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The Predictive Role of Hyposmia in Alzheimer's Disease

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1. Introduction

Loss of olfactory function starts at 60 years and become significantly worse after 70. In many cases olfactory disorders may be a consequence of a disease. Different types of olfactory deficit may be revealed by smell evaluation. *Anosmia* is defined as inability to perceive all odors (total) or some odors (partial). *Hyposmia* or *microsmia* is a decreased sensitivity to odors. *Dysosmia* is a distorted smell percpeption. *Olfactory agnosia* is defined as failure to identify odors in presence of normal detection and discrimination. Olfactory allucinations are named *phantosmias*.

Many common diseases may compromise the sense of smell, permanently or temporaneally. The range of diseases causing olfactory disorders varies from the common cold to neurodegenerative diseases. Most common causes of olfactory loss are local nasal diseases (allergic rhinitis, nasal polyposis, sinus disease), head trauma, viral and bacterial infections of upper airways. Some neurodegenerative diseases like Alzheimer's disease (AD) and various forms of Parkinson's disease (PD) are accompanied, even from their earliest stages, by olfactory disorders.

Dementia is defined by the American Academy of Neurology as a progressive and permanent decline in cognitive function and affects nearly 15% of people who live up to 65 years and 35% of those who reach the age of 85. The Alzheimer's Disease International (ADI) in Alzheimer World Report published in 2010 provides that an aging population with dementia - the most common form is AD which is currently estimated to affect 35,6 million of people - will nearly double in 20 years to reach 66 million in 2030 with a higher concentration in poor countries leading to enormous social costs.

The research on AD is now oriented to an early diagnosis which is essential before the development of the irreversible and typical changes due to AD. In AD patients, a reduced capacity for olfactory detection, discrimination and identification is usually found and confirmed by several studies (Mesholam et al., 1998; Hawkes, 2003; Kovacs, 2004; Albers et al., 2006; Westervelt et al., 2007).

In this chapter we present a review on the predictive role of hyposmia in the early diagnosis of AD patients.

2. Central mechanisms of smell

Humans can detect more then 10.000 different odorants (Ressler KJ et al, 1994).

Odorants may be perceived through sniffing (ortonasal olfaction) and through the mouth (retronasal olfaction) (Heillmann S & Hummel T, 2004). The anatomical area covered by olfactory neuroepithelium is estimated between 100-400 mm^2 (Moran DT et al, 1982).

The human olfactory neuroepithelium is localized in the superior turbinate, in the dorsal areas of the nasal vault and in the superior part of the nasal septum. Olfactory mucosa is composed of olfactory sensory neurons (OSNs), supporting cells, basal cells and Bowman's glands.

The OSNs are bipolar cells with a dendrite that ends in a knob with 10-25 projecting cilia.

These cilia are covered by a layer of mucus which extends over the neuroepithelium and represent the site of sensory transduction. The cilia contain G-protein-linked receptors that bind to the odour molecules (Jones D & Reed RR, 1989): the expression of these receptors is still unclear.

These receptors are proteins encoded by a family of 1,000 genes in the mammals (Buck L & Axel R, 1991) while in the humans 60% of OR genes appear to be pseudogenes (Sosinsky A et al, 2000). The G-protein activates an adenylyl cyclase that converts ATP into the second messenger cyclic adenosine 3' monophosphate (cAMP) which is the major messenger for olfactory signaling.

The cAMP opens a cyclic nucleotide-gated (CNG) channel. Cations (Na+ and Ca2+) entering through the CNG channels cause a membrane depolarization and generate an action potential which is propagated along the olfactory axon. The olfactory axon crosses the lamina propria and became an unmyelinated axon that penetrates the foramina of the cribriform plate and synapses in the glomerulus of the olfactory bulb where signals are integrated. In the glomeruli, the axons of the olfactory sensory neurons form synapses with the dendrites of the mitral and the tufted cells (second-order of neurons). The axons originated in the mitral and tufted cells leave the olfactory bulb and project to the olfactory tract, to the anterior olfactory nucleus, to the piriform lobe (prepiriform cortex, periamygdaloid cortex and entorhinal cortex) and to the limbic system (amygdala and hippocampus).

