4° CONGRESSO NAZIONALE SIONG

SOCIETÀ ITALIANA OTONEUROGERIATRIA

IL RUOLO DELL'OLFATTO NELL'INVECCHIAMENTO E NELLE PATOLOGIE NEURODEGENERATIVE

Luca D'Ascanio

Direttore

U.O.C. di Otorinolaringoiatria

AST Pesaro-Urbino

Ospedale Santa Croce- Fano

Ospedale San Salvatore - Pesaro

Direttore Dott L. D'Ascanio

ast PESARO URBINO MARCHE

GIORNATE ITALIANE DI OTONEUROLOGIA
MANIFESTAZIONE UFFICIALE DELL'A.O.O.I.
CON IL PATROCINIO DELLA
SOCIETÀ ITALIANA DI OTORINOLARINGOIATRIA

L'OLFATTO: ATTUALI ACQUISIZIONI DI FISIOPATOLOGIA E DI OLFATTOMETRIA OBIETTIVA

a cura di G. Perfumo

SORRENTO (NA)
31 Marzo - 1 Aprile 1990
CENTRO CONGRESSI SORRENTO PALACE HOTEL

1990

Comitato Simposi Scientifici della Dott. FORMENTI S.p.A. - Milano
in collaborazione con
PUROPHARMA S.r.l. - Milano

GRUPPO ALTA ITALIA
di OTORINOLARINGOIATRIA
CHIRURGIA CERVICO-FACCIALE

Presidente
Matteo Richichi

L'OLFATTO:
IL SENSO DIMENTICATO

2010

LVI Raduno

Milano, 27 novembre 2010

INTRODUZIONE

L'olfatto: il senso dimenticato

Dimenticato perché tra i cinque sensi è stato certamente quello che più ha perso significato, dal punto di vista funzionale, nel corso dell'evoluzione della razza umana attraverso i millenni. È noto come l'uomo primitivo, pur essendo un animale microsmatico, affidasse all'odorato compiti importantissimi per la propria sopravivenza, quali la difesa dai pericoli, la ricerca del cibo e l'eccitazione dell'appetito sessuale. E poi che cosa è successo? È successo che, condizionati da una mentalità visivo-acustica che per 2500 anni ha determinato il nostro modo di sentire e di pensare, abbiamo relegato l'olfatto fra i sensi minori. Prova ne sia che dei 1000 geni (individuati nel genoma umano) dedicati alla codifica dei recettori olfattivi, il 43% sono dei "pseudogeni" cioè non codificano.

Se il primo a spiegare che la diversità degli odori si collegava alla diversità delle molecole fu Democrito, abbiamo dovuto attendere il 1991 perché due scienziati come Axel e Buck (insigniti dal Premio Nobel nel 2004) riuscissero ad individuare i recettori molecolari dell'olfatto ed a descriverne i più intimi meccanismi della percezione.

Oggi l'olfatto costituisce un modello privilegiato di studio per la comprensione dei processi molecolari di trattamento dell'informazione sensoriale.

Ed allora oggi dobbiamo abituarci a rivalutare il significato clinico dei disturbi dell'olfatto, laddove la disosmia sembra acquisire un valore semiologico forte come sintomo di allarme per malattie non solo rinosinusali, ma anche sistemiche o neurodegenerative.

Ed ancora dobbiamo chiarire il ruolo dell'olfattometria: a tutt'oggi non vi sono criteri obiettivi pienamente condivisibili per misurare l'olfatto come quelli, per intenderci, usati per la vista e l'udito.

Ma forse è proprio questo il fascino dell'olfatto e che lo rende il senso più intimo: il suo regno resta confinato al cervello di chi annusa, anche se una scena olfattiva può essere descritta usando una metafora: comunque sempre si evidenzierà la disparità tra la ricchezza del mondo percepito con l'olfatto e la povertà del linguaggio!

The Nobel Prize in Physiology or Medicine 2004

"for their discoveries of odorant receptors and the organization of the olfactory system"

Richard Axel

◑ 1/2 of the prize

USA

Columbia University
New York, NY, USA

b. 1946

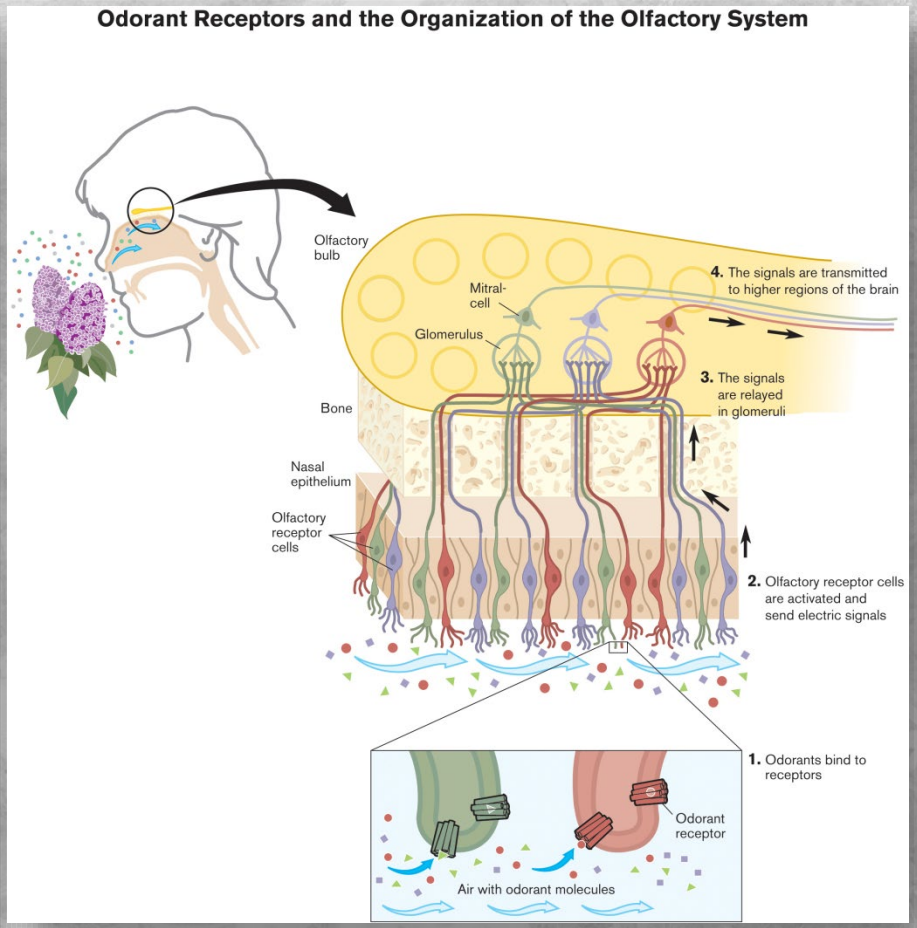
Linda B. Buck

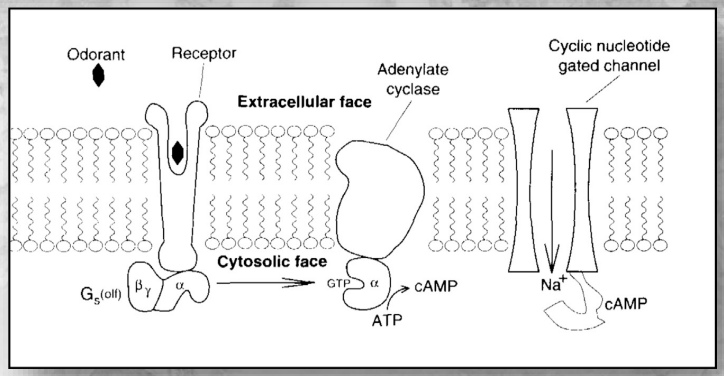
◑ 1/2 of the prize

USA

Fred Hutchinson Cancer Research Center
Seattle, WA, USA

b. 1947





Cell, Vol. 65, 175–187, April 5, 1991, Copyright © 1991 by Cell Press

A Novel Multigene Family May Encode Odorant Receptors: A Molecular Basis for Odor Recognition

Linda Buck* and Richard Axel*†
*Department of Biochemistry and Molecular Biophysics
†Howard Hughes Medical Institute
College of Physicians and Surgeons
Columbia University
New York, New York 10032

Summary

The mammalian olfactory system can recognize and discriminate a large number of different odorant molecules. The detection of chemically distinct odorants presumably results from the association of odorous ligands with specific receptors on olfactory sensory neurons. To address the problem of olfactory perception at a molecular level, we have cloned and characterized 18 different members of an extremely large multigene family that encodes seven transmembrane domain proteins whose expression is restricted to the olfactory epithelium. The members of this novel gene family are likely to encode a diverse family of odorant receptors.

Intro

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vision, involves only a few odor receptors, each capable of interaction with multiple odorant molecules. Alternatively,

the sense of smell may involve a large number of distinct receptors each capable of associating with one or a small number of odorants. In either case, the brain must distinguish which receptors or which neurons have been activated to allow the discrimination between different odorant stimuli. Insight into the mechanisms underlying olfactory perception is likely to depend upon the isolation of the odorant receptors and the characterization of their diversity, specificity, and patterns of expression.

The primary events in odor detection occur in a specialized olfactory neuroepithelium located in the posterior recesses of the nasal cavity. Three cell types dominate this epithelium (Figure 1A): the olfactory sensory neuron, the sustentacular or supporting cell, and the basal cell, which is a stem cell that generates olfactory neurons throughout life (Moulton and Beidler, 1967; Graziadei and Monti Graziadei, 1979). The olfactory sensory neuron is bipolar: a dendritic process extends to the mucosal surface, where it gives rise to a number of specialized cilia that provide an extensive, receptive surface for the interaction of odors with the cell. The olfactory neuron also gives rise to an axon that projects to the olfactory bulb of the brain, the first relay in the olfactory system. The axons of the olfac-
subcortical and corti-
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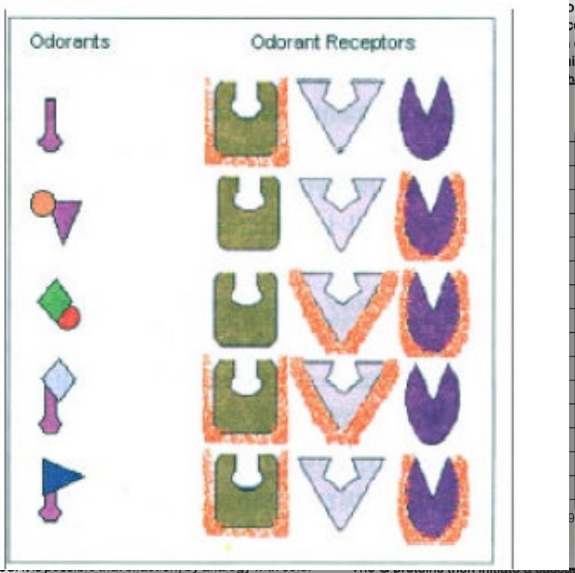
specific receptors on



The G proteins then initiate a number of intracellular signaling events leading to the generation of an action potential that is propagated along the olfactory sensory axon

Cell
Leading Edge

CellPress

BenchMarks

What Makes a Discovery Successful? The Story of Linda Buck and the Olfactory Receptors

Ann-Sophie Barwich[1,*]
[1]Indiana University, Bloomington, IN, USA
*Correspondence: abarwich@iu.edu
https://doi.org/10.1016/j.cell.2020.04.040

In 1991, Buck and Axel published a landmark study in *Cell* for work that was awarded the 2004 Nobel Prize. The identification of the olfactory receptors as the largest family of GPCRs catapulted olfaction into mainstream neurobiology. This BenchMark revisits Buck's experimental innovation and its surprising success at the time.

A Tale of Two Tales

This is the story of how the largest multigene family in the mammalian genome was found. The story of the discovery of the olfactory receptors (ORs) by Linda Buck and Richard Axel is really a tale of two tales: the first is the birth of olfaction as a model for neurobiology, and the second is a methodological breakthrough in the bench life of Buck. At the core of this discovery sits its experimental design, raising the question: what makes discov-
ery tools fit their tasks? Why are some

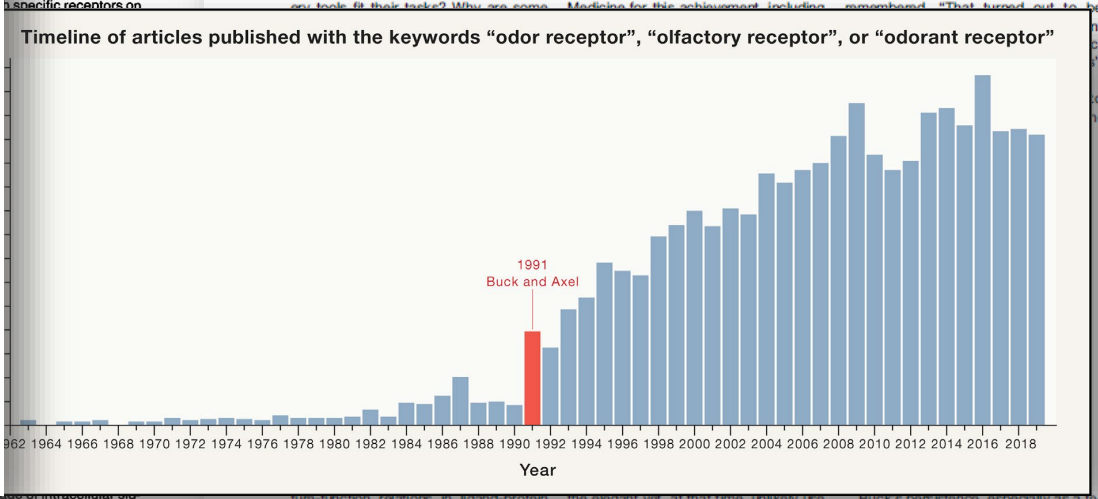
targeting (Firestein, 2001). The identification of ORs as members of the superfamily of GPCRs changed the significance of olfaction in mainstream science: GPCRs are part of many fundamental cell-signaling processes; up to 50% of drugs target GPCRs. ORs are of special interest for studying GPCRs because they present their largest, most diverse class.

It's hard to overstate the importance of this discovery. Buck and Axel received the 2004 Nobel Prize in Physiology or Medicine for this achievement, including

Finding a Particular Needle in a Stack of Other Needles

The Race Begins

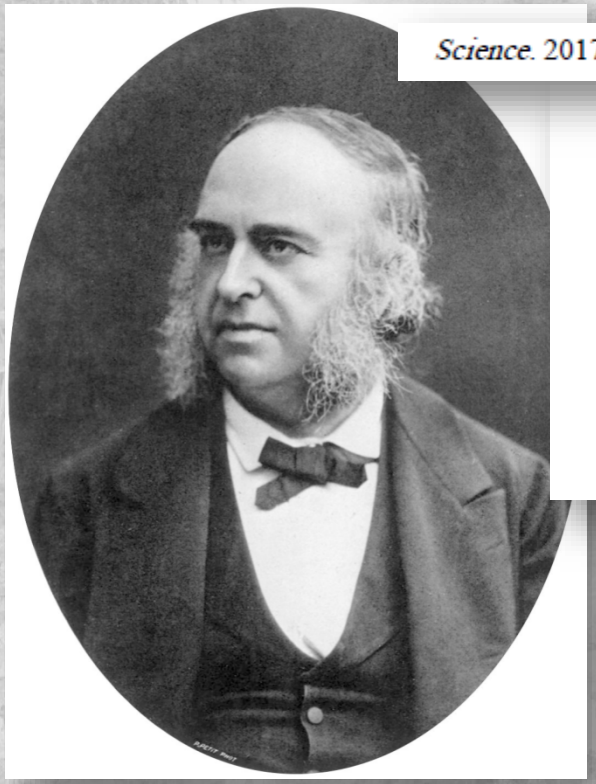
Smell long constituted a niche subject. "When I first came into the field," Gordon Shepherd remembered, "olfaction was way off to the side" (Barwich, 2020). Shepherd recognized the investigative potential of olfaction for sensory signaling early on. His intuition was proven right, if not outdone by the OR discovery. Stuart Firestein, Shepherd's former postdoc,
remembered, "That turned out to be



ture-function relations in ligand-protein interactions, gene regulation, and axon

the elegant yet, at that time, unlikely use of a method.

Buck's persistence, especially as a female early-career researcher in the



Science. 2017 May 12; 356(6338): . doi:10.1126/science.aam7263.

