al 2006) and with a high incidence of parosmia (Konstantinidis et al. 2013, Lötsch et al. 2016). Indeed, anosmia and phantosmia, occurs when there is lost function in important brain regions while parosmia is more complex, requiring injured and undamaged brain regions at the same time (Lötsch et al. 2016).

One study showed that, after traumatic brain injuries, up to 20% of the patients may develop olfactory impairment (Proskynitopoulos et al. 2016). As said, it happens when there is some degree of the lesion on the olfactory fibers around the lamina cribrosa or in cases of brain lesions in specific areas related to olfaction (Hummel et al. 2011, Hüttenbrink et al. 2013). Recently, it was identified by Lötsch et al., that lesions in the right olfactory bulb are the first and most important decisive MRI finding associated with anosmia (Lötsch et al. 2015). Research over the past years has suggested that the entorhinal cortex (located in the medial temporal lobe) and the olfactory bulb are neuronal structures that display neuroplasticity and have the potential for significant regeneration (Kern et al. 2000, Wang et al. 2004).

Although, it is believed that the recovery rate of any olfactory function depends on many clinical aspects other than just the anatomical location of the lesion alone (Proskynitopoulos et al. 2016, Kern et al. 2000). Indeed, different recovery rates have been reported in these patients with olfactory loss following head trauma (Konstantinidis et al. 2013). There is a propensity that younger patients have a higher olfactory improvement rate. This finding was supported by Jiang et al, 2010, who found that younger patients had a better response to oral steroid treatment and had a better improvement of olfactory function. Also, in younger patients were found to have a better proliferation of neurons in the olfactory neuroepithelium (Fan et al. 2015). It was also reported that for both groups (post-infectious and post-traumatic) significantly improved scores for the olfactory function was found when compared to baseline (Konstantinidis et al. 2013).

There is enough evidence showing that repeated exposure to different odors may modulate the olfactory system, a procedure called olfactory training (OT). It is performed twice daily, at leats for 12 weeks, with the use of four odors (phenyl ethyl alcohol [rose], eucalyptol [eucalyptus], citronellal [lemon], and eugenol [cloves]). The use of these fragrances represents the four significant odor categories: flowery, fruity, aromatic, and resinous (Hummel et al. 2007). OT is considered a very promising therapeutic treatment for olfactory loss, especially in patients with smell loss after an upper airway infection (Hummel et al. 2007, Hummel et al. 2009, Konstantinidis et al. 2013, Damm et al. 2014) and after a post-traumatic event (Konstantinidis et al. 2013).

In a study from 2014, Kollndorfer et al., showed that OT can induce alterations in functional connectivity networks and may lead to neural reorganization processes. The same author demonstrated in 2015, that an OT program can

reorganize functional networks, although, initially, no differences in the spatial distribution of neural activation is observed. After the OT, the sensitivity to detect odors significantly increased in the anosmic group, which was also manifested in modifications of functional connections. Finally, in a recent large systematic review and meta-analysis, about the efficacy of OT in patients with the olfactory loss, from 2016, Pekala et al. suggested that it may be an effective treatment for olfactory dysfunction in many different etiologies, including post-infectious, post-traumatic, and Parkinson's disease. The neuronal basis of the OT remains poorly understood (Kollndorfer et al. 2014). At the behavioral level, OT mainly affected the odor detection threshold, the most basic function of olfactory performance (Hummel et al. 2009, Kollndorfer et al. 2014).

Smell Loss Etiology	**Typical starting age**	**Onset of smell disorder**	**Loss of Smell**	**Chance to occur parosmia**	**Chance to improve with treatment**
Advanced Age	60-70 years	Very slow	Variable	?	No improvement
Chronic Rhino-Sinusitis	30-60 years	Slow	Moderate	Not Frequent	Very often (but usually short term)

Upper Airway Virus Infection	>50 years	Fast	Moderate	Very Frequent	Often
Head Trauma	20-50 years	Fast	Severe	Frequent	Less Often

Fig. 5. Adapted from Hummel et al. 2011.

In addition to the three main causes of olfactory dysfunction, there are several other situations that may cause smell disorders. The olfactory decline has been associated with several neurodegenerative diseases, leading to central olfactory dysfunction; although its role as a predictor or marker of disease onset has not yet been clearly established (Pinto 2011). Smell dysfunction is often an early important manifestation of neurodegenerative diseases, such as Parkinson's disease (PD), Alzheimer's disease (AD) (Zou et al. 2016), Multiple Sclerosis (MS) (Caminiti et al. 2104b), Huntington's disease, motor neuron disease and its evaluation can be useful for diagnosis knowing that olfactory decline may precede the more severe manifestations of these diseases. (Pinto 2011, Hummel et al. 2011, Doty and Kamath 2014). They are present in over 95% of patients with idiopathic Parkinson’s syndrome when compared to the smell function of young and healthy persons (Hummel et al. 2011). The Guidelines of the “Deutsche Gesellschaft für HNO-Heilkunde” state that a neurological examination is recommended for patients with idiopathic smell disorders, because may be a

predictor of subsequently development of PD or AD (Hummel et al. 2011, Hüttenbrink et al. 2013, Zou et al. 2016). In PD, the smell loss is concomitant with atrophy of the olfactory bulbs and this atrophy is attributed to an increase in the number of dopaminergic cells in the olfactory bulbs that will inhibit the olfactory inflow (Leboucq et al. 2013). The olfactory impairment in MS has also been reported, but it still remains unclear whether olfactory loss occurs as an early symptom of MS. (Caminiti et al. 2104b). Furthermore, AD is a common neurodegenerative disorder, which accounts for 60%-80% of all cases of dementia (Zou et al. 2016). In fact, olfactory dysfunction is an early symptom of dementia and has a high prevalence in various types of dementia, reaching up to 100% in AD, 90% in PD dementia, 96% in frontotemporal dementia, and 15% in vascular dementia (Duff et al. 2002, Pardini et al. 2009). In many cases the olfactory impairment in the unconscious. Only 6% of AD patients complained of a decline in olfactory function during the early stage of the disease, but 90% of AD patients demonstrated in an olfactory test, a significant impairment of olfactory function. (Devanand et al. 2000). Combining olfactory tests and conventional diagnostic methods could possibly improve the sensitivity and specificity of AD diagnosis and early recognition (Velayudhan 2015).

The olfactory training (OT) can be also effective in patients with PD. Indeed, in a study conducted by Haehner et al., in 2013; Parkinson's patients were exposed over a period of 12 weeks, twice daily to four odors (phenyl ethyl alcohol: rose, eucalyptol: eucalyptus, citronellal: lemon, and eugenol: cloves). Compared to baseline, trained PD patients experienced a significant increase in their olfactory function, while it was unchanged in PD patients who did not perform OT (Haehner et al. 2013). It is interesting to note that odor discrimination, but not odor

threshold, improved in response to olfactory training. Perhaps a possible reason could be that odor discrimination appears to involve higher-level cognitive abilities compared to odor threshold. Therefore, it is possible that OT may bring positive effects on cognitive processing of olfactory information. (Haehner et al. 2013).

Decreased olfactory function is very frequent in the older population. It is presented in over half of those between the ages of 65 and 80 years and in over three-quarters of those over the age of 80 years (Lafreniere and Mann 2009, Doty and Kamath 2014). Since olfactory dysfunction may manifest early in neurodegenerative diseases, it represents a remarkable early clinical symptom suggestive of neurodegeneration (Gallarda and Lledo 2012). In a relevant study with 2800 subjects (see Murphy et al. 2002) revealed that between 53 and 59 years old, the prevalence of smell dysfunction reached 6.1%, whereas in 80- to 97-year-old people, it reached 62.5%.

In fact, ageing is thought to represent an important influence on the olfactory decline in the general population, and olfactory degradation is a part of normal aging (Mullol et al. 2012, Wilson et al. 2014). Indeed, this has been confirmed by biopsy studies that show degeneration of the olfactory epithelium with age. At present, the exact factors that modulate age-related loss of smell are not completely understood. (Pinto 2011). Another author, in 2001, studying functional magnetic resonance imaging (fMRI) in elderly volunteers, showed decreased activation in brain regions related to olfactory processing (Suzuki et al. 2001).

According to Attems et al., three main changes ought to be considered in olfactory loss. First, changes in the olfactory neuroepithelium, followed by changes in the OB and finally, changes in brain regions involved in olfactory processing (Attems et al. 2015). In this context, it is believed, that multiple factors

may contribute to age-related smell disorders, including: altered nasal engorgement, increased propensity for nasal disease, a decrease in mucosal blood flow, imbalance of the sympathetic/ parasympathetic mode of olfactory sensibility (Attems et al. 2015), cumulative damage to the olfactory epithelium from viral and other environmental insults, replacement of the olfactory epithelium by respiratory epithelium, decrements in mucosal metabolizing enzymes, ossification of cribriform plate foramina, loss of selectivity of receptor cells to odorants, decreased number of glomeruli and mitral cells in the olfactory bulb (Meisami et al. 1998), reduction of the volume of olfactory bulbs (Sinding et al. 2014), changes in neurotransmitter and neuromodulator systems, and neuronal expression of aberrant proteins associated with neurodegenerative disease (Doty and Kamath 2014). Changes in the OB and in the brain regions involved in olfactory processing due to the deposition of pathological proteins associated with various neurodegenerative diseases such PD and AD (Attems et al. 2015). Reduced odor identification in elderly population has important practical consequences on daily life activities because it is related with a reduction in global cognition and in episodic memory (Wilson et al. 2006).

In a 2004 study with 445 patients with chemosensory dysfunction, many whom were elderly, 37% of those with olfactory impairment informed having experienced an olfaction-related hazardous event at some point in their lives, as compared to only 19% of those with no such impairment. In addition, cooking-related incidents were most common (45%), with ingestion of spoiled food (25%), lack of ability to detect leaking natural gas (23%), and inability to smell a fire (7%) being less frequent (Santos et al. 2004). In other more recent study from Sinding et al, it was found that there is a difference among odors of the “Sniffin’ Sticks”

test, in response to ageing, related to pleasantness. Interestingly, the authors revealed that unpleasant odors were age invariant, whereas pleasant odors showed sensitivity to ageing. (Sinding et al. 2014). Confirming other studies, elderly women showed a less age-related decline in olfactory abilities when compared to old men at the equivalent ages (Oliveira-Pinto et al. 2014). Perhaps because there is a significant sex-related difference in the absolute number of total, neuronal and non-neuronal cells in the OB, favoring women around 40%, even when corrected for mass (Oliveira-Pinto 2014).

Also relevant, is that the ability to identify olfactory stimuli is significantly correlated with measures of memory, language, and other cognitive abilities; identification involves detection, discrimination, recognition, and retrieval of a name. Therefore, age-related differences in olfactory ability in the identification test might be the level of development of cognitive abilities. (Sorokowska et al. 2014).

Many drugs/ medications may rarely be the cause of smell disorders. Both, anosmia, (the loss of smell), and ageusia (the loss of taste) are rare side effects that can happen because of administration of practically all classes of medications (Elterman et al. 2014). This rare complication has the overall incidence estimated to be 0.05% (Pinto 2011). Medications such as steroids, anti hyper tonic drugs (diltiazem, nifedipine), cancer chemotherapy, antibiotics (aminoglycosides, macrolides, tetracycline, streptomycin), antithyroid medication, opioids (remifentanil, morphine), antidepressants (amitriptyline) sympathomimetics, psychopharmaceuticals (amphetamines, alcohol) and L-dopa may all cause olfactory impairments (Hummel et al. 2011, Pinto 2011). Indeed, patients undergoing chemotherapy may suffer from taste and smell

changes. In a study conducted with 518 patients, mainly breast, gynecologic, and GI cancer patients, the patients reported taste and smell changes (75%), oral problems (56%), depressed mood (49%), nausea (39%), appetite loss (22%), and vomiting (10%) (Bernhardson et al. 2008). Chemicals such as benzene, menthol, sulfur dioxide, carbon disulfide, heavy metals, and even dust have also been linked to olfactory loss (Pinto 2011). A recent study from Mizera et al., with 100 chronic pain patients and 95 controls, suggested that the chronic use of pain medication is associated with reduced olfactory perception of intranasal trigeminal stimuli compared to age-matched controls that do not use analgesics - without difference between non-opioid and opioid drugs. The precise mechanism of how these chemicals and medications affect olfactory abilities are not completely known in humans. (Mizera et al. 2016).

Cases of anosmia and/or ageusia have also been reported to occur after administration of various anesthetic agents. In this regard, the incidence of anosmia or ageusia after an anesthetic has been estimated to be approximately 1.8% (Elterman et al. 2014). Possible approaches of avoiding or minimizing the risk of this rare complication include avoidance of intranasal ketamine and limitation of the duration of exposure of the olfactory cleft to lidocaine at concentrations equal to or greater than 4%. Fortunately, in most cases, the symptoms are temporary because the olfactory receptor cells are often capable of regenerating themselves after injury. (Elterman et al. 2014).

Furthermore, endocrine changes including pregnancy, diabetes, Addison's disease, vitamin deficiency (primarily vitamins A and B and thiamine), as well as renal and liver disease are associated with olfactory dysfunction. (Pinto 2011). Other diseases like granulomatous inflammatory disorders (sarcoidosis,

Wegener's granulomatosis) or even autoimmune/immune-mediated diseases, such as poly dermatomyositis, recurrent spontaneous abortion, and hereditary angioedema and Sjögren's syndrome may induce hyposmia (Strous and Shoenfeld 2006). Genetic susceptibility and hormonal and environmental factors may play a role in these conditions. It is known that olfactory receptor gene clusters are located near to key locus of susceptibility to autoimmune diseases, suggesting not only a physic linkage but a functional association (Perricone et al. 2013).

Tumors, especially benign tumors, most often found are olfactory meningiomas and those of the small sphenoid ridge may also result in olfactory impairment (Leboucq et al. 2013). It is also important to notice that partial olfactory seizures are infrequent, but when presented, they are often related to structural alterations to the amygdala (Medrano et al. 2004). Patients with olfactory seizures may report generally unpleasant smells during the ictal phase. (Chen et al. 2003, Medrano et al. 2004).