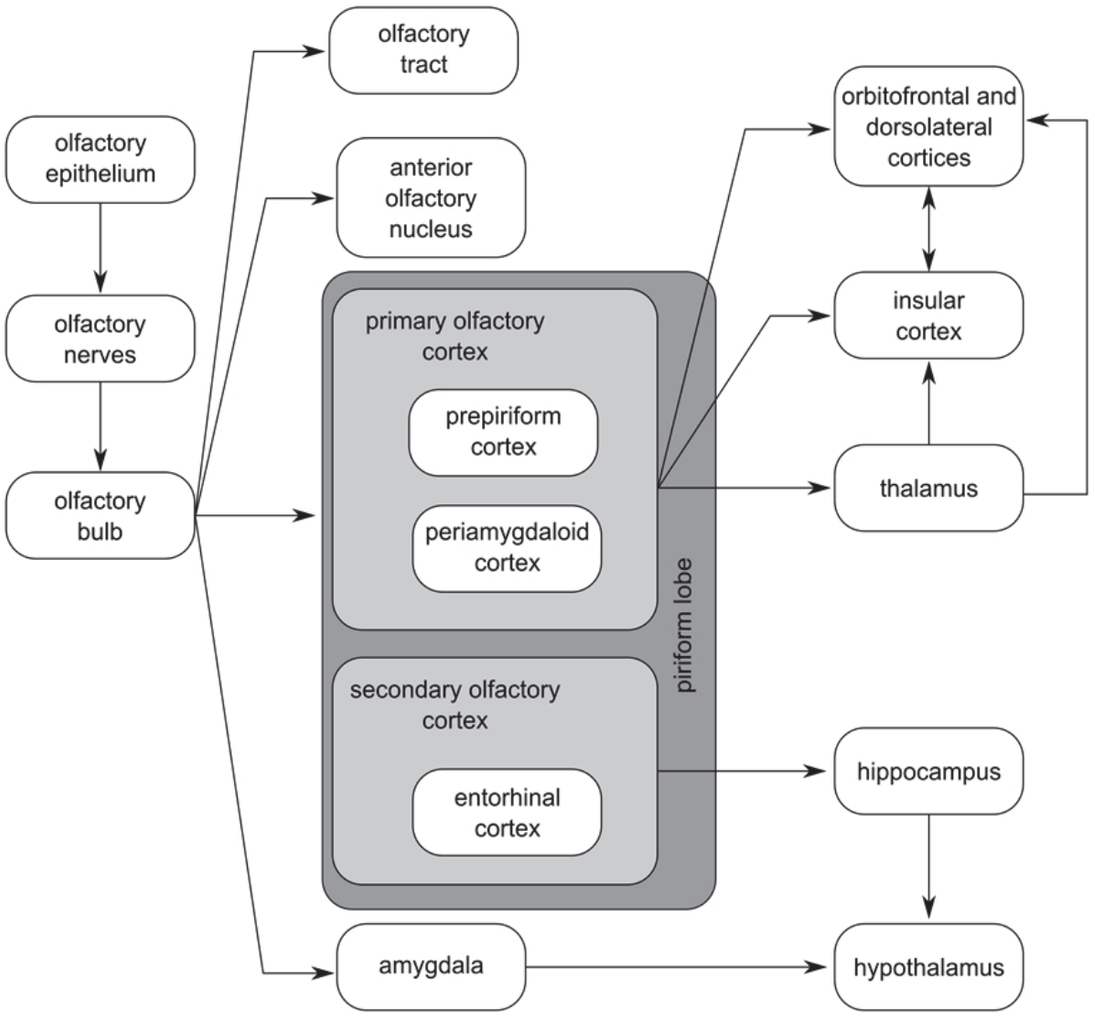
The prepiriform cortex and the periamygdaloid cortex represent the primary olfactory cortex while the entorhinal cortex, which represents the secondary olfactory cortex, receives olfactory fibres from the primary olfactory cortex (Graph 1).

When medication molecules come in contact with this specialized olfactory mucosa they are rapidly transported directly into the brain and achieved cerebrospinal fluid levels (faster than if the drug is given intravenously).

This concept of molecules transfer from the nose to the brain is referred to the so called nose-brain pathway and has implications when centrally acting medications such as sedatives, anti-seizure drugs and opiates are delivered nasally (Hussain AA, 1989; Dale O et al., 2002; Westin et al, 2006).

In this way the absorptive surface is not the intestinal mucosa so the drug is not subjected to hepatic metabolism and lead to early effects. Recently, Dale O (Dale O, 2010) indicated Intranasal fentanyl spray (INFS) as an effective treatment of breakthrough cancer pain; this formulation has been investigated as a new and convenient route of administration that may offer a rapid onset and short duration of analgesic effect.

Many studies based on the functional imaging in humans, point to the role of the piriform cortex in odor classification and differentiation (Li et al. 2006; Howard et al. 2009).



Graph 1. Central olfactory pathways of the olfactory system

The role of temporal lobe structures in olfactory memory was investigated (Dade LA et al., 2002) by the convergent approach of examination of odour learning and memory in patients who had undergone resection from a temporal lobe (including olfactory regions) for the treatment of intractable epilepsy, as well as studying these aspects in the healthy brain, through the use of the PET.

Some studies have also examined olfactory memory in patients with epilepsy before and after surgical intervention in different brain regions, and only subjects with resection within temporal lobe and orbitofrontal regions have shown impairments (West SE& Doty RL, 1995).

The piriform lobe may have an active role not only in odour perception but also in odour memory processing without hemispheric superiority among patients with resection from the left or right temporal lobe regions (Dade LA et al. 2002).

2.1 Diagnostic approaches for detecting olfactory disorders

An accurate evaluation starts with an history to establish the type of olfactory disorder (hyposmia, anosmia), the onset (rapid, slow) and progression, the presence of concomitant

nasal diseases, previous trauma and neurological symptoms, occupational exposure, medications, alcohol and tobacco consumption. A nasal examination is necessary to exclude signs of nasal diseases.

