TASTE AND SMELL DISORDERS IN CLINICAL NEUROLOGY

OUTLINE

A. Anatomy and Physiology of the Taste and Smell System

B. Quantifying Chemosensory Disturbances

C. Common Neurological and Medical Disorders causing Primary Smell Impairment with Secondary Loss of Food Flavors
   a. Post Traumatic Anosmia
   b. Medications (prescribed & over the counter)
   c. Alcohol Abuse
   d. Neurodegenerative Disorders
   e. Multiple Sclerosis
   f. Migraine
   g. Chronic Medical Disorders (liver and kidney disease, thyroid deficiency, Diabetes).

D. Common Neurological and Medical Disorders Causing a Primary Taste disorder with usually Normal Olfactory Function.
   a. Medications (prescribed and over the counter),
   b. Toxins (smoking and Radiation Treatments)
   c. Chronic medical Disorders (Liver and Kidney Disease, Hypothyroidism, GERD, Diabetes,)
   d. Neurological Disorders(Bell's Palsy, Stroke, MS,)
   e. Intubation during an emergency or for general anesthesia.

E. Abnormal Smells and Tastes (Dysosmia and Dysgeusia): Diagnosis and Treatment

F. Morbidity of Smell and Taste Impairment.

G. Treatment of Smell and Taste Impairment (Education, Counseling ,Changes in Food Preparation)

H. Role of Smell Testing in the Diagnosis of Neurodegenerative Disorders

BACKGROUND

Disorders of taste and smell play a very important role in many neurological conditions such as; head trauma, facial and trigeminal nerve impairment, and many neurodegenerative disorders such as Alzheimer's, Parkinson Disorders, Lewy Body Disease and Frontal Temporal Dementia. Impaired smell and taste impairs quality of life such as loss of food enjoyment, weight loss or weight gain, decreased appetite and safety concerns such as inability to smell smoke, gas, spoiled food and one's body odor. Dysosmia and Dysgeusia are very unpleasant disorders that often accompany smell and taste impairments. Prognosis and treatment knowledge is very important so we can treat our patients.

Smell Testing has been helpful in the diagnosis of Idiopathic Parkinson's Disease vs Parkinson's Plus disorders, who with Amnestic Mild Cognitive Impairment will Likely Develop Alzheimer's Disease, Pseudodementia vs True Dementia, and Vascular Dementia vs Degenerative Dementias.

Standardized smell and taste testing is inexpensive, gives a lot of useful information and is another source of reimbursement for neurologists in the required setting. Standardized smell and taste testing is rarely done by ENT and primary health care physicians.

FACULTY

Richard Doty PHD is the director of the University of Pennsylvania Taste and Smell Center in Philadelphia, in internationally recognized and has published numerous articles on smell and taste dysfunction in many neurological disorders. He wrote the section on the anatomy, physiology and office testing of altered taste and smell.

Dr Ron Postuma is a neurologist and specialist in Movement Disorders at the Montreal General Hospital and has published many papers on the value of smell testing in the Diagnosis of neurological conditions such as Parkinson's and Parkinson's plus conditions, and who with REM Sleep Behavioral Disorder will likely develop Parkinson's disease in the future.

Dr Ronald Devere FAAN is director of the Taste and Smell Disorders clinic and the Alzheimer's Disease and Memory Disorders Center initially in Houston and now Austin Texas for the last 25yrs. He has published a number of papers in the Diagnosis and treatment of neurological smell and taste disorders. He is the author of the Neurology Now and AAN publication in 2011 of the book entitled "Navigating Taste and Smell Disorders". This book is very user friendly and written for patients, caregivers and all health care providers.

A. Anatomy and Physiology of the Smell and Taste Systems

Smell

After inhalation or passive diffusion, odorant molecules dissolve in the mucus covering the olfactory epithelium, a neuroepithelium that lines the cribriform plate and sectors of the superior septum, superior turbinate, and middle turbinate. They then bind to cilia that extend from the dendrites of the ~ 6 million bipolar olfactory receptor cells. These cells are surrounded by supporting (sustentacular) cells. Other cells within this epithelium include microvillar cells (which likely secrete nitric oxide and serve an antibacterial function), duct cells of Bowman glands (the major source of mucus in the region which contain high levels of enzymes such as those of the P-450 family), and basal cells from which the other cell types are derived and which replace cells when damage to them occurs. In humans, ~ 350 receptor proteins are expressed on the long cilia of the receptor cells (Figure 1), with each cell expressing only one type of receptor. Odor receptor genes are found in ~ 100 locations on all chromosomes except 20 and Y, and the olfactory subgenome spans 1-2% of the total genomic DNA. Most olfactory receptors are activated by multiple chemicals, resulting in overlapping fields of chemical responsitivity.

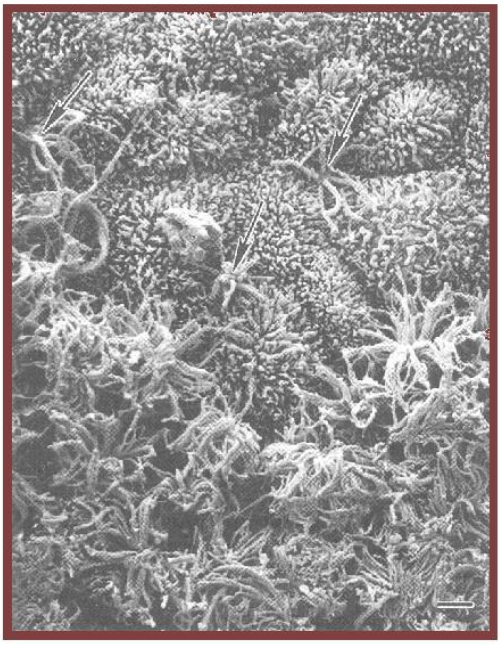


Figure 1. A transition zone between the human olfactory epithelium (bottom) and the respiratory epithelium (top). Arrows signify two examples of olfactory receptor cilia dendrites with cilia that have been cut off. Bar = 5 µm. From Menco and Morrison (2003). Copyright © 2003 Richard L. Doty.

Unlike the receptor cells of other sensory systems, those of the olfactory system serve as both the receptor cell and the first order neuron, synapsing within globe-like structures, termed glomeruli, within the outermost sector of the olfactory bulb at the base of the brain. These cells express glutamate which activates both NMDA and AMPT receptors on the second order neurons. Their activity is modulated via cells that surround the glomeruli (periglomerular cells) by dopamine, GABA, and possibly cholecystokinin and somatostatin. Interestingly, each glomerulus receives axons from receptor cells that express the same receptor protein, making each of them, in effect, a function unit representative of a specific class of such proteins. The glomeruli, which number over a thousand in young persons, often are indistinguishable and frequently disappear in older persons. As shown schematically in Figure 2, the glomeruli make up one of the several relatively distinct layers of the bulb. The bulb proper is comprised of afferent and efferent nerve fibers, multiple interneurons, microglia, astrocytes, and blood vessels.

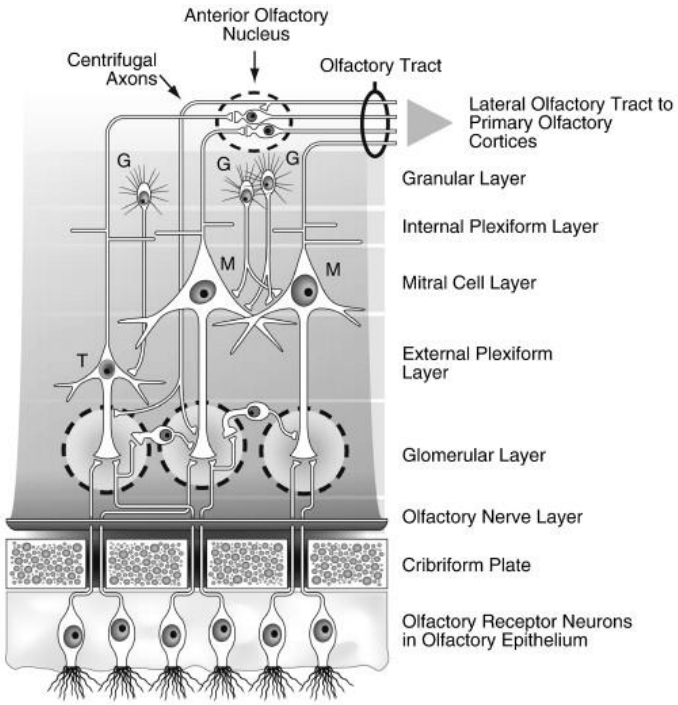


Figure 2. Schematic of the major layers of the olfactory bulb and their interactions among cell types therein. Reprinted with permission from Duda (2010). G: granuel cells; M: mitral cells; T: tufted cells. Copyright © 2010 Elsevier B.V.

The activity of the output neurons of the olfactory bulb – the mitral and tufted cells -- is influenced not only by input from receptor cells, but also from input from local neurons and from centrifugal fibers located outside of the bulb. The secondary dendrites of these cells reciprocally interact with GABAergic granule cells – cells which constitute much of the core of the olfactory bulb.

Granule cells, in turn, are modulated by input from cholinergic and other types of cells whose cell bodies are located outside of the olfactory bulb. While granule cells receive most of the centrifugal input, centrifugal fibers also terminate on cells within the external plexiform, internal plexiform, and glomerular layers.

Like the olfactory receptor cells, a number of cells within the olfactory bulb undergo replacement over time.[2] These include granule and periglomerular cells. Neuroblasts generated from astrocyte-like stem cells within the subventricular zone of the brain undergo restricted chain migration along the rostral migratory stream, terminating largely within the granule cell layer and within the periglomerular region.

Among the central brain structures that receive projections from the mitral and tufted cells are the anterior olfactory nucleus, the piriform cortex, the anterior cortical nucleus of the amygdala, the periamygdaloid complex, and the rostral entorhinal cortex (Figure 3). These structures have reciprocal relations with one another and numerous other brain structures. Indeed, the entire length of the hippocampus is innervated by fibers from the entorhinal cortex. Pyramidal cells from the anterior olfactory nucleus project to both ipsilateral and contralateral brain structures, the latter via the anterior commissure. Despite the fact that it is generally accepted that the olfactory system projects directly to cortical structures without first connecting in the thalamus, the thalamus does serve as a olfactory relay station between the entorhinal and orbitofrontal cortices.

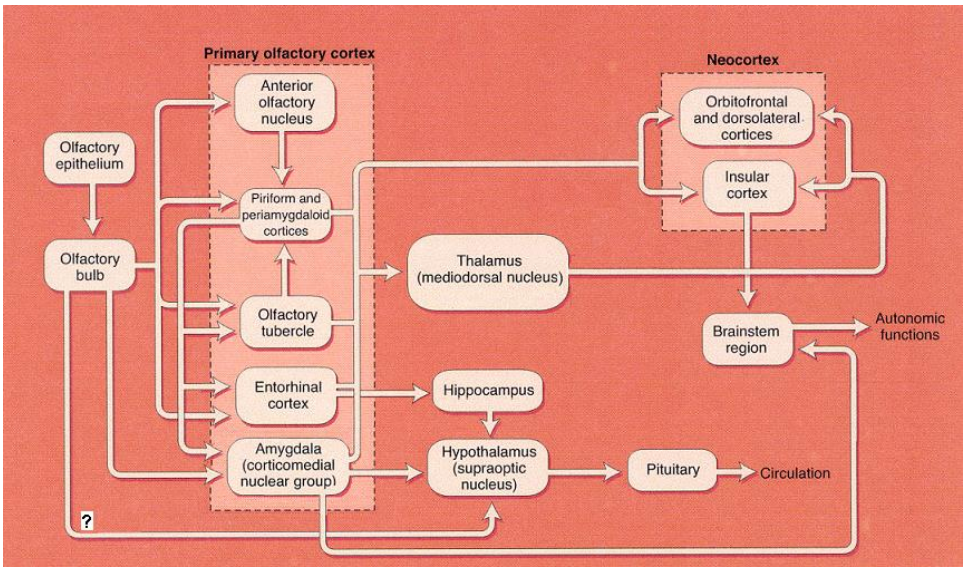


Figure 3. The major central afferent olfactory projections of the olfactory system. Reciprocal efferent projections not shown. Direct connections between the olfactory bulb and hypothalamus may not be present in humans and some other mammals. Copyright © 2010 Richard L. Doty

The various roles played by central olfactory structures are poorly understood and may be largely overlapping. Basic odor perception and detection occurs within the posterior piriform cortex, whereas the anterior piriform is likely involved in odor hedonics, as is the amygdala.[3] The orbitofrontal cortex appears to integrate information about concepts (e.g., an orange) across several modalities (e.g., color, touch, taste and smell).