According to World Health Organization, in 2015, over 1,1 billion people smoked tobacco. It is indeed, a huge world health problem. Regarding the relation between the smell dysfunction and tobacco, most of the researchers confirm it. In 1990, Frye et al. concluded that a large inverse relation between pack-years and olfactory test score when cumulative cigarette smoking dose was evaluated. And also that smoking causes long-term changes in the olfactory system. According to this study, improvement in smell function appears to occur following cessation of smoking, but not in a short-term period (eg. for a two-pack-per-day smoker, the restoration of smell function to normal levels requires the same number of years as the number of years smoked). In another study

(Katotomichelakis et al. 2007), it was found a clear decrease in olfactory threshold, discrimination and identification ability in smokers compared to non-smokers. Especially the olfactory threshold ability in smokers presented a 14.1% reduction. In addition, depending on the duration and the number of cigarettes smoked, smokers were found to be nearly six times as likely to have a smell impairment compared to nonsmokers (Katotomichelakis et al. 2007). Smoking, in general, is associated with an increased risk of hyposmia but not always with gustatory dysfunction. However, heavy smoking of 20 or more cigarettes per day is clearly related to the impairment of both senses. (Vennemann et al. 2008).

Even race may play a role in the smell loss genesis. In 2014, a study by Pinto et al., pointed that African Americans are more likely to suffer from olfactory loss, a disparity not explained by gender, education, cognition, physical or mental health, and health behaviors. This study showed that African Americans had a markedly worse olfactory function (controlling for gender and age) when compared with whites ($p < .001$).

Some anatomical abnormities like septal deviations and turbinate hypertrophy are sometimes implied in olfactory loss although there is conflicting literature evidence concerning whether and how septal and turbinate deformations or nasal surgery exactly can influence the smell function. Many studies show that septal deviation and turbinate hypertrophy cause olfactory dysfunction due to a physical obstruction in the nasal airways (Choi et al. 2016). Others studies demonstrate variable results as regards olfactory function after a surgical treatment due to turbinate hypertrophy or septal deviation. In the case of Kimmelman, 1994, there was no statistical significance in smell capability in patients who underwent septoplasty. On the other hand, Damm et al. in 2003 showed that about 80% of

patients improved odor identification after the surgery; result also agreed by other studies (see Sanchez-Vallecillo et al. 2012 and Choi et al. 2016). Other nasal surgeries such as endonasal surgeries can also lead to smell impairment. In a recent study from 2015, Wang et al. suggested that microscopic endonasal transsphenoidal pituitary surgery impairs olfactory function in most patients for at least 4 months after surgery. Moreover, many studies indicate that certain intranasal volumes are significantly associated with an olfactory function (Jun et al 2010). Thus, in patients following nasal surgeries (ESS, septoplasty), changes in intranasal airflow pattern, direct trauma to, or vascular compromise of, the olfactory epithelium may be responsible for olfactory loss, even when it is performed at a distance from the olfactory epithelium (Pfaar et al. 2004, Chen et al. 2013, Choi et al. 2016).

Around 3% of all olfactory dysfunctional cases are defined as congenital anosmia. They were born without a sense of smell (Keller and Malaspina 2013) and most of them are isolated deficits (isolated congenital anosmia) (Leopold et al. 1992). Many rare congenital abnormalities can lead to olfactory disorders. Facial anomalies are mainly hypoplasia or absence of nose (arrhinia) is a very unusual medical condition that originates smell loss. The absence of olfactory lobes, called arhinencephaly, may be isolated or associated with various anomalies involving the face and brain. The brain malformations are hypoplasia or agenesia of the corpus callosum, impairment of the hypothalamic-pituitary axis, lobar holoprosencephaly or even fronto-naso-ethmoidal encephalocele. Hypoplasia of the olfactory bulbs may be included in multi mal formative syndromes such as the CHARGE syndrome (coloboma, cardiopathy, choanal atresia, retarded growth and development, genital and ear anomalies), Kallmann syndrome (Pinto 2011)

or even cranioencephalic dysplasia. Kallmann syndrome associates hypogonadotropic hypogonadism with anosmia (Leboucq et al. 2013).

In most cases, a detailed medical history (anamnesis), nasal endoscope examination, olfactory testing, and imaging will aid to establish an appropriate diagnosis. Even so, none of the above causes of smell dysfunction can be found in 6% of patients (Forster et al. 2004), and this situation is called smell loss with idiopathic cause. Additionally, according to Hummel and Welge-Lüssen, only after excluding all already mentioned diseases and failure to respond to cortisone, the diagnosing idiopathic olfactory dysfunction can be done (Hummel and Welge-Lüssen 2008). Obando et al., in 2009, raised the question that, these idiopathic cases require the physician's special attention and suggested perform further image investigation (such as MRI).

Not all cases of olfactory loss are permanent. In upper airway post viral etiology and in a younger patient with smell dysfunction, partial spontaneous recovery should be expected. Remarkably, spontaneous recovery can happen years after the symptoms appeared, but the probability of recovery decreases with the duration of smell impairment. Although treatment options may be limited, physicians should provide more information and counseling about the risks and hazards linked with loss of the olfactory impairment. (Costanzo and Miwa, 2006).

2.4.3.1 Test Methods

There are numerous functional and structural approaches available for assessing the integrity of the olfaction system. They include psychophysiological,

electrophysiological (olfactory event-related potentials), and imaging tests (MRI and CT). Psychophysiological tests may evaluate odor sensitivity, identification, and discrimination (Attems et al. 2015). In most cases, this category of tests relies on the patient collaboration and cooperation (fig. 7)

The University of Pennsylvania Smell Identification Test (UPSIT) are a validated and well-known test to assess olfaction. It is a pure identification test with high test-retest reliability ($r > 0.90$), however, without evaluation of the olfactory threshold and discrimination. This test is a 40-question forced-choice test (total score: 0-40), where the microencapsulated fragrances are released by scraping and identified on the basis of multiple choice (so-called "Scratch and Sniff") (Litvack et al. 2009). This test has the disadvantage in its single time applicability compared to the reusable smell pins that have about 6 months of durability. (Doty et al. 1984).

Another important screening test is the Cross-Cultural Smell Identification Test (CCSIT), a limited version of the University of Pennsylvania Smell Identification Test (UPSIT). It is a 12-odor test where the applicant must choose between four options (multiple forced-choice methods). The selection of odors was made based on the existence of the American, European, and Asian culture. Odor familiarity is a very important component while evaluating olfactory function because a person should be familiar with an odor to identify it correctly (Veyseller et al. 2014). The microencapsulated applied to paper scents are released by rubbing. An advantage is that this test may be performed by the subject in a relatively short time (Doty et al. 1996; Hummel and Welge-Lüssen 2008).

There are also described the Connecticut Chemosensory Clinical Research Carried out Test (CCCRC). This test includes threshold determination and identification although without discrimination investigation (Cain et al. 1988). The fragrances are released using squeezable polypropylene or glass bottles (Hummel and Welge-Lüssen 2008). The threshold tests the perception of n-butanol in ascending concentration. The score is recorded, for each nostril, when the subject identified accurately the same butanol concentration five times in a row. The scores for both nostrils are averaged to arrive at the final score (Veyseller et al. 2014). The identification test is conducted with the subjects selecting from a printed list containing the correct items as well as an equal number of distractor items. The forced choice items include the following: Vicks, burnt paper, wood shavings, coffee, baby powder, peanut butter, spearmint, cinnamon, soap, chocolate, mothballs, grape jam, ketchup, black pepper, and rubber. The ability to sense Vicks shows intact trigeminal nerve function. Scores for the butanol threshold test and identification tests are averaged to arrive at a composite score for an orthonasal olfactory ability (Veyseller et al. 2014).

In 1995, Kobal and Hummel have developed the Sniffing Sticks Test that allows a detailed determination of the olfactory sense (Kobal et al. 1996). It is a complete and validated test of nasal chemosensory performance based on pen-like odor dispensing devices (Hummel et al. 1997). It includes three tests of olfactory ability, including tests for odor threshold, discrimination, and identification (Hummel et al. 1996). It is believed that different tests examine different regions of the olfactory function. Threshold tests measure only the periphery of the olfactory system, identification and discriminatory tests greater and more complex

processing levels (Hummel & Welge-Lüssen 2008). Compared to other tests it has some clear advantages such as being reusable, portable, and not an expensive test. Odorants are presented in commercially available (unfilled) felt-tip pens with the length of 14 cm and the inner diameter of 1.3 cm. The tampon pen is filled with 4 ml of liquid odorants or odorants dissolved in propylene glycol. For odor presentation, the cap is removed by the experimenter for 3 seconds and the pen's tip was placed about 2 cm in front of both nostrils (Hummel et al. 1997, Kobal et al. 2000). In a previous study, no pathogenic microorganism's contamination in the sticks was detected (Hummel et al. 1997). The relatively small number of 16 odorants was selected to avoid time-consuming (Hummel et al. 1997). Odor thresholds are assessed using n-butanol (Hummel et al. 1997, Kobal et al. 2000) or phenyl ethyl alcohol (PEA) (Hummel et al. 2011) as the odorant, because of their minimal trigeminal components. PEA is often used in olfactory research because is considered to be a pure odorant. Only 1 of 15 anosmic subjects could detect PEA (Doty et al. 1978). It has, therefore, repeatedly been used to investigate subjects' ability to localize pure odorants. But it is also known that even PEA may cause some trigeminal activation, especially with long stimulus durations (Doty et al. 1978, Kobal and Hummel 1991). In this test subjects were blindfolded to prevent visual identification of some of the odorant containing sticks.

As described by Doty et. al in 1991, using a triple-forced-choice procedure, detection thresholds are determined by employing a single staircase method. Three sticks are presented to each subject in a randomized order, two contained the solvent and the third the odorant, at a certain dilution (Kobal et al. 2000). The

task of the subject is to indicate which stick has the odorant (Doty et al. 1991, Hummel et al. 1997, Hummel et al. 2013). To prevent olfactory desensitization, triplets are presented at intervals of 20 seconds (Hummel et al. 1997, Kobal et al. 2000). The rose-like odor PEA or n-butanol dissolved in distilled water presented in 16 successive 1:2 dilution steps starting from a 4% solution. The test starts at the lowest concentration and it increases until the examiner has two consecutive correct answers; then the staircase is reversed and move downward (sample with lower concentration). The threshold is defined as the mean of the last four out of seven staircase reversal points (Hummel et al. 1997, Kobal et al. 2000, Hummel et al. 2007, Hummel et al. 2013). The duration of this procedure can vary between 10 and 20 minutes and subject's score can range from 1 to 16. (Hummel et al. 1997). The 'Sniffin' Sticks' are definitely suited for olfactory testing. The coefficient of correlation between test and retest was 0.73 for odor identification, 0.61 for odor thresholds and 0.54 for odor discrimination. (Hummel et al. 1997). In another study, (see Hummel and Mayer 2003), the coefficient of correlation for measures of test-retest reliability has been found at $r = 0.94$ (very strong correlation) for odor thresholds and at $r = 0.76$ (strong correlation) for odor identification.

The odor discrimination is also performed with 16 sets of triplets' odorants. It is important to notice that these odors are in a suprathreshold concentration. (Hummel et al. 2007, Hummel and Welge-Lüssen 2008a). After blindfolded with a sleeping mask, the subject must choose, among the three samples offered, which one has the different odor (Hummel et al. 1997, Kobal et al. 2000). Three criteria are required for the selection of odorants: first, they must have a similar intensity. The odors must be similar regarding their hedonic tone, defined by the

Oxford Dictionary as the “degree of pleasantness or unpleasantness associated with an experience or state”. Finally, in healthy subjects, correct discrimination of each fragrance must be higher than 75%. In this part of the test, the subject can sample the odorant just once to avoid time-consuming. The subjects’ scores can range from 0 to 16. There is a standardization about the interval time between the presentations of the fragrances. Each individual stick is presented at an interval of 3 seconds and between the triplets, the waiting time is around 20 to 30 seconds (Kobal et al. 2000, Hummel et al. 2007).

For odor identification, there are 16 common odorants, multiple forced choice from four verbal items per test odorant. In this part of the test, the patient must recognize a total of 16 different fragrances based on a shortlist of four terms, and just one is the correct answer (Hummel at al. 2013). Also, in this exam, the fragrances are presented in suprathreshold concentration. Different from the other steps, subjects may sniff the odorants as much as necessary to make a judgment. In order to prevent olfactory desensitization, there is also an interval of 20 to 30 seconds between each odorant presented by the examiner (Hummel et al. 1997). Again, the subjects’ scores ranged from 0 to 16. Criteria for the selection of odorants are the same as described above for odor discrimination. All odorants should be familiar to the subjects, must be similar regarding intensity and hedonic tone, and the rate identification of each odorant should be higher as 75% (in healthy subjects) (Hummel et al. 1997).

Finally, the sum of the scores from the three subtests determines a composite “TDI score” (“Threshold Discrimination Identification”) considered the final result

of the olfactory ability (Wolfensberger et al. 2000). The TDI can be compared with standard value tables. Established standard criteria of olfactory diagnosis establish that normosmia occurs when TDI is bigger than 30,5; hyposmia with TDI between 16,25 and 30,5 and functional anosmia are indicated by TDI less than 16,25 (Hummel et al. 2007) (fig.6).

Normosmia	TDI > 30,5
Hyposmia	30,5 ≥ TDI ≥ 16,25
Functional Anosmia	TDI < 16,25

Fig. 6 According to Hummel et al 2007.

In 1975, Takagi and Toyota developed in Japan a sniff test known as T & T-test (Kondo et al 1998). In this evaluation, five odorants - β-phenylethyl alcohol, methyl cyclopentenolone, iso-valeric acid, γ-undecalactone, and scatole - adhered to paper strips in eight different concentrations, are presented to the subject, starting with the lowest offered (Hong et al. 2011). The concentration at which a scent is perceived for the first time corresponds to the threshold of perception, concentration, from which a fragrance is correctly allocated, indicates the detection threshold (Hummel & Welge-Lüssen, 2008). It is important to notice that this test has some important limitations like the unpleasant odors that are used contaminate the test environment, and because of that, the test usually needs expensive ventilation facilities (like a chemical hood). Furthermore, it lacks

forced-choice response alternatives, which may lead to many responses variations (Hong et al. 2011).

Psychophysiological Test	How the fragrance is offered	What kind of smell evaluation
University of Pennsylvania Smell Identification Test (UPSIT)	Micro-encapsulated applied to paper fragrances released by scraping	Identification test
Cross-Cultural Smell Identification Test (CCSIT)	Micro-encapsulated applied to paper fragrances released by scraping	Identification test
Connecticut Chemosensory Clinical Research Carried out Test (CCCRC)	The odors are released using squeezable bottles	Threshold and identification test
Sniffing Sticks Test	Pen-like odor dispensing devices	Threshold, discrimination, and identification test

T & T-test	Fragrance adhered to paper strips	Threshold test

Fig. 7 Most used psychophysiological tests.