Sophisticated investigations like computed olfactometry and electrophysiological tests are available. Computed olfactometry provides the precision of the stimulus presentation and data collection but it is expensive and it requires a long time for administration. That is why it is restricted to specialized centers. The electrophysiological tests such as the odor event-related potentials evaluate the integrated electrical activity at the surface of the scalp but require a complex stimulus presentation and recording equipment.

For this reason in the last 20 years many practical and reliable psychophysical tests of olfactory function have been developed and largely diffused (Table 1).

Olfactory tests	Olfactory function tested
University of Pennsylvania Smell Identification Test (UPSIT)	Identification
Sniffin' Sticks (SS)	Identification, discrimination, threshold
Cross-Cultural Smell Identification Test (CC-SIT)	Identification
Quick Smell Identification Test (Q-SIT)	Identification
Odorant confusion matrix	Identification
Biolfa olfactory test	Identification
Brief Smell Identification Test (B-SIT)	Identification
Smell diskettes test	Identification
Smell Threshold Test (STT)	Threshold
T&T Olfactometer	Threshold
Olfactory Perception Threshold Test (OPTT)	Threshold
Sniff Magnitude test	Psycolfaction
12-item Odour Memory Test	Odorant Memory, discrimination

Table 1. Olfactory tests and respective olfactory function tested

Most of modern olfactory tests are brief and easy to use. Unilateral test with occlusion of the nostril controlateral to the tested side is preferred to evidence a monolateral anosmia which can be undervalued with a bilateral test.

In regard to cross-cultural differences in olfactory assessment, several olfactory tests have been proposed over the years to study smell function and its quantifiable parameters such as threshold, identification, discrimination and memory.

The *odor threshold* test measures the lowest concentration of a stimulus that can be discerned. Modern olfactory tests evaluate the detection threshold which is the lowest odorant concentration where such a presence is detected but not recognized (Stevens JC et al., 1988; Kobal G et al., 2000).

The *odor discrimination* test evaluates the ability to differentiate between odorants and requires the subject to decide whether two stimuli are similar or different (Kobal G et al., 2000)without requiring the identification.

The *odor identification* test evaluates the subject's ability to identify an odorant at the supra-threshold level. The multiple-choice identification test is the most sensitive and specific procedure to assess identification. In this type of test the subject identifies the stimulus from a list of odor names (Doty RL et al., 1984; Cain WS et al., 1988; Simmen G et al., 1999; Kobal G et al., 2000).
To evaluate *odor memory*, the subject is required to smell an inspection odorant and to select the same odorant from a set of alternatives choices after a delay period of 10, 30 or 60 seconds (Campbell IM et al., 1972).
Several threshold tests are available like the Smell Threshold Test (Doty RL, 2000), the odor threshold test of Sniffin' Sticks (Hummel T et al, 1997) and the T&T olfactometer (Toyota B et al. 1978).
In most cases a marked variability in threshold values depends on the techniques of stimulus presentation, interstimulus time, method of stimulus dilution, number of trials presented, confusion of the subject between detection and recognition of the stimulus.
Currently the most widely identification tests used are screening tests, as the Brief Smell Identification test (Doty et al., 1995) (B-SIT) and the Sniffin 'Sticks Screening Test (Kobal G et al.,1996;Hummel et al., 2001) (SSST) (Burghart GmbH, Wedel, Germany) and complete tests as the University of Pennsylvania Smell Identification Test (Doty et al., 1984) (UPSIT) (Sensonics, Inc., Haddon Heights, New Jersey, USA) and the Sniffin 'Sticks Extended Test (Hummel et al., 1997) (SSET). Therefore it is recommended a full assessment of respiratory function with naso-pharyngeal nasal endoscopy and rhinomanometry. After examination, further diagnostic investigations such as citology, CT or MRI of the nose and paranasal sinuses, may be prescribed to verify an insufficient ventilation in the presence of nasal or sinus diseases which make the olfactory test less reliable by substantially reducing its specificity and sensitivity.

2.1.1 Sniffin' Sticks

The SSST is a test of olfactory identification by the administration of 12 odors presented in felt-tip pens (sticks) (Hummel et al., 2001). Few hours prior to the test food intake is limited only to water. The subject is asked to identify among 4 written names of different odours the one smelled on a specific single odour stick. Based on the final score, adjusted per age and sex, subjects are classified in three categories: normosmic (>12) hyposmic (< 10) and anosmic (< 6). As opposed to neuropsychological tests the smell test is not influenced by the level of schooling. Our experience in administering the SSS test also showed that almost all of the test odors are familiar to Italian subjects except for cloves. In fact 23 of 102 normal subjects tested by us with the SSS test didn't know the cloves but they correctly identified it with the aid of the four possible answers.
The SSET provides for the assessment of olfactory identification, discrimination and threshold (Kobal et al., 2000).
The olfactory identification is evaluated with 16 odors which are presented to the patient using a 4-alternative forced-choice task with presentation of a list of 4 descriptors for each pen (normal value: ≥12 correct identifications).
The olfactory threshold is achieved by presenting the patient 16 triplets of sticks: only one of three sticks contains a smell, not the other two and the patient must recognize that stick smells unlike the other 2. The 16 odors presented to the patients for the threshold, are 16 dilutions of n-butanol. Odor threshold was represented by the mean of the last 4 out of 7 staircase reversals (normal values: >6 for men, >6.5 for women).