Taste

The sense of taste is intimately involved in detecting, accepting, or rejecting nutrients (e.g., sugars) and poisons (e.g., bitter tasting alkaloids). However, we now know, as described in more detail below, that receptor proteins found in taste buds, generally termed taste receptor proteins, are found not only within mouth, but within the stomach, intestine, oropharynx, larynx, and the upper esophagus.[4, 5] among the functions served by these "taste receptor" proteins are insulin release, bacterial inactivation (via secretion of nitric oxide), chemical absorption, and the facilitation of the digestion and metabolism of swallowed foods and beverages. One type of taste receptor (T2R38) is found in the upper respiratory epithelia of humans, where it induces the secretion of nitric oxide in response to acyl-monoserine lactone quorum-sensing molecules secreted by *Pseudomonas aeruginosa* and other gram-negative bacteria. Importantly, differences in T2R38 functionality are related to susceptibility to upper respiratory infections.[6] Taste-related receptor proteins in the gut may explain why ingesting glucose releases more insulin from the pancreas than occurs following its injection into the bloodstream. It may also help to explain why gastric bypass patients have an immediate decline in their underlying insulin resistance.[7]

The conscious perception of taste results from activation of taste receptor located in flask-like taste buds embedded in lingual papillae, save the small pointed *filiform papillae* (Figure 4). On average, humans have ~ 7,500 taste buds, although large individual differences are apparent. In most persons, tastants are perceived on both the front and the back of the tongue, with the back being more sensitive to bitter and the front to other taste sensations. The chorda tympani division of the facial nerve (CN VII) supplies the taste buds on the *anterior folliate papillae* and *fungiform papilla.* The glossopharyngeal nerve (CN IX) supplies those on the *posterior folliate papillae* and on the large *circumvallate papillae*. Those on the soft palate are supplied by the greater superficial petrosal division of CN VII, whereas those in the throat and digestive tract are supplied by the vagus (CN X). Free nerve endings of the trigeminal nerve (CN V) project into the papillae and other oral mucosa surfaces, where they signal

sensations of touch, pain, and temperature – other components of flavor (e.g., the fizziness of carbonated drinks and the warmth of coffee).

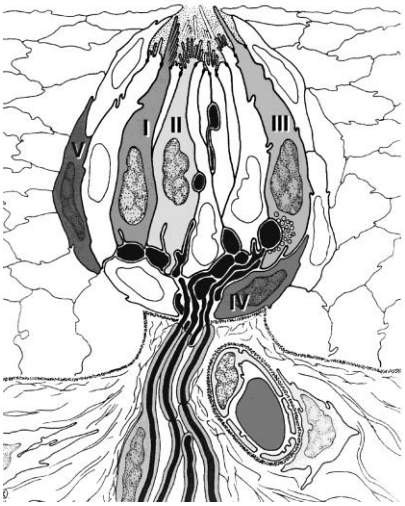


Figure 5. Idealized drawing of longitudinal section of mammalian taste bud. Cells of type I, II and III are elongated and form the sensory epithelium of the bud. These cells have different types of microvillae within the taste pit and may reach the taste pore. Type IV are basal cells and Type V are marginal cells. Synapses are most apparent at the bases of type III cells. The connecting taste nerves have myelin sheaths. From Witt et al (2005).

Three general classes of taste-responsive cells within taste buds have been identified (Figure 5).[8] Those largely responsible for the salty taste are Type I cells. Na^+ ions active these cells via specialized membrane channels such as the amiloride-sensitive Na^+ channel.[9] Substances that taste sweet, bitter and savory (monosodium glutamate-like) activate Type II cells. Some of these cells express a family of ~ 30 G-protein-coupled receptors (GPCRs), the T2R receptors, that are responsible for bitter sensations.[10-12] Three GPCRs are associated with sweet and savory taste sensations (T1R1, T1R2, and T1R3 receptors). Type III receptors are specialized for detecting sour tastes via H^+ ions that pass through specialized proton channels.[13] A number of ion channels are involved in the transduction of sour sensations induced by acids, including acid-sensing ion channels, potassium channels, and ENAC-like channels.[14]

The brain stem's nucleus tractus solitarius receives projections from the taste nerves (i.e., CN VII, IX and X). Connections are subsequently made to the upper regions of the ventral posterior nuclei of the thalamus via the medial lemniscus and then to the amygdala, anterior-insular cortex, and the orbitofrontal cortex, where broader concepts become formulated. Neurons within the orbitofrontal cortex respond to taste, touch, and in some cases odors. In some cases, such neurons become conditioned following the pairing of activation of these modalities during deglutition. Flavor perception

ultimately reflects multimodal integration of information and the participation of a number of brain regions.

B. Quantifying Chemosensory disturbances.

Quantitative testing, which is easy to perform in the clinic, should be employed in assessing chemosensory function of patients. Most people are surprisingly inaccurate in assessing less-than-total smell or taste loss. They either do not recognize the problem, or either underestimate or overestimate its magnitude. Moreover, quantitative testing allows for the detection of malingering on the basis of improbable responding in forced-choice tests and also defines whether the degree of dysfunction is normal for someone of a given age or sex. It is extremely therapeutic for older persons, for example, to be told that while, in an absolute sense, they have dysfunction, the degree of such dysfunction is normal for a person of their age and sex. Half of the time such a person can be told that their remaining function exceeds that of others in their peer group – a very therapeutic endeavor. Quantitative testing makes it possible to accurately monitor the influences of medical or surgical interventions, as well as to establish whether spontaneous recovery from such etiologies as viral insults or head trauma has occurred or is occurring.

Smell

While electrophysiological smell tests are available, they require complex stimulus presentation and recording equipment and are generally less sensitive that other types of olfactory tests. Hence, they are not discussed in this course. Psychophysical tests, i.e. tests that require a conscious response on the part of the patient, are most practical and a number are commercially available. Among such tests are those of odor detection, identification, discrimination, memory, and suprathreshold intensity perception. In smell identification tests, many of which can be self-administered (Figure 6), odorants known to be familiar to most people are presented and the subject selects the name of the odor from written alternatives. Such tests have been developed for different cultures, given differences in the familiarity to certain stimuli (e.g., the odors of pumpkin pie and skunk are unknown in most countries outside of North America).

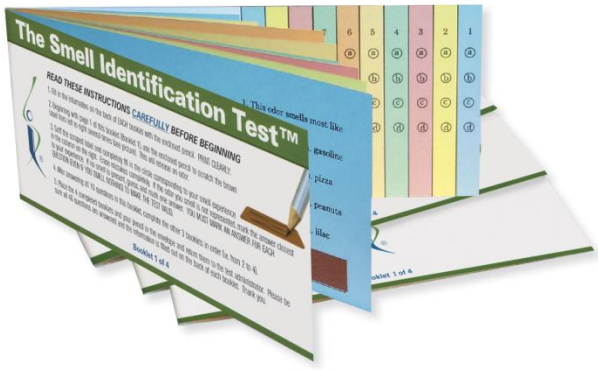


Figure 6. The self-administered University of Pennsylvania Smell Identification Test. This test consists of 4 test booklets, each containing 10 odors with 4 corresponding response alternatives. Norms based upon ~ 4,000 persons permit accurate assessment of smell loss in both an absolute sense and in terms of age- and sex-related normative values. Photograph courtesy of Sensonics International, Haddon Heights, NJ USA.

In addition to an absolute determination of function (e.g., normal or mild, moderate, severe, or total loss), sex- and age-related normative data are available for some tests, making it possible to determine a patient's percentile rank relative to peers [15]. Smell threshold tests are akin to pure-tone hearing threshold tests, except that odors, rather than tones, are presented. (Figure 7) The goal is to determine lowest concentration that a subject can reliably detect, although distinctions are to be made between detection (something vs. nothing) and recognition (experience of an odor quality) [16]. Recent developments in computer technology make self-administration of threshold tests possible (Figure 8).

Figure 7. Two examples of modern detection threshold kits. Left: The Smell Threshold Test utilizing squeeze bottles to present different odorant concentrations of phenyl ethyl alcohol (rose oil) or amyl acetate (banana). Photo courtesy of Sensonics International, Haddon Heights, NJ USA. Right: Sniffin' Sticks. Phenyl ethyl alcohol or n-butanol odorants presented by felt-tip markers. Photo courtesy of Burghart Messtechnick GmbH, Wedel Germany.

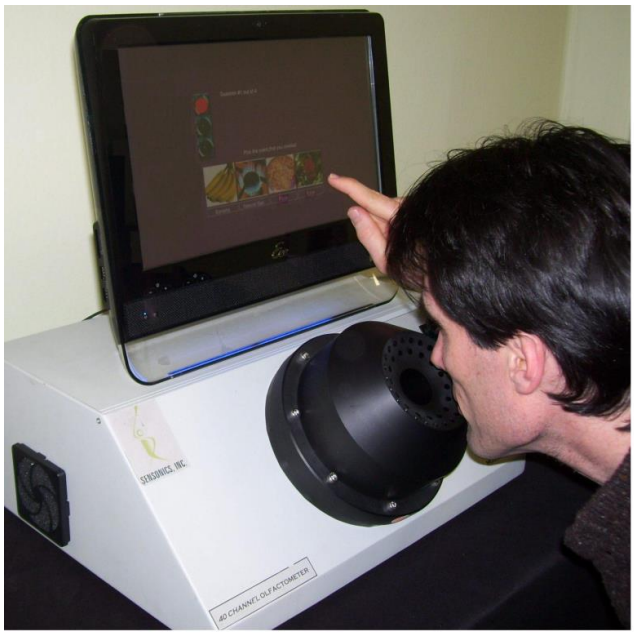


Figure 8. A modern self-administered computerized smell threshold testing device. On a given trial, a pair of stimuli are presented one after the other with a 10-sec interval interspersed. The task of the patient is to indicate which of the two stimuli smells strongest. When misses occur higher concentrations are presented, and when correct responses occur, lower concentrations are presented, in accord with a staircase algorithm. Although programs can also assess odor identification and memory, the main feature of this device is the production of staircase threshold values without the intervention of a tester. Photo courtesy of Sensonics International, Haddon Heights, NJ USA.

Odor discrimination tests typically require the patient to identify the "odd" stimulus from a set of foils, whereas odor memory tests measure a patient's ability to recognize previously experienced odors over

various intervals of time [17]. With the exception of tests of suprathreshold intensity and pleasantness, the majority of olfactory tests are correlated with one another, with the size of the correlations among test largely being determined by the reliability of the least reliable test. In most cases olfactory dysfunction can be rather completely characterized by the administration of a single reliable olfactory test, although, in the case odor threshold tests, some odorants may be more consistently influenced by dysfunction than others. In general, tests of odor identification are more sensitive and reliable than other types of tests. This reflects a number of factors, including the tapping of the function of multiple components of the olfactory system – presumably components of a system that evolved in aggregate. Thus, perturbations anywhere within the system are more likely to be detected by such a test. The weight of the evidence suggests that individuals have a "general olfactory acuity" factor similar to the general intelligence factor proposed for various tests of intelligence.[18, 19]

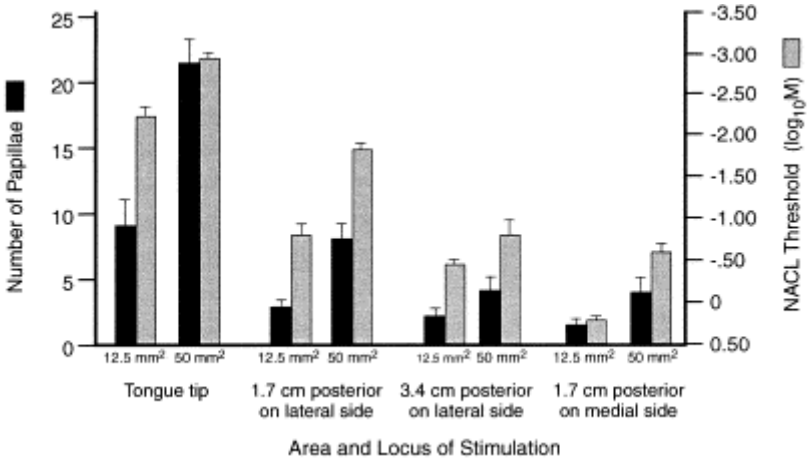
From the point of view of practicality, it is important to point out that a number of screening tests are available to the neurologist to allow for a determination as to whether gross dysfunction is present before administering more detailed tests. Most such tests are self-administered identification tests that employ microencapsulation (“scratch and sniff”) technology. These include 3- and 4-odor versions, such as those being employed in the current National Health and Nutrition Examination Survey (NHANES) Survey, and the 3-item Quick Smell Identification Test available from the American Academy of Neurology. Screening tests are, however, less sensitive than longer tests in detecting less-than-total deficits and cannot be relied upon for detecting malingering.