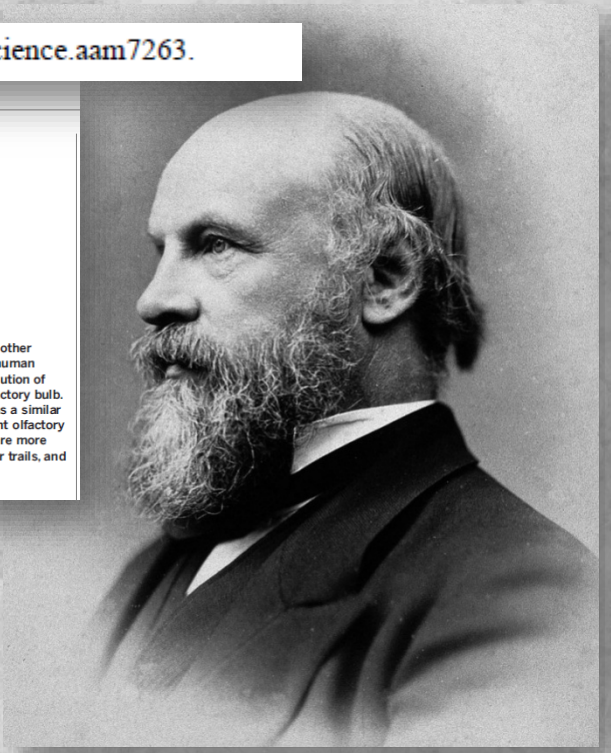
REVIEW

NEUROSCIENCE

Poor human olfaction is a 19th-century myth

John P. McGann*

It is commonly believed that humans have a poor sense of smell compared to other mammalian species. However, this idea derives not from empirical studies of human olfaction but from a famous 19th-century anatomist's hypothesis that the evolution of human free will required a reduction in the proportional size of the brain's olfactory bulb. The human olfactory bulb is actually quite large in absolute terms and contains a similar number of neurons to that of other mammals. Moreover, humans have excellent olfactory abilities. We can detect and discriminate an extraordinary range of odors, we are more sensitive than rodents and dogs for some odors, we are capable of tracking odor trails, and our behavioral and affective states are influenced by our sense of smell.



Paul Pierre Broca
1824 -1880

William Turner
1832 -1916

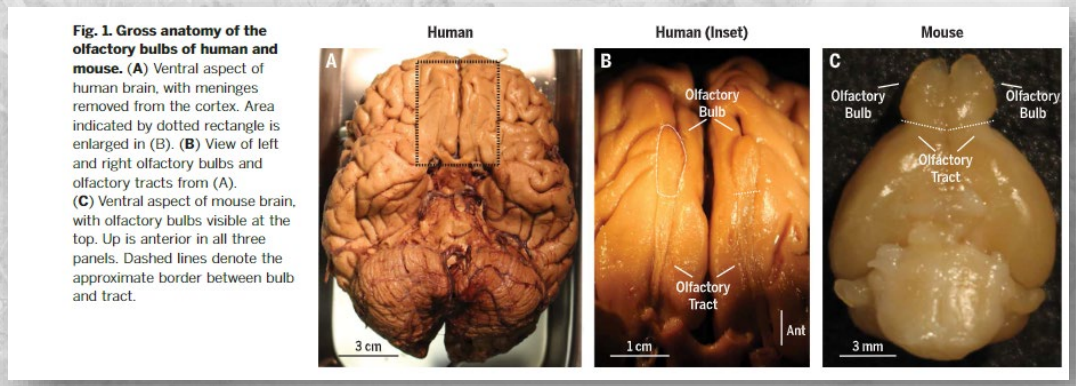


Fig. 1. Gross anatomy of the olfactory bulbs of human and mouse. (**A**) Ventral aspect of human brain, with meninges removed from the cortex. Area indicated by dotted rectangle is enlarged in (B). (**B**) View of left and right olfactory bulbs and olfactory tracts from (A). (**C**) Ventral aspect of mouse brain, with olfactory bulbs visible at the top. Up is anterior in all three panels. Dashed lines denote the approximate border between bulb and tract.

RESEARCH

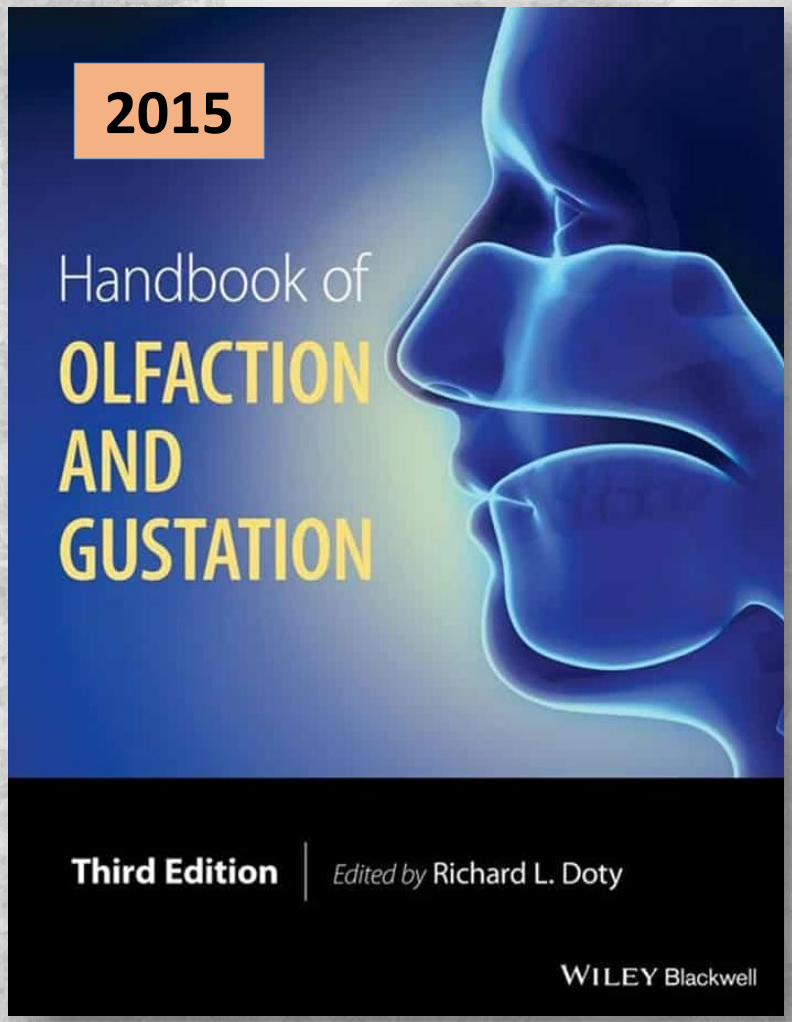
REVIEW

NEUROSCIENCE

Poor human olfaction is a 19th-century myth

John P. McGann*

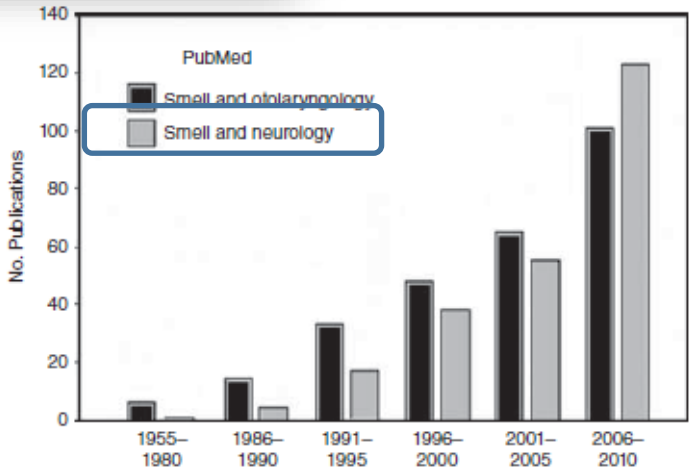
It is commonly believed that humans have a poor sense of smell compared to other mammalian species. However, this idea derives not from empirical studies of human olfaction but from a famous 19th-century anatomist's hypothesis that the evolution of human free will required a reduction in the proportional size of the brain's olfactory bulb. The human olfactory bulb is actually quite large in absolute terms and contains a similar number of neurons to that of other mammals. Moreover, humans have excellent olfactory abilities. We can detect and discriminate an extraordinary range of odors, we are more sensitive than rodents and dogs for some odors, we are capable of tracking odor trails, and our behavioral and affective states are influenced by our sense of smell.



52 capitoli (1197 pagine)

Capitolo 17: «Clinical Disorders of Olfaction» . 27 pagine

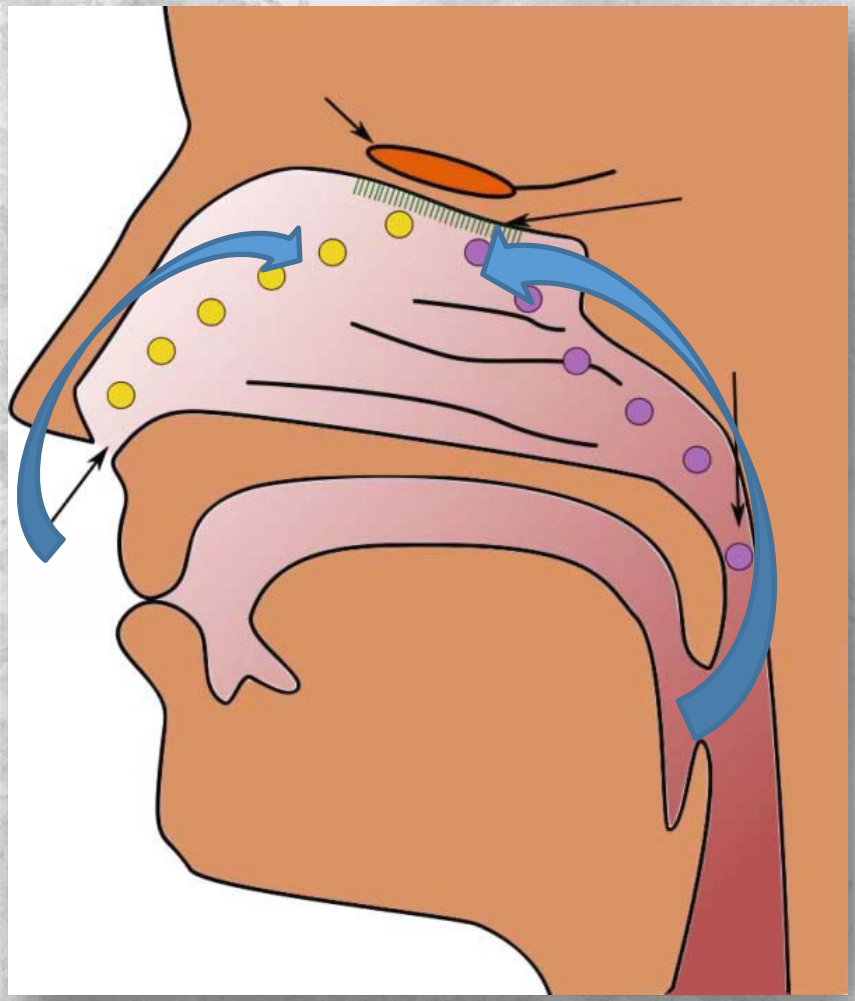
Preface

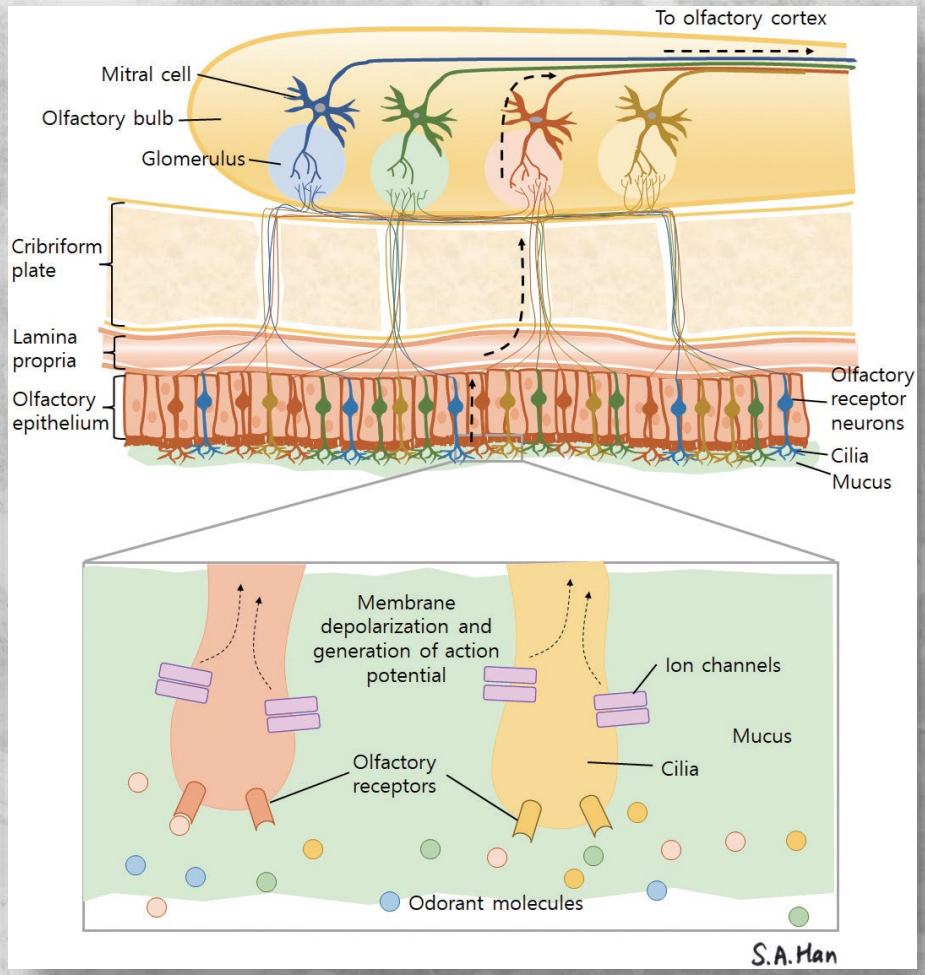


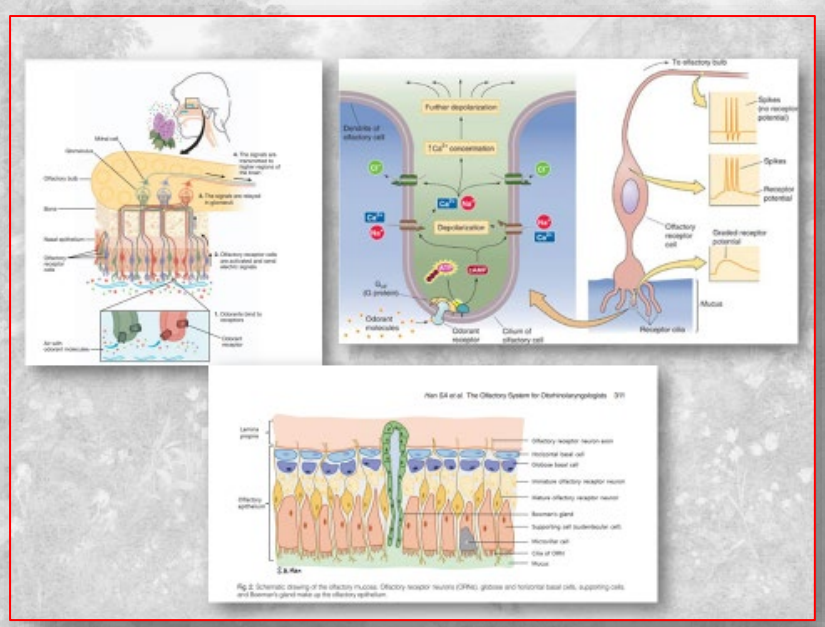
It is important to emphasize that biology, neuroscience, and the clinical specialties are not the only fields where the chemical senses are current centers of focus.

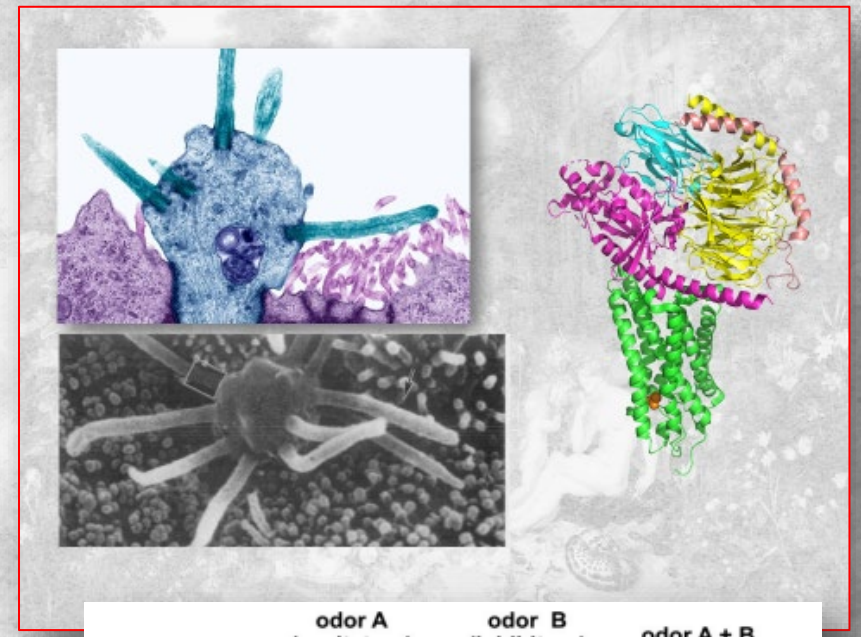
The food and beverage industries are increasing, at great cost, research efforts to enhance the flavor of their products and, importantly, to maintain such flavor in light of developing government regulations to minimize the amount of salt, sugar, and other ingredients in their products. Continued interest in olfaction by marketers of perfumes and personal care products goes without saying.