Results from psychophysical, electrophysiological and imaging studies suggest that are clear differences in the perception of orthonasal and retronasal stimuli (Kent et al. 1996). Some patients exhibit good retronasal olfactory function with little or no orthonasal function available, and *vice versa* (Hummel 2008). In order to determine specifically the retronasal olfactory function, in 2004, a device was created (Heilmann and Hummel 2004). It allows the release of odors directly into the epipharynx above the soft palate. This avoids concomitant oral gustatory, thermal and mechanical stimulation. This device is connected to outlets of a computer-controlled air-dilution olfactometer and then the gathered data can be further analyzed. These previously mentioned test methods serve the diagnosis of quantitative olfactory disorders such as hyposmia and anosmia. Objective tests for diagnosis of qualitative olfactory disorders such as Parosmia or Phantosmie are so far, not available. As already said, routine assessment of parosmia appears to be feasible by using instruments based on questionnaires regarding daily life problems (Frasnelli and Hummel 2005).

Objective testing of smell disorders can be performed using olfactory event-related potentials (OERPs). This method allows observing changes in olfactory function in an objective way, independent from patients' response bias (Caminiti et al. 2014b). In 1978, Kobal and Plattig introduced this device capable of

delivering transient chemosensory stimuli over the olfactory neuroepithelium and allowing to explore how the human brain processes odors. It is remarkably important that this device delivers pulses of odorant embedded within a constant airflow, air temperature, and humidity, thus avoiding concomitant mechanical (trigeminal) stimulation of the nasal mucosa (Hummel et al. 2007). Moreover, using specific fragrances, the device can be used to activate olfactory and trigeminal chemosensory receptors relatively selectively. For example, 2-phenylethanol (PEA) is related to activation of olfactory afferents. One should, however, test specifically trigeminal chemoreceptors, using carbon dioxide. The presence of OERP clearly signifies the presence of olfactory function (Caminiti et al. 2014b), however, the absence of OERP does not surely indicate the lack of the olfactory input. In one study, for example, OERPs were not identifiable in nearly a third of subjects with no olfactory deficits (Lotsch and Hummel, 2006). This technique is the result of sequential activation of different brain regions, from olfactory bulbs and tracts to the orbitofrontal and insular cortices, along with rostrum-medial regions of the temporal lobe (Caminiti et al. 2014b). The fragrances are the patient manually or under computer control in the nose applied. The latest methods allow the monitoring of the propagation of olfactory activation in the brain on the millisecond scale, meaning that a different evaluation of smell disorders can be feasible (Hummel et al. 2011). Some disadvantages of OERPs are that they are relatively expensive and time-consuming. (Hummel et al. 2007 and Hummel & Welge-Lüssen 2008).

In addition to these studies, mucosal biopsies of the olfactory region can be done to analyze the presence and organization of the neuroepithelium. The endoscopic olfactory mucosal biopsy is described as a reproducible and safe surgical

technique for obtaining human olfactory mucosa (Kachramanoglouet al. 2013). Holbrook et al, in 2016, showed that it is a doable and safe procedure, done in the office, with topical anesthesia. The results of the biopsy vary according to the olfactory loss etiology.

For example, in post-traumatic olfactory disorders, a disorganization of the olfactory epithelium, individual degenerated cells and overall thickening of the epithelium can be found. In postviral anosmia it is possible to observe a reduction of olfactory sensory neurons (OSN). In a sinonasal conditional initially normal epithelium may be found at first, but, in long term, squamous or fibrosis can be presented. (Hummel & Welge-Lüssen 2008a). In the case of smell loss due to the ageing process, the olfactory epithelium is progressively replaced by respiratory epithelium, which contains no more ORS (Hummel et al. 2007).

There are specific situations where is important and necessary to measure the volume of the olfactory bulb. And, in other cases, the objective is to determine which brain areas are being activated during an olfactory stimulus. To achieve these goals some image exams can be performed.

Positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) are useful for studies of olfactory functions. Both PET and fMRI studies repeatedly indicate an engagement of limbic structures during the passive smelling of fragrances (Savic 2005). The routine clinical smell loss investigation using fMRI will rarely be applied. In fMRI method, with the so-called BOLD effect (Blood Oxygenation Level-dependent effect), blood oxygenation could be detected, so it is possible to determine which areas are being activated/ has neuronal activity, as a response to olfactory stimuli (Hummel & Welge-Lüssen,

2008a). Most often, the activations cover the amygdala, piriform, orbitofrontal and insular cortex (see Savic 2005). Curiously, activation is seen in similar areas in elderly subjects but the degree of activation is significantly lower in regions receiving primary olfactory projections (piriform cortex, entorhinal cortex, and amygdala) (Cerf-Ducastel and Murphy 2003). Simple MRI exam may also be useful in the search for a cause of the olfactory disorder. Patients with hypoplastic or aplastic olfactory bulbs need MRI to confirm the congenital anosmia diagnosis. Furthermore, it is known that the bulbus volume is linked with the decrease of olfactory abilities (Hummel and Welge-Lüssen, 2008a) and especially in patients with post-infectious and post-traumatic disorders, lower bulbus volume may be found – when compared with healthy volunteers. Although in diseases like idiopathic Parkinson syndrome, no significant decrease of bulbus volume is usually observed (Hummel et al. 2007).

3. Materials and Methods

This retrospective study was submitted by the institutional ethical committee board approved by the number EK 122032011, in accordance with the principles of the Helsinki Declaration. The complete data were collected by one post-graduation student, under the supervision of Professor Doctor Thomas Hummel, in the Smell and Taste Clinic at the Medical Faculty of the Technical University of Dresden (Germany).

3.1 Participants

A total of 288 randomized eligible subjects, 120 males (41.7%) and 168 females (68.3%) were retrospectively evaluated in this study. The minimal age was 18 years old and the maximum age was 89 years old, with a mean age of 58.54 years old (SD= 14,33).

Two groups were formed; The first with patients with smell dysfunctional complaint (n= 240) including 101 men and 139 women, mean age 59.24 (SD= 13.96). The second group was formed by 48 persons without smell complaint. (control group), including 19 men and 29 women, mean age 55.04 (SD= 15.74). To be part of the control group the subjects should not have smell complaint, although could present other nasal conditions (such as rhinitis and rhinosinusitis) or taste disorders.

From the group with smell complaint, four subgroups were formed, based on the probable etiology: idiopathic, post head trauma, post upper airway infection and chronic rhinosinusitis (CRS) with or without polyposis (fig.8). The participants' age was not used as criterion to organize the subgroups.

There were some exclusion criteria such as subjects less than 18 years old, pregnant and lactating women, those who have undergone a nasal surgery three months prior to the test exam and having a cold or flu during the exam.

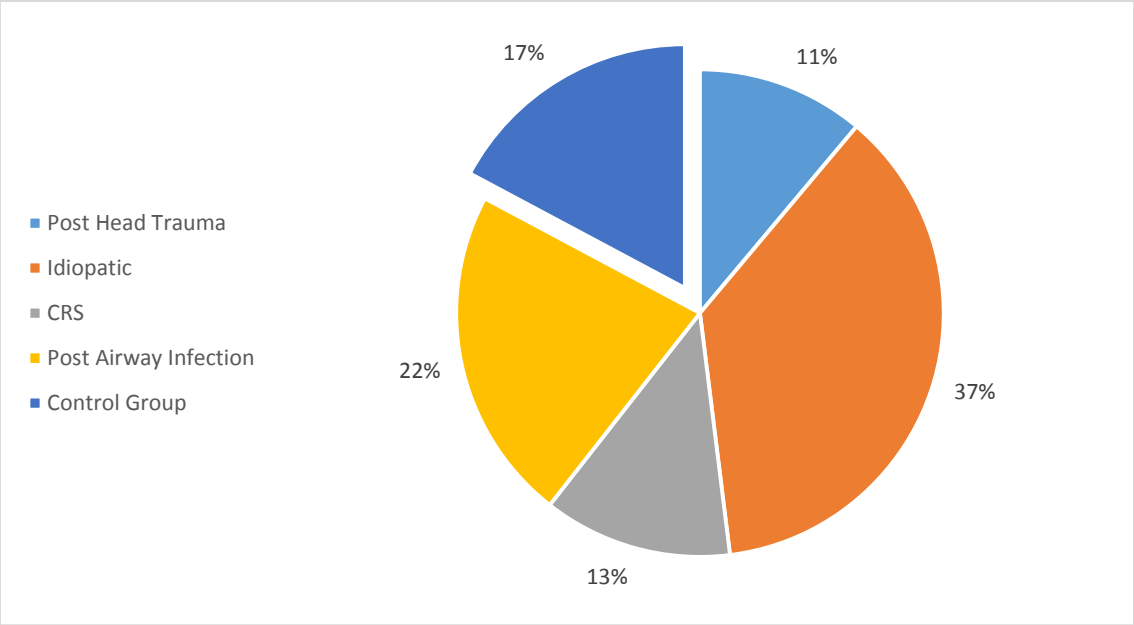


Fig. 8. Distribution of analyzed subgroups based in the probable etiology of smell complaint. Control Group (17%) had no smell complaint.

3.2 Research Design

All the statistical analyses were performed using a commercially available software, R Core Team 2016. Any p values ≤ 0.05 were considered statistically significant. The comparison between groups was done using paired and non-paired samples. If the samples were drawn from a normal distribution it was used parametric tests, if not, non-parametric tests were applied. Some statistical tests were used in order to compare the means (medians) for one, two, three or more groups/samples: t-test, Wilcoxon test, Mann-Whitney test, Chi-square test and ANOVA test.

3.3 Data Collection and Analysis

All data collection, including the answer to the questionnaire, Sniffing Sticks Test, and nasal endoscopy evaluation were made in the same facility in the “Smell and Taste Clinic” at the University of Dresden (TUD). Before the evaluation started, all patients have been well informed about how the exam was conducted. All patients were evaluated according to the following order: questionnaires answer, smell test (Sniffing Stick Test) and finally, the nasal endoscopic evaluation with a main focus in the OC, made by the same otolaryngologist. Each part of the evaluation will be carefully addressed in the following pages.

3.3.1 Questionnaires

As said by Nguyen et al. in 2017: “The aim of a QOL questionnaire is not necessarily to measure each symptom exactly but rather to obtain a global assessment of the impact of the various symptoms on the patient’s QOL.”

To be trustful, a questionnaire must include adequate levels of reliability, validity, and responsiveness (van Oene et al. 2007). Reliability happens when it consistently produces similar results in a specified situation - also called reproducibility. (Bowling 1997, Snoek 2000). Validity occurs when an instrument behaves according to underlying hypotheses. Finally, responsiveness is the ability of an instrument to perceive change when the change occurs (van Oene et al. 2007).

In this study, all questionnaires were paper and pencil tests, without a maximum time limit to finish it. Patients completed the tests by themselves, in the waiting area of the Smell and Taste Clinic of the Department of Otorhinolaryngology at the University of Dresden Medical School.

There is plenty evidence showing that 'QOL assessment' can be considered as adjuvant to clinical and physiological evaluations in many chronic conditions (Asadi-Lari et al. 2004). Two QOL related questionnaires were used in this study and were fulfilled by the subjects: a specific smell disorders questionnaire and SNOT 20 GAV questionnaire.

3.3.1.1 Specific Smell Disorders Questionnaire

To evaluate QOL in patients with olfactory complaint, it was applied a specific smell disorder questionnaire (*Fragebogen zu Riechstörungen*). It was used a simplified and modified version of the questionnaire that has been published by Frasnelli and Hummel in 2005 called ‘‘Questionnaire for Olfactory Dysfunction’’. This version has 29 statements distributed as follows: 6 questions about social desirability, 4 specific questions about parosmia and 19 questions about complaints and the degree to which patients suffer from smell dysfunction (see Appendix A, B, C, D). These statements have four answers possibilities: agree (3 points), partly agree (2 points), partially disagree (1 point) and disagree (zero points). For a complaint, a maximum score of 57 points could be reached, for parosmia a score of 12 points and for social desirability a maximum score of 24

points. ‘‘Socially desired’’ statements, indicates if patients give answers that they believe they are expected to give.

In addition, there are also seven visual scale questionnaires, graded from 1 to 10. The average of the first five questions reveals a number ranging from 1 to 10 (visual analogue scale score) that means the possible impact that the olfactory disturbance have in the daily life. The two final questions, also graded from 1 to 10, are the subjective subject’s impression about nasal blockage and overall self rating smell capability (olfactory function score).

3.3.1.2 SNOT 20 Questionnaire

The Sino-Nasal Outcome Test (SNOT-20) is one of the most widely used QOL questionnaires for patients with sinonasal conditions, especially those with chronic rhinosinusitis (Piccirillo et al. 2002). Nevertheless, may be used also in many others sino nasal situations (Pynnonen et al. 2009). Also notorious is the SNOT 20 GAV, the German validated adapted version of the SNOT 20 (Baumann et al. 2007, Baumann et al. 2008). The Sino-Nasal Outcome Test-20 German Adapted Version (SNOT-20 GAV) is a translated and adapted version of SNOT-20. It is the first reliable, validated and sensitive German instrument for measuring health-related QOL in patients with CRS. (Baumann et al. 2007). Validated QOL instruments are very useful to assess the subjective outcomes of patients. SNOT-20 does not inquiry all the major symptoms of CRS, whereas SNOT-20 GAV meets this requirement. (Baumann 2009). Although just one question address directly olfactory loss complaint (*riechminderung*), SNOT 20 GAV was one of the

questionnaires selected in this study by its importance and acceptance (see Appendix E).

In this questionnaire, there are twenty QOL related questions with five possible answers. The scores can range from 0 (no problem) to 5 (as bad as it can be), with a higher score indicating a greater rhinosinusitis-related health complaint. It is easy to complete and takes about 5 to 10 minutes to finish it (Pirccillo et al. 2002).

Although not used in this study it is known that the division of the SNOT 20 into four groups (rhinological symptoms, ear and/or facial symptoms, psychological function and sleep function) may be useful. It would increase the instrument precision and could allow the identification of each domain separately (Pynnonen et al. 2009).