Taste

From a clinical perspective, accurate testing of taste function is more difficult than that of olfactory function, since there are multiple nerves involved and taste receptors are variably distributed over the tongue and other regions of the oral cavity. Moreover, taste thresholds are sensitive to stimulus duration, size, and a multitude of other factors. For practical reasons, only some tongue regions are usually tested, such as sectors of the left and right sides of the anterior tongue (CN VII) and, in some cases, the posterior tongue (CN IX). Testing of the taste buds on the roof of the mouth, i.e., the anterior and posterior regions of the soft palate, can be tested using electrogustometry, although in most clinical situations this is not done. Taste buds within the esophagus and on the epiglottal surface are never tested clinically. Clearly, compromises in terms of taste testing must be made.

Although whole-mouth testing provides a good assessment of the overall taste experience, it is insensitive to damage to individual taste nerves. Bornstein[20] stated the following when it comes to clinical taste testing (p. 137):

> To detect pathological alterations of taste, neither the whole-mouth methods nor examinations of only one area of the tongue are applicable because, in organic lesions, different parts of the tongue are usually involved in different manners and degrees. Therefore, separate examinations of the several areas of the tongue are necessary. For this purpose, the tongue is divided into right and left halves, and each half into three regions, namely, tip, border, and base.



Taste stimuli can be presented to subjects via (a) cups, beakers, or flasks from which whole-mouth 'sipping & spitting', or in some cases swallowing, can occur, (b) medicine droppers, syringes, pumps, or micropipettes that allow for assessing small regions of the tongue, (c) paint brushes or Q-tips dipped in taste solutions, and (d) small discs or strips made of filter paper or methylcellulose polymers impregnated with tastants. In 1955, Hara developed paper discs for the assessment of regional taste function[22] and since then such discs have been standardized and routinely used in Japanese hospitals. Recently dissolvable disks made from methylcellulose polymers have been developed that largely confine the stimulus to the region of interest.[23] As shown in Figure 9, taste thresholds are very sensitive to the tongue regions which are evaluated and are highly correlated with the number of papillae located in a given tongue region.

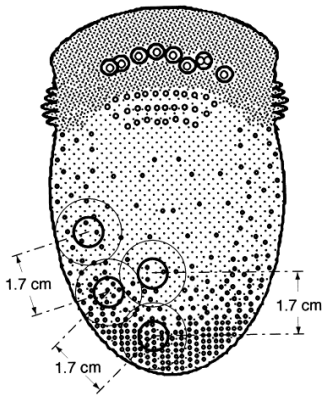


Figure 9. Left: Tongue regions where stimulators were centered. Right: Mean (± SEM) threshold values obtained from 8 subjects for NaCl presented to the four tongue regions for two stimulation areas (12.5 and 50 mm^2). The number of papillae counted under videomicroscopy is indicated by the dark bars, and the threshold values by the gray bars. From [1]

The most practical clinical taste tests employ electrical stimulation. In electro-gustometry, a small stainless steel electrode is placed on a tongue region and a weak (< 100 μA) current applied for a half second or so. If the taste nerve is working well, only a few μA of current induces a subtle but noticeable perception. Although such stimulation does not produce all taste qualities (e.g., sweetness is never induced by an anodal electrode), thresholds obtained using electrogustometry correlate well with thresholds using chemical tastants. Normative electrical threshold data are available for thresholds obtained using a staircase procedure on the anterior, posterior, and palate tongue regions.

A major problem in clinically assessing taste thresholds is the lack of standardization of procedures and accurate normative data that takes into account the effects of age and sex. Like olfaction, older persons have somewhat higher average taste thresholds than younger ones, an effect that is most noticeable when small regions of the tongue are tested. Those taste tests for which at least some normative data are available include the whole-mouth three-drop threshold test of Henkin,[24,25] a five-drop procedure described by Wen[26] for a control sample of 600 persons, a filter-paper test using dried tastants by Landis normed on 537 persons,[27] and validated edible “taste strips” made from pullulan combined with the polymer hydroxypropyl methylcellulose.[28]

As with olfaction, suprathreshold measures of taste function are becoming more popular, in part because of their greater practicality and their ability to measure ‘real world’ sensations. Unfortunately, norm development for such tests has lagged behind that of threshold tests, so published normative data

are lacking for such instruments.[29,30] Reviews of several modern taste testing procedures used clinically and electrogustometry are provided by Frank.[31, 32]

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C. Common Neurological and Medical Disorders with Primary Olfactory and Secondary Taste Dysfunction

There are a number of neurological and non-neurological disorders that a neurologist encounters in clinical practice involving impairment of olfactory function, and secondarily, the perception of "taste" as viewed by the patient. The smell system, which detects and recognizes odors, is also responsible for flavor recognition. The taste system itself is made up of numerous taste receptors located in the mouth and on the tongue that are innervated by cranial nerves V, VII, IX, and X. It is responsible for the perception of five basic taste qualities of sweet, sour, bitter, salt and umami (Japanese word for savory that is the taste of monosodium glutamate or MSG. The trigeminal sensory system of the mouth is responsible for the recognition and appreciation of texture, temperature, and spice sensation.

a. Post Traumatic Anosmia

AR was a 40yr old truck driver who was stopped at a red light when he was rear-ended by a car. He was wearing a seat belt and remembers the impact; then he blacked out. He remembers someone banging on the door and asking him if he was alright. He also remembers headaches and neck pain. He was taken to the ER and evaluated by the ER physician. He was noted to have a bruise on his forehead and tender neck muscles, and an otherwise normal neurological exam. Scans of the brain and cervical spine were also normal. He was sent home with a prescription for pain medication and muscle relaxants and told to return to work in a few days. Three days later, AR noticed his morning coffee had no taste or smell. He also noticed he could not smell gasoline when he went to fill his car. He also was unable to "taste" many of the foods he ate. He was referred to an ENT physician. He ordered a CT scan of the sinuses and performed a nasal endoscopy to search for nasal fractures, or possible injury to the upper nasal airway and olfactory organ. All these tests were normal. AR was given a nasal steroid spray to help reduce any nasal inflammation that may have developed. Also, because of his headaches and impaired smell and taste, he was referred to a neurologist.

His neurological exam was normal. He was given the University of Pennsylvania Smell Identification Test (UPSIT) and he scored 14/40 (normal >37/40) and is indicative of total anosmia. He was also given a taste strip test that measures the basic tastes of sweet, sour, bitter, salt, which proved to be normal. An MRI of the brain was done with special views of the olfactory bulb, orbital frontal and medial temporal lobes (important central regions for olfactory function) to determine if there was any injury in

these regions. The MRI was reported as normal. AR was told by the neurologist that he had post traumatic anosmia from his auto accident and likely head injury. He was told he could expect some improvement over the next three to twenty four months.

Of all the causes of smell impairment and secondary taste complaints (flavor loss) observed in a neurology clinic, 10-20% will be due to head trauma. This includes injuries to facial and nasal structures and any part of the skull. It is the most common cause of patient recognized smell loss observed in clinical neurology. It occurs in 7% of all head trauma cases, but increases to 60% with a skull fracture with spinal fluid leakage.

Since head injury is often associated with memory impairment, the injury may have been forgotten, so history from family and friends is necessary to confirm the diagnosis. If injury is suspected, an MRI of the olfactory system (cribiform plate, olfactory bulb and tracts, gyrus rectus, orbital frontal lobe, and medial temporal lobe) should be performed. These particular regions need to be mentioned on the requisition sheet. 80% of individuals with traumatic anosmia, and secondarily impaired flavors, complain within one to five days and 17% within three to sixteen weeks of injury (often secondary to other injuries and/or memory loss.) Total smell loss occurs in 60-80% tested, and 20-40% have mild to moderate smell loss.(1) Interestingly, some patients only become aware of their smell loss much later, likely reflecting gradual damage to the receptor cells or subsequent comorbid causes.

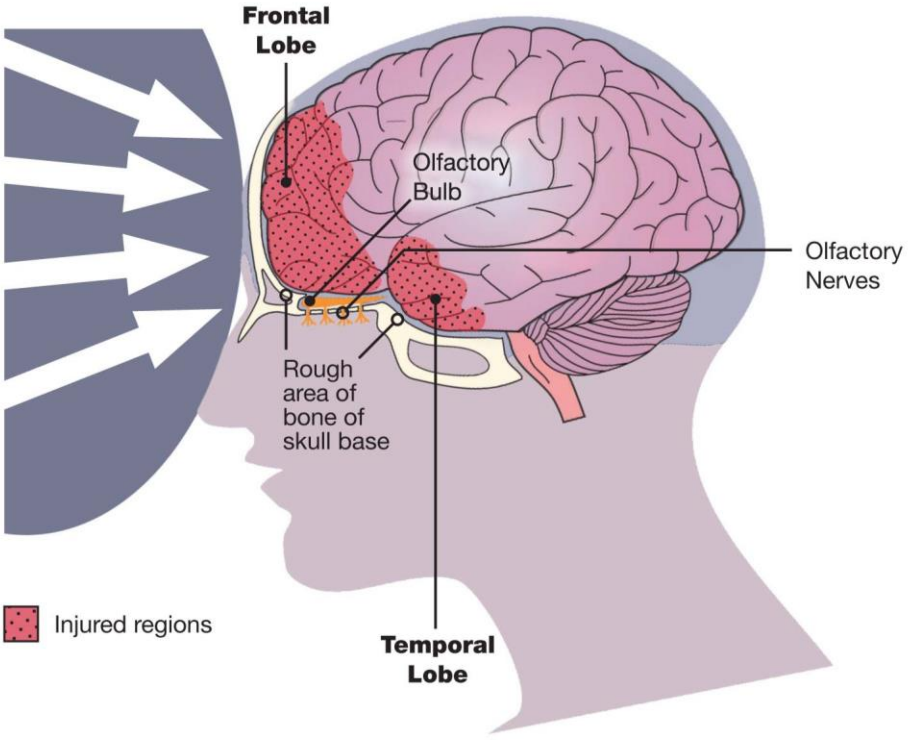
There are four mechanisms associated with smell loss in head trauma:

1. Direct injury to the face and nose which can block the transit of odorant molecules to the olfactory receptors or injure the olfactory organ and olfactory nerves.
2. Trauma to the skull with injury to the olfactory nerves and sparing injury to frontal and temporal brain regions.
3. Trauma to the skull with injury to the olfactory nerves, plus frontal and temporal lobes of the brain.
4. Any combination of 1, 2, and 3 above (see Figure 1).