For the assessment of olfactory discrimination 16 triplets of odors are presented to the patient. In each triplet two sticks have the same smell and a stick has a different smell: the patient must recognize the stick with different smell (normal value: ≥11 correct discriminations). The execution time of SSET varies from 25 to 45 minutes.
The sum of the three scores in the evaluation of threshold, discrimination and identification gives us the total score (TDI score) and classifies the subject as normosmic (> 30.5), hyposmic (≤ 30.5) or anosmic (≤ 15.5)(Hummel et al., 2007).
The SS test is largely used to evaluate olfactory dysfunction in neurodegenerative disorders like Parkinson's disease (Daum RF 2000), Alzheimer and MCI (Peters JM et al., 2003).

2.1.2 UPSIT

The UPSIT is a scratch and sniff test used in North America since 1984 (Doty et al., 1984). The UPSIT is a multiple-forced-choice odor identification test available in 11 languages. For each odorant there are four alternative responses and the subject is required to choose one of these even if no smell is perceived. It requires 10 to 15 minutes to be administered. This test consists of 40 odorants at the supra-threshold level embedded in microencapsulated crystals in four booklets, each containing 10 odorants. Every odorant is located on brown strip that is "scratched" with a pencil. The UPSIT detects most olfactory disorders (anosmia, severe microsmia, moderate microsmia, mild microsmia) and also identifies malingerers on the basis of improbable responses. Malingerers avoid the correct response more often than expected on the basis of the chance (zero score detects a malingerer). The test-retest reliability is high (r=0.92) (Doty RL et al., 1989). Normative data for the UPSIT include a score on a scale of 0-40 to evaluate olfactory dysfunction and percentile ranks for men and women across the entire age span.
Some odorants of the UPSIT as root beer, skunk, fruit punch and pumpkin pie may be unfamiliar to patients outside of the USA. Although the UPSIT is a self-administered test, we underline the great importance of a ENT evaluation before each test administration because many pathologies involving nose and paranasal sinuses can interfere with the mechanical transport of the odorants to the olfactory areas with the consequent test failure. The 40-item UPSIT has been used to test olfactory dysfunctions in many neurodegenerative disorders like AD (Doty RL et al., 1987; Hawkes C. 2003), MCI (Devanand DP et al., 2000, Wang QS et al., 2002), Parkinsonism (Hawkes C. 2003), multiple sclerosis (Doty RL et al., 1999).

2.2 General diseases causing olfactory disorders

Few studies have investigated the real prevalence of olfactory disorders in the population (Deems DA et al., 1991). According to a recent study the prevalence of measured olfactory impairment is 24.5% overall, but among elderly people it can be high as 70% (Murphy C et al., 2002). Disorders of the sense of smell are caused by conditions that interfere with the access of the odorant to the olfactory neuroephytelium (transport loss), injure the receptor region (sensory loss), or damage the central olfactory pathways (neural loss). Smell disorders may be typically intermittent or permanent. When the smell disorder is intermittent there are usually some conditions that interfere with the access of the odorant to the olfactory neuroephytelium and in these cases we suppose a transport loss. Most frequent causes of transport loss are nasal diseases and polyposis. The onset of hyposmia is more gradual and intermittent, the recovery is possible with an adequate medical or surgical treatment. Conversely, a permanent olfactory dysfunction may be secondary to an injure of

the receptor region when there is a sensory loss (like in prior upper respiratory infections and toxic exposure) or secondary to a damage of the central olfactory pathways in case of neural loss (like in head trauma). A temporary hyposmia often occurs with a prior upper respiratory infection but in a small percentage of cases olfaction never returns. Temporary or permanent hyposmia due to toxic exposure can occur through modification of neurotransmitter levels or anatomical damage to the olfactory receptor. Even a minor head trauma can produce a total anosmia and recovery occurs in fewer than 10 %, most occurring several months. Olfactory impairment is a common occurrence in aging and may be an early signal of neurodegenerative disease. Olfactory loss caused by aging and diseases effects both quality of life and personal safety. Aging as well as prior upper respiratory infections, head trauma (approximately 5-10% of adult patients with head trauma report olfactory loss to be in anosmic range) and nasal and/or sinus diseases lead to smell dysfunction but frequently the cause of the olfactory loss remains unknown (idiopathic smell dysfunction). Disorders of olfactory function have been also associated with the exposure to toxic chemicals, tobacco smoking, endocrine disorders (hypothyroidism, diabetes, Kallmann's syndrome, Cushing syndrome) and neurodegenerative diseases (Table 2). Among these, Alzheimer's disease (AD) is one of the earliest to be reported and studied in detail.

Nasal/sinus diseases
Head trauma
Prior upper respiratory infections (viral, bacterial)
Idiopathic
Toxic exposure (drugs, airbone compounds like metals, dusts, ecc.)
Neurodegenerative diseases
Congenital
Endocrine disorders (hypothyroidism, diabetes, Kallmann's syndrome, Cushing syndrome)
Tumors (olfactory groove meningioma, temporal lobe glioma, nasopharyngeal carcinoma)

Table 2. Main disorders associated with smell dysfunction

2.3 Clinical and pathological features of hyposmia in different CNS diseases

Hyposmia is one of the markers of a future cognitive decline but it is not specific for AD because it can also precede other neurological diseases, like PD and multiple sclerosis (Table 3).