3.3.2 Olfactory Test (*Riechtest*)– "Sniffing Test"

Olfactory function was assessed using the Sniffin' Sticks Test (Burghart GmbH, Wedel, Germany) (fig. 9,10 and 11) (see Appendix F). This is a complete olfactory test that evaluates olfactory threshold, odor discriminatory and odor identification, in this order (Kobal et al. 1996, Hummel et al. 1997, Hummel et al. 2007). They were performed with a three-minute interval between tests. For fragrance presentation, the pen cap was removed by the examiner for about 3 seconds and the pen tip was placed approximately 2 cm in front of the subjects' nostrils. All patients were blindfolded to prevent visual identification of the target pens. As previously said, the threshold was demarcated as the concentration at which n-

butanol (highest concentration 4%, 1:2 serial dilutions to 16 steps) was properly identified four times in a row. For discriminatory evaluation, triplets of odorants (two were the same odor, one different) were presented and subjects were asked to select the different odorant. The identification test included 16 familiar fragrances, using a multiple-forced choice procedure. Finally, the sums of the three tests are known as Threshold-Discrimination-Identification score (TDI).

Fig. 9. Sniffing Sticks: Identification Test

Fig. 10. Sniffing Sticks: Thresholds Test

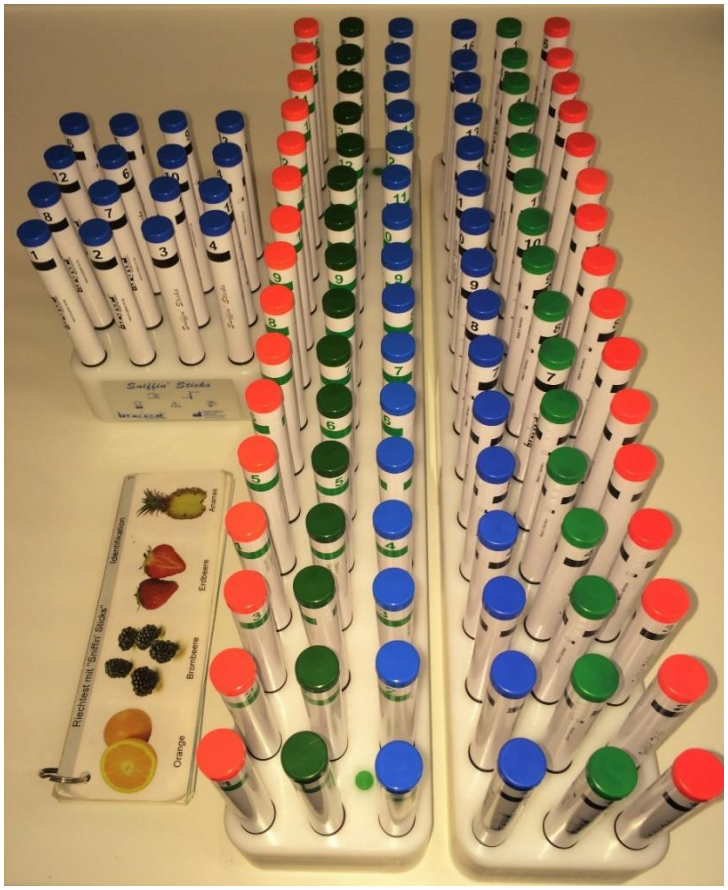


Fig. 11. Sniffing Sticks: Threshold, Discrimination, and Identification Test

3.3.3 Endoscopic Nasal Examination

According to the American Rhinologic Academy (retrieve from *http://care.american-rhinologic.org/nasal_endoscopy*) nasal endoscopy is usually performed with a 30 degree endoscope using the “three pass” technique. In the first pass the nasal floor and the nasopharynx are observed. The endoscope is then brought out and turned upwards and sideways in order to view the middle and superior meati and the spheno-ethmoidal recess. In the third pass the endoscope is used to view the roof of the nose and specifically the area of the olfactory cleft.

The equipment to perform all nasal endoscopies was a 2.7 mm, 30 degrees Karl Storz endoscope, a halogen Karl Storz light source and a conventional light cable. No video system was used in these exams and no record was performed. To nasal evaluation, the patients were told to stand still, in a seated position, and with a slightly extended head position. The average time to perform the nasal endoscopy was 2 to 3 minutes. To avoid any exam misinterpretation or bias, some measures were carefully made: the same equipment (endoscope, light source, and light cable) was used in all exams; no systemic or topical medicament, such as nasal drops or sprays were used before or during the exam; the same ENT physician made all endoscopic exams, under similar conditions and using the same evaluation method (using the “three pass” technique) and following the same analysis criteria.

Also, very relevant, is the fact that, among the patient group, the examiner did not know the possible olfactory loss etiology prior or during the endoscopic exam (blinded). However, the examiner knew prior the endoscopy evaluation, which where the control and patient group, that eventually could lead to a risk of bias.

3.3.3.1 General Nasal Endoscopic Findings

The endoscopic examination includes some important nasal areas, already commented in this paper, including inferior and medial turbinates, inferior and medial meatus, sphenoethmoidal recess and choana, on each side. The Lund Kennedy endoscopic grading system is widely used in many papers in the literature (see Vaid et al. 2007, Wright and Agrawal 2007, Rahman et al. 2016, Schlosser et al. 2016), and provides an accurate nasal endoscopic anatomical evaluation.

In this study it was used a modified Lund-Kennedy endoscopic scoring system that added mucosal redness to the following findings: the presence of polyps, mucosal edema, secretion discharge, fibrosis, and crusting. Each of these findings could receive from 0 to 2 points; being 0 absence, 1 mild and 2 severe pathological finding degree (see Lund and Kennedy 1995). The sum of these findings (also known as mean composite score) gave us a general nasal endoscope score for each side, that ranged from 0 (no pathological findings) to a maximum of 12 points.

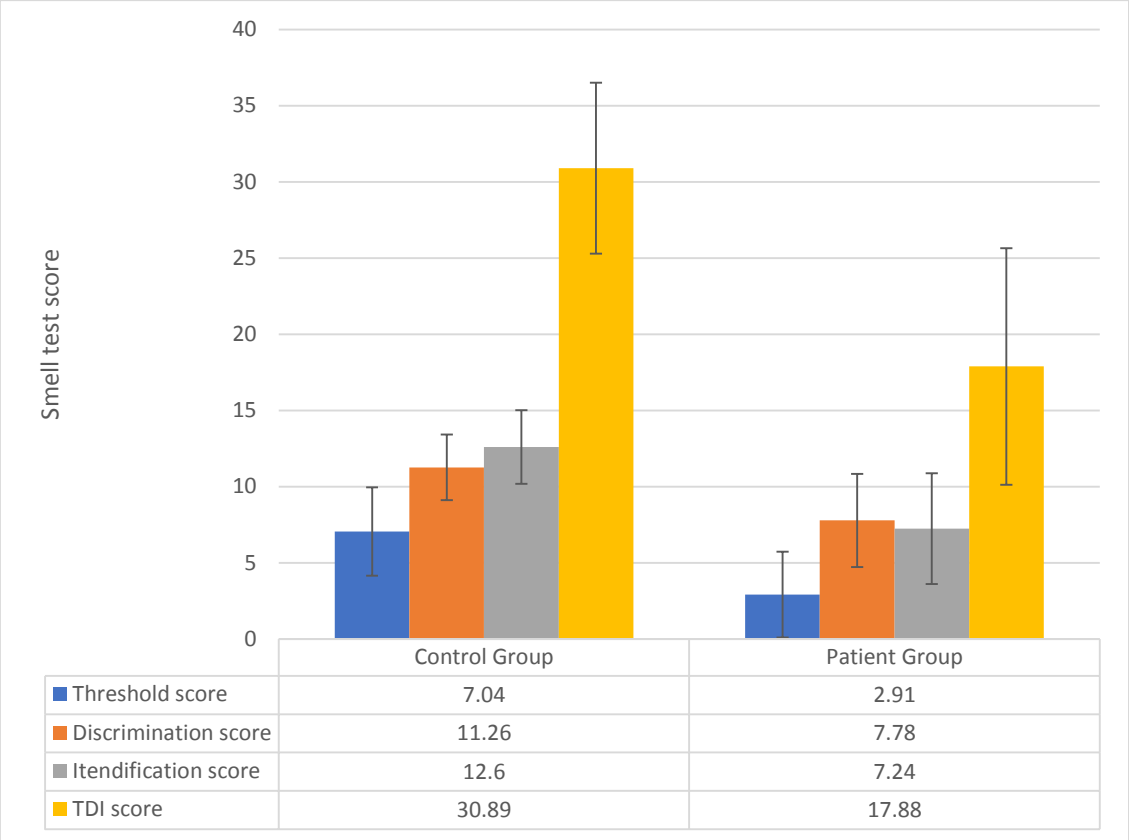
3.3.3.2 Specific Olfactory Cleft Endoscopic Findings

The primary focus and priority of the nasal endoscopy in this study was the proper visualization and evaluation of the OC in both sides. Once this is the main region covered by the OE, it was the most important site to be observed and evaluated. The criteria used to classify the OC was an area that is covered by the olfactory mucosa, featuring the cribriform plate and 1 cm^2 on each side, on the medial aspect of middle turbinate and on the upper septal wall. As already said, pathological findings in this area could lead to smell impairment (see Litvack et al. 2009, Vandenhende-Szymanski et al. 2015, Nguyen et al. 2013, Nguyen et al. 2015, Soler et al. 2016). In many cases, only the anterior aspect of the OC could be seen in the nasal endoscopic examination.

The evaluation criteria used here was the same applied in the general nasal endoscopic findings. So, the findings that were evaluated in this part was: the presence of polyps, mucosal redness, mucosal edema, discharge, fibrosis, and crusting. Each of these findings could receive from 0 to 2 points; being 0 absence, 1 mild and 2 severe pathological finding degree (see Lund and Kennedy 1995). Equal to the general nasal endoscopy score, the sum of these findings (also known as mean composite score) gave us a specific OC endoscope score for each side, that ranged from 0 (no pathological findings) to 12 points (all severe pathological findings).

4. **Descriptive Results**

As expected, when analyzing, using Man-Whitney test, there was a statistical difference (p<0,001) between the patient and control group regarding threshold, identification, discrimination and TDI result in the Sniffing Sticks Test (fig. 12).

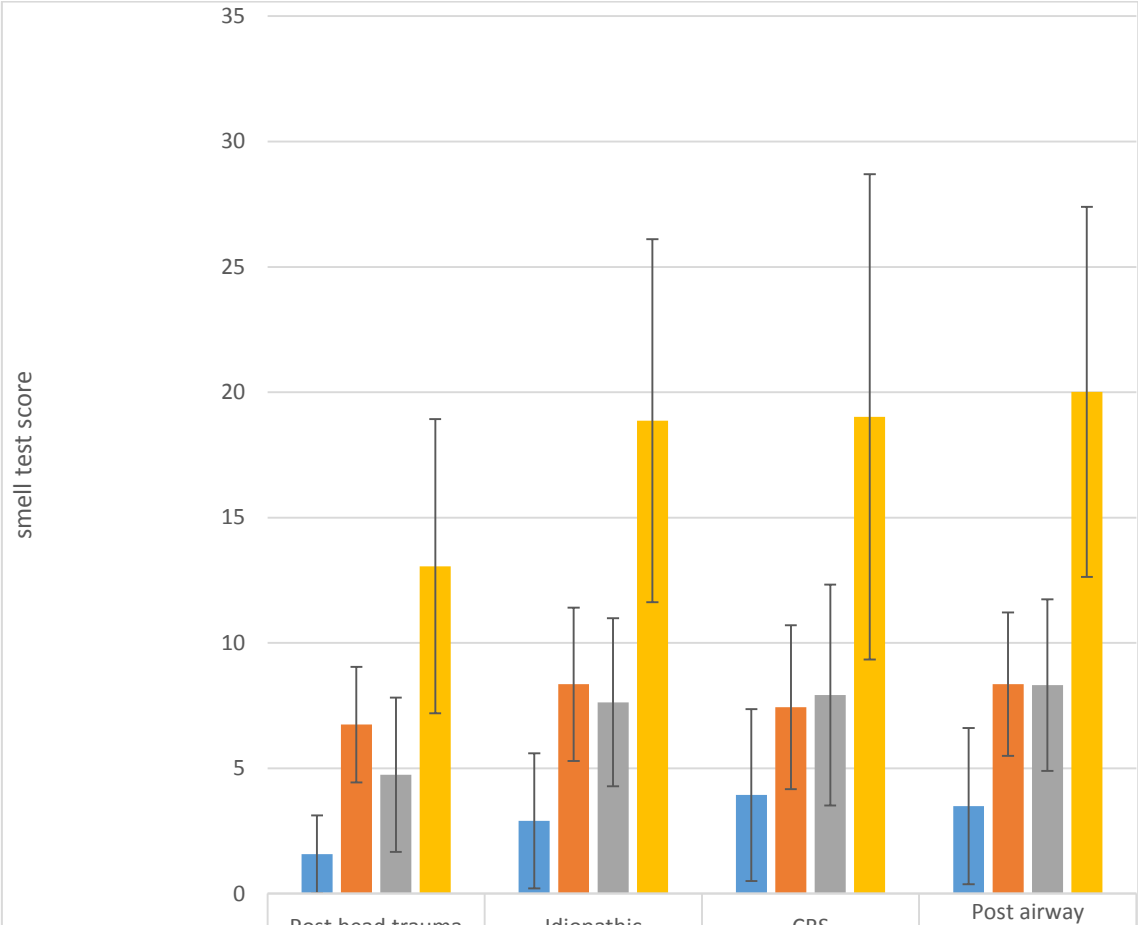


	Control Group	Patient Group
Threshold score	7.04	2.91
Discrimination score	11.26	7.78
Itendification score	12.6	7.24
TDI score	30.89	17.88

Fig. 12. Comparison between control and patient group regarding Sniffing Sticks Smell Test results.

All smell test scores (Threshold, Discrimination, Identification and TDI score) were significantly lower in the head trauma subgroup of patients when compared with the other causes of smell loss (p<0.05) (fig.13). It was not observed any

specific endoscopic finding, with statistical relevance, in this subgroup, when compared with the other subgroups of subjects with smell complaint (p>0.05).



	Post head trauma	Idiopathic	CRS	Post airway infection
Threshold score	1.57	2.9	3.93	3.49
Discrimination score	6.74	8.35	7.44	8.35
Identification score	4.74	7.63	7.92	8.32
TDI score	13.06	18.87	19.02	20.01

Fig. 13. Comparison between subgroups of subjects with an olfactory complaint regarding smell test results.