In direct facial and skull injuries, the brain is shifted backward and forward due to acceleration and deceleration forces that can lead to contusion of the frontal and temporal lobes along with a shearing injury of the olfactory nerves traveling through the cribiform plate. Studies have shown that occipital

and side head trauma is five times more likely to cause olfactory impairment due to some protective effect of the frontal sinus and cartilage present in frontal injuries. (1) Prognosis of olfactory impairment in head trauma has been traditionally considered dismal, but most studies have lacked standardized smell and taste testing and did not take into account subjective improvement. Doty, et al, found in 268 cases of head trauma patients presenting to a specialized smell and taste center, that improvement in smell function testing occurred in 36% at two years. The remainder slightly worsened or remained the same. (1) In a small study of twenty patients, Duncan and Seiden found that 35% improved over one to five years. (2). London, et al, in 2004, followed one hundred and six cases of post traumatic smell loss over twenty three years with careful smell and taste evaluation. Of sixty nine patients with total smell loss, 44% made moderate improvement and 11% returned to normal. Of those who were hyposmic (moderate smell loss 37 cases), 45% improved, but only 27% improved to the normal age related change. (3)

Figure 1: Brain injury at base of skull



Blunt force to the face, nose and head causes the brain to move backward and forward. This causes a stretch injury to the olfactory nerves which are anchored to the cribiform plate. Frontal and temporal lobes become bruised from moving across the irregular base of skull.

Three important points arose from this study:

1. The time between post traumatic olfactory loss and baseline smell testing is directly correlated with improvement. The longer the period, the better the improvement. Greater smell improvement occurs within the first six to nine months of injury with subsequent improvement very slow or not at all.
2. The lower the olfactory loss at the initial visit, the better the prognosis. People with mild to moderate smell loss are twice as likely to improve into the normal range as those with severe smell loss.
3. Patients older than seventy four years of age are less likely to improve than younger patients due to factors of aging on normal olfactory function. These include changes in olfactory mucosa, sclerosis of the cribiform plate with compression of the olfactory nerves, and frequently, underlying neurodegenerative disorders like non-motor and motor Parkinson's disease, mild cognitive impairment or Alzheimer's disease.

THE USE OF ORAL STERIODS IN ALL CASES OF POST TRAUMATIC SMELL IMPAIRMENT SHOULD BE STRONGLY CONSIDERED. TAPERING HIGH DOSE ORAL STEROIDS OVER A TWO WEEK PERIOD MAY UNCOVER SOME INFLAMMATION AND SWELLING AND PARTIAL CONDUCTION BLOCK IN THE HIGHER NASAL PASSAGE AND AROUND THE OLFACTORY ORGAN WHICH COULD IMPROVE OLFACTION. HIGH DOSE ORAL STEROIDS HAVE SHOWN TO BE MUCH BETTER THAN NASAL SPRAY STEROIDS.

b. Medications (prescribed and over-the-counter)

Medications that have been suspected to cause smell impairment have been documented in the Physician Desk Reference (PDR) without a reference or only recognized in isolated case reports. Some directly interfere with the olfactory transmission or cell regeneration. Major offenders may be calcium channel blockers and statins, although these drugs usually affect taste more than smell. (4)

Carol had been having infrequent migraine headaches since her teens. Now in her mid-forties, she began having more frequent headaches. Her neurologist started her on dilitizam, which helped to control her high blood pressure. When this did not prevent her migraines satisfactorily he added topiramate. This combination of drugs treated her migraines and blood pressure well. However, one month after topiramate was added Carol noticed when she drank a can of cola, it tasted unpleasant and

flat. She also noticed she could not smell brewing coffee. Her husband told her not to wear so much perfume when she went out. Carol's neurologist was aware that smell loss can be caused by medications, especially dilitizam. She was given the University of Pennsylvania Smell Identification Test (UPSIT) to self-administer, and she scored 30 out of 40, which put her into the mild to moderate impairment category (should be >35/40). Her neurologist was also aware that topiramate can cause primary altered taste. He recommended she start on propanalol, which can also help control blood pressure and migraine headaches, and has no effect on smell and taste. Over the next four months Carol's smell and taste returned to normal. During this time period she learned to add flavors to her food in twice the normal concentration, and to use small amounts of monosodium glutamate (a savory taste, one of the five taste sensations) instead of regular salt. She was also told to experiment with different spices to enhance her food enjoyment. (See section on Food Preparation.) The literature is not clear as to time of onset of smell/taste impairment with offending medications or the length of time it takes to improve once the offending medication is stopped. However, three months to a year is not an unreasonable time to develop chemosensory impairment from prescribed medications; and it may take three to nine months or longer to improve or return to normal once the offending medication is discontinued. Below is a list of different classes of medications that can impair smell and cause secondary taste dysfunction. This list is by no means exhaustive, and if you suspect a medication not listed, it should be reviewed in the PDR to see if chemosensory dysfunction is mentioned in the side effects.

- Antibiotics -- penicillins, tetracylines
- Antihistamines -- chlorphenarimine maleate (used in decongestants and cough syrup)
- Calcium channel blockers -- dilitizan, nifedipine
- Cholesterol lowering drugs-- atorvastatin, pravastatin
- Opiates -- codeine, morphine
- Chemotherapy – methotrexate
- Sympathomimetics -- amphetamines
- Local Nasal Anesthetics -- cocaine
- Gastric acid inhibitors -- cimetadine

- Antidepressants -- amytriptiline, paroxitine
- Antiepileptic -- phenytoin
- Diuretics -- furosemide
- Non-narcotic sleeping agents -- eszopiclone

c. Alcohol Abuse

Since the 1970's smell impairment has been known to occur in heavy alcohol users. In 2003, Rupp, et al, noted that 50% of chronic alcohol users had difficulty with odor identification in the absence of memory and cognitive impairment. The evidence suggested that impairment of the brain's olfactory connections (prefrontal and orbital frontal lobes) was involved rather than impairment of the olfactory organ and bulb. (5) In 2004, the same authors showed, that discontinuation of alcohol allowed for some improvement of olfactory function. (6)

d. Neurodegenerative Disorders

The role of smell testing in the diagnosis of neurodegenerative disorders is described in detail later in this presentation. In this section we briefly discuss the olfactory and secondary taste impairments associated with common neurodegenerative disorders. Clinical research in olfaction has revealed impairment in greater than ninety percent of patients diagnosed with many neurodegenerative disorders such as Alzheimer's, Parkinson's disease, Parkinson dementia, Lewy body and frontal-temporal dementia. It is also very important to note clinically that greater than ninety percent of individuals with these disorders often do not have any spontaneous smell or taste complaints. Careful questioning of the patient and caregiver in regard to changes in appetite, enjoyment of eating and tasting food, and weight changes may often give clues to a disturbance in smell and/or taste. Most physicians attribute these changes to medications, gastrointestinal disorders, or even cancer, resulting in extensive and frequently unnecessary work ups.

1. Alzheimer's Disease

Smell abnormality in Alzheimer's disease has been described in the literature since the mid-1980s. It develops early on, and has been shown to be impaired in the majority of patients with amnestic cognitive impairment (AMCI), disorders that often progress to Alzheimer's. In many

cases, the severity of smell loss correlates with the worsening of dementia. The UPSIT is usually <30/40. Age related normals are >35/40. (7, 8) Pathological studies have shown amyloid plaque and neurofibrillary tangles, especially in the medial temporal lobe (entorhinal and pyriform cortex), but also in the olfactory bulb, tract, and anterior olfactory nucleus. Smell testing can help separate the diagnosis of Alzheimer's disease from vascular dementia and the pseudodementia of depression where the patient has normal smell or only mild impairment. (7, 9)

2. Parkinson's Disease

Smell impairment in idiopathic Parkinson's disease (PD) was first described in 1975, (10) and found to be present in ninety percent of patients. It did not correlate with motor impairment, severity of the disease, or treatment; however, it correlated with disease type. Tremor dominant PD showed less smell impairment than the rigid akinetic type. Ninety percent of patients have asymptomatic smell loss that does not progress with time because the maximum impairment appears to be reached early on. (11) Pathology is centered in the olfactory bulb and anterior olfactory nucleus, and in later stages of the disease, in the medial temporal lobe (entorhinal and pyriform cotex). Although this may also occur in AD, some accounts suggest that AD, unlike PD, reveals earlier involvement of pathology within the medial temporal lobe. In Parkinson-plus disorders such as Lewy body dementia, progressive supranuclear palsy, cortical basal degeneration, multiple system atrophy, and vascular PD, smell impairment is much milder. Testing shows smell scores of > 30/40. The UPSIT score of < 25/40 was found to be 77% sensitive and 85% specific for idiopathic Parkinson's disease. (11) The AAN guidelines state that if an individual is suspected of PD, and has a normal or mildly abnormal smell test, then Parkinson-plus or some other disorder should be suspected. Asymptomatic smell loss has been shown to be a premotor finding of Parkinson's disease and can predate Parkinson's disease onset by 4 years. (12)

3. Frontal/temporal Dementia

Frontal temporal dementia (FTD) has also shown to have asymptomatic smell loss in seventy percent of cases, but less research on smell dysfunction has been done with these disorders. It is not clear, for example, if smell loss worsens with time. Unlike AD and PD, the olfactory receptor, bulb, and tracts are normal pathologically, suggesting a disturbance in the frontal

(orbital, etc.) and temporal lobes in the brain. Much more work needs to be done in this regards in this disorder. (13)

4. Multiple Sclerosis

Thirty to fifty percent of Multiple Sclerosis (MS) patients have mild to moderate smell impairment on testing, and ninety percent of those are asymptomatic, similar to the neurodegenerative disorders. Doty, et al, showed an inverse correlation between UPSIT scores and the number of MS plaques in the sub frontal and sub temporal regions. He followed many of these MS patients for two years and showed that the UPSIT score waxed and waned in correlation with the number of MS plaques seen on MRI. In rare cases, short- lived taste changes can be the first symptom of a MS attack. (14)

5. Migraine

Smell complaints have been long recognized in people with migraine. They will often say that their migraines are triggered by certain odors. The most common triggers are perfume and gasoline. Many migraine patients complain that every day smells make their headaches worse. In a 2004 study of migraine patients, twenty five percent (mostly women) reported their migraines were triggered by a strong odor. (15) Spontaneous bad smells (phantosmia) also can replace spots and flashing lights as part of an aura, but this reportedly occurs in less than one percent of migraine patients.

6. Chronic Medical Disorders

Most neurologists see many patients with underlying chronic (diagnosed or undiagnosed) primary medical disorders. These disorders may or may not explain their neurological symptoms. Among such disorders are: Diabetes, hypothyroidism, chronic liver and kidney disease, and vitamin B_{12} and/or folate deficiency.

Hypothyroidism may reduce smell and taste sensitivity, although hedonic distortions appear to be more common.

Low thyroid more frequently causes a burning mouth syndrome (20% of cases) and an unpleasant taste that may or may not recover with repletion of thyroxine. The cause is likely due to combination of saliva changes and disturbance of olfactory cells and their brain connections. (16)

Over fifty percent of diabetic patients have a change in their smell and taste function. They are less sensitive to common odors and many different tastes, especially sugar. The cause is not definitely clear, but is likely due to a neuropathy of the cranial nerves that subserve smell and taste. (17)

Chronic kidney disorders lead to decreased sensitivity to common smells and tastes. This is likely due to multiple factors including medications, and metabolic changes that occur in kidney disease (increased Bun, creatinine, etc.) Dialysis and medication changes with correction of possible low zinc and other metabolic abnormalities usually lead to improvement. (17)

Chronic liver disease is often associated with impaired smell and taste, which like chronic kidney disease, is due to a combination of metabolic and medication factors. Evidence suggests that smell and taste receptor cells and their central connections in the brain are impaired. (17)

D. **Common Neurological and Medical Disorders Causing Primary Taste Impairment with (Usually) Normal Olfactory Function**

a. Medical Disorders

Less than ten percent of patients with altered taste who see a neurologist or other physician will have a primary taste disorder. This is because most impairment of taste are due to impairment of olfaction, with secondary loss of flavor recognition. The public does not really understand the difference between the words “flavor” and “taste”. Altered taste or impaired enjoyment of food is more likely due to impaired olfaction, independent of whether the patient complains of smell dysfunction. It is important; however, for the neurologist to understand what role primary taste disorders play in our patients. As noted earlier, the five primary tastes are: sweet, sour, bitter, salt, and umami (Japanese word for savory) represented by MSG.