Although genetic predisposition in undoubtedly relevant in AD (older people with Down syndrome inevitably developed AD) environmental agents cannot be ignored (Table 4).

Particular attention should be paid to recent theories suggesting the olfactory neuroepithelium as a major point of invasion by external pathogens such as viruses, ionized metals (cadmium, gold, manganese) and nanoparticles to the central nervous system (Charles et al., 1995; Itzhaki et al., 2004; Doty, 2008).

Alzheimer's disease	Mild Cognitive Impairment
Idiopathic Parkinson's disease	Guam Parkinson's disease-dementia complex
Dementia with Lewy bodies	Down syndrome
Amyotrophic lateral sclerosis	Huntington's disease
Multiple sclerosis	Motor neuron disease
Pallidopontonigral degeneration	Korsakoff's psychosis
Multiple system atrophy (type-P)	Friedreich's ataxia

Table 3. Neurodegenerative diseases associated with olfactory dysfunction

Viruses
Toxic metals (cadmium, iron, manganese)
Air pollutants
Herbicides (rotenone)
Defoliants

Table 4. Possible environmental agents implicated in the "olfactory vector hypothesis"

The "olfactory vector hypothesis" suggests that certain viruses could be transported directly from the olfactory epithelium to the olfactory bulb and the central regions of the limbic system, without intermediate synapses, not causing damage to the epithelium, but only using this route to reach the brain (Youngentoub et al., 2001).
The "olfactory vector hypothesis" may explain how some neurodegenerative diseases like AD and PD may be caused by external patogenes that damage the olfactory system and enter the brain through the nose possibly in accordance with genetically determined substrates (Youngentoub et al., 2001).
Different brain cells may be infected by viruses in the presence or absence of certain specific receptors to which the virus would bind. However the entry of a pathogen through the nose seems more feasible as a cause of PD than AD.

2.3.1 Alzheimer's disease

In the preclinical phase which can precede over decades the disease, the presence of typical lesions of AD as amyloid plaques and neurofibrillary tangles have been demonstrated, even at the level of brain areas involved in olfactory function. Until few years ago it was thought that the beta-amyloid, the first 42 aminoacids of the amyloid precursor protein (APP), was just an inactive storage without biological activity. Recent researches have shown that the Aβ-42 provides cellular cascades and it's an initiator of the degeneration of neurons. The hyperphosphorylation of tau protein from which neurofibrillary tangles originate would be determined by the action of Aβ42. Autoptic studies conducted in the olfactory neuroepithelium in the past proposed the hypotesis that the diagnosis of AD would be confirmed by the finding of typical lesions at this periferic level (Lovell et al., 1982; Talamo et al., 1989; Arnold et al., 2010). However, following studies showed that these changes were not specific for AD because they where similar to those found in other neurodegenerative

diseases and in control elderly subjects (Trojanowski et al., 1991; Kishikawa et al., 1994; Smutzer et al., 2003). The presence of amyloid plaques and neurofibrillary tangles has been widely described in all layers of the olfactory bulb and in the central olfactory pathway of patients with AD (Kovacs et al., 2001) with a significant association between the peripheral olfactory and cortical degenerative changes (Christen-Zaech S et al., 2003). However it is not yet determined whether the olfactory involvement first appears at peripheral levels, in the olfactory bulb or in the temporal cortex.

There is a strict relationship between the loss of cells in the anterior olfactory nucleus, the development of anosmia, the extent of neurofibrillary degeneration and the severity of AD. It has long been known that the typical lesions of AD are early and selectively localized in rhinencephalon. This is not surprising when one considers that the rhinencephalon plays a key role in all processes of memory and that the first symptom in AD, the most important and included in all diagnostic systems as deemed necessary, is the early deficit of memory.

Some authors point out in many patients with AD the presence of early anosmia with slowly progressive deterioration of cognitive disorder. According to some authors, the olfactory deficit in AD could be based on a genetic predisposition. The allele ε4 of apolipoprotein E gene is a known genetic marker of hereditary AD with a low prevalence and it is the subject of ongoing researches. Schiffman (Schiffman SS et al, 2002) found that at-risk relatives of AD patients had higher detection thresholds and decreased odor memory than control subjects with an ApoE-4 status not associated with at-risk status. Conversely Graves (Graves et al., 1999) showed an increased risk of cognitive decline in patients with olfactory deficit and allele ε4, greater in males but with a trend also evident in females.

The transentorhinal area is early impaired in AD and it would be the point of passage of the sensory cortical afferents to the hippocampus, followed by the involvement of the anterior parahippocampal cortex or the entorhinal area (Braak&Braak, 1998).

In general terms, therefore, the entorhinal cortex receives a constant flow of informations from cognitive and sensory associative areas, that move towards the hippocampus to recover in a consolidated form. These informations are transmitted to the associative areas where they are encoded in the form of memory traces.

In contrast with the hypothesis of early involvement of the transentorhinal area, Kovacs (Kovacs, 2001) argues that neurofibrillary tangles are present in the anterior olfactory nucleus prior to the first changes observed in the entorhinal cortex.