«meccanismi della percezione olfattiva»









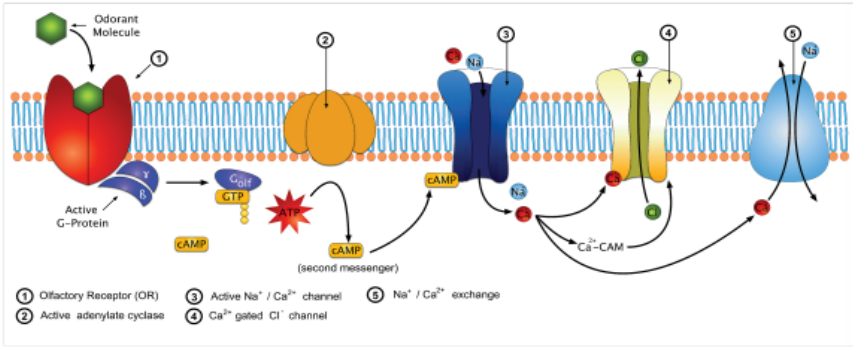


Figure 2 Schematic representation of the olfactory signal transduction pathway within OSNs cilia

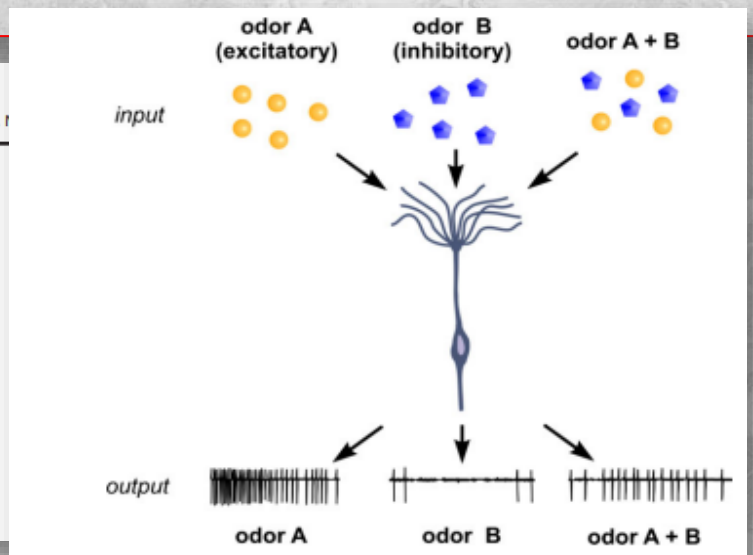


Figure 1 Diagram of a hypothetical mammalian ORN that is excited by odor A, inhibited by odor B, and intermediately excited by a mixture of odor A and B. Note that the output of such an ORN would integrate the relative proportion of odors A and B. This figure appears in color in the online version of *Chemical Senses*.

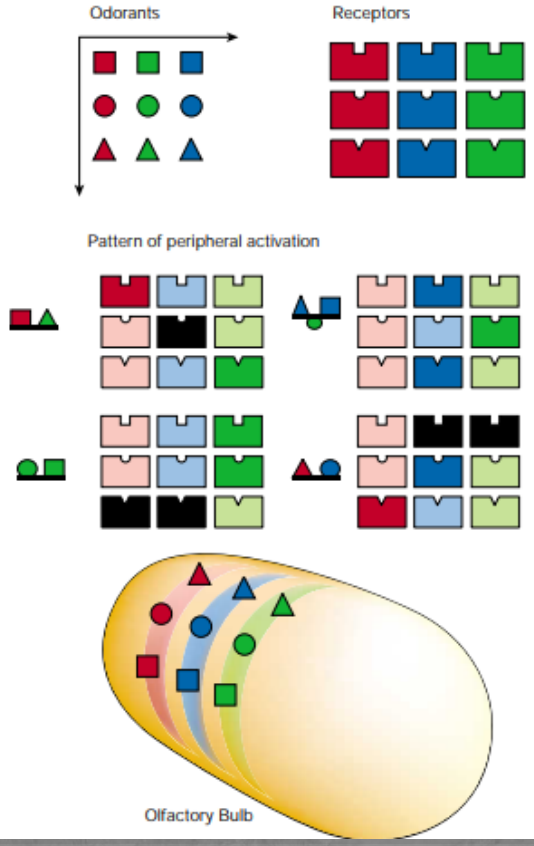
How the olfactory system makes sense of scents

NATURE | VOL 413 | 13 SEPTEMBER 2001

Stuart Firestein

Box 1

A code in the nose



Although there are some 1,000 ORs, dete
repertoire of odours requires a combinato
odour molecules are recognized by more
(perhaps by dozens) and most receptors
odours, probably related by chemical pro
the figure represents a current consensus
numerous molecular features, two of whi
here by colour and shape. Receptors are
different features of molecules, and a part
compound may also consist of a number
'determinants' that possess some of thes
recognition of an odorant molecule deper
receptors are activated and to what exter
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example, functional group or molecular le
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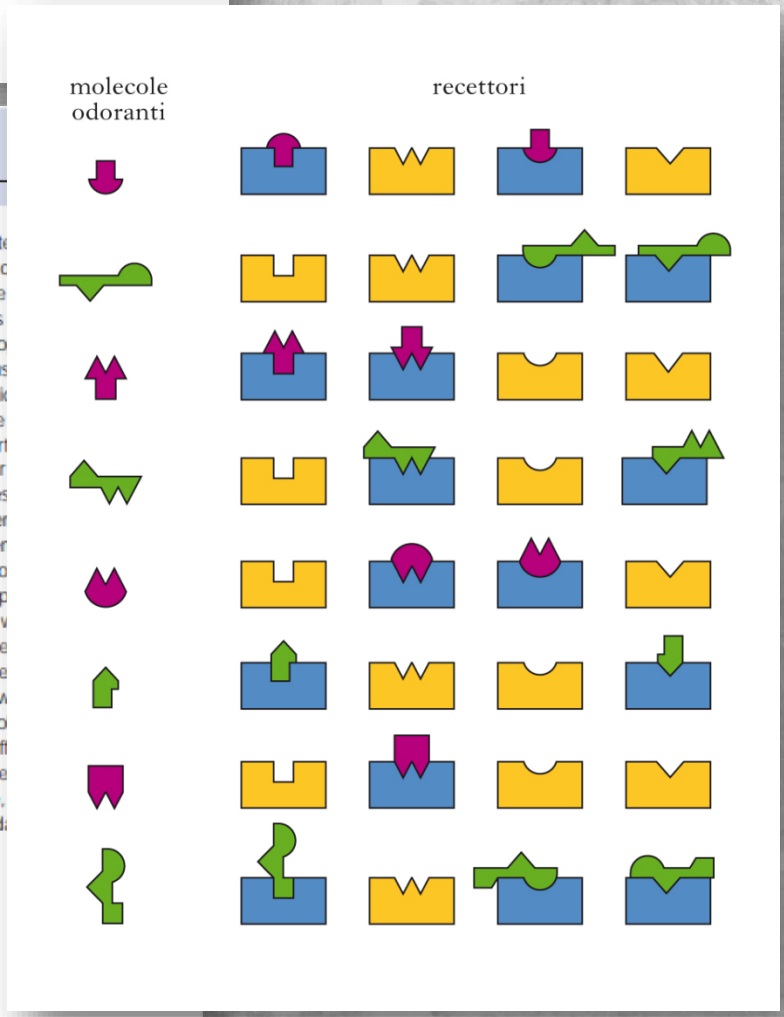
undergo considerable revision as more da



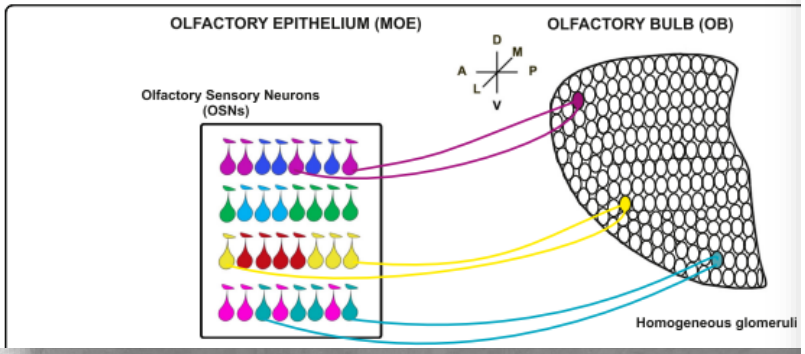
Francia and Lodovichi *BMC Biology* (2021) 19:174
https://doi.org/10.1186/s12915-021-01116-y

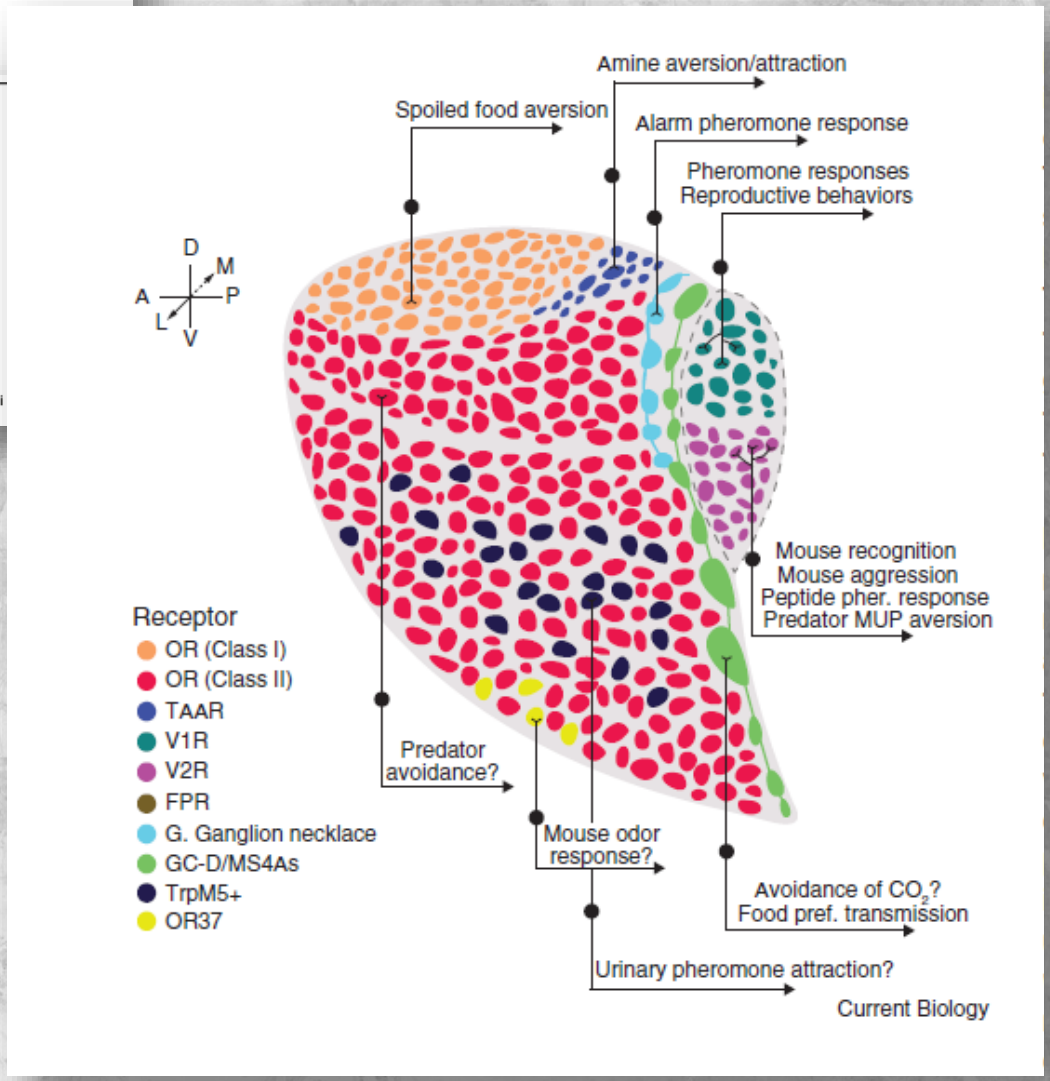
BMC Biology

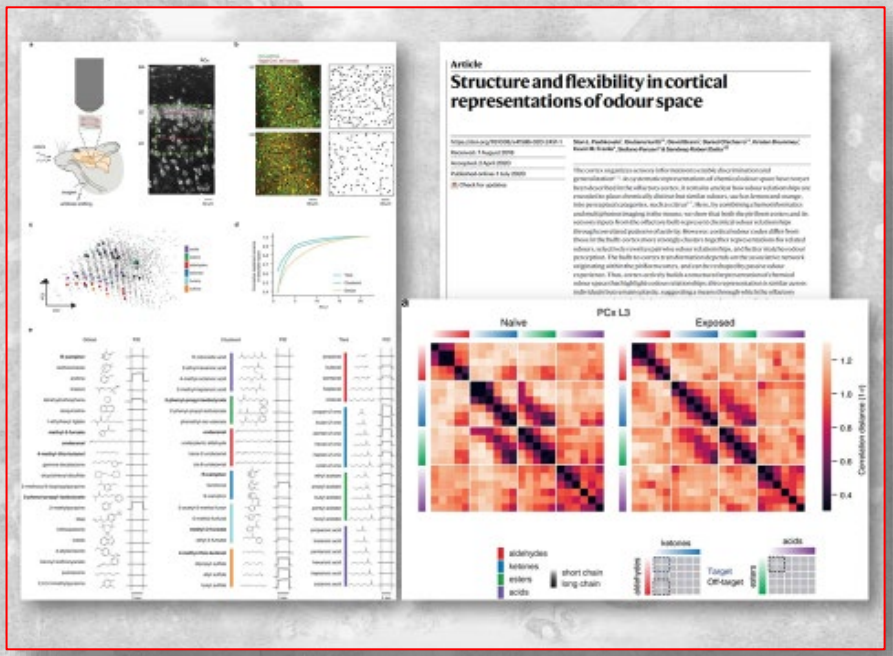
REVIEW Open Access

The role of the odorant receptors in the formation of the sensory map

Simona Francia[1,2] and Claudia Lodovichi[2,3,4,5*]