What are the causes of a primary taste disorder that a clinical neurologist might encounter? These include medications, chemicals and toxins (smoking and radiation exposure), local disorders of the mouth (poor oral and dental hygiene), insufficient saliva, and GERD. Common medical disorders such as hypothyroidism, diabetes, and chronic liver and kidney disease, as mentioned in the previous section

can also cause a primary taste disorder. Neurological disorders such as Bell's palsy, multiple sclerosis, and some brainstem strokes and brain tumors can (rarely) cause a primary taste disorder. Emergency intubation or intubation for general anesthesia can injure the trigeminal nerve (lingual nerve), glossopharyngeal nerve, and the tongue in general, and can cause a primary taste disorder. (19)

b. Medications (prescribed and over the counter) and Toxins

Medications and toxins are one of the most common or contributing factors in primary taste impairment. (18) The PDR reports taste alteration as a side effect of many prescribed medications. Medications can alter taste by many different mechanisms. (19)

- Reduced quality and quantity of saliva
- Interference with taste bud and taste receptor function
- Inflammation of the epithelial lining of the mouth, tongue and pharynx
- Alteration of the cranial nerves and their central connections that subserve taste (cranial nerves V, VII, IX & X)

Table 1 shows some examples of medication classes, and names of medications known to cause primary taste impairment.

Table 1

Category of medication	Examples of medication
Anti-inflammatory	allopurinal
Non-steroidal anti-inflammatory	ibuprofen
Antibiotic	tetracycline, penicillin
Anticholinergic	detrol, amytriptiline, paroxitine
Calcium channel blockers	nifedipine, dilitizam
Ace inhibitors	captopril, lisinopril
Antiarrythmic	propanalol, amiodarone
Antihistamines	diphenhydramine
Cancer drugs	methotrexate
Cholesterol lowering drugs	atorvastatin, pravastatin

Diuretics	hydrochlorothiazide, furosemide
Hypoglycemic agents	phenphormin, glipizide
Antiparkinson	L-dopa, selegeline
Antiseizure	Topiramate, diphenylhydantoin, Carbamepazine
Sleeping agents	Eszopiclone

Many medications in Table 1 impair taste by inhibiting saliva production and by interfering with acetylcholine. These include the specific anticholinergic medications used in treating bladder urgency (Detrol) and tricyclic antidepressants (amitryptiline). Some medication classes used to control high blood pressure and heart failure inhibit zinc action in the salivary glands and taste receptor cells. Zinc is necessary for saliva's action and digesting food and normal function of the taste receptors. (17) The best medication examples of drug induced impairment are captopril and lisinopril, both ACE inhibitors, and popular for blood pressure control. Inflammation of the connective tissue lining the mouth, tongue and pharynx can cause impaired taste. This is common in people with poor oral and dental hygiene and includes gum disease and tooth decay.

Gastroesophageal reflux disease (GERD) is a common ailment that can lead to altered taste through a similar inflammatory mechanism. It can be due to secondary irritation caused by gastric acid in the mouth, tongue and pharynx or due to the bitter taste of the gastric acid itself. Neuro medications like L-dopa, phenytoin, and carbamazapine interfere with taste receptor function and their central pathways. Topiramate, in a similar fashion, causes carbonated beverages to taste flat or metallic or both. Cholesterol lowering medications such as atorvastatin and pravastatin cause altered taste, but the mechanism is unclear.

Examples of toxins that impair primary taste function include smoking and radiation of the head and neck for cancer. Radiation therapy damages the salivary glands, taste receptors, and sometimes, the facial nerve. This can lead to secondary mouth infections with direct injury to the taste buds and taste receptors. Heavy smoking can cause taste loss, but it is usually mild. It is believed to be due to the chemicals in cigarettes themselves. Often these mechanisms overlap to impair primary taste.

c. Neurological Disorders

There are several neurological disorders that can directly cause a primary taste disorder.

Idiopathic Bell's palsy infrequently can impair taste because the taste sensation from the anterior two thirds of the tongue (lingual nerve) joins the chorda tympani in the middle ear canal to join the facial nerve. This taste impairment is usually very mild because taste is usually only impaired on one side of the tongue and the other side is normal; the facial paralysis is much more disabling. These taste changes usually recover completely even if the facial paralysis does not.

Taste complaints in brainstem and cerebral disorders such as stroke, brainstem tumor, and MS are very uncommon. (18) They are seldom mentioned or noticed because other symptoms are so much more debilitating, such as paralysis, double vision, etc. In very rare cases primary taste loss can be a presenting symptom of MS. Smell impairment with secondary taste impairment is much more common. Neurodegenerative diseases like AD, PD, LBD and PDD have only rarely been reported to have a primary taste disorder.

Clinically, complaints of taste impairment in neurological disorders are usually due to a combination of the area of brain affected, medications used in symptomatic treatment, and underlying associated medical conditions, such as diabetes and hypothyroidism. Common medical conditions can cause primary taste impairment. Fifty percent of patients with hypothyroidism and normal smell function develop taste complaints (16). The ability to taste all five primary tastes is impaired, with the bitter taste being most affected. This usually recovers with thyroid treatment. Patients with chronic liver and kidney disorders, with or without diabetes, often have primary taste complaints. Those medical conditions reduce sensitivity to all five primary tastes. Additional factors frequently present that can add to the taste impairment are use of other medications for symptomatic treatment, possible low zinc levels, reduced saliva production, and impaired cranial nerve function (I, V, VII, IX and X).

Neurologists might see a patient with Sjorgens disease for peripheral neuropathy or brain involvement. Taste complaints are not uncommon due to impaired saliva production, which is a common complication in this Disorder. (16)

During general anesthesia or emergency intubation, the lingual nerve can be injured. It can cause sensory loss to the tongue and mild taste impairment. It is usually mild since the other lingual nerve is intact and recovery usually occurs with time.

E. Abnormal Smells and Tastes (Dysosmia and Dysguesia): Diagnosis and Treatment

Abnormal smell and tastes can be a major disturbance in quality of life in patients with chemosensory abnormalities. Let us first define the appropriate terminology used in these abnormal sensory disturbances. Altered smells are referred to as dysosmia. If the altered smell is triggered by another odor, the term used is parosmia. If the altered smell occurs spontaneously without a trigger, it is referred to as phantosmia.

Altered taste is referred to as dysgeusia. If the altered taste is triggered by another taste it is termed parageusia. If the altered taste occurs spontaneously, it is termed phantageusia.

The majority of altered smells and tastes are usually very unpleasant and interfere with quality of life by decreasing appetite, impairing enjoyment of eating and can lead to unintended weight loss and depression.

John is 73 years old. A year ago he developed a very unpleasant odor that resembled feces. The smell was usually triggered by other environmental smells and lasted 10-15 minutes. It recurred numerous times a day. Over the next three months he developed decreased appetite and lost fifteen pounds. He did not enjoy eating because food odors would trigger this bad smell. He became very depressed. About the same time he developed the bad smell, he also noted a horrible metallic taste when he put food in his mouth. This added to his loss of interest in eating and impaired his quality of life. His past history was unremarkable except for high blood pressure, for which he was taking Lisinopril.

He was initially seen by an ENT physician who did a nasal endoscopy and a MRI of the brain. These tests were normal. Smell testing using the UPSIT, showed a low score of 18/40 that put him in the category of severe smell loss. Taste testing using the taste strip test showed a low score of 4/16 tastes correctly identified. Further studies to find the etiology included sedimentation rate, ANA, B_{12} and folate, zinc level, thyroid and a metabolic profile. All these tests were normal. John was given a trial of intranasal saline to see if it reduced the bad smells, but it did not help very much. He was started on zinc Gluconate, 40mg, TID and a trial of gabapentin starting at 300mg at bedtime, and increasing slowly to three times a day. After three weeks the bad smell and taste began to subside, and completely

subsided in three months. His appetite returned, and he regained the weight he had lost, and he was no longer depressed.

Review of the literature on dysosmia and dysguesia reveals mostly case reports with some large studies. In 2005, Bonfils (20) studied 56 patients with parosmia. The duration of parosmia ranged from three months to twenty two years with an average of fifty five months. All patients reported olfactory impairment. Seventy five percent had hyposmia and twenty five percent had total smell loss. All cases described their parosmia as foul, rotten, sewage, or burned smell. Eighty percent of patients were able to indentify the trigger. They included gasoline (30%), tobacco (28%), coffee (28%), perfumes (22%), fruits (mainly citrus 15%), and chocolate (14%). Ninety percent of these patients were unable to identify flavors. The causes of the parosmia in this series were: upper respiratory infection (43%), chronic paranasal sinus disease (12%), head trauma (10%), toxic chemical exposure (7%), nasal surgery (2%), and Idiopathic (26%). The temporal relationship between olfactory impairment and development of parosmia varied. In 57% of cases it occurred simultaneously. In the remainder (43%), it developed in three months (34%) and after three months (9%). The mean time was 1.5 months after olfactory impairment.

The cause of parosmia is possibly explained by two theories: peripheral and central. In the peripheral theory, evidence suggests that abnormal olfactory neurons are unable to form a complete picture of an odorant. This goes along with the evidence that all parosmic patients have a smell loss. In 2002, Leopold (21) stated that the peripheral theory is supported by the histology of the olfactory organ, which shows a decreased number of neurons, more immature neurons, and distorted growth of olfactory axons. In patients who develop immediate parosmia with olfactory loss, ephaptic transmission between disconnected axons and others that innervate the olfactory bulb might result in a distorted signal in response to the odorant.

A central theory of parosmia states that the integrative or interpretive centers in the brain form parosmia. The support for a central theory is that olfactory auras can accompany seizures and that excising the olfactory epithelium in some patients still leaves a feeling of the “bad” smell coming, but it never occurs. (21) The fact that gabapentin or other anti-seizure medications can improve parosmia in some patients and that this drug acts peripherally and centrally supports both of these theories.

Treatment of Dysosmia

Patients need to be reassured that their condition is not progressive, and that in most cases, will eventually disappear. Since smell impairment accompanies dysosmia, patients need to be counseled about safety issues such as installing smoke, gas and carbon monoxide detectors in their homes, not eating open foods that are not date labeled, and also to have family members monitor perfume and deodorant use.

In 2002, Leopold (21) states that use of normal saline in the nose may help reduce the bad odor in 50% of his patients. In my experience it is much less (25%). This treatment takes 10cc's of normal saline into a syringe and while sitting with the head down at the level of the knees, gently squirt the saline into each nostril, wait 10 seconds, and sit up. Do not sniff and let the extra saline drip out of the nose and wipe. Sniffing is not allowed so that the saline remains in the upper nasal passage and works as a partial block for entering odors. This should be done four times a day for 4-5 days, or as long as needed, if it works.

Anticonvulsant usage in dysosmia is mostly anecdotal and without a published series. Leopold (21) describes its use, but does not describe any details. I have used gabapentin in many of my patients when nasal saline treatment fails or is not very successful. I usually begin with 300mg at bedtime and increase the dose by 300mg every 4-5 days until total doses reach 900mg to 2400 mg per day in divided doses. Side effects may limit the total dose, but going slowly works better. If there is improvement which can range from 25% to 90%, the total dose is continued for three to six months. A slow taper should be done to see if the bad smell returns. If it does, the medication should be restarted at the same total dose. Repeated tapering of the gabapentin should be done every three to six months until the bad smell disappears permanently. I also have used zonisamide in a few cases, reaching 100 mg per day with positive results.

The most aggressive treatment for the treatment of dysosmia was also reported by Leopold. (21) He has been excising the olfactory epithelium by nasal endoscopy, mainly in intractable phantosmia. He has treated over 18 cases in a thirteen year period. He used pre-op intranasal cocaine to see if the bad odor is eliminated temporarily. The majority had the surgery only in one nostril that appeared to be the source for the bad smell. All cases except one made a complete recovery and eliminated the phantosmia. The purpose of the surgery was to cut all connections between the olfactory

organ and the olfactory bulb. Follow up smell tests in his patients showed no change (5/10), improved (2/10), and decrease from baseline (3/10). Why some olfactory function returned in some of these cases when all the nerves were cut is a puzzle.