The primary olfactory cortex would also be less severely affected than medial orbitofrontal cortex (associative area) and there would be a correlation between the pathology of the olfactory bulb and some areas not involved in olfactory processes.

2.3.2 Parkinson's disease

PD is a progressive neurodegenerative disease characterized by a loss of dopaminergic neurons in the substantia nigra. In the majority of cases it's clinically diagnosed as idiopathic Parkinson's disease (IPD). In the IPD the impairment of smell has been well documented in the early stages with the use of psychophysical tests (Doty et al., 1992; Daum et al., 2000, Muller et al., 2002; Ponsen MM et al., 2004; Haehner et al., 2007) and olfactory evoked response (Barz et al., 1997).

Olfactory dysfunction is a non-motor symptom of PD which includes deficits in odor detection, discrimination and identification without any relationship with the duration or severity of parkinsonism and with the nigrostriatal dopamine depletion.

As confirmed by autoptical studies (Beach TG et al., 2009) the presence of α-synucleinopathy in the olfactory bulb predicts, with greater than 90% sensitivity and specificity, the existence of neuropathologically confirmed PD.
Recent findings support the association between anosmia and autonomic failure, like orthostatic hypotension, in sporadic PD so they might provide biomarkers of the pathogenetic process. (Kaufmann H et al., 2004; Goldstein D et al., 2010).
Once IPD has become clinically manifest, olfaction appears to be already severely compromised, which is in line with the absence of longitudinal changes of olfactory function during IPD progression (Herting et al. 2008).
In a recent study (Wattendorf E et al., 2009) gray matter atrophy was investigated using morphometric analysis of magnetic resonance images voxel-based morphometry (VBM) and it was related to psychophysically measured scores of olfactory function in early PD patients, moderately advanced PD patients and age-matched healthy controls. Cortical atrophy in olfactory-related brain regions (mainly in the right piriform cortex in early PD patients and in the right amygdala in moderately advanced PD patients) was shown in PD patients, but not in controls, and it was specifically correlated with the olfactory dysfunction.
A selective hyposmia in PD patients correlated with hippocampal dopamine innervation as shown by DAT (dopamin transporter) PET binding was also demonstrated (Bohnen NI et al., 2008). These findings support the hypothesis of selective deficits in odor identification correlating with dopaminergic activity in the hippocampus, an area related to cognitive and memory processing.
Dopamine replacement therapy, does not improve olfaction in PD, suggesting that hyposmia cannot be explained by dopamine deficiency alone (Doty RL et al.,1992).

2.3.3 Multiple sclerosis

Multiple sclerosis (MS) is a demyelinating disease of the central nervous system. In MS (Doty et al., 1999) the olfactory abilities decline progressively over the course of the disorder. The presence of olfactory dysfunction in MS is confirmed by studies with UPSIT and olfactory evoked potentials (Hawkes CH et al., 1997) and with Sniffin' Sticks (Fleiner F et al., 2010). An important role could be entrusted to the association of olfactometric and neuropsychological measurements with imaging.

2.3.4 Epilepsy

The presence of olfactory deficits is also well known in epilepsy. Chen (Chen C et al.2003) in a study on patients who underwent temporal lobectomy for medically intractable temporal lobe epilepsy (TLE) found olfactory auras in 12 (5.5%) patients. The conclusion of this study is that the mesial temporal sclerosis is the most common aetiology rather than tumors and that the mesial temporal structures, especially the amygdala, may play an important role in the genesis of olfactory auras.

2.4 The role of olfactory test in Alzheimer's disease

The olfactory identification tests are considered more sensitive and specific in distinguishing patients with AD from control subjects. Although it is not possible to determine how early the olfactory deficit appears in the course of AD, it is well established that its presence is an early and consistent element before the clinical diagnosis (Devanand et al., 2000; Royall et

al., 2002; Swan et al., 2002; Wilson et al., 2009). Some studies highlighted the increase in olfactory threshold in AD subjects rather than in the control group (Nordin et al., 1997) while other studies showed that the olfactory identification is compromised earlier than the perception.

Anosmia, alongside at least one allele of Apo-E 4 may be associated with a risk five times higher to develop a subsequent cognitive decline (Graves et al., 1999). Wilson et al. (Wilson et al., 2007a) in a recent study showed a deficit of olfactory identification inversely related to AD (in particular with NFT in the entorhinal cortex and hippocampus) in elderly patients. The autopsy outcomes suggested that in elderly the olfactory identification deficit is partly due to the accumulation of NFT in the primary olfactory cortex.

Hyposmia can predict the next start of mild cognitive impairment (MCI) in patients with a not yet measurable cognitive impairment (Wilson et al., 2007b) and an increased risk of AD was demonstrated in MCI patients with hyposmia associated with unawareness of the olfactory deficit (Devanand et al., 2000). Conversely Bahar-Fucks et al. suggest that unawareness of olfactory deficit does not improve the identification of patients with MCI progressing to AD (Bahar-Fuchs et al., 2011).