Article
Structure and flexibility in cortical representations of odour space
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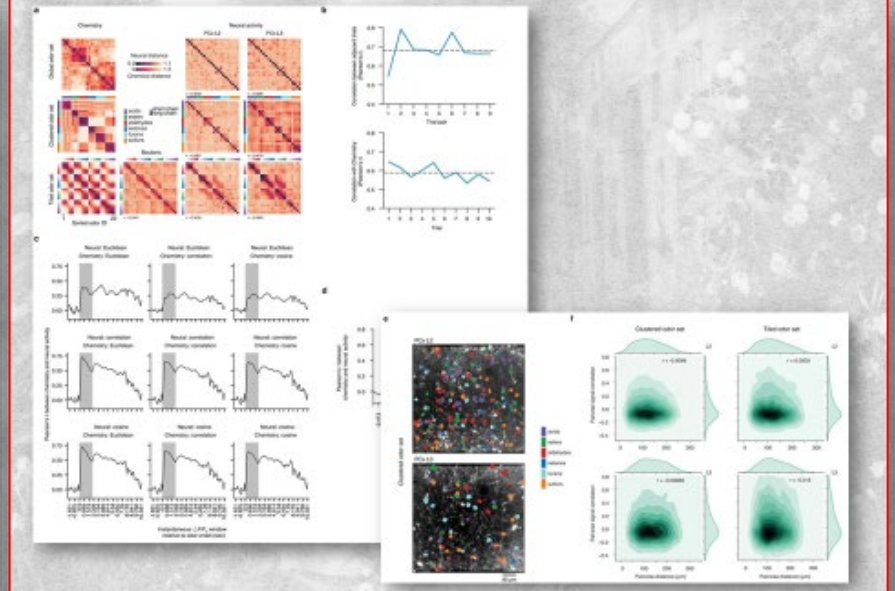
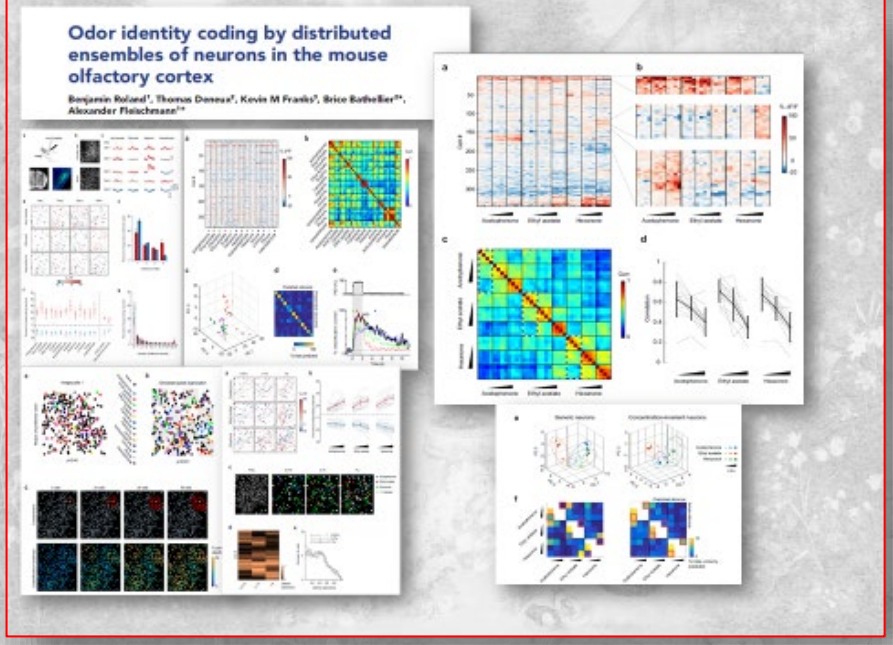
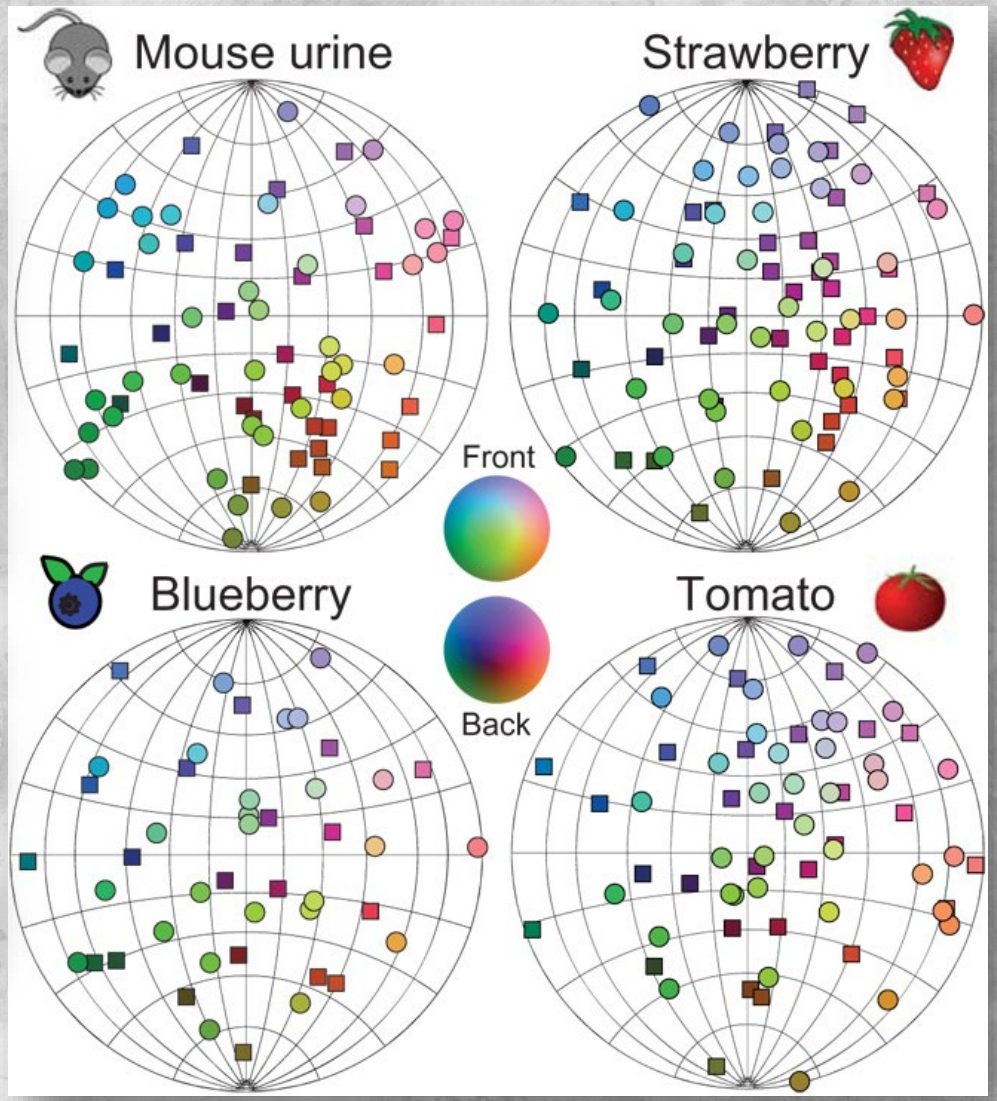
short chain
long chain
Target
Off-target

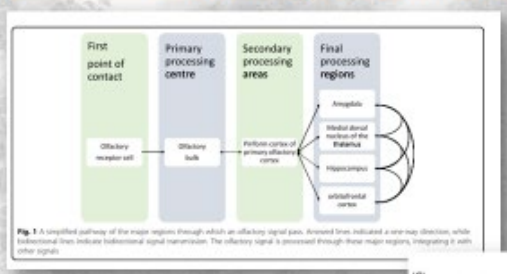


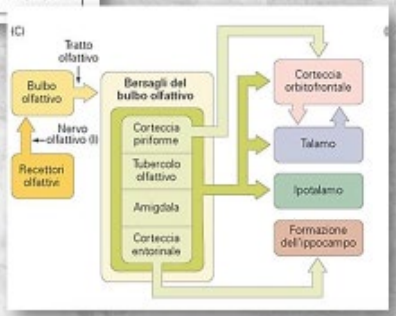

Odor identity coding by distributed ensembles of neurons in the mouse olfactory cortex
Benjamin Roland[1], Thomas Deneux[2], Kevin M Franks[3], Brice Bathellier[2]*, Alexander Fleischmann[1]*

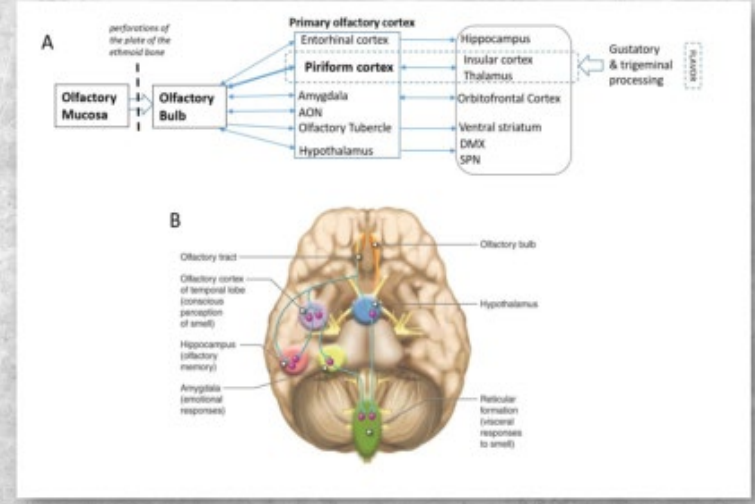

Science
A principal odor map unifies diverse tasks in olfactory perception
Principal Odor Map
Principal Odor Map (POM)
Training Data Counts
Test data counts


Mouse urine
Strawberry
Front
Blueberry
Back
Tomato

«modello di percezione nerusosensoriale»

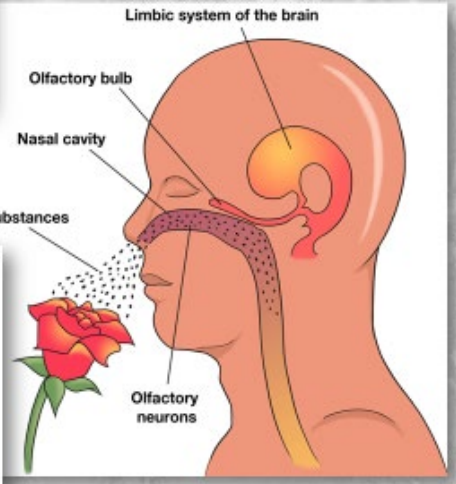


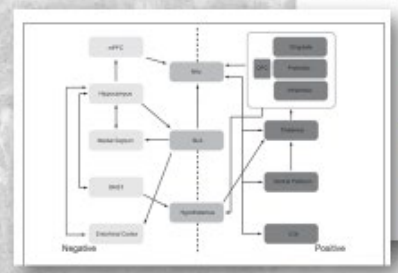




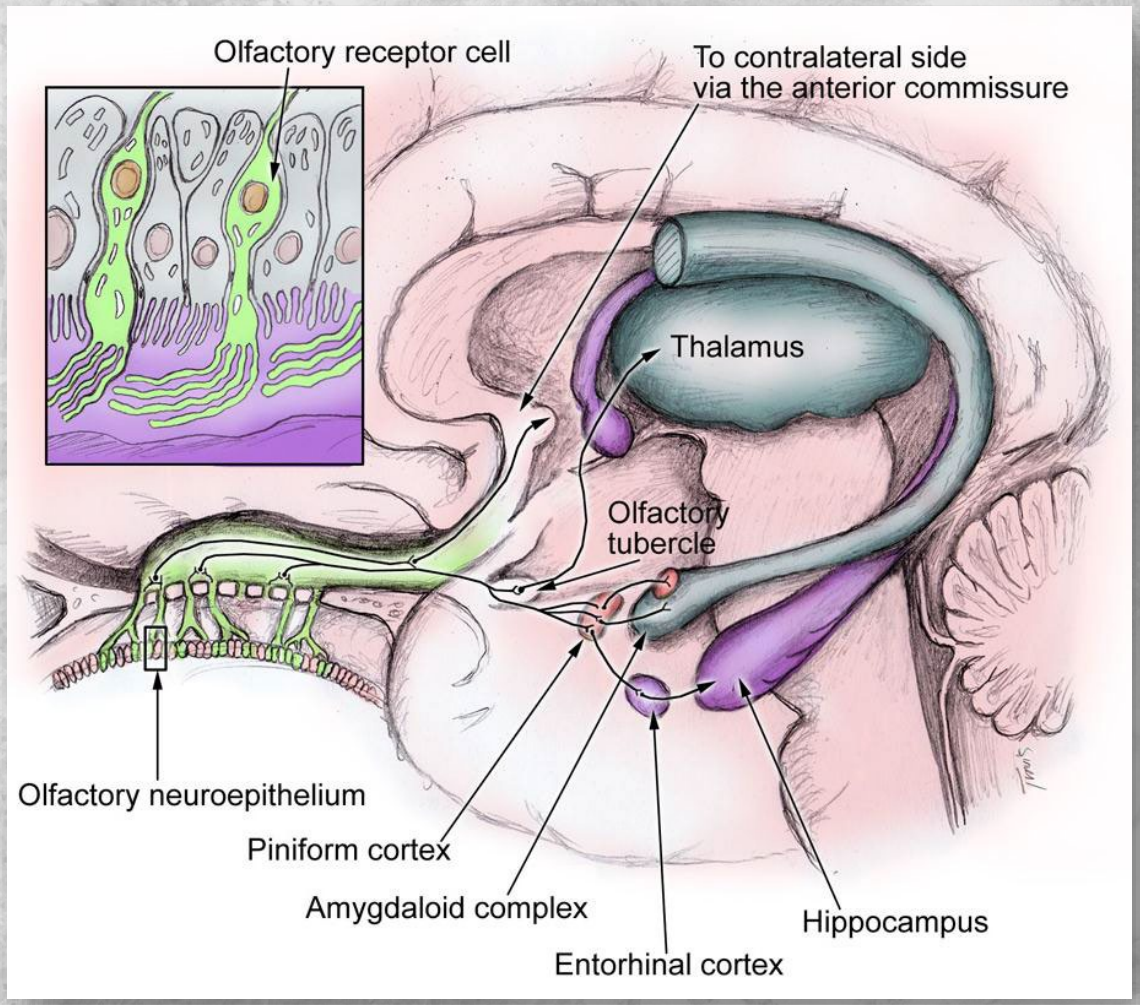

Progress in Neurobiology

Human hippocampal connectivity is stronger in olfaction than other sensory systems





«modello di percezione nerusosensoriale»



È **responsabile dell'elaborazione delle informazioni emozionali, dell'apprendimento legato alle emozioni e della regolazione delle risposte emotive**. Inoltre, è coinvolto nell'integrazione delle emozioni con la memoria, la motivazione e l'attenzione, fornendo una base per la nostra esperienza emotiva complessiva.

«Cervello emozionale»

Chapter 15

Olfactory Memory

THERESA L. WHITE, PER MØLLER, E. P. KÖSTER, HOWARD EICHENBAUM, and CHRISTIANE LINSTER

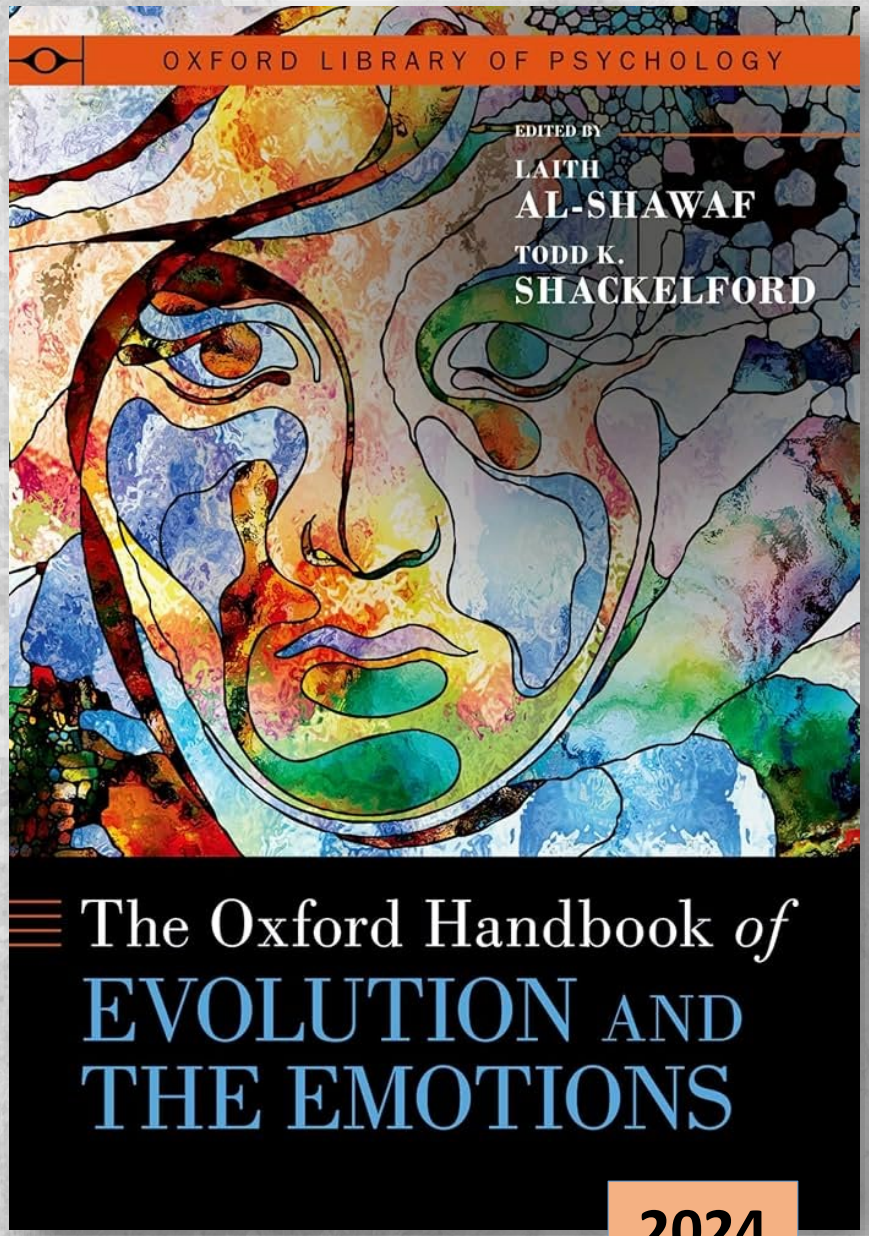
15.1 INTRODUCTION

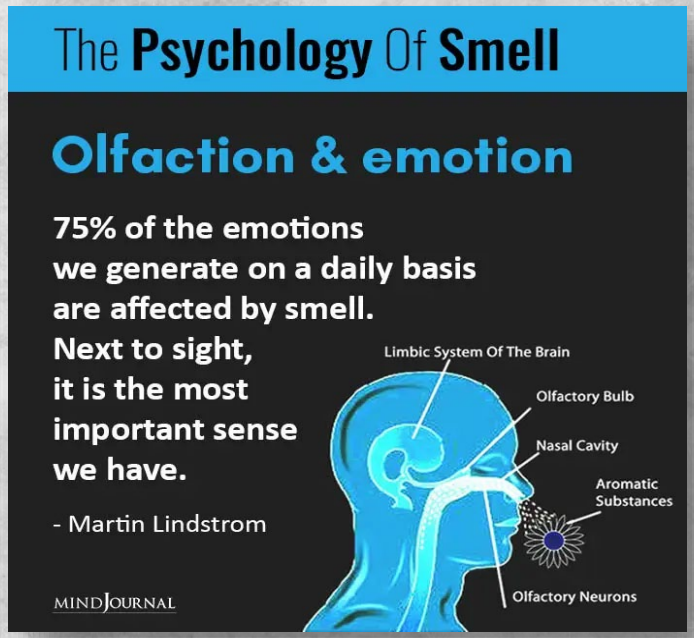
Olfactory memory plays an important role in the everyday lives of both animals and humans, even if people generally attend much less than animals to incoming olfactory information. Each of the three main functions of olfaction outlined by Stevenson (2010) would be impossible without odor memory: ingestive behaviors (e.g., food detection, flavor determination, breast finding), avoiding environmental hazards (e.g., fear related, disgust related), and social communication (e.g., reproductive behaviors, emotional contagion, territorial demarcation). Whether trying to remember whether the fruit of a tree is edible or toxic, or trying to determine friend from foe, the past experiences accessed through olfactory memory are critical in making the decision.