Treatment of Dysguesia

In 2005, Heckman (22) reported on dysgeusia in 116 patients. In this series, fifty were idiopathic and the remainder was due to allergy of dental material, poor oral and dental hygiene, poorly controlled diabetes, decreased saliva due to medications or diseases of the salivary gland, low zinc, and side effects of many medications. The following are predominantly anecdotal treatments and others referenced in a study:

- Cepacol lozenges with benzocaine. Have the patient take them before meals; they may help paraguesia.
- Xylocaine, 0.5-1% mouth gel, apply twice a day.
- Gabapentin anticonvulsant. This likely works by altering or blocking abnormal electrical discharges arising from the peripheral damaged smell or taste organ as well as altered central connections. Begin at 300mg at bedtime and increase slowly over 21 days to 900-2000 mg per day.
- Zonisimide anticonvulsant. Start at 50mg daily in am and after one week increase to 100mg/day.
- Zinc gluconate 140mg/day, is moderately effective. Improved taste, mood, and dysgeusia in 50% of patients (22)
- Ice cube stimulation. Put one small ice cube in the mouth for one minute just before meals. (See below)
- For insufficient saliva, try artificial saliva before each meal.
- Mirtazapine, 15mg, at bedtime. (See below.)

Fujiyama described an elderly patient who lost ability to sense sweet. (23) Whenever she ate foods that were sweet she developed a bad sour taste. Her taste test showed high threshold for saltiness. The author decided to put an ice cube in her mouth for one minute, which lowers the oral temperature by five degrees. They retested her taste for salt and her recognition improved, and the

sour taste decreased. She was told to place an ice cube in her mouth before each meal. After a month she could recognize sweets again, and the sour taste disappeared. There is some evidence that gustatory nerve fibers are sensitive to temperature changes by thermo sensitive ion channels. A thermo sensitive channel called TRPM5 is present in taste bud cells and can confer a steep temperature dependence on the processing of taste perception. The recovery of her taste sensitivity in this patient may be caused by interaction between taste and cold signals. The authors also speculate that cold treatment may improve circulation in the tongue and taste sensitivity recovers. More studies are needed to see if many patients improve and how it works.

Kalpana reported a case of an elderly woman who developed otitis media. She was given antibiotic, levofloxacin, 500mg, per day. After ten days she developed a spontaneous metallic taste. Her food tasted like bile causing loss of appetite and weight loss. The dysguesia continued three weeks after her antibiotic was stopped. She had a long history of depression and was on fluoxitine for years. A psychiatrist changed the fluoxitine to mirtazapine and in 5 days the patient reported complete resolution of her dysguesia. (24)

Mirtazapine is a noradrenergic and seritonergic antidepressant. How and why it helped the dysgeusia is not clear. More studies are needed.

Even though many of these treatments suggestion are not backed by good scientific studies, the symptoms of altered unpleasant taste impair quality of life of our patients and should prompt us to try these treatments singly or in combination.

F. Morbidity of Smell and Taste Disorders

Poor quality of life for people with taste and smell disorders has been recognized for many years, but more studies have been published in the last 10 years.

In 2001, Miwa, et al, found that 75% of patients with impaired smell had impaired detection of spoiled foods, 61% could not detect gas leaks, 50% could not detect smoke, and 30% could not detect burned food. (25)

In 1995, Duffy, et al, found in their cases decreased interest in cooking, eating less food variety, decreased appetite, and increased eating of sweeter and saltier foods (worsened hypertension and diabetes). (26)

In 2007, Aschenbrenner et al, studied 176 smell and taste impaired cases and found 21% gained weight (2.5 kg) searching for better tasty foods), 11% lost weight (5kg), 35% had fewer home dinner parties, and 47% stopped going to restaurants. (27)

Depression has been noted in over 50% of individuals with taste and smell disorders. Many do not enjoy eating because of impaired recognition of flavors. Individuals who depend on normal taste and smell to work at a job can be very depressed as it impairs their livelihood (chefs, neonatal nurses, fireman, wine tasters, etc.). Others worry about their body odor and the inability to smell gas and smoke.

G. Treatment of Smell and Taste Disorders

For many years, and still today is the common belief that the chance of recovering smell and taste impairments was nil to very poor. In the last twenty years more information is available on this topic. We now know that nerve cells in the olfactory organ and bulb can regenerate, although regeneration times are dependent upon multiple factors. Newer long term studies have shown gradual improvements in many of the causes of these disorders.

1. Education and Counseling

Most individuals, as previously mentioned, are either depressed or very unhappy because of impaired smell and/ or taste. It is important that the treating physician spend extra time with them discussing the cause(s) of their taste and smell disorder along with prognosis. Going over very simple anatomy of the taste and smell system and how it works will go a long way to relieve anxiety and increase understanding. Many individuals believe their condition will continue to decline. Reassurance that a number of smell and taste disorders often improve with time can also help relieve anxiety of the unknown. If education about the disorders does not help, then the addition of an antidepressant and professional counseling can be very helpful. Awareness of health and safety concerns due to these

disorders is also a very important part of education. The following important factors should be thoroughly discussed with each individual and family member.

- Be sure there is a working smoke, natural gas, carbon monoxide or propane detector.
- Date all perishable foods and store in the refrigerator to prevent accidental food poisoning.
- Be sure all chemical and cleaning solutions are properly labeled.
- While cooking, one should be very attentive to prevent food from burning and starting a fire.
- Bathe and shower, use underarm deodorant and wash and dry clothes regularly. Especially important for people who live alone.
- Use body fragrances and perfume sparingly and check with family and friends to be sure not in excess
- Those caring for young children should monitor frequently the need for diaper change.

2. Important Changes in Food Preparation

As previously mentioned, altered taste and food flavors in taste and smell disorders are the most frustrating and most unhappy outcome. Changes in food preparation to attempt to make food more enjoyable, is one of the most important interventions. The most important points to remember in understanding changes in food preparation is to know the function and sensory actions of the taste and smell system previously mentioned at the beginning of this course.

- The olfactory system identifies odors and also plays a major role in recognizing different flavors (chocolate, vanilla, etc.)
- The taste system is responsible for recognizing five basic tastes: sweet, sour, bitter, salt and umami (savory like MSG)
- The trigeminal sensory system in the mouth is responsible for recognizing texture, temperature, and spice sensation.

Remember that primary taste disorders are very uncommon compared to disorders of smell. This means that most individuals will have intact basic tastes and trigeminal function with impaired

flavor recognition. For example, an individual with post traumatic anosmia will likely have very impaired smell and impaired appetite and eating enjoyment with increased or decreased weight because they cannot identify flavors. Their primary taste and trigeminal function is normal. During the clinical evaluation it is important to know what the individual usually eats during mealtime.

If a patient normally eats toast, eggs and bacon, along with coffee for breakfast, those foods will likely have no flavor or very little flavor. Suggestive modification of this meal to try to improve food enjoyment would be to increase the strength of the coffee and use an artificial sweetener instead of sugar (normal taste receptors), add a cold glass of orange or grapefruit juice with lots of pulp (stimulates sour and sweet taste receptors), and temperature and texture (trigeminal system). The eggs, regardless how prepared, could benefit from salt and pepper, salsa with variable spiciness (stimulating taste and trigeminal receptors). Dry toast with butter will likely have no flavor. Adding sugar free jam, cinnamon, or crunchy peanut butter can improve texture and tastes.

If one is used to eating a salad for lunch, the vegetables will likely have little to no flavor. Adding different kinds of salts or spicy salad dressing like balsamic vinaigrette or honey mustard dressing will stimulate the normal taste and trigeminal system.

Individuals with mild smell loss (hyposmia) are often able to detect some flavors, but need higher flavor concentrations to enjoy their food. The ability to detect all tastes and trigeminal function is usually normal. People with hyposmia or anosmia usually increase their use of salt and sugar to compensate for partial loss of flavors, which can aggravate hypertension and diabetes. Artificial sweeteners, small amounts of MSG and normal amounts of spices should be used instead. Artificial food flavors are available and should be used when necessary in twice the normal concentration and adjusted up or down according to preference.

Individuals who have normal smell and primary loss of taste is much less common compared to primary smell disorders. Individuals in this category also have mild difficulty recognizing flavors because of altered primary taste. They will need higher concentrations of the basic tastants. Changes in food preparation should include adding spices (spared trigeminal function) and higher concentration of flavors and basic tastes.

Suggestions to improve food preparation regardless of smell or taste impairment:

- Choose and prepare foods that smell and look good.
- Use foods with different colors and textures.
- Chew slowly and move the food slowly around the mouth so all taste and sensory receptors are stimulated.
- Alternate bites of different foods during the meal.
- Add spicy condiments like peppers, horseradish, mustard or salsa.
- Use tart foods and beverages such as oranges, lemons and grapefruits.
- Increase the savory (umami) taste by using small amounts of MSG or eating food rich in MSG such as tomatoes, Parmesan cheese, and corn.

In the AAN book entitled, *Navigating Taste and Smell Disorders*, there are numerous recipes contributed by patients with taste and smell disorders and other recipes that were developed and studied in a group of smell-impaired patients and normal controls. These recipes were more concentrated in normal basic tastes and for trigeminal function. These changes in food preparation and highlighting many recipes have helped to improve quality of life in many individuals with smell and taste impairments. (28)

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H. Role of Smell testing in the Diagnosis of Neurodegenerative Disorder

There is now convincing evidence that olfaction is impaired in a variety of neurodegenerative disorders. Among the common diseases, Parkinson's disease, Alzheimer Disease, and Dementia with Lewy Bodies are particularly affected[1]. Olfaction is lost in the majority of patients affected by these conditions.

There have been suggestions that the nature of the deficit may differ according to the underlying cause. Whereas all conditions appear to have reduced odor detection, discrimination, identification, and recognition, some researchers have argued that patients with dementia (AD) may have relatively more difficulty with identification and recognition tests whereas PD patients may have relatively more difficulty with detection tests[1]. However, such tests have not been equated for such basic factors as reliability or effort, and differences among groups in their ability to comprehend test instructions and task demands have rarely been taken into account. Regardless, nearly all such measures of olfactory function, most of which are correlated strongly with one another are abnormal in most cases, and it is unclear at the present time whether the administration of more than one type of nominally distinct olfactory test has any practical advantage.

1) Parkinson's disease

Olfactory loss is experienced by the majority of patients with PD, and has been documented in nearly 200 studies. Moreover, olfactory loss appears to be relatively specific for PD compared to other parkinsonian disorders. This suggests that olfaction can potentially be useful in differential diagnosis of parkinsonian disorders and distinction of true parkinsonism from parkinsonism mimics. In order for olfaction to be used in differential diagnosis of parkinsonism, two essential criteria must be met. First, olfactory loss must be prevalent in PD, including early stages, when clinical differential diagnosis is most difficult (i.e. high sensitivity). Second, olfactory loss must be uncommon in the general population and in other parkinsonian disorders (i.e. high specificity).

Prevalence of Olfactory Loss - Comparisons with Normal Controls

The first step in assessing diagnostic utility is to compare PD patients to normal controls. This comparison allows assessment of sensitivity of a potential olfactory diagnostic test, and also measures

the maximum specificity that would be achievable in differential diagnosis (assuming that any alternate condition is not associated with olfactory loss).

Although it is abundantly clear that PD patients have more olfactory loss than controls and patients with many other neurodegenerative diseases, the true proportion of PD patients with discrete, identifiable olfactory loss varies somewhat between studies, and sensitivity and specificity are not always directly tested. Even in well-designed studies, there can be sources of bias. These can include:

1) Incorrect clinical diagnosis may be in important confound, particularly in early stage PD, in which up to 20% of clinical diagnoses are incorrect. Since clinical misdiagnosis would result generally in a false-negative finding, the true prevalence of olfactory loss in PD may be higher than studies estimate.

2) Comparison to age-matched controls can be confounded by the fact that a substantial proportion of elderly controls may in fact be in preclinical stages of Alzheimer disease or PD - this would also tend to underestimate sensitivity and specificity of olfactory testing.