There was no relation between smokers and no smokers in the TDI score (p=0.636). It was also not found a relation between TDI score and gender

(p=0.178). In our study, using Pearson Correlation, it was found a weak correlation (ρ= - 0.231, with p<0.001) between age and TDI score (fig.14).

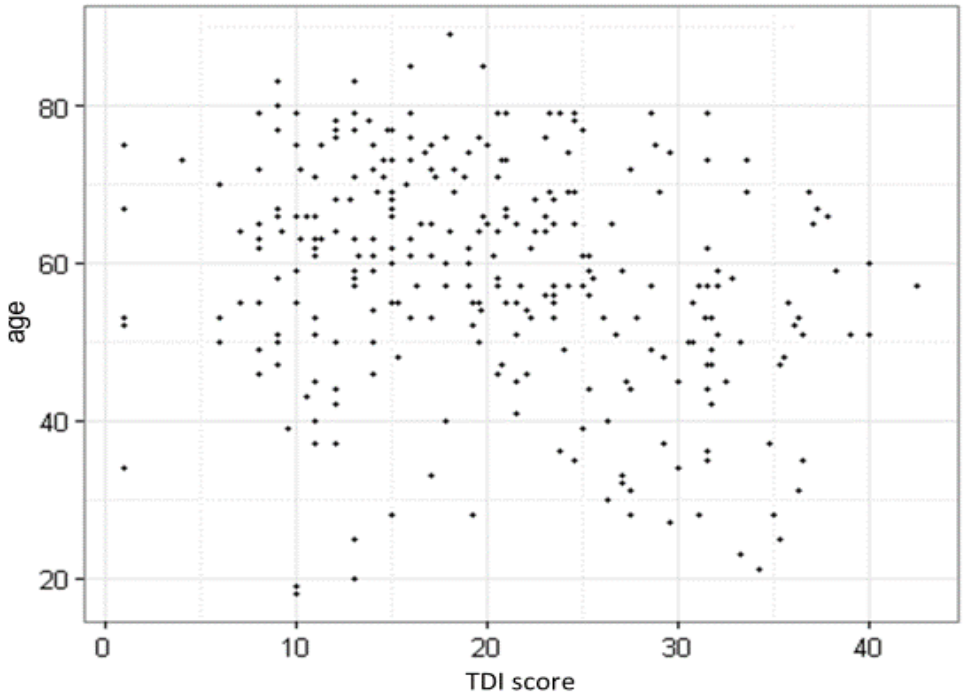


Fig.14. Dispersion graph showing a weak inverse relation (ρ= - 0.231) between age and smell test result (TDI score).

Regarding the general endoscopic nasal findings, mucosal redness (27.2% on the left side and 26.5% on the right side) and mucosal edema (29.6% on the left side and 32.3% on the right side) were the most frequent endoscopic findings in this studied population. Using the Wilcoxon test, there was no statistical difference between patients and control regarding general endoscopic nasal findings (p>0.05). That's probabily occurred because in the control group there were also many patients with nasal pathologies, except smell complaint.

Concerning specifically the olfactory cleft (OC) findings in the whole studied population (controls + patients) , mucosal redness (33.1% on the left side and 32.2% on the left side), followed by mucosal edema were the most frequent endoscopic findings (fig. 15 and 16).

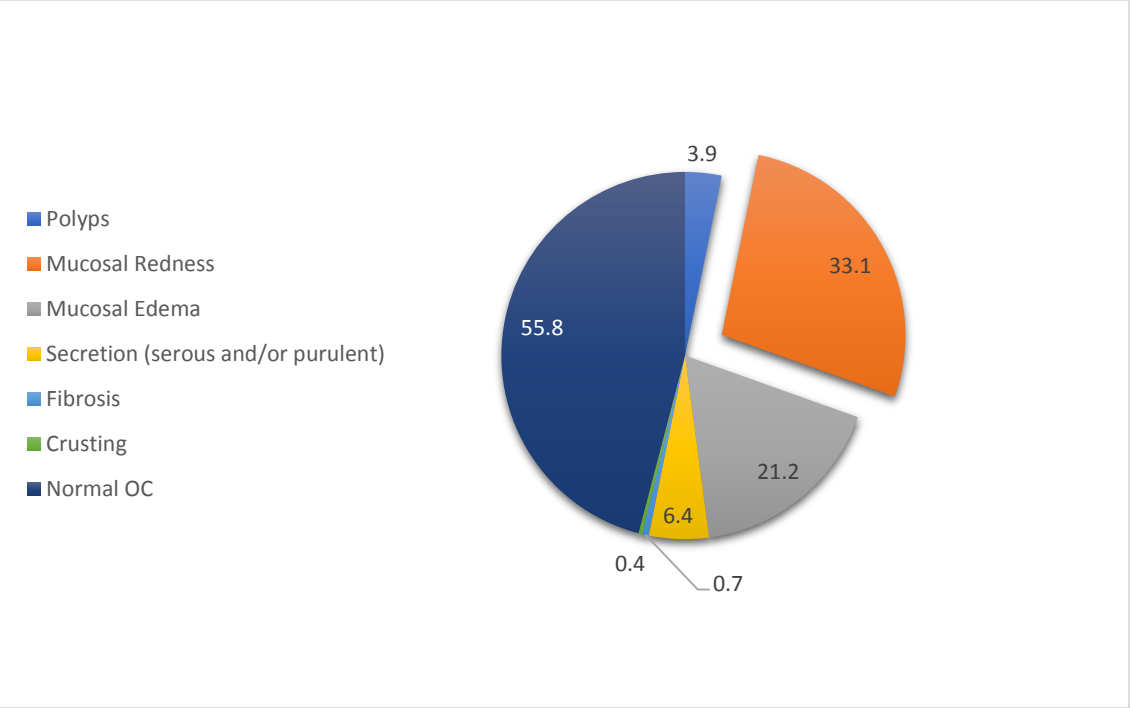


Fig. 15. Percentages of endoscopic findings in the left olfactory cleft (in the whole studied population).

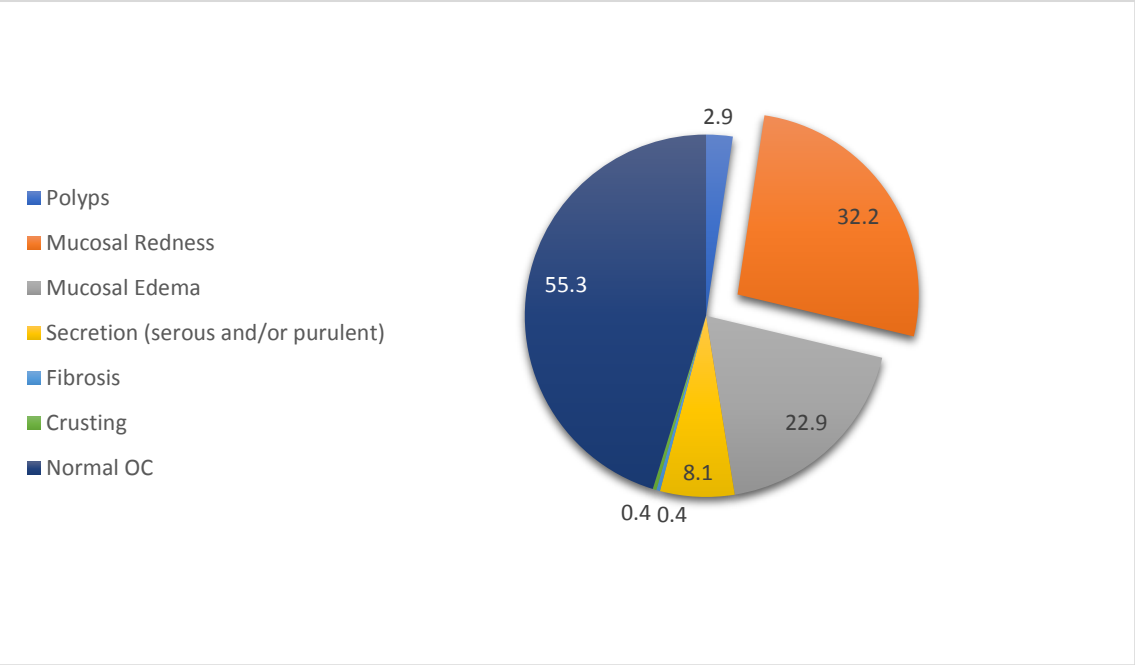


Fig. 16. Percentages of endoscopic findings in the right olfactory cleft (in the whole studied population)

Using Wilcoxon statistical test, it was found the presence of mucosal redness in the OC with statistical significance in both sides (p=0,006 on the left side and p=0,014 on the right side) in the group of the subjects with olfactory complaint (patient group), compared with the control group. These results were also observed using Chi-square statistical test, with $p<0.05$ ($p=0.021$ on the left side and $p=0.046$ on the right side). This was undoubtedly the most important finding in this study. These data points to a possible relation between olfactory complaint and the presence of mucosal redness seen in the OC during endoscopic evaluation (fig. 17 and 18).

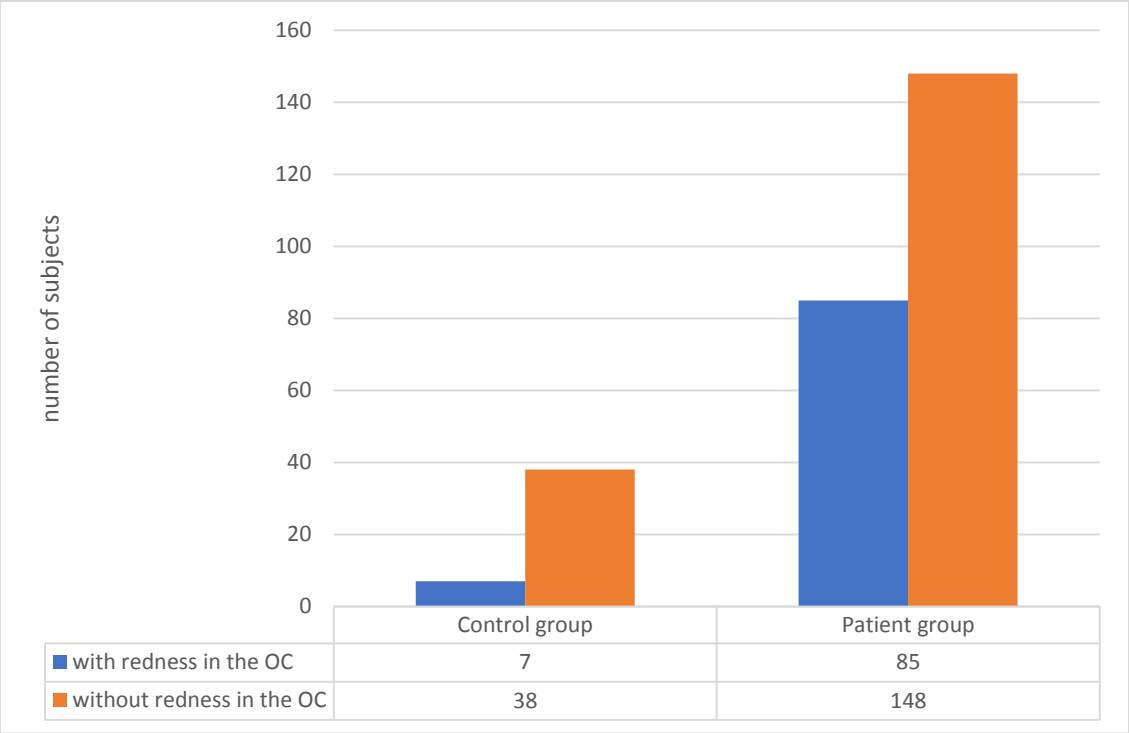


Fig. 17. Redness presented in the left OC.

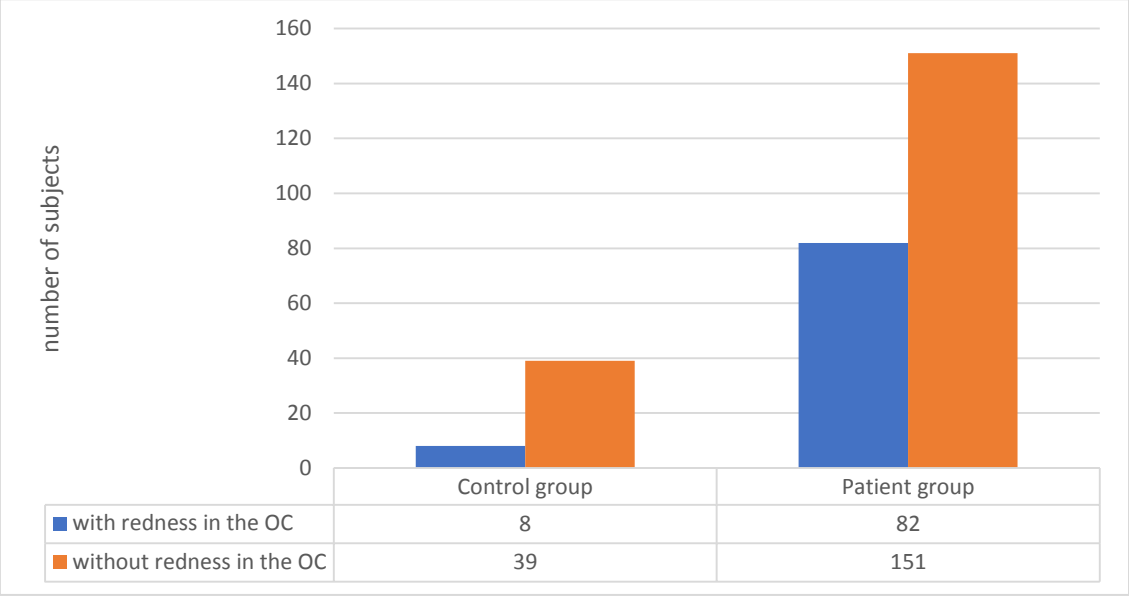


Fig. 18. Redness presented in the right OC.

As expected, it was found more endoscopic findings in patients with CRS compared with other subgroups with olfactory complaints ($p<0.001$). Although it was not found worse TDI score in this subgroup compared with other subgroups with olfactory complaints ($p=0.545$) (fig.13). The nasal airflow score was, as anticipated, lower in this group of patients ($p=0.005$) (fig.21).

When comparing, using Wilcoxon statistical test, the idiopathic subgroup with the other groups together. There was no statistical difference regarding TDI score and endoscopic findings ($p>0.05$).