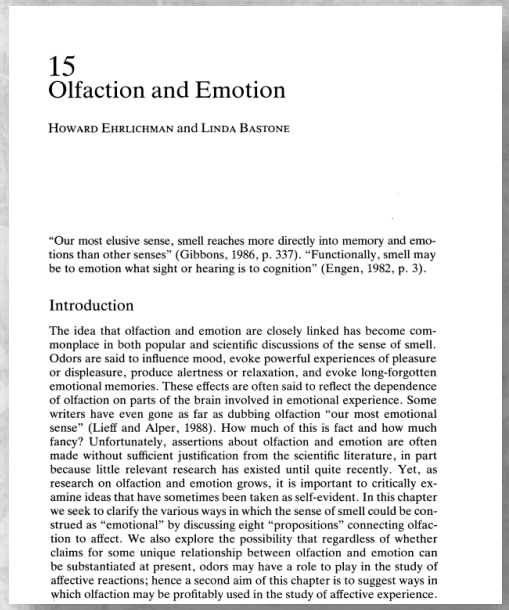
The phrase "odor memory" generally has two meanings. The first meaning reflects "odor-evoked memory". Most of us are familiar with "Proustian effects" (Proust, 1928), or the ability of odor memory to evoke rich recollections of times and events gone by (Chu and Downes, 2000; 2002; Willander and Larsson, 2006; 2007; 2008; Herz and Schooler, 2002). Although these effects emphasize the episodic nature of olfactory memory, the memories in question are multi-sensorial, making them odor-evoked memories (Herz, 2012; Herz and Cupchik, 1992; 1995). This meaning of odor memory also illustrates the way that odors are associated with a variety of other stimuli through experiences and learning (Wilson and Stevenson, 2006). The second meaning of "odor memory" concerns the way that the odors themselves are remembered and recognized at a later time. Historically, the study of this type of odor memory has been dominated by tasks that have their counterparts in the study of vision, such as discrimination, recognition and identification (e.g., Engen and Ross, 1973; Mozell, 1972; Goldman and Seamon, 1992; Jehl et al., 1994). These studies have led to some theories related to this meaning of odor memory that place odor semantics into prominence by invoking "odor objects" (Wilson and Stevenson, 2006), a form of internal representation that can be changed by such processes as odor-odor and odor-taste learning. Thus, from this theoretical viewpoint, recognition and identification of the "odor object" seem to be the most important tasks of olfactory learning and memory. Other theoretical views concerning the way that odors are remembered have emphasized the implicit and episodic nature of olfactory cognition (e.g., Zucco, 2003), and question the role of odor percept recollection in everyday memory use (Köster, 2005).

Rather than attempting to dissociate theoretical viewpoints, this chapter focuses on recognition memory and learning paradigms useful in characterizing the olfactory memory system. Since the basic anatomy and physiology of the olfactory system is well known and is described in great detail elsewhere in this volume (Chapters 1–10), only brief mention of anatomical structures critical for odor memory is made in the sections that follow. Among the brain regions most critical for odor memory are the hippocampus and the piriform, entorhinal, and orbitofrontal cortices, each of which seems to contribute to different memory-related functional properties (Eichenbaum, 1997; Petrulis and Eichenbaum, 2003a; Gottfried, 2010).

Handbook of Olfaction and Gustation, Third Edition. Edited by Richard L. Doty.







15
Olfaction and Emotion

Howard Ehrlichman and Linda Bastone

"Our most elusive sense, smell reaches more directly into memory and emotions than other senses" (Gibbons, 1986, p. 337). "Functionally, smell may be to emotion what sight or hearing is to cognition" (Engen, 1982, p. 3).

Introduction

The idea that olfaction and emotion are closely linked has become commonplace in both popular and scientific discussions of the sense of smell. Odors are said to influence mood, evoke powerful experiences of pleasure or displeasure, produce alertness or relaxation, and evoke long-forgotten emotional memories. These effects are often said to reflect the dependence of olfaction on parts of the brain involved in emotional experience. Some writers have even gone as far as dubbing olfaction "our most emotional sense" (Lieff and Alper, 1988). How much of this is fact and how much fancy? Unfortunately, assertions about olfaction and emotion are often made without sufficient justification from the scientific literature, in part because little relevant research has existed until quite recently. Yet, as research on olfaction and emotion grows, it is important to critically examine ideas that have sometimes been taken as self-evident. In this chapter we seek to clarify the various ways in which the sense of smell could be construed as "emotional" by discussing eight "propositions" connecting olfaction to affect. We also explore the possibility that regardless of whether claims for some unique relationship between olfaction and emotion can be substantiated at present, odors may have a role to play in the study of affective reactions; hence a second aim of this chapter is to suggest ways in which olfaction may be profitably used in the study of affective experience.

Chem. Senses 35: 3–20, 2010

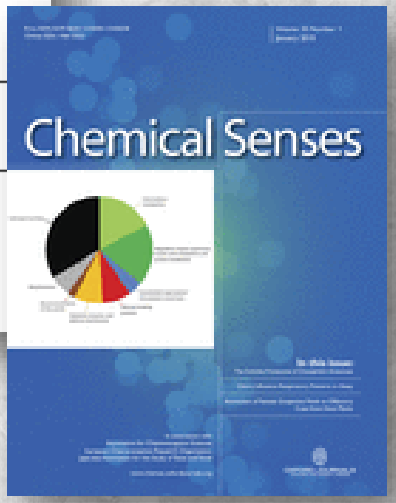
doi:10.1093/chemse/bjp083
Advance Access publication November 25, 2009

REVIEW

An Initial Evaluation of the Functions of Human Olfaction

Richard J. Stevenson

Department of Psychology, Macquarie University, Sydney, NSW 2109, Australia



Three major classes of function were identified

1. **Ingestive behaviors**: Detection/identification prior to ingestion; Detection of expectancy violations; Appetite regulation; Breast orientation and feeding.
2. **Avoiding environmental hazards** (Fear related; Disgust related)
3. **Social communication** (Reproductive [inbreeding avoidance, fitness detection in prospective mates]; Emotional contagion [fear contagion, stress buffering]).

Cell and Tissue Research (2021) 383:559–567
https://doi.org/10.1007/s00441-020-03367-7

REVIEW

The importance of the olfactory system in human well-being, through nutrition and social behavior

Sanne Boesveldt[1] · Valentina Parma[2,3]

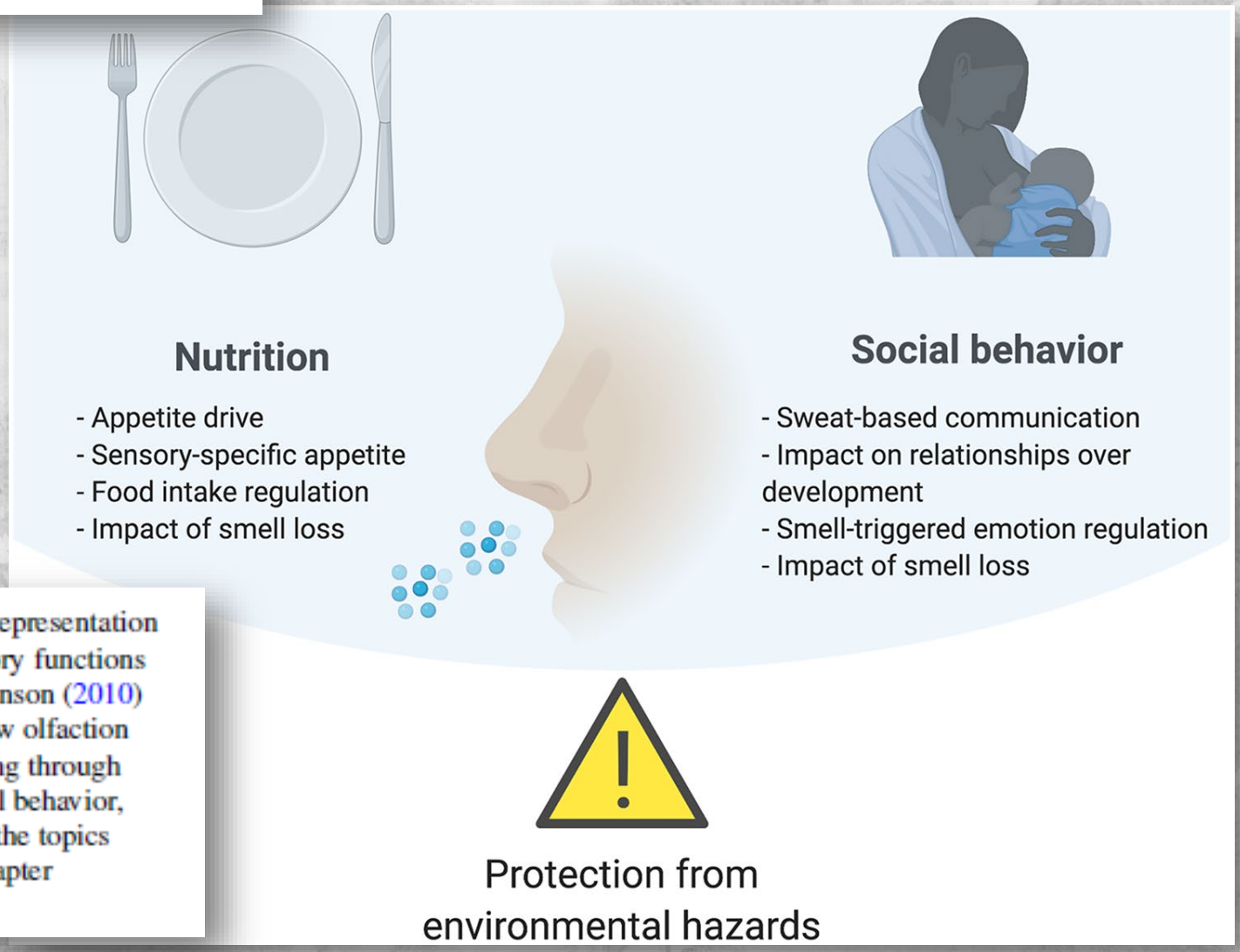


Fig. 1 Schematic representation of the three olfactory functions described by Stevenson (2010) with a focus on how olfaction promotes well-being through nutrition and social behavior, with an outline of the topics reviewed in the chapter

Chem. Senses 39: 185–194, 2014

doi:10.1093/chemse/bjt072
Advance Access publication January 15, 2014

Olfactory Disorders and Quality of Life—An Updated Review

Ilona Croy[1,3], Steven Nordin[2] and Thomas Hummel[3]

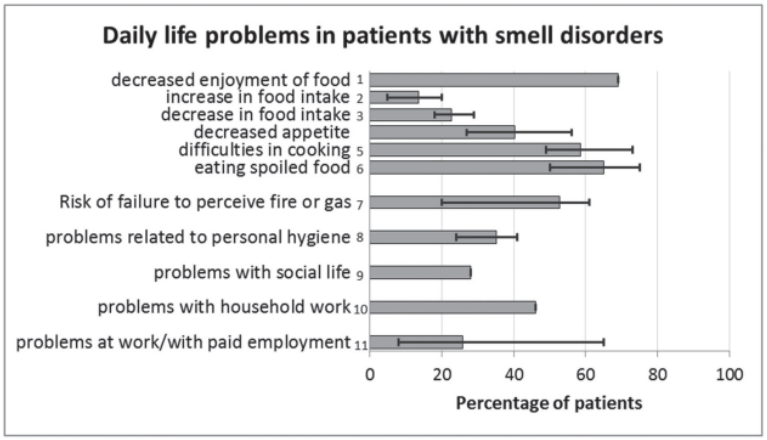


Figure 1 Daily life problems in patients with smell disorders. Results of 8 studies are included. The bars visualize the mean percentage of patients affected weighted by the number of participants per study. The error bars sh
on the following studies: Temmel et al. (2002), *n* = 278 (items 4–6
Nordin et al. (2011), *n* = 50 (item 4); Ferris and Duffy (1989), *n* =
n = 72 (item 4); Aschenbrenner et al. (2008), *n* = 176 (items 2,3).

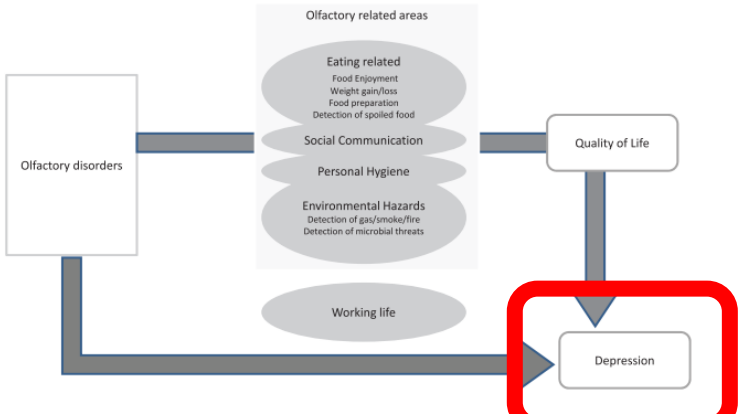


Figure 2 Pathways of depression in olfactory disorders. Olfactory impairment leads to restrictions in olfactory related areas, which can affect Quality of life and, by this pathway, enhance depression likelihood. Working life is directly affected in professions depending on olfactory ability, such as perfumers, firemen, or cooks. However, working life is also impaired in professions where olfactory-related areas play a major role, such as detecting microbial threats in nurses. A second pathway refers to potentially altered brain functioning in olfactory disorders.

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Journals of Gerontology: Medical Sciences
cite as: *J Gerontol A Biol Sci Med Sci*, 2017, Vol. 72, No. 8, 1072–1079
doi:10.1093/gerona/glx054
Advance Access publication April 21, 2017

OXFORD

Research Article

Prevalence and Correlates of Olfactory Dysfunction in Old Age: A Population-Based Study

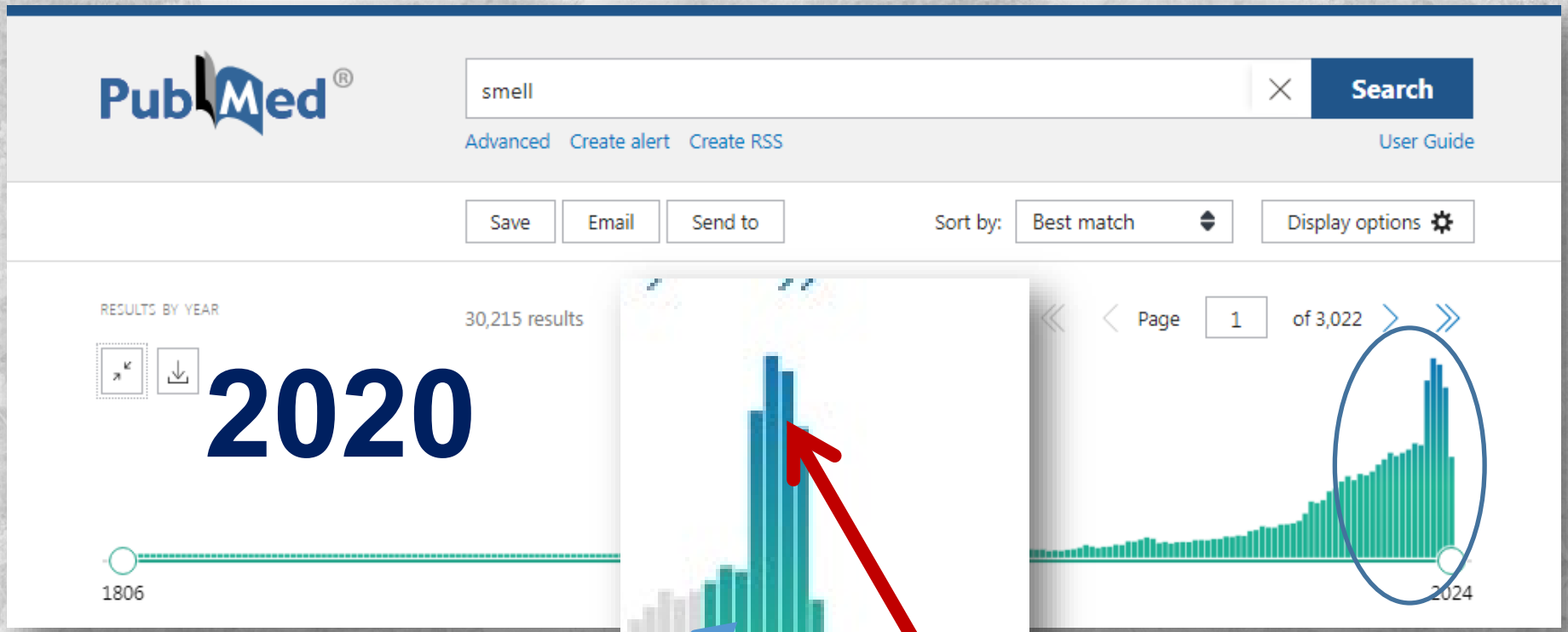
Janina Seubert,[1,2] Erika J. Laukka,[1] Debora Rizzuto,[1] Thomas Hummel,[3] Laura Fratiglioni,[1,4] Lars Bäckman,[1,4] and Maria Larsson[5]