3) Although olfaction is abnormal in many cases of PD due to single gene mutations, some mutations (in particular *parkin*), are associated with normal olfaction[3, 4].

4) For most studies, sensitivity and specificity estimates are presented at the optimal cutoff for that particular study - this would bias towards better results than may be found in real-world application to a different patient population.

Most studies have suggested that that potential sensitivity and specificity of olfactory loss are high, although this varies somewhat depending on olfactory technique, cutoffs for defining abnormality and patient population. For this review, we have selected only those studies which contained at least 40 patients and for which sensitivity and specificity calculations could be calculated. There are numerous such studies, which supply generally convergent estimates of diagnostic utility. Results are summarized in Table 1.

Doty *et al* obtained sensitivity and specificity estimates of the UPSIT in differentiating 180 PD patients from 612 healthy controls. Age and sex related effects were observed with the highest sensitivity and specificity occurring in men 60 years of age or less (sensitivity= 0.91, specificity=0.88). The poorest sensitivity and specificity occurred in men over the age of 70 years (sensitivity= 0.76, specificity = 0.78). Double *et al* obtained 82% sensitivity and 82% specificity using the 12-item Brief Smell

Identification test. Hawkes found that 74% of PD patients had decreased olfaction, using a stringent cutoff of below 95% threshold control values in olfactory testing[6]. In a Brazilian study, Silveira-Moriyama *et al* observed 81% sensitivity and 89% specificity for Sniffin Sticks, and 82% sensitivity and 84% specificity of the UPSIT[7]. Silveira-Moriyama also found a 91% sensitivity and 93% specificity of a 12-item Sniffin Sticks adaptation in Sri Lanka[8]. Haehner *et al*, in a large cohort of 400 patients assessed with Sniffin sticks found that 96% of patients had some olfactory loss compared to normative data for young controls[9]. However, when results were compared to normative age-matched controls, 75% of patients were identifiably hyposmic. Bohnen *et al* found 80% sensitivity and 93% specificity of the UPSIT in patients with a 3.5-year disease duration[10]. Boesveldt *et al* achieved 83% sensitivity and 82% specificity of odor identification alone using Sniffin Sticks in 400 PD patients[11] - in a separate study, this improved to 90% sensitivity and 92% specificity in a 52-patient group for whom odor detection and odor identification were combined[12]. Deeb *et al* estimated sensitivity of 86% for diagnosis in early PD (mean duration = 1.5 years) using the 40-item UPSIT[13]. Using the UPSIT, Berendse *et al* estimated that 94% of 96 patients were either hyposmic or normosmic[14]. Suzuki *et al* found that he OSIT-J at a cutoff of 7 distinguished PD patients from controls with 81% sensitivity and 100% specificity[15]. Rodriguez-Violante *et al* found a 71% sensitivity of olfaction in PD, with specificity of 86%[16]. Finally, Maremmani et al using a 33-item Italian 'scratch-and-sniff' test modeled after the UPSIT, found 93% of subjects tested below threshold value, with specificity of 99%[17].

Table 1 - Sensitivity/Specificity of Olfactory Testing in PD vs. controls

Citation	n (PD patients)	Test Used	Sensitivity	Specificity
Doty, 1995[5]	180	UPSIT	79-91	82-88
Hawkes, 1997[6]	73	home-made	74	95
Silveira-Moriyama, 2008[7]	95	UPSIT Sniffin Sticks	82 81	84 89
Double, 2003[18]	49	B-SIT	82	82
Silveira-Moriyama, 2009[8]	89	Sniffin-Sticks adapted	91	93
Haehner, 2009[9]	400	Sniffin-Sticks	75	
Bohnen, 2008[10]	45	UPSIT	80	93

Boesveldt, 2008[11]	404	Sniffin Sticks	83	82
Boesveldt, 2009[12]	52	Sniffin Sticks	90	92
Deeb, 2010[13]	73	UPSIT	86	
Berendse, 2011[14]	96	UPSIT	96	
Suzuki, 2011[15]	94	OSIT-J	81	100
Rodriguez-Violante, 2011[16]	70	B-SIT	71	86
Maremmani, 2012[17]	133	Italian Olfactory Identification test	93	99

Although combining studies with diverse methodology can be problematic, this analysis nonetheless clearly shows that most patients with PD have olfactory loss. Sensitivity of olfactory testing ranges from 70-96%, with a median estimate of 82%. Sensitivity in early disease duration is presumably lower, and sensitivity may also change depending on olfactory testing technique (although no clear trends can be seen in this data). Specificity compared to normal controls is generally higher at 82-99%, with a median of 90.5%. So, although olfactory testing is not definitive, results compare favorably to diagnostic test standards for other neurologic disorders. Olfactory testing can be therefore considered as a means of supporting a diagnosis of parkinsonism.

b) Olfactory loss in differential diagnosis of PD from other causes of Parkinsonism

Differential diagnosis of PD involves two separate diagnostic decisions. The first is whether the patient has a true parkinsonian disorder (as opposed to a dystonic tremor, essential tremor, etc.). There are few studies directly comparing PD to non-parkinsonian conditions. Shah *et al* found olfaction in essential tremor was indistinguishable from normal controls. Moreover, they found that olfaction could distinguish essential tremor from parkinsonism; using the UPSIT (cutoff=25) they could diagnose PD with 83% sensitivity and 94% specificity[19]. Other direct studies are limited. However, it is presumed that results should be similar to what would be found when comparing to normal controls, assuming that the alternate conditions do not have associated olfactory loss.

The second diagnostic decision is whether PD is the cause of the parkinsonism, as opposed to parkinsonian conditions such as progressive supranuclear palsy (PSP), multiple system atrophy (MSA),

vascular parkinsonism, etc. This task is usually more difficult for experienced clinicians; therefore, it is this area that may have the most clinical potential. Of the major alternate conditions, only MSA (another synucleinopathy) has demonstrated olfactory abnormalities in some patients; in general these are much milder than what is found in PD[3]. Some patients with drug-induced parkinsonism can also have olfactory loss[3, 20] - however, as many cases of drug-induced parkinsonism may in fact be unmasked preclinical PD, the significance of this finding is uncertain. All such studies share the common difficulties noted in the preceding section, including uncertainty of clinical diagnosis, possibility for olfactory loss due to subclinical PD/AD, etc.

Studies that directly test olfaction in differential diagnosis of parkinsonian conditions are relatively few, but are encouraging (see Table 2). Suzuki *et al* found that olfaction could distinguish PD from PSP with 81% sensitivity and 71% specificity[15]. In the same study, MSA could be diagnosed with 81% sensitivity and 73% specificity. Kikuchi *et al* obtained 74% sensitivity and 86% specificity in differentiating PD from MSA[21]. Goldstein *et al* compared patients with PD and MSA and found that the UPSIT could distinguish the conditions with 78% sensitivity and 80% specificity[22]. Wenning *et al* found that the UPSIT could distinguish PD from atypical parkinsonism (PSP, MSA, corticobasal degeneration) with 77% sensitivity and 85% specificity[23]. Katzenschlager *et al* in a smaller study (18 and 14 patients in each group) found that an UPSIT-40 score <22 could identify PD vs. vascular parkinsonism with 89% sensitivity and 86% specificity)[24]. Muller *et al* in prospective study in early disease found that olfactory dysfunction could identify eventual PD diagnosis with 78% sensitivity and 100% specificity[25], compared to patients with MSA and other parkinsonian syndromes. Busse *et al* used Sniffin Sticks to compare PD patients (average disease duration=9 years) to patients with atypical parkinsonian conditions (vascular parkinsonism, parkinsonism in depression, essential tremor), and found a sensitivity of 75% and a specificity of 70[26]. This low specificity was especially related to a high prevalence of olfactory loss (50%) in vascular parkinsonism - since many cases of idiopathic PD could have additional vascular lesions contributing to clinical presentation, it is possible that some of these also had idiopathic PD. In a subgroup assessment of patients with early disease, sensitivity decreased to 54%.

Table 2 - Sensitivity/Specificity of Olfactory Testing Compared to Other Parkinsonian conditions

Citation	n (PD patients)	Test Used	Comparison Condition	Sensitivity	Specificity
Shah, 2008[19]	64	UPSIT	Essential Tremor (59)	83	94
Wenning, 1995[23]	118	UPSIT	MSA (29), PSP (15), CBD (7)	77	85
Muller, 2002[25]	37	Sniffin' Sticks	MSA (8)	78	100
Goldstein, 2008[22]	77	UPSIT	MSA (57)	78	80
Katzenschlager, 2004[24]	18	UPSIT	Vascular Parkinsonism (14)	89	86
Kikuchi, 2011[21]	42	OSIT-J	MSA (42)	74	86
Suzuki, 2011[15]	94	OSIT-J	MSA-P (15) PSP (7)	81 81	73 71
Busse, 2012[26]	385	Sniffin' Sticks	Other Parkinsonism (Mixed - 132)	75	70

Therefore, the sensitivity and specificity of olfaction in diagnosis of PD, although not optimal, are nonetheless reasonably high. Median sensitivity from these studies is 78%, with median specificity of 86%. This implies, that if a patient has parkinsonism of unclear cause, with an estimated 50% pretest probability of PD vs. another disorder, the presence of olfactory loss implies an 86% chance that PD is the underlying cause. Olfactory testing is simple and inexpensive, especially compared to other potential diagnostic tests such as neuroimaging. Therefore, although never definitive, olfactory testing provides a separate, independent (i.e. non-motor) marker that can help diagnose cases that are uncertain. This concept is beginning to have broad acceptance - olfactory testing was recently recommended as a useful diagnostic procedure for PD by a European Federation of Neurological Sciences taskforce[27].

2) Dementia

Olfactory loss is affected in several types of dementia syndromes. The most important of these are Dementia with Lewy Bodies (DLB) and Alzheimer disease.

a) DLB - Dementia with Lewy bodies occurs in up to 20% of pathologic dementia series. Symptoms overlap most closely with AD and with PD dementia (many consider DLB and PD dementia to be subtypes of a similar underlying disease process[28]). Diagnosis during life is based upon presence of hallucinations, fluctuations in attention and alertness, parkinsonism, neuroleptic sensitivity and REM sleep behavior disorder[29, 30]. Diagnostic criteria are relatively specific but are insensitive - therefore, many persons with a clinical diagnosis of AD may in fact have DLB. This should be considered when considering studies of prevalence and severity of olfactory loss in AD.

Olfactory loss in DLB is highly prevalent and likely more severe and consistent than in AD. McShane *et al* assessed severe anosmia (on a test of odor detection) in 92 patients, all of whom eventually had autopsy confirmation of diagnosis[31]. In this analysis, DLB was associated with severe anosmia (41% vs. 6% of controls), but AD was not (16%). Correlation analysis disclosed a strong correlation between cortical Lewy body burden and anosmia. Olichney *et al*, in another pathologically-confirmed study, found that DLB patients had a significantly higher olfactory threshold than AD patients, with 65% of DLB patients demonstrating anosmia compared to 23% of AD patients[32]. Olfactory threshold could identify the presence of Lewy bodies on autopsy with 65% sensitivity and 78% specificity. In a clinical series of patients with mild dementia using Sniffin Sticks, Williams *et al* found that DLB patients had significantly lower olfactory identification, with a trend towards lower olfactory threshold. Severe anosmia could differentiate DLB from AD with 66% sensitivity and 66% specificity (cutoffs at milder olfactory loss improved sensitivity (81%) but reduced specificity 41%)[33]. Chiba *et al* found higher self-reported olfactory loss in DLB patients (41%) compared to AD patients (2%) - note that olfactory deficits are very commonly asymptomatic, and no objective testing was performed[34]. Finally, Sato *et al* also found a reduced olfactory score in 38 clinically-diagnosed DLB patients compared to AD patients[35]; severe hyposmia (defined as a score $\leq$2 on a 12-item battery) could differentiate DLB from AD with 47% sensitivity and 81% specificity.

3) Alzheimer disease

Abundant evidence from over 80 studies demonstrates that olfactory dysfunction analogous to that observed in PD is also common in AD.