Also, using Wilcoxon test, a significant statistical difference ($p<0.001$) between patient and control group was observed regarding QOL parameters: parosmia score, complaint score, visual scale score (fig. 19) and rating olfactory function (self-rated smell ability) (fig. 20).

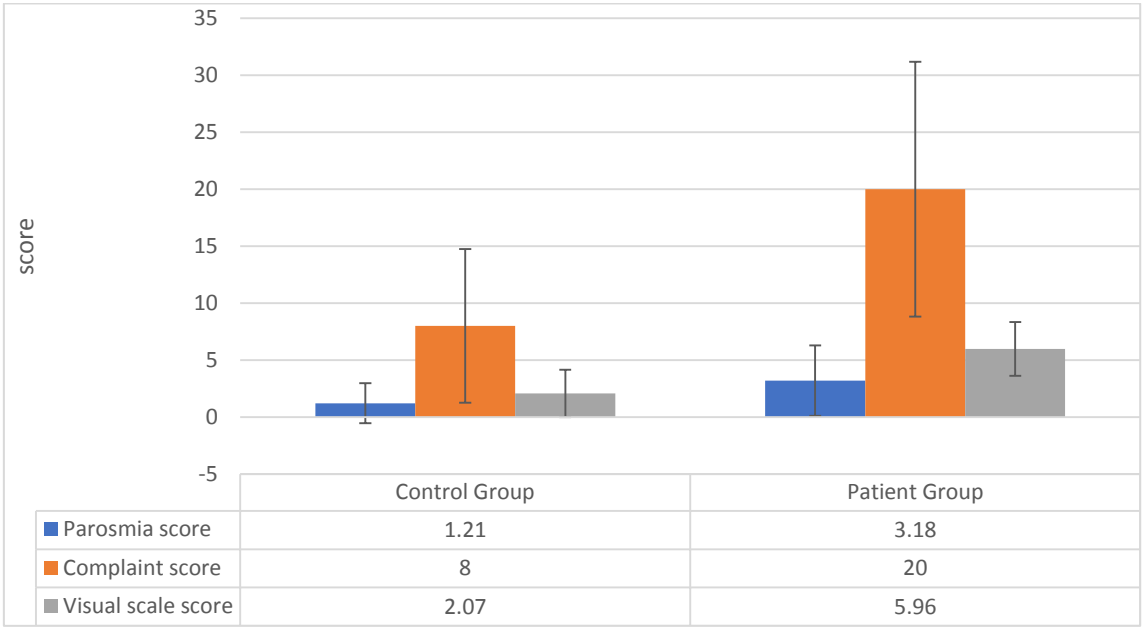


Fig. 19. Comparison between control and patient group regarding QOL parameters: parosmia score, complaint score, and visual scale score.

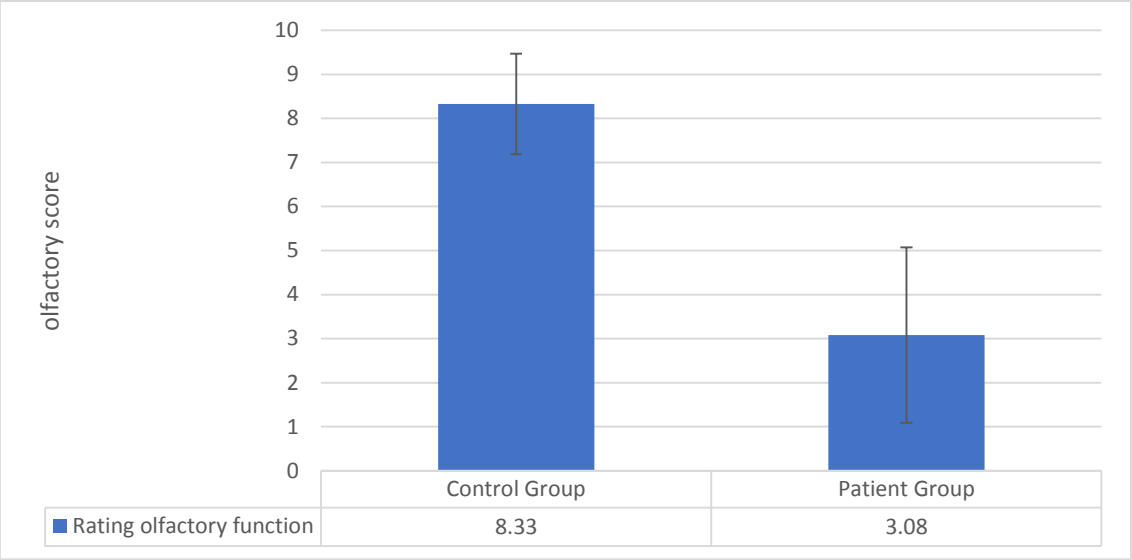
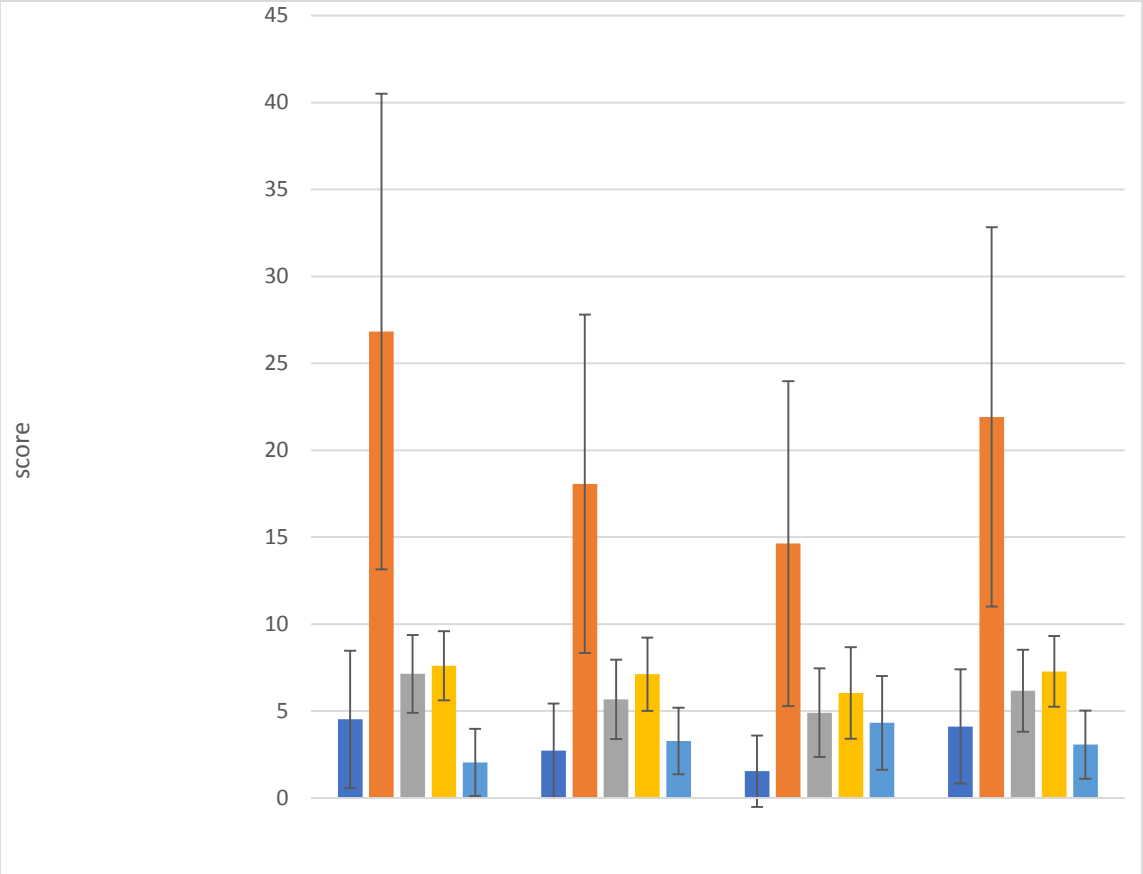


Fig. 20. Comparison between control and patient group regarding rating olfactory function (self-rated smell ability).

Also, using Wilcoxon test and Chi-square test, it was found higher parosmia score in the post airway infection and in the post head trauma subgroups, with similar results, compared with the other causes of smell impairment ($p<0.05$) (fig.21).

It was clearly found that in the post head trauma subgroup, the rating olfactory functional (self-rated smell ability) was statistically lower ($p<0.001$), and the complaint score was higher ($p<0.05$), when compared with the other causes of smell impairment (fig 21).



	Post head trauma	Idiopathic	CRS	Post airway infection
Parosmia score	4.52	2.73	1.54	4.11
Complaint score	26.83	18.07	14.63	21.92
Visual scale score	7.14	5.67	4.9	6.17
Rating nasal airflow	7.61	7.12	6.04	7.28
Rating olfactory function	2.04	3.28	4.32	3.07

Fig. 21. Comparison between subgroups of subjects with olfactory complaint regarding parosmia score, complaint score, visual scale score, ratings of nasal airflow, and ratings of olfactory function score (self-rated smell ability).

Confirming literature data, in this study, subjects with parosmia (n=205) had worse complaints scores, visual scale score and olfactory function score compared with those without parosmia (n=81) ($p<0.001$) (fig.22), reflecting a possible negative impact on QOL.

Also, using Wilcoxon test it was demonstrated that subjects with parosmia had worse discrimination score (p=0.047), identification score (p=0.031) and TDI score (p=0.028) compared with those without parosmia. The threshold, however, was not statistically different between these groups (p=0.064).

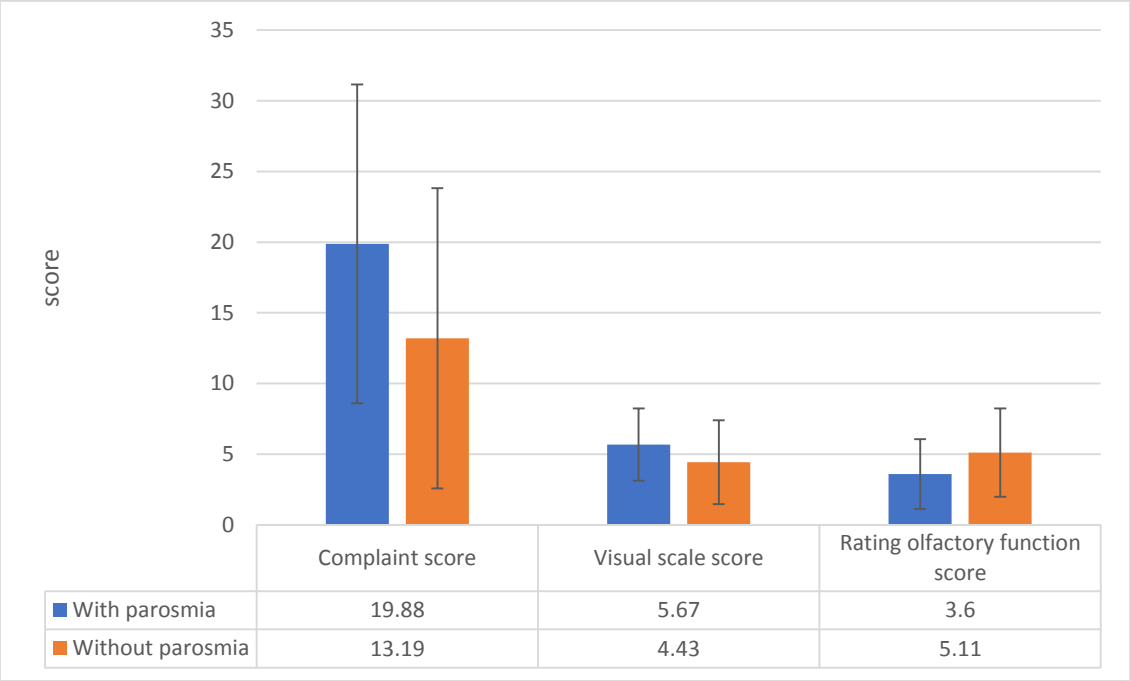


Fig. 22. Comparison between subjects with and without parosmia regarding complaint score, visual scale score, and rating olfactory function score (self-rated smell ability).

It was not found a clear relation between age (p=0.662) and gender (p=0.957) regarding parosmia. The gathered data, also indicated that the presence of parosmia was not a good predictor of the presence of any nasal endoscopic finding (p>0.005).

Using ANOVA statistical test, there was no statistical difference in the SNOT 20 GAV score among all cause of smell loss (p>0.05). Although using t-test, it was

found a statistical difference in the SNOT score, between control group and patients group ($p<0.001$).

Finally, the data analyses in this study showed clearly that subjects with smell complaint had, in the nasal endoscopy evaluation, more frequently, the occurrence of mucosal redness in the OC. Also, confirmed some findings already described in the medical literature such as: subjects with smell loss after head trauma had worse parosmia score, worse TDI score, worse rating olfactory function (self-rated smell ability) and higher complaint score, consequently, suggesting worse QOL, compared to other causes of smell complaint. This study also suggested that parosmia was related to low QOL. However, different from most of the studies in the literature, smoking habits and gender could not be associated to worse smell test result (TDI score) and age had a weak inverse relation.

5. Discussion

In the present study, the relation between olfactory complaint and anatomical endoscopic findings in the OC has been the main goal to be investigated. It was also the aim of the study to observe if there where any specific population (persons with smoking habits, elderly population and gender based population), with worse smell test result. Additionaly, which subgroup of subjects with smell complaint presented lower smell test result? Besides, other relevant aspects related to the quality of life and parosmia were examinated.

In this study, data analyses indicated that the mucosal redness in the OC was clearly observed more and with statistical significance in subjects with smell

complaint (patient group), compared with those without the olfactory complaint (fig. 16 and 17). It is definitely not a pathognomonic sign of olfactory impairment, once could also be found in subjects without smell complaint – however, much less observed in the control group (see fig. 15 and 16).

Overall, mucosal redness/ erythema is usually interpreted as an inflammatory state of the mucosal. According to the free online medical dictionary (retrieve from *http://medical-dictionary.thefreedictionary.com/erythema*) erythema is defined as "redness due to capillary dilation, usually signaling a pathologic condition (e.g. inflammation, infection)". It is known that inflammation process in the olfactory epithelium itself may cause olfactory dysfunction despite adequate delivery of odorants (Turner et al. 2010, Nguyen et al. 2013, Soler et al. 2015). Some papers also suggest that some inflammatory cytokines, such as TNF-α can lead to physiologic dysfunction of OSN (see Turner et al. 2010, Sultan et al. 2011, Pozharskaya et al. 2013). According to these papers, TNF-α may act on inhibition of proliferation on OSN and progenitor cells.