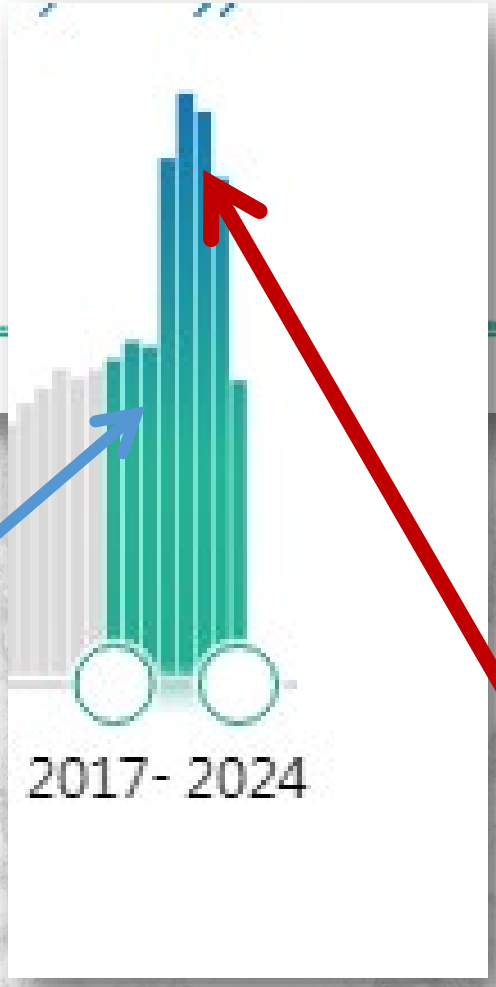
	Women						Men					
Age	% OD (*n*/total)		hyposmic		anosmic		% OD (*n*/total)		hyposmic		anosmic	
60	8.6	(31/361)	8.3	(30)	0.3	(1)	14.6	(42/288)	12.5	(36)	2.1	(6)
66	10.3	(28/272)	8.1	(22)	2.2	(6)	19.8	(40/202)	14.9	(30)	5.0	(10)
72	17.9	(40/224)	17.0	(38)	0.9	(2)	28.8	(45/156)	23.1	(36)	5.8	(9)
78	29.2	(62/212)	23.6	(50)	5.7	(12)	48.5	(48/99)	32.3	(32)	16.2	(16)
81	43.8	(39/89)	27.0	(24)	16.7	(15)	45.8	(22/48)	31.3	(15)	14.6	(7)
84	36.8	(28/76)	26.3	(20)	10.5	(8)	58.1	(25/43)	48.8	(21)	9.3	(4)
87	53.7	(29/54)	40.7	(22)	12.9	(7)	75	(18/24)	41.6	(10)	33.3	(8)
90	66.2	(43/65)	49.2	(32)	16.9	(11)	66.7	(14/21)	42.9	(9)	23.8	(5)

	OD, P% (*n*)			
Characteristic	No (*n* = 1,680)		Yes (*n* = 554)	
Gender				
male	37.3	(627)	45.8	(254)
female	62.7	(1053)	54.2	(300)
Education (mean)	*M* = 12.8		*M* = 11.3	
APOE (ε4 Carrier)	27.6	(442)	33.2	(169)
BDNF (Val/Val Carrier)	65.3	(986)	71.5	(348)
Heart failure	5.9	(99)	15.3	(85)
Coronary heart disease	12.9	(216)	24.2	(134)
Atrial fibrillation	11.5	(193)	19.3	(107)
Cerebrovascular disease	5.8	(98)	10.1	(56)
High cholesterol	13.8	(226)	9.8	(53)
Hypertension	46.9	(787)	59.1	(327)
Migraine	4.0	(67)	1.4	(8)
Depression	3.0	(50)	5.6	(31)
Inadequate physical activity	22.0	(369)	29.8	(165)
Manufacturing occupation	17.2	(289)	24.7	(136)
BMI				
underweight	1.1	(18)	3.6	(19)
Nutritional status	10.7	(144)	15.2	(67)
Poor appetite	0.2	(3)	1.4	(8)

The present study examined the prevalence of OD, and its associations with demographic, genetic, clinical, and behavioral factors, in an urban elderly population-based sample free from neurodegenerative disease.

In older adults, olfaction, but not visual or hearing impairment, is associated with increased mortality





2019
1179
pubblicazioni

2021
2118 pubblicazioni

Dal 2020 7882 lavori
(26% delle pubblicazioni sull'olfatto negli ultimi 4 anni)

Olfactory Dysfunction in COVID-19 Patients: Prevalence and Prognosis for Recovering Sense of Smell

Luca D'Ascanio, MD[1]*, Manlio Pandolfini, MD[1], Cristina Cingolani, MD[1], Gino Latini, MD[1], Paolo Gradoni, MD[1], Maria Capalbo[2], Gabriele Frausini, MD[3], Massimo Maranzano[4], Michael J. Brenner, MD[5]*, and Arianna Di Stadio, MD, PhD[6]*

Received June 8, 2020; accepted June 30, 2020.

Materials and Methods

The study was conducted at Santa Croce Hospital AORMN (Fano-Pesaro, Italy) from February 1, 2020, to April 24, 2020. All patients were >18 years and underwent diagnostic testing for COVID-19 using SARS CoV-2 RNA quantitative reverse transcription polymerase chain reaction (RT-qPCR) viral detection via nasopharyngeal swab.[13-16] For patients who came to the hospital, nasopharyngeal swabs were performed by the emergency department nurse, and patients who tested positive were admitted and enrolled to the hospitalized group. For patients not requiring emergency care,

1. Did you have a decreased sense of smell before the start of COVID-19 pandemic?
   Yes No
2. Did your sense of smell decrease with COVID-19? (If no loss of smell, skip all other questions)
   Yes No
3. Do you have a partial or complete loss of smell?
   I cannot smell anything at all I have partial decrease in sense of smell
4. When did your sense of smell decrease in relation to testing positive for COVID-19?
   At least a day before I tested positive | On the same day I tested positive | At least a day after I tested positive
5. Have you experienced headache in association with loss of smell alteration?
   Yes No
6. For how long has your decreased sense of smell persisted?
   < 5 days | 5 to 10 days | > 10 days
7. Is your sense of smell still decreased now?
   Yes No

60%

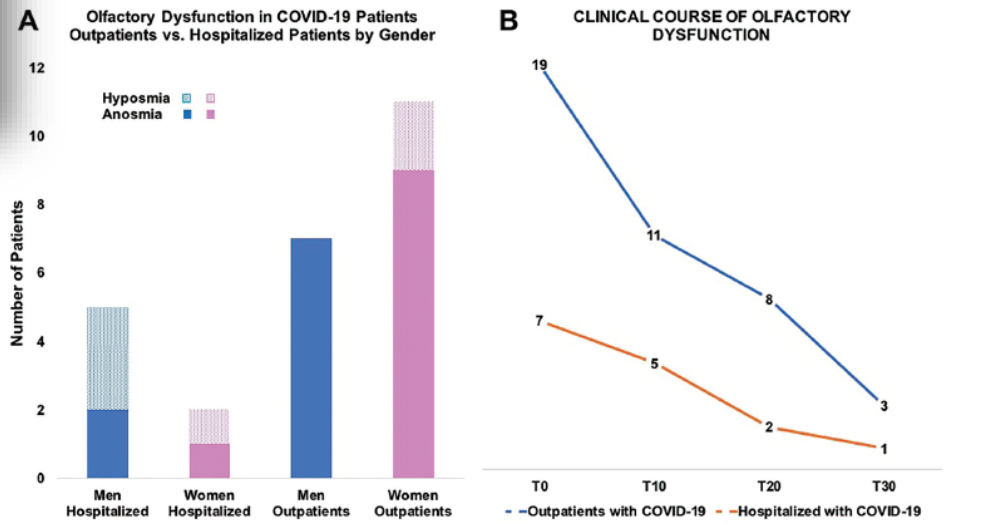


Figure 2. Olfactory dysfunction and clinical course. (A) Anosmia and hyposmia in patients with coronavirus disease 2019 (COVID-19), broken down by sex and inpatient vs outpatient status. (B) Clinical course of olfactory dysfunction in patients with COVID-19. The blue interrupted line corresponds to outpatients, and the orange line is inpatients.

Otolaryngology Head Neck Surg 2021, Vol 164(1): 82-86.

Art. 1.11349-PM 254

European Review for Medical and Pharmacological Sciences 2022; 26:

Hyperosmia after COVID-19: hedonic perception or hypersensitivity?

A. DI STADIO[1], L. D'ASCANIO[2], P. DE LUCA[3], D. ROCCAMATISI[4], I. LA MANTIA[1], M.J. BRENNER[5]

brain sciences MDPI

Article

Olfactory Dysfunction, Headache, and Mental Clouding in Adults with Long-COVID-19: What Is the Link between Cognition and Olfaction? A Cross-Sectional Study

Arianna Di Stadio [1,*,†], Michael J. Brenner [2], Pietro De Luca [3], Maria Albanese [4], Luca D'Ascanio [5], Massimo Ralli [6], Dalila Roccamatisi [7], Cristina Cingolani [5], Federica Vitelli [5], Angelo Camaioni [8], Stefano Di Girolamo [9] and Evanthia Bernitsas [10,†]

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CLINICAL TRIAL STUDY

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Ultramicronized Palmitoylethanolamide and Luteolin Supplement Combined with Olfactory Training to Treat Post-COVID-19 Olfactory Impairment: A Multi-Center Double-Blinded Randomized Placebo-Controlled Clinical Trial

Arianna Di Stadio[1,*,#], Luca D'Ascanio[2], Luigi Angelo Vaira[3,4], Elena Cantone[5], Pietro De Luca[6], Cristina Cingolani[2], Gaetano Motta[5], Giacomo De Riu[3], Fe [illegible] Marco De Vincentiis[9], Angelo Camaioni[10], Ignazio La Ma [illegible] Brenner[11,#]

Di Stadio A, D'Ascanio L, La Mantia I, Ralli M, Brenner MJ. Parosmia after COVID-19: olfactory training, neuroinflammation and distortions of smell. Eur Rev Med Pharmacol Sci. 2022 Jan;26(1):1-3.

Comment > JAMA Otolaryngol Head Neck Surg. 2023 Jul 1;149(7):650.

doi: 10.1001/jamaoto.2023.1134.

Visual-Olfactory Training and Patient Preference in Treatment of COVID-19 Olfactory Loss-How Salient Stimuli Might Support Recovery of Smell

Arianna Di Stadio [1 2], Luca D'Ascanio [3], Michael J Brenner [4]

European Archives of Oto-Rhino-Laryngology (2024) 281:3671–3678
https://doi.org/10.1007/s00405-024-08548-6

RHINOLOGY

Check for updates

Persistent COVID-19 parosmia and olfactory loss post olfactory training: randomized clinical trial comparing central and peripheral-acting therapeutics

Elena Cantone[1] · Luca D'Ascanio[2] · Pietro De Luca[3] · Dalila Roccamatisi[4] · Ignazio La La Mantia[5] · Michael J. Brenner[6] · Arianna Di Stadio[5,7]

COVID-19, food supplements and pediatricians. Knowledge of the products and their use: a national survey.

A Della Volpe, L D'Ascanio, A Di Stadio,

Eur Rev Med Pharmacol Sci 25(24):

Rhinology in review: from COVID-19 to biologicals*

Wytske J. Fokkens[1], Basile N. Landis[2], Claire Hopkins[3], Sietze Reitsma[1], Ahmad R. Sedaghat[4]

[1] Department of Otorhinolaryngology, Amsterdam University Medical Centres, location AMC, Amsterdam, The Netherlands

[2] Department of Otorhinolaryngology, Geneva University Hospitals, Geneva, Switzerland; Faculty of Medicine, University of Geneva, Geneva, Switzerland

[3] Department of Otorhinolaryngology, Guy's Hospital, London, UK

[4] Department of Otolaryngology – Head and Neck Surgery, University of Cincinnati College of Medicine, Cincinnati, Ohio, USA

Rhinology 59: 6, 490 - 500, 2021

https://doi.org/10.4193/Rhin21.424

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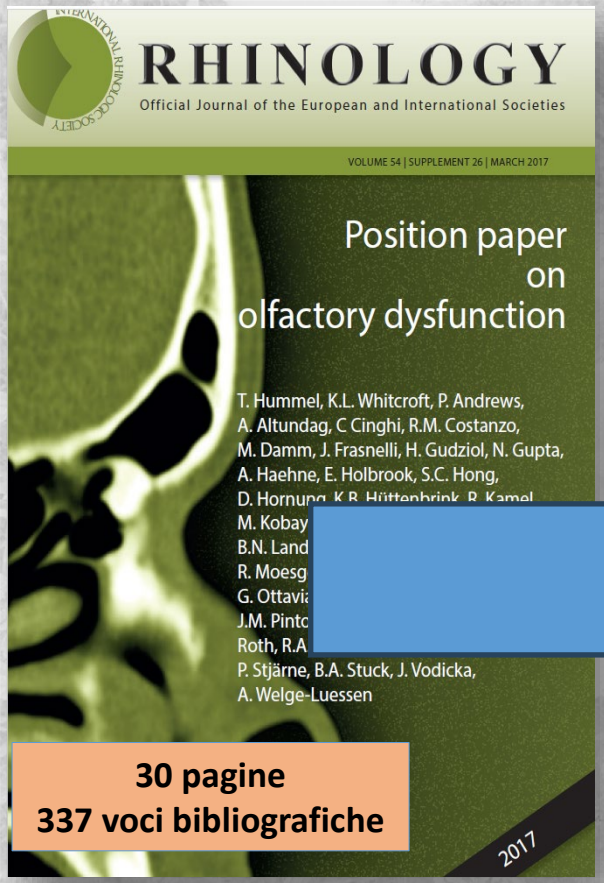
November 12, 2021

Accepted: November 16, 2021

2021

Abstract

We look back at the end of what soon will be seen as an historic year, from COVID-19 to real-world introduction of biologicals influencing the life of our patients. This review describes the important findings in Rhinology over the past year. A large body of evidence now demonstrates loss of sense of smell to be one of the most common symptoms of COVID-19 infection; a meta-analysis of 3563 patients found the mean prevalence of self-reported loss to be 47%. A number of studies have now shown long-term reduced loss of smell and parosmia. Given the high numbers of people affected by COVID-19, even with the best reported recovery rates, a significant number worldwide will be left with severe olfactory dysfunction. The most prevalent causes for olfactory dysfunction, besides COVID-19 and upper respiratory tract infections in general, are trauma and CRSwNP. For these CRSwNP patients a bright future seems to be starting with the development of treatment with biologics.



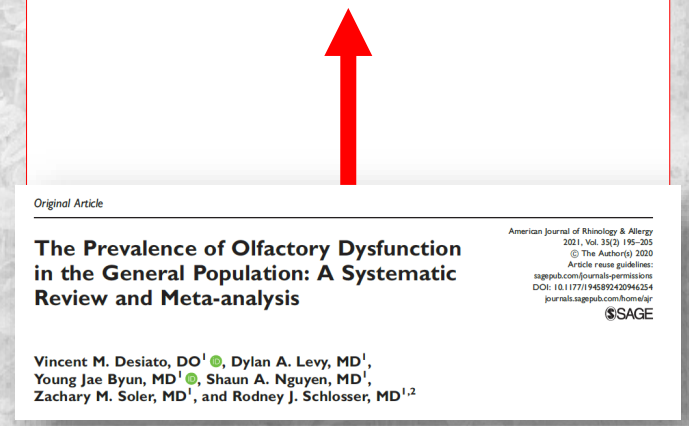
30 pagine
337 voci bibliografiche

116 pagine
725 voci bibliografiche

Executive summary

Since publication of the original Position Paper on Olfactory Dysfunction in 2017 (PPOD-17), the personal and societal burden of olfactory disorders has come sharply into focus through the lens of the COVID-19 pandemic. Clinicians, scientists and the public are now more aware of the importance of olfaction, and the impact of its dysfunction on quality of life, nutrition, social relationships and mental health. Accordingly, new basic, translational and clinical research has resulted in significant progress since the PPOD-17. However, the overall quality of evidence, particularly for the management of olfactory dysfunction (OD), continues to lag behind that of other sensory impairments.