Hyposmia incurs with a latency of less than 10 years since the beginning of clinical manifestations of the disease in patients with AD and autosomal dominant mutation of the presenilin-1(Nee et al., 2001). Another explanation could be that the olfactory deficit is predictive only of sporadic forms of AD.

In a recent study (Luzzi et al., 2007) the smell was measured in patients with mild semantic dementia, with frontotemporal dementia, with corticobasal degeneration and with mild AD. As expected, patients with AD showed lower scores in the discrimination, denomination and visual recognition. Patients with semantic dementia showed a normal discrimination but a marked reduction in denomination and olfactory agnosia. In patients with frontotemporal dementia and corticobasal degeneration there was a slight deficit of naming and discrimination.

Compared to the olfactory tests the role of olfactory event-related potentials (OERPs) is considered useful in the diagnosis of AD (Morgan&Murphy, 2002).

The results of olfactory tests are supported by functional imaging techniques (CT, MRI, PET) which show a reduced activation of the central olfactory structures (Wang et al., 2010), mainly on the right side (Kareken et al., 2001) and an atrophy of hippocampus (Jack et al., 1992;Yousem et al., 2001) and olfactory bulb (Thomann et al., 2009).

Murphy et al. (Murphy et al., 2003) studied olfactory function (odor threshold and odor identification) and volumetric MRI measures of mesial temporal areas (hippocampus, the parahippocampal gyrus and the amygdala) in patients with probable AD. They found strong relationships between mesial temporal lobe volumes and olfactory functional measures, particularly between the left hippocampal volume and the performance on the odor identification task so they concluded a left-hemisphere prevalence for verbally mediated olfactory tasks.

2.5 The role of olfactory test in Mild Cognitive Impairment

In a recent study we highlighted the role of olfactory test in early diagnosis of dementia (Fusetti et al, 2010).

The early identification of those patients which can develop a dementia before its clinical appearance has become a priority since they could benefit from therapeutic and preventive

options. For this reason in our researches we selected patients with Mild Cognitive Impairment (MCI).

The term MCI defines a transient condition that occurs along the progression from normal aging to dementia and comprises a broad clinical spectrum of pre-dementia stages. Standard MCI diagnostic criteria are the following:

1. subjective symptoms of memory loss
2. pathologic performance in mnemonic testing in relation to age and level of schooling
3. normal activities of daily living
4. normal cognitive functions
5. absence of dementia
6. lack of other diseases which impair or may alter memory (Petersen et al., 2001).

The discriminant role of the olfactory test was determined by the outcomes of a study on a group of patients with amnesic Mild Cognitive Impairment (aMCI) which is the category with the higher risk of conversion in AD (Peters et al., 2003). aMCI progresses to AD with a prevalence of 15% annually and they are identified clinically with neuropsychologic testing to determine isolated memory loss.

In our study 29 patients diagnosed with aMCI were selected and reassessed at 18 months (T1) after the first visit (T0). Exclusion criteria were considered neuropsychiatric disorders different from aMCI (Parkinson's disease, schizophrenia, multiple sclerosis and depression), head trauma (with loss of consciousness greater than 15 minutes), maxillofacial surgery, rhinosinusitis, nasal polyposis, chronic obstructive pulmonary disease, asthma, active hepatitis, cirrhosis, chronic renal failure, vitamin B12 deficiency, alcohol and drug abuse, cerebral vascular accidents, insulin dependent diabetes mellitus, hypothyroidism and Cushing syndrome.

The patients underwent an assessment by the SSST and the SSET and a neuropsychological evaluation using the Mini Mental State Examination (MMSE) and the Mental Deterioration Battery (MDB).

The MMSE is a quick, simple and reliable screening test used to explore cognitive functions and to evaluate disease progression. However its applicability in differential diagnosis shows limitations as well, due to the low reliability in individualizing specific profiles of cognitive deficit. The MMSE requires 5-10 minutes and it provides a score between 0 and 30 points adjusted according to the age and years of education in the Italian population. The MMSE score >24 was used as cut-off to distinguish between MCI and early dementia.

The MDB discriminates with a high degree of accuracy AD patients from normal aging subjects and it provides qualitative informations on the cognitive deficit. The MDB is a battery including seven tests that measures memory function and other cognitive abilities. This test is easily reproducible and lasts between 45 and 75 minutes.

Further inclusion criteria were the diagnosis of "questionable demented" (score=0.5) according to the CDR. Depressive symptoms were rated using the GDS with a score > 6 as cut off to discriminate patients with depression. All patients underwent CT scan or MRI of the brain to assess the presence and degree of cerebral atrophy and causes of secondary dementia.

Patients with aMCI showed a lower score in the ability of olfactory identification and discrimination worse than 18 months from first visit. The percentages of normosmic, hyposmic, anosmic patients at T0 and T1 based on the mean TDI score are reported in Table 5. We demonstrated that all patients (100%) who developed AD were hyposmic at T0 while

of 20 patients who didn't develop AD 12 (60%) were hyposmic and 1 (5%) was anosmic based on TDI score.

aMCI patients	*T0*	*T1*
9 with AD, n (%) Score on TDI	9 hyposmic (100%)	9 hyposmic (100%)
20 without AD, n (%) Score on TDI	7 normosmic (35%) 12 hyposmic (60%) 1 anosmic (5%)	5 normosmic (25%) 14 hyposmic (70%) 1 anosmic (5%)

Table 5. Percentages of normosmic, hyposmic, anosmic patients at T0 and T1 based on the mean TDI score

The correlation between individual neuropsychological tests of the MDB and the 3 olfactory functions (threshold-discrimination-identification) evalueted with the SSET was examined with the Spearman correlation.