Contrasting to other papers that have made a relation between smell tests results, QOL, CT findings and nasal endoscopic scores, using Lund-Kennedy endoscopic scoring system (see Litvack et al. 2009, Soler et al. 2016), this study used a modified Lunk-Kennedy endoscopic grading system, for the first time. This grading system added mucosa redness together with the existing five endoscopic findings (polyps, mucosal edema, discharge, crusting and scaring). Additionally, most of the developed grading systems often focus on the middle meatus or the nasal cavity in general, without specific consideration to the OC (Soler et al. 2016). A study with the inclusion of mucosal erythema in this endoscopic grading system, specifically to evaluate the OC, has never been published. It is certainly

a refined finding that we chose to investigate whether or not would have any relation with this phenomenon described with relevance in inflammatory processes.

Moreover, mainly in those subjects with CRS and allergy, the inflammatory state of the nasal mucosal in the OC, may lead to worse smell capability, even in patients without great edema and secretion in the OC region. One could hypothesize that most of the subjects in this study had CRS or nasal allergie, explaining the frequence that mucosal redness was found in the OC. On the contrary, however, only 13% of the study overall population had in fact CRS (fig.8). Also, apart from these patients with CRS, only 4.3% had nasal allergie.

Other endoscopic findings like polyps/ tumors, fibrosis, secretion discharge, scarring and mucosal edema (that usually are responsible for OC opacification in the CT scan), related to worse olfactory performance have been many times described in the medical literature, in the past years. For instance, Chang et al., in 2009, found that OC opacification was more predictive of objective olfactory ability than sinus-specific opacification. Other study from Kuperan et al., in 2015, suggested that OC polyp surgery improves olfactory function outcomes. Also confirmed in the same year by Soler et al. and Vandenhende-Szymanski et al. that correlated OC opacification with objective olfaction. It is interesting to notice, however, that patients, without OC opacification in the CT scan, can still have smell loss because a malfunction in the level of the OE.

Furthermore, the relation between olfactory complaint and the presence of the mucosal redness in the OC has not yet been described in the medical literature. This probably occurred because mucosal redness is a difficult sign to quantify, once the normal nasal mucosal already has a “normal redness”, specifically a

light red or pink color. According to the Pocket Atlas of the Nose and Paranasal Sinuses (for retrieve: *http://rhinitis.hawkelibrary.com/album05/34_G*): “Normal nasal mucous membranes have a healthy pink color and appear slightly moist.” Thus, quantifying mucosal redness is a subjective evaluation and examiner dependent. However, other subjective endoscopic signs, as mucosal edema and secretion discharge, are already, for long time, used in the Lund Kennedy endoscopic grading system. (Lund and Kenney 1995). In this study, it was not used a color (red) grading scale to quantifying the redness found in the nasal mucosal. Perhaps, forthcoming studies about this theme could also apply a red grading scale to make the evaluation more accurate.

Some considerations about how the groups were organized are also pertinent. As already described, the two main groups in this study were formed based on the smell complaint. One group with, and another one, without the smell complaint. However, this does not mean that some patients with smell complaint, would have normal smell tests (rare) and, subjects without smell complaint (included in the control group), would have an abnormal smell test result. For instance, our result analysis showed that 15 out of 48 subjects (31.25%) from the control group presented with TDI score lower than 30.5, defined as hyposmia. A total of 9 subjects (18.75% of the controls) presented with TDI even lower than 27.5. On the other hand, just 12 out of 240 subjects (5%) from the patient's group presented TDI equal or higher than 30.5, meaning normal smell test score. This emphasizes that many subjects self-evaluated as having normal smell sense (included in the control group) had, in fact, abnormal smell tests results, confirming smell loss unconsciousness, many times described in the medical

literature (see Murphy et al. 2002; Shu et al. 2011, Keller and Malaspina 2013, Croy et al. 2014 and Philpott and Boak 2014).

As a suggestion, perhaps future studies about this theme should organize the groups not based on the olfactory complaint criterion, but rather based on a more objective parameter, like the TDI result. Following this parameter of group division - the TDI score - further studies could maybe reach different outcomes. In this context, the approach to the patient would be more direct and objective, instead of following a subjective sense (smell complaint) to divide the groups.

In addition, it is important to notice, that the control group in this study, was made purposely by subjects with many different kinds of nasal pathologies (such as allergic rhinitis, CRS, nasal septal deviation and turbinate hypertrophy) but without the smell complaint. This explains why there wasn't found any statistical difference between patients and control group, regarding general endoscopic nasal findings ($p>0.05$).

Also, one limitation of this study would be the fact that the examiner already knew, before the nasal endoscopy, which was the control group and the patient group (though did not know which of the subgroups were being evaluated). This could have lead to some tendency towards the endoscopy result. Perhaps future analyses should be done blinded in order to minimize the influence that this might have. Another limitation of this research is given by the transversal study design that does not test the same subjects after a period of time, in order to evaluate, if there where any modification in the endoscopic OC analyses. In this context, maybe subjects without mucosal erithema in the OC could develop it and vice-versa, changing the study conclusion.

Further studies are necessary to confirm if there is a relation between olfactory complaint and the presence of mucosal redness in the olfactory cleft. In this case, maybe mucosal redness in the OC may be used in the daily nasal endoscopic exam routine and would be recognized as a frequent endoscopic sign related to the olfactory complaint. Additionally, it may possibly be used even as a diagnostic and prognostic information.

Although the SNOT-20 is considered a validated CRS disease-specific QOL instrument, in terms of olfaction evaluation has had limited representation (Litvack et al. 2009). Only one question is related specifically to olfaction, accounting for only 5% of the overall score. Regarding SNOT-20 GAV, this questionnaire also showed no statistical importance to differentiate the four studied etiologies of smell loss (CRS, post head trauma, post airway infection and idiopathic). However, demonstrated worse smell test results in those subjects with smell complaint ($p<0.05$). Although it is a well accepted and widely used questionnaire in various nasal diseases, specially in CRS (Baumann et al. 2007, Baumann et al. 2008), the SNOT 20 GAV is probably not a valuable questionnaire to precisely evaluate the consequences of the olfactory impairment in the QOL.

On the other hand, the specific smell disorder questionnaire (*Fragebogen zu Riechstörungen*) used in this study (see Appendix A, B ,C, D), is a similar but simplified version of the ‘‘Questionnaire for Olfactory Dysfunction” that has been published by Frasnelli and Hummel in 2005. It appeared to be a suitable tool to verify the impact that the olfactory complaint have in the QOL. This questionnaire addresses differents dominions: parosmia, degree of the complaint, possible impact that the smell impairment has in the daily life (visual scale score), and also, the subjective subject’s impression about nasal blockage and overall self

rating smell capability (olfactory function score). One feature about this questionnaire is that it is time consuming, and sometimes, not feasible to be used in the daily practice. Future authors will have the difficult task to develop an accurate, but less time consuming questionnaire, that will be able to quantify the loss of the QOL related to the olfactory disturbance.

Parosmia (distorted perception of an olfactory stimulus) has been many times in the literature associated with depression and worse QOL (see Leopold 2002, Bonfils et al. 2005, Keller and Malaspina 2013, Croy et al. 2014, Kohli et al. 2016). In this study, it was confirmed that patients with parosmia had poor QOL (presented by worse complain score, visual scale score, and olfactory function score), compared with those without parosmia (fig. 22). This study also showed worse Sniffing Sticks Test results in this group of subjects. In fact, except for threshold test, all other smell tests evaluations (discrimination, identification and TDI score) were statistically worse in subjects with parosmia. These findings confirms that this qualitative smell disorder should not be neglected and deserve additional consideration and better counseling by the physicians (Kivity et al. 2009, Landis et al. 2009).

Confirming literature (see Konstantinidis et al. 2013, Proskynitopoulos et al. 2016) the subgroup with smell loss after head trauma had poor quality of life. In this subgroup was found statistically higher parosmia score, worse visual scale score and worse complaint score compared to other subgroups with smell complaint. To develop parosmia, considered a complex symptom, one must have damage in certain brain regions and the absence of lesions, specifically, a lower prevalence of damage in the temporal lobe (Lötsch et al. 2016). In addition, rating olfactory functional, a subjective index of smell capability, was statistically lower

in these subjects (fig. 21). This was confirmed when analysed the Sniffing Sticks Test results. All olfaction test parameters (Threshold, Discrimination, Identification and TDI score) were significantly lower in the head trauma subgroup of patients (fig.13). These data may suggest a greater impact in QOL in these patients with smell loss following head trauma. This certainly confirms most of the literature data that presents the olfactory loss after head trauma as being severe, with sudden onset (see Harris et al. 2006 and Hüttenbrink et al. 2013), with poor prognosis (Fan et al. 2015) and with high incidence of parosmia (Konstantinidis et al. 2013, Lötsch et al. 2016).

Although significant, with $p<0.001$, a weak inverse relation ($\rho = -0.231$), between age and TDI score was found. This information differ from most of the literature data, that emphasize a strong inverse relation between them (Murphy et al. 2002, Lafreniere and Mann 2009, Pinto 2011, Mullol et al. 2012, Doty and Kamath 2014, Sinding et al. 2014, Wilson et al. 2014, Attems et al. 2015) (fig.14). In the paper from Fark and Hummel, the authors showed that the mean age for olfactory function decline, in patients with idiopathic olfactory loss, has been defined at 57 years (see Fark and Hummel 2013), nearly the same population mean age of our study that was 58.5 years old (SD=14,3).

Unlike most of the cases reported in the literature, the relations between gender (Hummel et al. 2007, Mullol et al. 2012, Oliveira- Pinto et al. 2014), and smokers / not smokers (Katotomichelakis et al. 2007, Vennemann et al. 2008), related to TDI score, were not proved to be true in this particular study ($p>0.05$). Concerning the smoking habits, this study had only 10.2% of smokers. A low number that may explain the reason why we could not find a clear relation between this habit and lower smell test results.

6. Conclusion

Olfaction is a remarkable neurosensory function that has become more investigated because it may directly influence QOL, behavior, and may assist to quantify disease severity in many neurodegenerative diseases (Doty and Mishra 2001, Alt et al. 2014). Apart from the pleasure linked to the smell and flavor of foods and beverages, the olfaction also protects us to perceive odors such as leaking natural gas, smoke, and spoiled food (Cheng et al. 2013, Doty and Kamath 2014).

In our study with 288 subjects; CRS, post upper airway infection, post head trauma, and idiopathic causes were the most common etiologies found. Confirming literature data, this study showed that parosmia was clearly linked to worse QOL scores and worse results in the smell test. Among the subgroups of patients with smell complaint, those that occurred after head trauma confirmed to have worse results in the smell test as well as worse QOL scores.

Regarding the nasal endoscopic evaluation, the study found a relation, not yet described in the medical literature, between smell complaint and the presence of mucosal erythema in the OC. If confirmed by future investigations, the OC redness may be a new variable to be measured in the nasal endoscopic assessment, especially in terms of olfactory loss evaluation. Future long-term follow-up is necessary to determine if current findings carry useful diagnostic and even prognostic information.

7. Appendix: Survey Instruments

7.1 Appendix A

Fragebogen zu Riechstörungen

Dresden, 25. September 2002

Sehr geehrte Patientin, sehr geehrter Patient,

im Rahmen unserer Diagnostik würden wir Sie bitten, die folgenden Fragen zu beantworten. Dazu stehen hinter jeder Frage die Antwortmöglichkeiten „trifft zu", „trifft weitgehend zu", „trifft weitgehend nicht zu" und „trifft nicht zu".

Versuchen Sie, sich zu entscheiden, ob „trifft zu", „trifft weitgehend zu", „trifft weitgehend nicht zu" oder „trifft nicht zu" Ihre übliche Art zu Denken, zu Fühlen oder zu Handeln am besten beschreibt. Kreuzen Sie bitte die entsprechende Antwort schnell an und verwenden Sie nicht zu viel Zeit für einzelne Fragen. Wir möchten Ihre erste Reaktion erfassen und nicht das Ergebnis langer Überlegungen. Für den ganzen Fragebogen sollten Sie nicht mehr als ein paar Minuten brauchen. Vergewissern Sie sich bitte, dass Sie keine Frage ausgelassen haben!

Arbeiten Sie schnell und vergessen Sie nicht, auf jede Frage eine Antwort zu geben. Es gibt keine richtigen oder falschen Antworten. Dies ist kein Intelligenz- oder Fähigkeitstest, es sollen nur Ihre üblichen Verhaltensweisen erkennbar werden.
Vielen Dank für Ihre Mitarbeit!