Meta-analytic work demonstrates that olfactory dysfunction affects approximately 22% of the general population



Original Article

The Prevalence of Olfactory Dysfunction in the General Population: A Systematic Review and Meta-analysis

American Journal of Rhinology & Allergy
2021, Vol. 35(2) 195–205

DOI: 10.1177/1945892420946254
journals.sagepub.com/home/ajr
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Vincent M. Desiato, DO[1], Dylan A. Levy, MD[1], Young Jae Byun, MD[1], Shaun A. Nguyen, MD[1], Zachary M. Soler, MD[1], and Rodney J. Schlosser, MD[1,2]

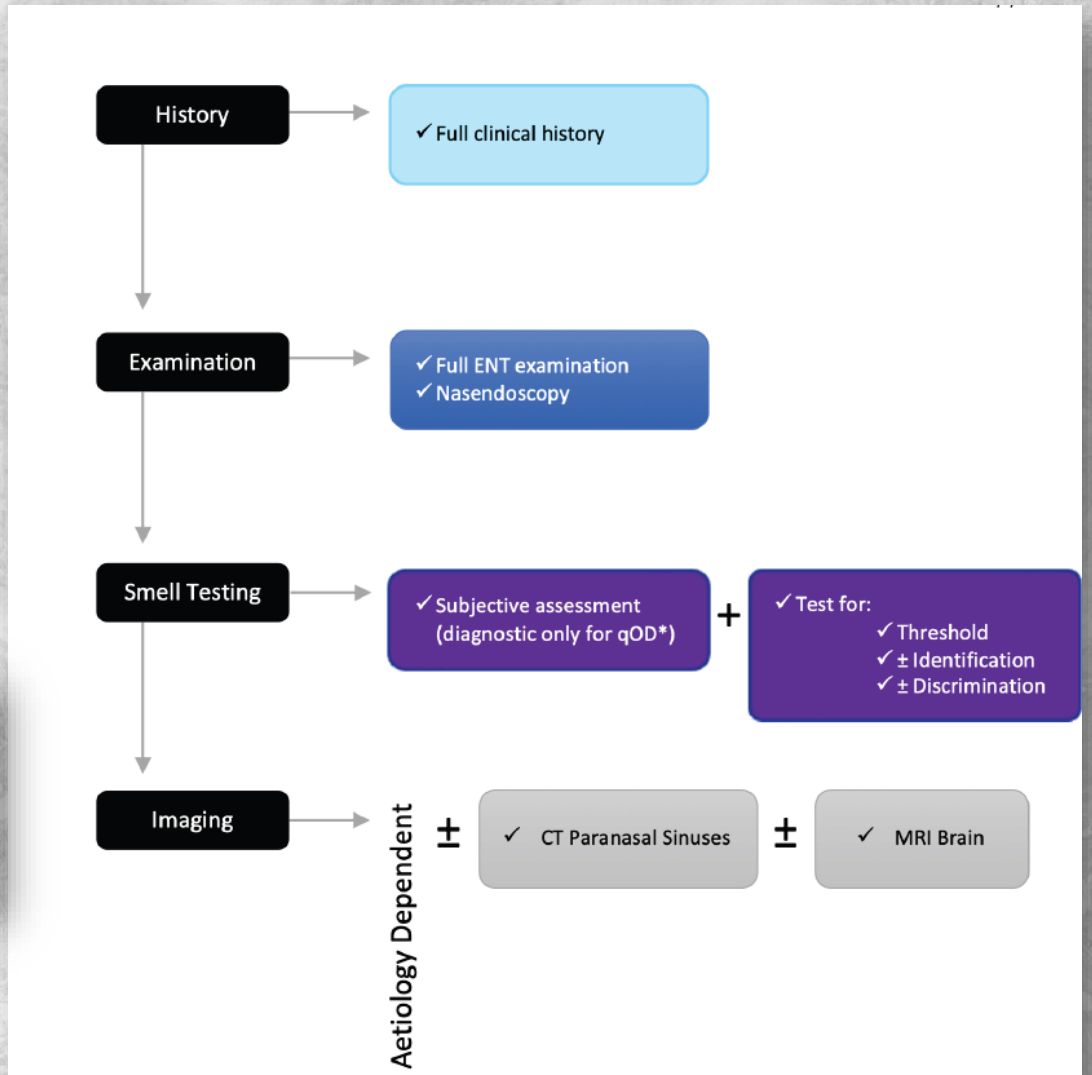
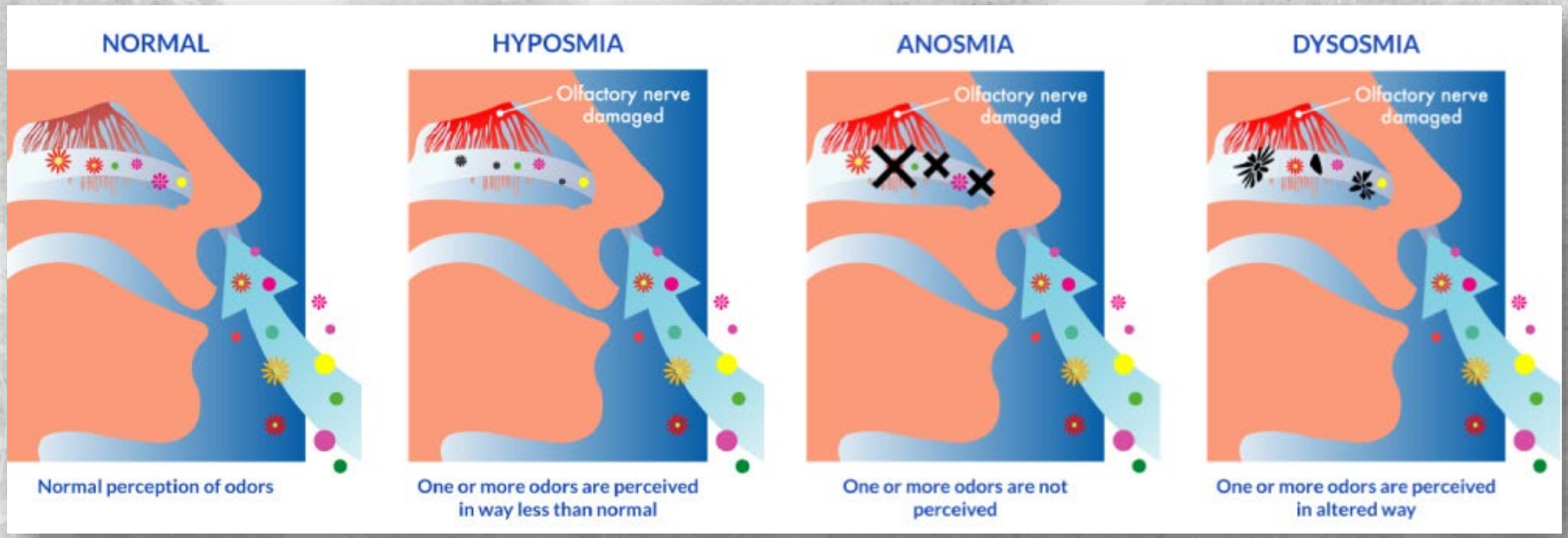
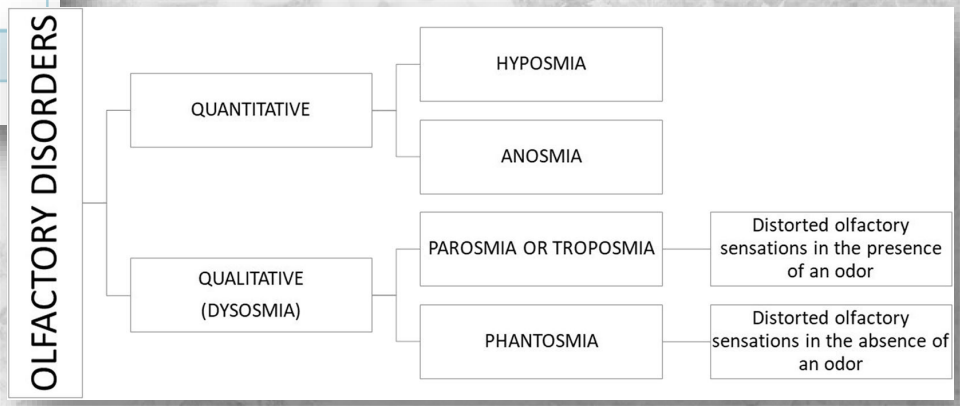


Figure e1. Basic summary flowchart of clinical assessment (for full flowchart see Figure 4).



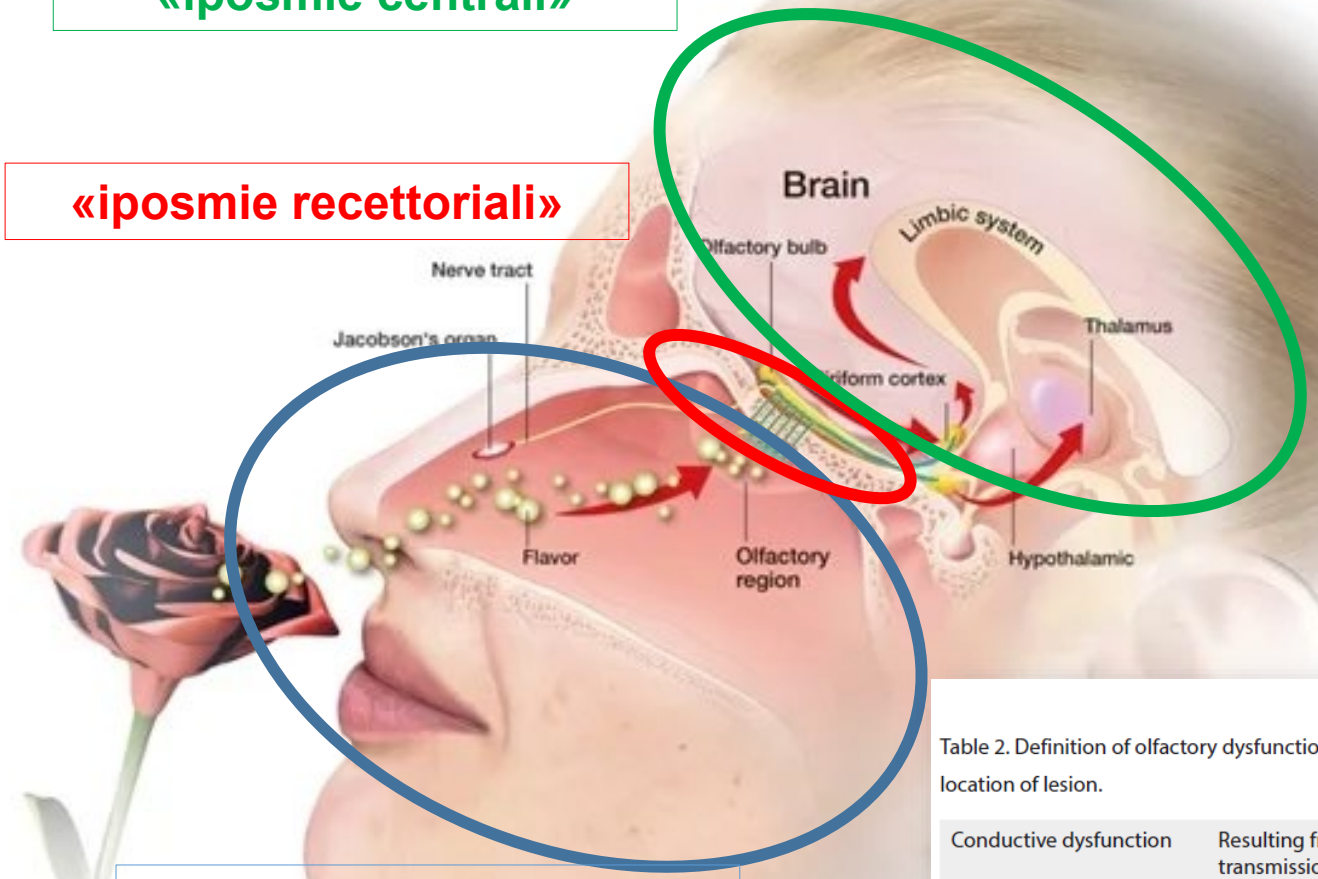
Types of Smell Disorders	
Presbyosmia	Smell loss due to aging
Hyposmia	Loss of only certain odors
Anosmia	Total loss of smell
Dysosmia	Change in the perception of odors. Familiar odors are distorted.
Phantosmia	Smell odors that are not present

Adapted from NIH Senior Health: Problems with Smell



«iposmie centrali»

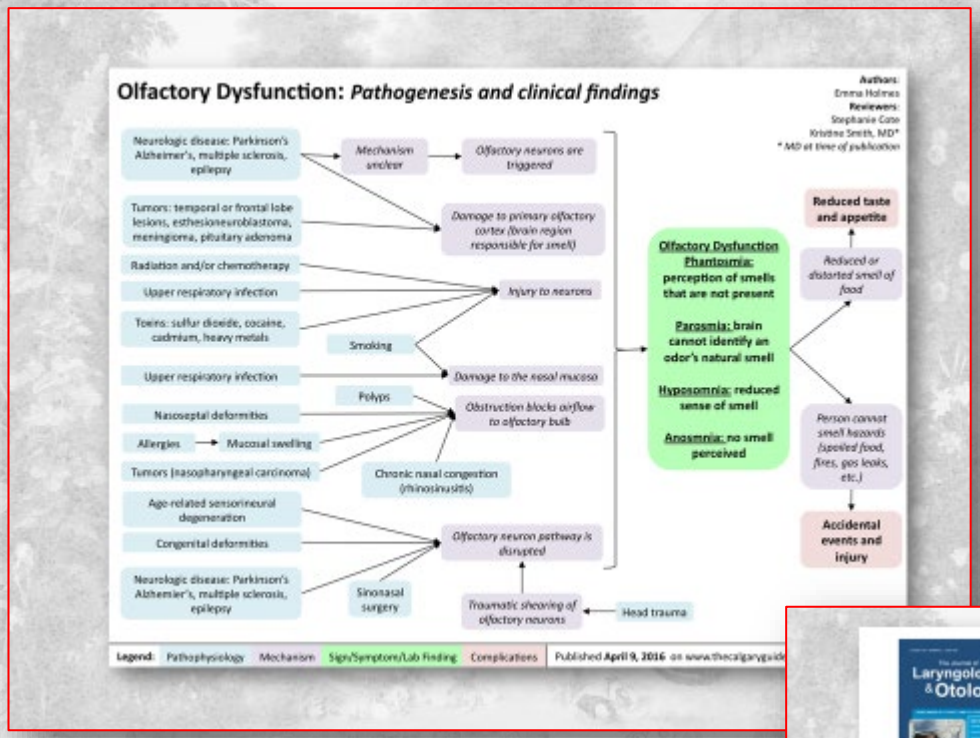
«iposmie recettoriali»

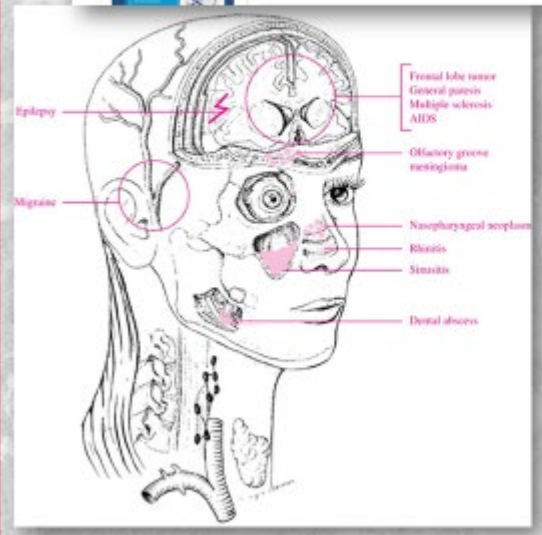


«Iposmie trasmissive»

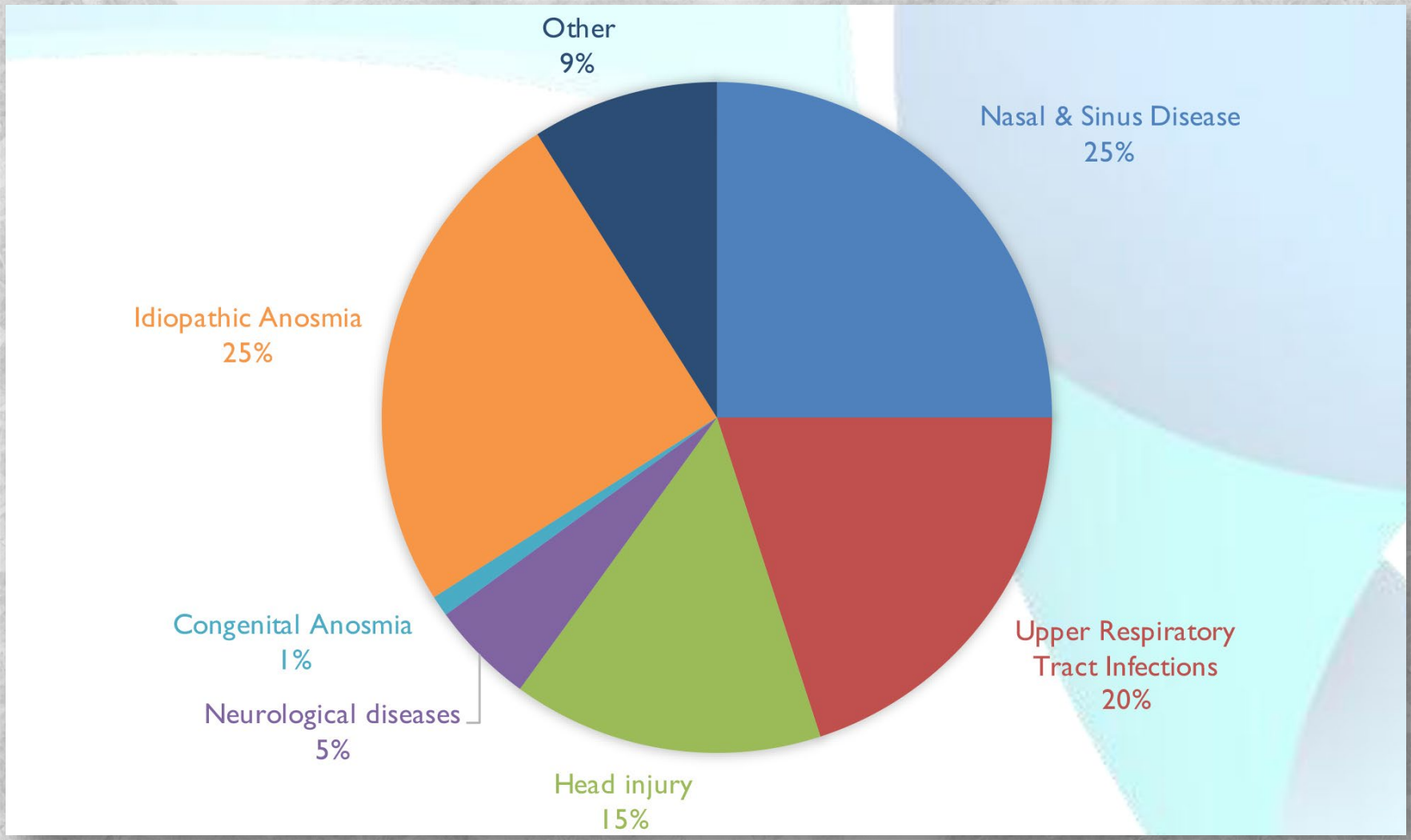
Table 2. Definition of olfactory dysfunction according to anatomical location of lesion.