The most statistically significant correlations were found between olfactory discrimination and copying designs with elements of programming, between olfactory discrimination and verbal fluency, between olfactory discrimination and immediate recall of Rey's 15 words and between olfactory identification and delayed recall of Rey's 15 words.

The olfactory test has been shown to be sensitive and in some cases statistically more reliable of neuropsychological tests such as the MMSE. Another fact that emerges from the results of our study is that the olfactory test appears to allow a prediction of conversion to AD in aMCI who show a worsening of 'olfactory identification at follow-up. 9 of 29 patients with aMCI (31%) developed AD, and all had a worse olfactory deficit to 18 months from the first survey showing also unawareness of their olfactory deficit.

This finding confirms the results of Devanand stating that the olfactory deficit associated with unawareness increase the risk of progression to AD.

Our data show an early olfactory deficit in aMCI patients and suggest to introduce the study of the smell in early evaluation of aMCI patients. At follow-up we evidenced a more rapid cognitive than olfactory decline but they must be confirmed on the basis of further studies on a larger sample population. We also demonstrated a significant progression from hyposmia to anosmia in aMCI patients which have developed AD after 18 months. This suggested the validity of the olfactory test as a possible early diagnostic marker of AD. Moreover we found in the 20 aMCI patients that did not developed AD an increase of the mean MMSE score at the 18 months follow-up. These findings is in concordance with epidemiological studies which suggest that the progression of MCI is heterogeneous and may be reversible, stable or progress to AD (Ritchie K et al., 2001; De Carli C., 2003). Förster et al. have instead shown in patients with early AD studied with SSET and FDG-PET a correlation between the scores in the identification, discrimination and olfactory threshold and different areas of brain activation (Förster et al., 2010). In our studies we confirmed the accuracy of the olfactory test to find an impairment of the olfactory identification function in the early stages of AD.

3. Conclusion

The olfactory tests are a useful and reliable diagnostic aid for the identification of olfactory deficit. They are easy to use, with a low cost, they don't take too much time for the administration and they are not influenced by the level of education. The ideal test should overcome the problem of the different ethnic and currently the most widely used standardized tests in clinical practice and research are the UPSIT and the SS. For a first rapid evaluation the screening identification test can be used but in case of abnormal results or if cognitive disorders are suspected a complete test is strongly reccomended.

The only olfactory test is obviously not sufficient for the early diagnosis of AD but its high sensitivity is now accepted and should be included into a full battery of neuropsychological tests and other diagnostic aids (ApoE, PET or SPECT brain, functional MRI, etc..) commonly used to evaluate these patients.

The role of the ENT specialist in this area is very important as fundamental to ensuring the reliability of the olfactory test excluding with a careful selection of patients hyposmia secondary to malformations, acute and chronic inflammatory phenomena, allergy, exposure to irritants. We also recommend to avoid the self-administration expecially if the test is not for screening aims but is part of the clinical routine for diagnosis.

In conclusion, we can assert that the role of olfactory deficit in neurodegenerative diseases is still underestimated, mainly for the problem of an early and correct identification of a clinical disorder. Long-term studies can determine the real predictive value of hyposmia in AD and the efficacy of early treatment even on olfactory function.

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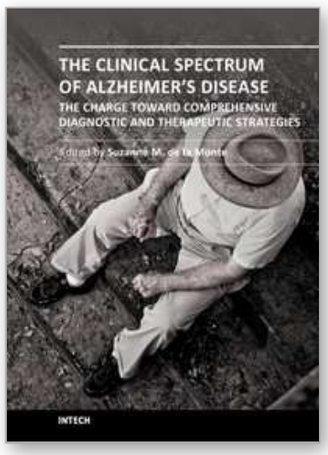

The Clinical Spectrum of Alzheimer's Disease -The Charge Toward Comprehensive Diagnostic and Therapeutic Strategies

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The Clinical Spectrum of Alzheimer's Disease: The Charge Toward Comprehensive Diagnostic and Therapeutic Strategies is highly informative and current. Acknowledged experts in the field critically review both standard and under-appreciated clinical, behavioral, epidemiological, genetic, and neuroimaging attributes of Alzheimer's disease. The collection covers diverse topics of interest to clinicians and researchers alike. Experienced professionals and newcomers to the field will benefit from the read. The strengths and weaknesses of current clinical, non-invasive, neuro-imaging, and biomarker diagnostic approaches are explained. The perspectives give fresh insights into the process of neurodegeneration. Readers will be enlightened by the evidence that the neural circuits damaged by neurodegeneration are much broader than conventionally taught, suggesting that Alzheimer's could be detected at earlier stages of disease by utilizing multi-pronged diagnostic approaches. This book inspires renewed hope that more effective treatments could be developed based upon the expanding list of potential therapeutic targets.

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