However, in contrast to PD, the proportion of AD patients with olfactory loss and the sensitivity and sensitivity of olfaction for identification of AD is less established - there are fewer studies with at least 40 participants that included controls for which sensitivity and specificity can be calculated. Serby *et al* found that 78% of AD patients had UPSIT scores <27, compared to 19% of controls (i.e. specificity 81%); sensitivity increased considerably with disease stage (68% for Stages 3 and 4, 100% for Stages 5 and 6)[36]. Moberg *et al* used the UPSIT, and found that olfactory loss could identify all AD patients, and correctly excluded 40/42 controls[37]. Suzuki *et al* tested a picture based smell identification test in 85 AD patients and 30 controls, finding a sensitivity of 94% with a specificity of 81%[38]. In the same population, the B-SIT obtained a sensitivity of 90%, but a much lower specificity (51%). In the largest and most comprehensive study to date, Tabert *et al* assessed olfactory loss using three different olfactory identification subtests in patients with AD and those with MCI who converted to AD, compared to controls and MCI patients who did not develop AD[39]. The UPSIT at a cutoff of 30 identified AD with 82% sensitivity and 81% specificity. The shorter B-SIT, performed less well than the UPSIT, from which the B-SIT items are derived, but 10 selected items from the UPSIT achieved 83% sensitivity and 89% specificity (note that these were selected post-hoc on the basis of performance in the same sample). Kjelvik *et al* found 97% sensitivity and 79% sensitivity of the B-SIT comparing 39 AD patients and 52 controls at a cutoff <9 (a cutoff <8 produced 79% sensitivity and 92% specificity)[40]. Finally, Westervelt *et al* studied 44 patients with AD compared to 21 controls with the B-SIT[41]. A cutoff of <10/12 could identify AD with 86% sensitivity and 71% specificity (values for other cutoffs were not provided).

Citation	n (AD patients)	Test Used	Sensitivity	Specificity
Serby, 1991[36]	55	UPSIT	78	81
Moberg, 1997[37]	42	UPSIT	100	95
Suzuki, 2004[38]	85	p-SIT B-SIT	94 90	81 51
Tabert, 2005[39]	209	UPSIT BSIT 10-item test	82 66 83	81 79 89

Kjelvik, 2007[40]	39	B-SIT	97	79
Westervelt, 2008[41]	44	B-SIT	86	71

Therefore, although studies are more limited than in PD, sensitivity and specificity of olfaction for identifying dementia (AD and DLB together) is relatively high. Estimates are relatively imprecise, but studies in AD approximate a median of 86% sensitivity and 79% specificity. Presumably, inclusion of DLB patients would improve sensitivity further.

4) Olfaction in Other Neurological diseases

Since they are common neurodegenerative disorders AD, DLB and PD make up the majority of patients with olfactory loss secondary to neurodegenerative disease. However, olfactory loss is note exclusive to these conditions, and several other neurological conditions have been associated with olfactory loss. Among movement disorders, these include Fragile X ataxia syndrome[42], the Parkinson-Dementia complex of Guam[3], Lubag[43], and Huntington's disease[43]. Also, as noted above, multiple system atrophy has been associated with mild olfactory loss, again less than seen in PD or AD[43]. Amyotrophic lateral sclerosis has been associated with mild hyposmia, substantially less severe than seen in PD or AD[3]. Finally, olfactory loss has also been linked with non-neurodegenerative disease, in particular myasthenia gravis - this may reflect the crucial relationship between cholinergic function and olfactory processing[44].

5) “Pre-clinical Prediction”?

If olfactory abnormalities are present in the majority of patients at diagnosis, then it is logical to presume that the abnormalities may have been manifest before diagnosis. Of all the potential benefits associated with olfactory research, the ability of olfaction to identify neurodegeneration at its earliest prodromal stages may have the greatest potential to benefit human health. One crucial barrier to the development of neuroprotective therapy is the fact that neurodegenerative processes are well-entrenched by the time a patient crosses the threshold into clinical disease[45]. A neuroprotective intervention with modest effect in established disease might be able to even prevent clinical disease if provided in early preclinical stages. If olfaction can identify early disease, it may be a way of steering patients

Olfaction as a Predictor of Parkinson's disease

Studies that directly test olfactory dysfunction in prodromal disease are few, mainly because they require large prospective studies. For relatively uncommon diseases like PD, massive population-based studies are needed to demonstrate even the most basic measure of predictive ability (i.e. to see if controls are different from prodromal disease). Based on known disease prevalence, in order to assess 20 PD patients at prodromal stages, 10,000 persons over 65 must be followed for at least 5 years. The most clinically relevant issues of sensitivity, specificity, and the amount of lead-time that can be gained require even larger and longer studies. Therefore direct evidence of predictive ability is relatively limited.

Despite the barriers to population-level research, there are some studies that have been performed in the general population. Perhaps the strongest evidence for olfaction as a predictor of PD comes from the Honolulu Asia Aging study, in which the B-SIT was assessed in large population, who was then followed with autopsy. Patients with olfactory loss had a 5.2-fold increased risk of developing PD[46]. Of note, over 25% of the population had olfactory loss at baseline, suggesting that olfaction is a non-specific predictor. Moreover, the predictive value of olfaction was lost when the interval between assessment and disease was greater than 4 years, suggesting that lead-time may be limited. In the PRIPS study, a prospective population-based follow-up of 1850 subjects, impaired olfaction was associated with a 3.94 odds ratio of developing PD[47]. However, positive predictive value was also low, suggesting olfactory loss by itself may not be a sufficiently powerful marker to warrant targeted neuroprotective therapy.

Another way to assess the potential of olfaction as a PD predictor is to look at incidental Lewy Body Disease (iLBD). This refers to patients who have no clinical signs of PD, but have deposition of Lewy bodies on autopsy. It is assumed that many of these persons would have developed PD (or DLB) if they had lived long enough (note that this assumption is by no means established - some suggest that for some patients, incidental Lewy bodies can be a sign of a successful battle against neurodegenerative synucleinopathy[48]). Regardless, many studies document olfactory dysfunction in iLBD. In the Honolulu Asia-Aging study, those in the worst tertile of olfaction had an 11-fold adjusted odds of having Lewy bodies on autopsy[49]. Among patients with iLBD in the Mayo Clinic cohort, a subset of 4 patients had olfactory testing before death - these had with lower UPSIT scores than those without iLBD[50]. From the Rush Aging Project, 26 patients with iLBD were compared to 175 without - there were strong differences

in olfactory function during life, particularly when limbic and neocortical areas were involved by Lewy pathology[51]. Note that most studies generally do not find motor abnormalities in iLBD; this suggests that olfactory loss can precede motor dysfunction.

Another approach to assessing olfaction as a predictor is to choose persons at high risk of disease. Prospective analysis of these samples allows direct assessment of predictive ability, with a more manageable sample size. Studies of this nature include:

a) Patients with single gene mutations for PD - Patients carrying mutations of LRRK-2 are at high risk of developing PD (30% penetrance by age 80), and PD patients carrying LRRK-2 mutations have olfactory loss (although perhaps less than those with idiopathic PD). One study assessed asymptomatic carriers of LRRK-2, and they did not have olfactory loss[52], suggesting that olfactory dysfunction may not be present very early in the disease course.

b) Family members of PD patients - Ponsen *et al* studied 400 first-degree relatives of PD patients to select a high risk group. Those with impaired olfaction had more evidence of dopaminergic denervation on ß-CIT SPECT[18]. Two years later, 4/40 of hyposmics developed PD, compared to 0/360 of normosmics[19], providing direct evidence that olfaction can predict PD. However, on 5-year follow-up, only one more hyposmic patient developed PD - this may again suggest that lead time may be limited (that is, olfactory dysfunction develops only soon before motor dysfunction[53]). The PARS study is a 5,000 patient study which has selected patients with family history of PD (although it has since expanded to include the general population) - in this study, approximately 15% demonstrated olfactory loss[54]. Olfaction was highly correlated with other potential markers of prodromal PD, including constipation, anxiety, depression and dream-enactment behavior (i.e probable REM sleep behavior disorder) and mild motor symptoms. Prospective follow-up of this cohort has not yet been reported[54].

c) Patients with other prodromal conditions - Another group of high-risk patients with considerable potential is those with REM sleep behavior disorder (RBD). Idiopathic RBD is a very strong marker of prodromal PD and DLB - over 50% of patients in sleep disorder clinics develop defined disease over 10 years[55]. Patients with RBD have a very high prevalence of olfactory dysfunction, with approximately 50% of patients testing in the hyposmic range[56-59]. Moreover, in a four-year prospective study, RBD patients who also had olfactory loss had a 65% chance of developing defined neurodegenerative disease, compared to only 14% of those with normal olfaction[60]. In this case,

olfactory abnormalities were present at least four years before disease onset, and were only slowly progressive in prodromal periods, suggesting that in this subgroup, olfactory loss may have a longer lead time than in the general population.

Olfaction as a Predictor of Dementia

Despite the strong evidence of the association with Alzheimer's disease and olfaction, studies directly assessing predictive ability of olfaction for dementia are relatively limited.

The Epidemiology of Hearing Loss study was a prospective 5-year population-based study which assessed an 8-item olfactory test at baseline, then correlated it with eventual risk of developing dementia five years later. This study was limited by unclear diagnosis of dementia (including all with dementia, not necessarily Alzheimer disease and DLB) defined only by MMSE <24 or proxy report[61]. Regardless, those with olfactory impairment had an odds ratio of 6.6 (adjusted OR=3.7) for dementia - positive predictive value was 16%, sensitivity and specificity were 55% and 84% (note that positive predictive value depends upon follow-up duration - one would predict an increase over time as more patients develop dementia). Jungwirth *et al* studied 488 elderly participants from the general population in a prospective study over a 3-year interval. The Pocket Smell Identification Test, a test of odor identification based on 3 UPSIT items, was significantly different in those who eventually developed AD (n=90) compared to those remaining dementia-free (1.56 items correct vs. 1.88, p=0.002), although differences were not significant after adjustment for other demographic/cognitive variables at baseline. Other prospective studies have found associations between olfaction and milder cognitive changes (not necessarily to the level of dementia). Graves *et al* found that impaired olfaction on the B-SIT was associated with a 1.2 to 1.9-fold odds ratio for significant cognitive decline on quantitative testing[62]. Wilson *et al* found that baseline olfactory dysfunction was associated with a subsequent decline in episodic memory and perceptual speed over a 3-year prospective follow-up period[63]. Subsequent follow-up disclosed that those with olfactory loss (25th percentile) were at 50% increased risk of developing defined mild cognitive impairment[64] compared to those in the 75th percentile of olfactory function. Another 359-patient 4.5 year prospective follow-up study by Swan *et al* demonstrated that impaired olfaction was associated with development of verbal memory impairment[65] over time. In a community sample of 303 persons, impaired olfactory discrimination was modestly associated with decline in the Cambridge Cognitive Evaluation score 3 years later[66]. Finally, the Honolulu Asia-Aging study reported an abstract in 2009 suggesting that patients in the lowest quartile of

olfactory function had a 5.7-fold increased risk of developing AD compared to those in the highest quartile[67].

There have been some prospective studies that directly assessed olfaction in high-risk groups. Devanand *et al*, in a follow-up to Tabert 2005[39] studied 147 patients with mild cognitive impairment in a 3-year prospective study. 26% developed AD, and 74% remained dementia-free[68]. UPSIT scores at baseline were lower in those who ultimately developed dementia ($p<0.001$). Positive predictive value was 73% (negative predictive value=83%), albeit with only 48% sensitivity.

Conclusion

Although much remains undefined, there is suggestive evidence that olfactory loss can be a predictor of AD and PD. In an age when neuroprotective therapy against neurodegenerative disease becomes available, it will be critical to detect disease as early as possible. This implies screening of the general population. For practical reasons, two-stage testing may be required - the first stage could involve a simple, inexpensive, but sensitive test. If positive, this could be followed up with more specific modalities (neuroimaging, CSF evaluation, etc). Given the simplicity of olfactory testing, olfaction is arguably the most promising modality for general-population first-stage identification of prodromal neurodegeneration.

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