P1	Wegen der Probleme mit dem Riechen schmecken Lebensmittel anders, als sie schmecken sollten.	trifft zu ☐ trifft weitgehend zu ☐ trifft weitgehend nicht zu ☐ trifft nicht zu ☐
P2	Ich habe immer einen schlechten Geruch in der Nase, egal ob eine Duftquelle in der Nähe ist oder nicht.	trifft zu ☐ trifft weitgehend zu ☐ trifft weitgehend nicht zu ☐ trifft nicht zu ☐
P3	Gerüche, die anderen angenehm sind, erscheinen mir unangenehm.	trifft zu ☐ trifft weitgehend zu ☐ trifft weitgehend nicht zu ☐ trifft nicht zu ☐
P5	Das größte Problem für mich ist nicht so sehr, dass ich Gerüche schwächer (oder gar nicht) wahrnehme, sondern dass sie anders riechen als sie riechen sollten.	trifft zu ☐ trifft weitgehend zu ☐ trifft weitgehend nicht zu ☐ trifft nicht zu ☐

7.2 Appendix B

Fragebogen zu Riechstörungen

1	Wegen der Riechstörungen gehe ich seltener ins Restaurant zusammen mit Verwandten oder Bekannten.	trifft zu trifft weitgehend zu trifft weitgehend nicht zu trifft nicht zu
4	Ich bin mir der Schwierigkeiten mit dem Riechen vom Aufwachen bis zum Schlafengehen bewusst.	trifft zu trifft weitgehend zu trifft weitgehend nicht zu trifft nicht zu
11	Die Schwierigkeiten mit dem Riechen schränken meine Genussfähigkeit ein.	trifft zu trifft weitgehend zu trifft weitgehend nicht zu trifft nicht zu
13	Ich mache mir Sorgen, ob ich jemals dazu in der Lage sein werde, mit diesem Problem fertig zu werden.	trifft zu trifft weitgehend zu trifft weitgehend nicht zu trifft nicht zu
14	Ich halte stets ein Versprechen, gleichgültig wie schwierig es auch sein könnte, das zu tun, was ich gesagt habe.	trifft zu trifft weitgehend zu trifft weitgehend nicht zu trifft nicht zu
15	Ich fühle mich wegen der Veränderungen meines Riechvermögens angespannter als früher.	trifft zu trifft weitgehend zu trifft weitgehend nicht zu trifft nicht zu
17	Ich habe gelegentlich Gedanken und Vorstellungen, von denen ich nicht möchte, dass andere sie erfahren.	trifft zu trifft weitgehend zu trifft weitgehend nicht zu trifft nicht zu
19	Fast alle meine Probleme sind durch die Schwierigkeiten mit dem Riechen bedingt.	trifft zu trifft weitgehend zu trifft weitgehend nicht zu trifft nicht zu
22	Die Schwierigkeiten mit dem Riechen stören mich beim Essen.	trifft zu trifft weitgehend zu trifft weitgehend nicht zu trifft nicht zu
23	Mein Benehmen ist immer gut und einwandfrei.	trifft zu trifft weitgehend zu trifft weitgehend nicht zu trifft nicht zu
26	Bekannte, Verwandte oder Nachbarn besuche ich wegen der Schwierigkeiten mit dem Riechen seltener als früher.	trifft zu trifft weitgehend zu trifft weitgehend nicht zu trifft nicht zu
27	Wegen der Schwierigkeiten mit dem Riechen fällt es mir schwerer, mich zu entspannen.	trifft zu trifft weitgehend zu trifft weitgehend nicht zu trifft nicht zu
28	Ich habe wegen der Schwierigkeiten mit dem Riechen Gewichtsprobleme.	trifft zu trifft weitgehend zu trifft weitgehend nicht zu trifft nicht zu

7.3 Appendix C

Fragebogen zu Riechstörungen

Schmecken & Riechen

31	Unter all den Leuten, die ich kenne, gibt es einige, die ich ganz und gar nicht ausstehen kann.	trifft zu trifft weitgehend zu trifft weitgehend nicht zu trifft nicht zu
32	Ich kann mir vorstellen, zu lernen, mit den Riechschwierigkeiten umzugehen.	trifft zu trifft weitgehend zu trifft weitgehend nicht zu trifft nicht zu
33	Die Schwierigkeiten mit dem Riechen führen bei mir zum Gefühl des Ausgeschlossenseins.	trifft zu trifft weitgehend zu trifft weitgehend nicht zu trifft nicht zu
34	Ich vermeide Gruppen von Personen wegen der Schwierigkeiten mit dem Riechen.	trifft zu trifft weitgehend zu trifft weitgehend nicht zu trifft nicht zu
35	Die Riechschwierigkeiten sind eines der Probleme im Leben, mit denen man zu leben hat.	trifft zu trifft weitgehend zu trifft weitgehend nicht zu trifft nicht zu
36	Ich bin noch nie zu spät zu einer Verabredung oder Arbeit erschienen.	trifft zu trifft weitgehend zu trifft weitgehend nicht zu trifft nicht zu
37	Wegen der Riechstörungen esse ich weniger/mehr als früher.	trifft zu trifft weitgehend zu trifft weitgehend nicht zu trifft nicht zu
39	Ich habe Angst, mich wegen der Schwierigkeiten mit dem Riechen bestimmten Gefahren auszusetzen (z.B. Haushaltsgas, verdorbene Nahrung).	trifft zu trifft weitgehend zu trifft weitgehend nicht zu trifft nicht zu
42	Durch die Schwierigkeiten mit dem Riechen ergeben sich Probleme bei alltäglichen Tätigkeiten.	trifft zu trifft weitgehend zu trifft weitgehend nicht zu trifft nicht zu
48	Ich rede manchmal über Dinge, von denen ich nichts verstehe.	trifft zu trifft weitgehend zu trifft weitgehend nicht zu trifft nicht zu
49	Die Schwierigkeiten mit dem Riechen machen mich gereizt.	trifft zu trifft weitgehend zu trifft weitgehend nicht zu trifft nicht zu
50	Durch die Schwierigkeiten mit dem Riechen ist meine Partnerbeziehung gestört.	trifft zu trifft weitgehend zu trifft weitgehend nicht zu trifft nicht zu

7.4 Appendix D

Fragebogen zu Riechstörungen Name Datum: . .2016

Bitte beurteilen Sie auf der untenstehenden Skala, wie lästig die Veränderungen ihres Riechvermögens für Sie sind.

Nicht lästig			Mittelmäßig				Extrem lästig		
1	2	3	4	5	6	7	8	9	10

Bitte beurteilen Sie auf der untenstehende Skala, wie oft sich die Veränderungen Ihres Riechvermögens bemerkbar machen.

Überhaupt nicht			Häufig				Immer		
1	2	3	4	5	6	7	8	9	10

Wie stark beeinträchtigten Sie die Veränderungen ihres Riechvermögens im letzten Monat im Beruf oder in der Arbeit?

Überhaupt nicht			Häufig				Immer		
1	2	3	4	5	6	7	8	9	10

Wie stark beeinträchtigten Sie die Veränderungen Ihres Riechvermögens im letzten Monat in der Freizeit oder in Ihrem gesellschaftlichen Leben?

Überhaupt nicht			Häufig				Immer		
1	2	3	4	5	6	7	8	9	10

Wie stark beeinträchtigten Sie die Veränderungen Ihres Riechvermögens im letzten Monat im Familienleben oder im Haushalt?

Überhaupt nicht			Häufig				Immer		
1	2	3	4	5	6	7	8	9	10

Wie würden Sie Ihre Nasenatmung beurteilen?

Schlecht			Mäßig				Sehr gut		
1	2	3	4	5	6	7	8	9	10

Wie würden Sie Ihre Riechfunktion beurteilen?

Schlecht			Mäßig				Sehr gut		
1	2	3	4	5	6	7	8	9	10

7.5 Appendix E

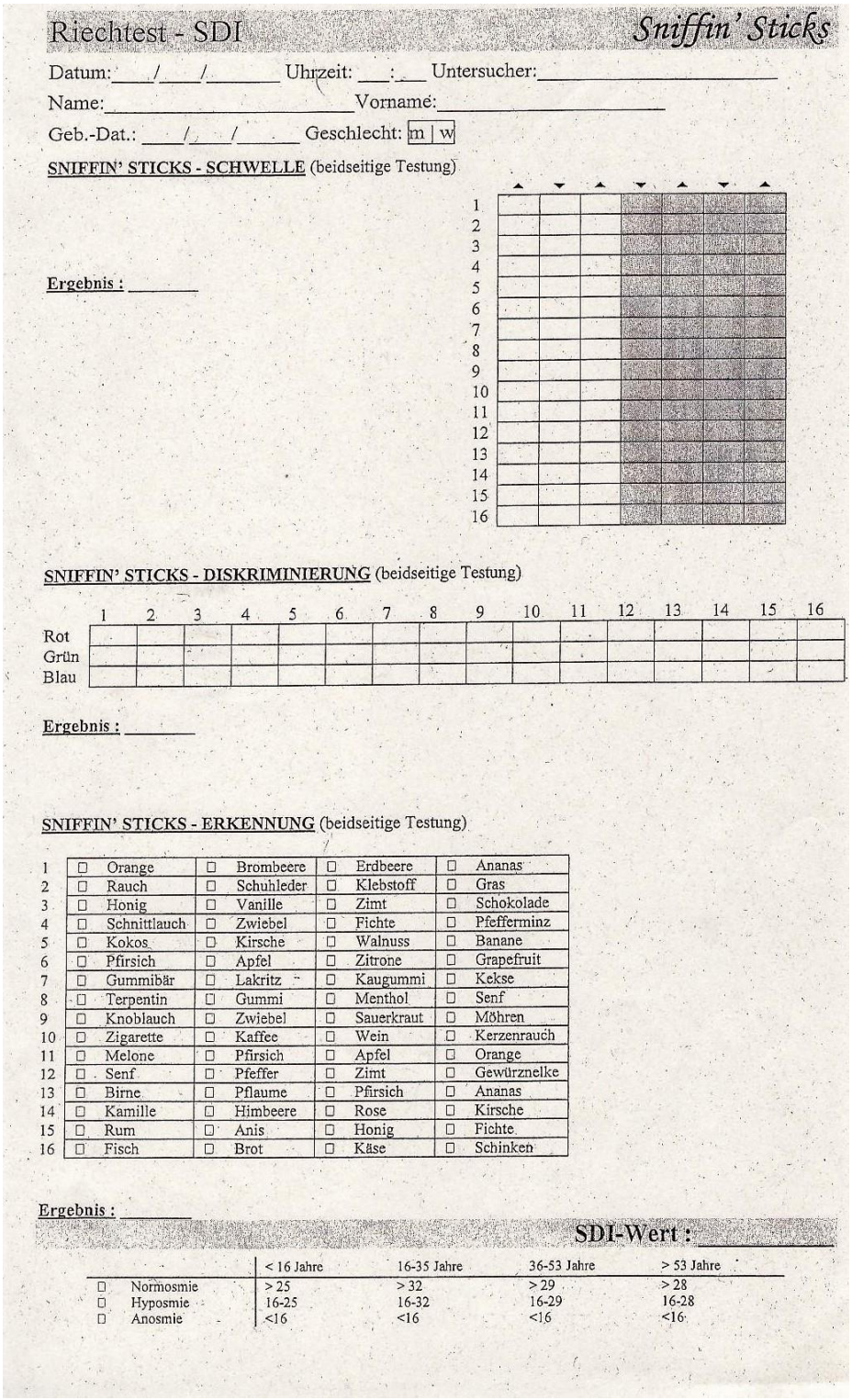
SINO-NASAL OUTCOME TEST 20 GERMAN ADAPTED VERSION (SNOT-20 GAV)

PatNr.: ☐☐☐

Unten finden Sie eine Liste von Symptomen und sozialen/emotionalen Folgen einer Nasennebenhöhlenerkrankung. Wir möchten gerne mehr über diese Probleme erfahren und bitten Sie, die Fragen nach bestem Wissen zu beantworten. Es gibt keine falschen oder richtigen Antworten, uns interessiert Ihre persönliche Sicht. Bitte beantworten Sie die Fragen in Bezug auf die letzten beiden Wochen. Vielen Dank für Ihre Teilnahme.

1. Um beurteilen zu können, wie stark die einzelnen Symptome ausgeprägt sind, kreuzen Sie bitte bei jeder einzelnen Frage die entsprechende Ziffer an.	Kein Problem	Sehr geringes Problem	Kleines Problem	Mittelgradiges Problem	Hochgradiges Problem	Schlechter kann es nicht mehr werden
1. Nasenatmungsbehinderung	0	1	2	3	4	5
2. Niesreiz	0	1	2	3	4	5
3. ständiges Naselaufen	0	1	2	3	4	5
4. Sekretfluß in den Rachen	0	1	2	3	4	5
5. dickes schleimiges Nasensekret	0	1	2	3	4	5
6. Räusperzwang, trockener Hals	0	1	2	3	4	5
7. Husten	0	1	2	3	4	5
8. Druckgefühl auf den Ohren	0	1	2	3	4	5
9. Ohrenschmerz	0	1	2	3	4	5
10. Riechminderung	0	1	2	3	4	5
11. Schwindelgefühl	0	1	2	3	4	5
12. Gesichtsschmerz, Druckgefühl im Gesicht	0	1	2	3	4	5
13. Probleme beim Einschlafen	0	1	2	3	4	5
14. Nächtliches Aufwachen	0	1	2	3	4	5
15. Tagesmüdigkeit	0	1	2	3	4	5
16. Verminderte Leistungsfähigkeit	0	1	2	3	4	5
17. Konzentrationsschwäche	0	1	2	3	4	5
18. Frustrationen/Rastlosigkeit/Reizbarkeit	0	1	2	3	4	5
19. Traurigkeit	0	1	2	3	4	5
20. Nebenhöhlenbeschwerden sind mir peinlich	0	1	2	3	4	5

7.6 Appendix F



Riechtest - SDI — Sniffin' Sticks

Datum: ___/___/_____ Uhrzeit: ___:___ Untersucher: _____

Name: _____ Vorname: _____

Geb.-Dat.: ___/___/_____ Geschlecht: m | w

SNIFFIN' STICKS - SCHWELLE (beidseitige Testung)

1							
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
13							
14							
15							
16							

Ergebnis : _____

SNIFFIN' STICKS - DISKRIMINIERUNG (beidseitige Testung)

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Rot																
Grün																
Blau																

Ergebnis : _____

SNIFFIN' STICKS - ERKENNUNG (beidseitige Testung)

1	☐ Orange	☐ Brombeere	☐ Erdbeere	☐ Ananas
2	☐ Rauch	☐ Schuhleder	☐ Klebstoff	☐ Gras
3	☐ Honig	☐ Vanille	☐ Zimt	☐ Schokolade
4	☐ Schnittlauch	☐ Zwiebel	☐ Fichte	☐ Pfefferminz
5	☐ Kokos	☐ Kirsche	☐ Walnuss	☐ Banane
6	☐ Pfirsich	☐ Apfel	☐ Zitrone	☐ Grapefruit
7	☐ Gummibär	☐ Lakritz	☐ Kaugummi	☐ Kekse
8	☐ Terpentin	☐ Gummi	☐ Menthol	☐ Senf
9	☐ Knoblauch	☐ Zwiebel	☐ Sauerkraut	☐ Möhren
10	☐ Zigarette	☐ Kaffee	☐ Wein	☐ Kerzenrauch
11	☐ Melone	☐ Pfirsich	☐ Apfel	☐ Orange
12	☐ Senf	☐ Pfeffer	☐ Zimt	☐ Gewürznelke
13	☐ Birne	☐ Pflaume	☐ Pfirsich	☐ Ananas
14	☐ Kamille	☐ Himbeere	☐ Rose	☐ Kirsche
15	☐ Rum	☐ Anis	☐ Honig	☐ Fichte
16	☐ Fisch	☐ Brot	☐ Käse	☐ Schinken

Ergebnis : _____

SDI-Wert : _____

	< 16 Jahre	16-35 Jahre	36-53 Jahre	> 53 Jahre
☐ Normosmie	> 25	> 32	> 29	> 28
☐ Hyposmie	16-25	16-32	16-29	16-28
☐ Anosmie	<16	<16	<16	<16

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9. Conflict of interest

There was no conflict of interest to disclose.

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