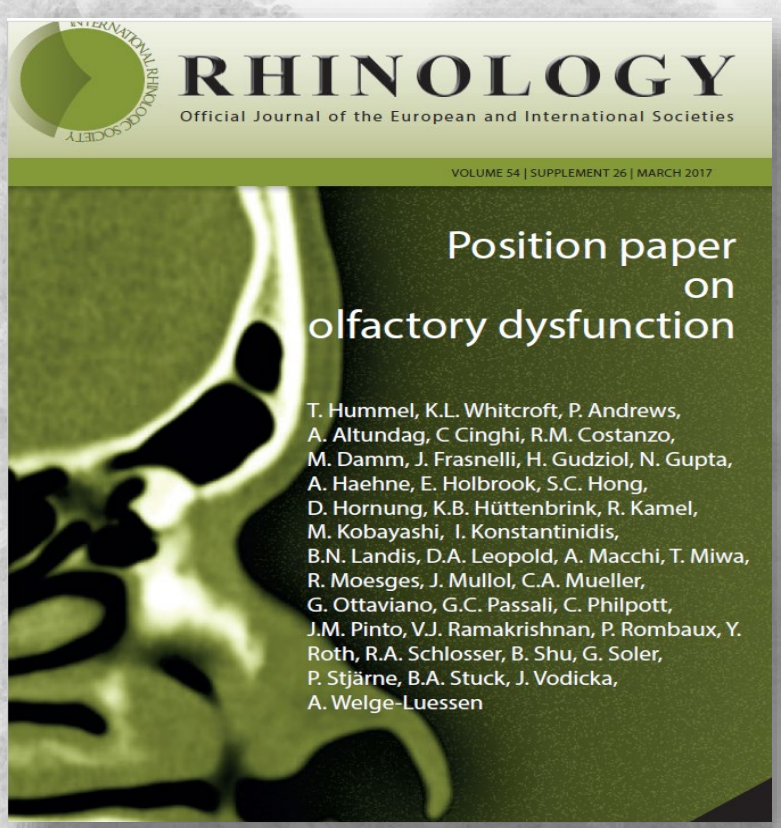
Conductive dysfunction	Resulting from blockage of odourant transmission to the olfactory neuroepithelium.
Sensorineural dysfunction	Resulting from damage/loss of the olfactory neuroepithelium or nerve.
Central dysfunction	Resulting from damage/loss of the olfactory processing pathways of the central nervous system.





Category	Disease
Neurological	Alzheimer's disease
	Down syndrome
	Epilepsy
	Multiple sclerosis
	Parkinson's disease
Congenital	Kallman syndrome
	Choanal atresia
Nutritional & metabolic	Chronic renal failure
	Liver disease
	Vitamin B12 deficiency
Endocrine	Diabetes
	Adrenal cortex insufficiency
	Hypothyroidism
	Cushing's disease
Trauma	Head injury
	Laryngectomy
Inflammatory	Rhinosinusitis or nasal polyposis
	Sarcoid
	Wegener's disease
Neoplastic	Olfactory neuroblastomas
	Anterior skull base tumours
Degenerative	Age
Infective	Acute viral hepatitis
	HIV
	Influenza-like
Other	Adenoid hypertrophy
	Familial
	Psychiatric


Other
9%
Nasal & Sinus Disease
25%
Idiopathic Anosmia
25%
Congenital Anosmia
1%
Neurological diseases
5%
Upper Respiratory
Tract Infections
20%
Head injury
15%



Olfactory Testing

The method used for assessing olfactory function and dysfunction is vitally important with respect to accurate diagnosis, outcome reporting and tracking of olfactory changes over time. A limitation of the current literature base is the heterogeneity of assessment techniques used, with consequent effect on definitions of impairment and improvement. As highlighted in the epidemiology section above, this can lead, for example, to large differences in estimated prevalence rates, and impacts significantly on the generalisability of results, especially where non-standardised and potentially unreliable tests are used.

In general, three different types of olfactory testing can be undertaken:

1. **Subjective**, patient reported olfactory assessment.
2. **Psychophysical olfactory assessment.**
3. **Olfactory assessment using electrophysiological studies or magnetic resonance imaging**

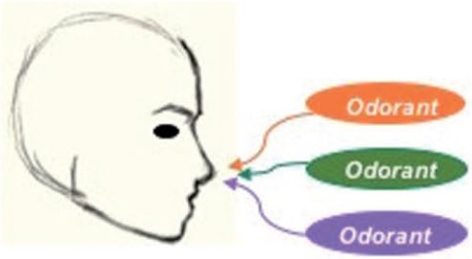
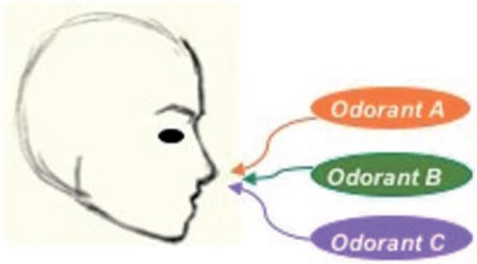
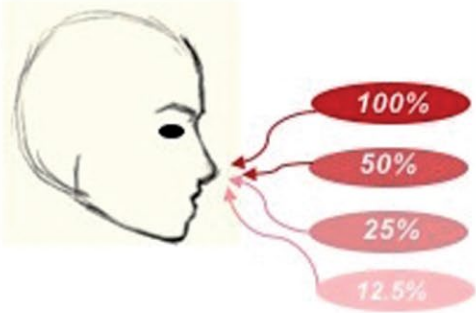
Psychophysical olfactory assessment

La **soglia** dell'odore è la concentrazione di un odorante in cui il 50% degli stimoli viene rilevato e il 50% rimane non rilevabile per un soggetto.

La **discriminazione** degli odori descrive la capacità non verbale di distinguere tra diversi odori.

L'**identificazione** degli odori comporta sia il riconoscimento di uno stimolo sia la comunicazione della sua identità corretta (vale a dire, la capacità di nominare un odore).

Psychophysical test	Olfactory components assessed
"Sniffin' Sticks" (original version)	Threshold, discrimination, identification
Connecticut Chemosensory Clinical Research Center Test	Threshold, identification
T & T Olfactometer	Threshold, identification
University of Pennsylvania Smell Identification Test	Identification
Smell Diskettes Test	Identification
Cross-Cultural Smell Identification Test	Identification
Pocket Smell Test	Identification
San Diego Odor Identification Test	Identification
Scandinavian Odour Identification Test	Identification
Smell Threshold Test	Threshold
Olfactory Perception Threshold Test	Threshold
Barcelona Smell Test (BAST-24)	Odour detection, identification, memory
Odourized Marker Test	Identification
Snap & Sniff Olfactory Test System	Threshold
Open Essence	Identification

Odor Identification	Odor Discrimination	Odor Threshold
		
This odorant smells like: *A.* *B.* *C.* *D.*	*Which odorant smells different?* *A.* *B.* *C.*	*Which concentration was hardest to detect?* *A.* *B.* *C.* *D.*
Subject is presented with different odorants (one at a time) and are required to identify the odor from a list.	To determine if subject can differentiate between odorants, subject must pick the odorant that smells different in a group.	Subject is provided with various concentrations of the same odorant and is asked to identify the hardest detectable concentration.

Servizio Sanitario Nazionale
Regione Marche
Azienda Ospedaliera
Ospedali Riuniti Marche Nord
Presidio Ospedaliero Santa Croce
Via Vittorio Veneto, 2 - 61032 Fano
Presidio Ospedaliero San Salvatore
P.le Cinelli, 4 – 61121 Pesaro

Direttore
Dr. Luca D'Ascanio
Segreteria Fano 0721 882853
Segreteria Pesaro 0721 382269

OTORINOLARINGOIATRIA

Data
Nome: Occupazione: Sesso:

Data di nascita:

Anamnesi:

THRESHOLD TEST

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

Punteggio:

DISCRIMINATION TEST

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

Punteggio:

IDENTIFICATION TEST

1	**Arancio**	Fragola	Mora	Ananas
2	Fumo	**Pelle/cuoio**	Colla adesiva	Erba
3	Miele	Vaniglia	Cioccolato	**Cannella**
4	Erba cipollina	**Menta**	Abete pino	Cipolla
5	Cocco	**Banana**	Noce	Ciliegia
6	Pesca	Mela	**Limone**	Pompelmo
7	**Liquirizia**	Ciliegia	Menta	Biscotto
8	Senape	Mentolo	Gomma	**Acqua ragia**
9	Cipolla	**Aglio**	Carota	Crauti
10	Sigaretta	Vino	Fumo	**Caffè**
11	Melissa	Pesca	Arancio	**Mela**
12	**Chiodo garofano**	Pepe	Cannella	Senape
13	Pera	Prugna	Pesca	**Ananas**
14	Camomilla	Lampone	**Rosa**	Ciliegia
15	**Anice**	Rum	Miele	Abete pino
16	Pane	**Pesce**	Formaggio	Prosciutto

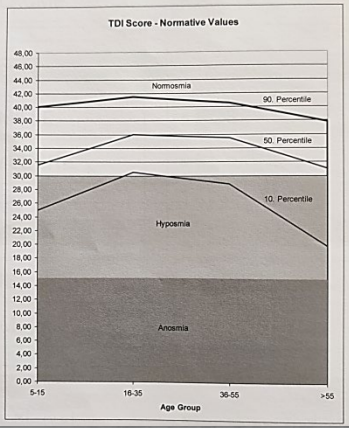
Punteggio:

TDI-SCORE:

TDI – Score

48 – 31 Normosmia
30 – 16 Hyposmia
<= 15 Functional Anosmia

The following graph can be used for an advanced evaluation. With it's help you can make additional statements about age-related evaluation.



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Olfactory dysfunction in aging and neurodegenerative diseases

Xiuli Dan[1], Noah Wechter[1], Samuel Gray[1], Joy G. Mohanty[1], Deborah L. Croteau[1], Vilhelm A. Bohr[1,2,*]

3. Measures of olfactory functions

3.1 Four major aspects of olfactory evaluation

Carefully designed behavioural tests are vital tools in characterizing OD. Many of the tests below were selected for their widespread use as reliable assays for basic olfactory functions shared by humans and most model organisms. The tests assess odor identification, discrimination, sensitivity, and habituation. Olfactory functions are regulated by different regions of the brain which are also relevant to aging, PD and AD (Fig. 3).

Odor identification is the detection and recall of a previous smell associated with an individual's knowledge or experience (Murphy, 2019). The key brain regions in humans and mammalian animal models involved in odor identification are the entorhinal cortex, hippocampus, insula, orbitofrontal cortex, inferior frontal gyrus, piriform cortex, thalamus, and amygdala (Kjelvik et al., 2012; Merrick et al., 2014; Wu et al., 2019). Odor identification is affected by sensitivity to different aspects of the odorant, integration of these aspects to define its qualities, and further integration with previous experiences to provide identity and significance. In humans, this is indicated by recognition and correct naming of an odor presented during the test. For animal models, this relies on a specific behavioural response on exposure, such as travel towards an attractive odorant, or away from a repellent one. Odor identification has been found to be a central deficit in early stages of AD and PD (Kjelvik et al., 2012), as well as in normal aging (Seubert et al., 2017).

Odor discrimination is the ability to distinguish between two or more odors (Hummel et al., 1997). It relies heavily on the hippocampus, piriform cortex, orbitofrontal cortex, and thalamus (Martin et al., 2007; Merrick et al., 2014; Tanabe et al., 1975; Wilson, 2009). Like odor identification, odor discrimination is tied closely to cognitive abilities and is thought to be developed through experiencing odors (Hedner et al., 2010). Essentially, an odor must be learned before it can be discriminated against other smells (Wilson, 2009). Similar to odor identification, odor discrimination declines with age (Hummel et al., 1997).

Odor sensitivity/threshold is the ability to detect an odor at a given concentration wherein the lowest detectable concentration is considered the threshold (Trimmer and Mainland, 2017). The brain regions involved in odor sensitivity include insula and hippocampus (Wabnegger et al., 2019). Odor sensitivity varies in individuals depending on the odorant qualities, pleasantness, and familiarity. Individual variation is also due in part to differences in the number of OSNs specific to that odorant. Sensitivity decreases with age, although the mechanism of this decline is not well understood. OSN sensitivity remains relatively consistent through age, as does axonal density and convergence on glomeruli (Lee et al., 2009; Richard et al., 2010). As such, peripheral changes of the olfactory system do not appear to provide sufficient explanation for changes in odor sensitivity with age.

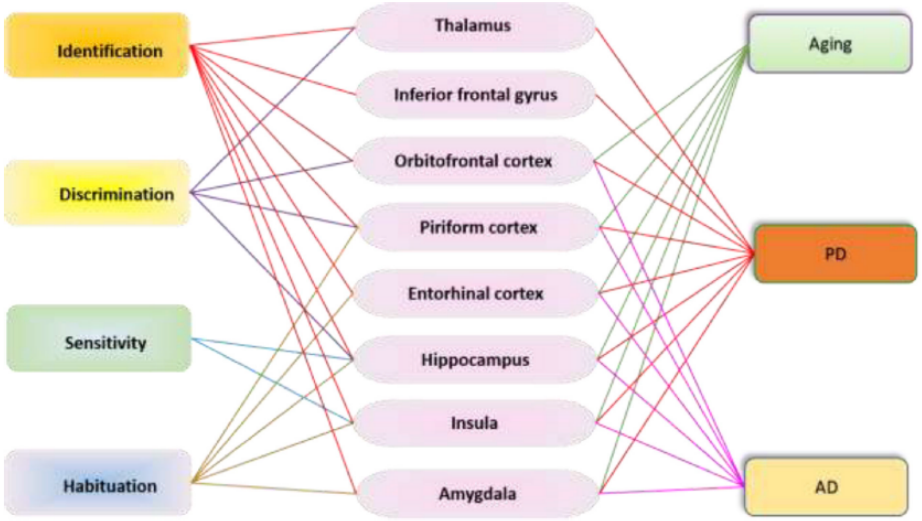
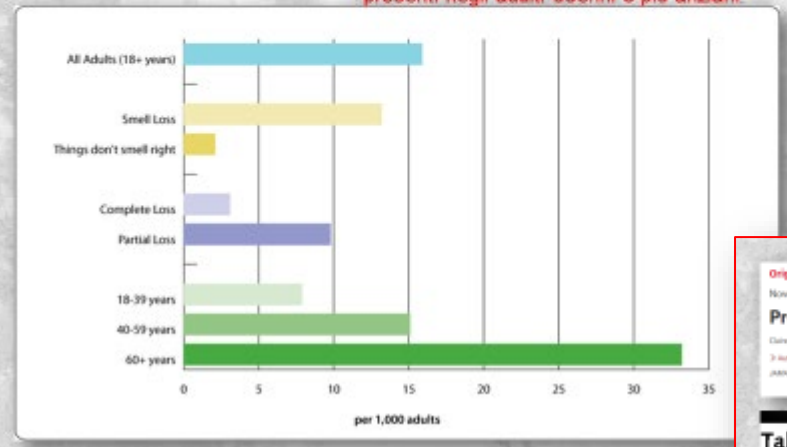


Fig.3.
The interconnection between different olfaction aspects and brain regions and the involvement of these brain region in aging, PD, and AD in human and mammalian animal models. Among the mentioned brain regions involved in olfaction, all are related with PD (Braak et al., 1994; Criaud et al., 2016; Henderson et al., 2000; Jia et al., 2019; Kobayakawa et al., 2017; Liu et al., 2019; Sancandi et al., 2018; Terada et al., 2018) and a majority (orbitofrontal cortex, piriform cortex, entorhinal cortex, hippocampus, insula, and amygdala) are related with AD (DeTure and Dickson, 2019; Saiz-Sanchez et al., 2015) and aging (Churchwell and Yurgelun-Todd, 2013; Gocel and Larson, 2013; Reagh et al., 2018; Resnick et al., 2007; St Jacques et al., 2010).

ANNALS OF THE NEW YORK ACADEMY OF SCIENCES

Age-Related Changes in the Prevalence of Smell/Taste Problems among the United States Adult Population: Results of the 1994 Disability Supplement to the National Health Interview Survey (NHIS)

Nel 1994 la National Health Interview Survey, prese random 42.000 famiglie tra una lista di famiglie precedentemente selezionate e riportò una stima nazionale della prevalenza dei problemi olfattivi e gustativi: i corretti tassi di prevalenza erano di 2,7 milioni di adulti (2,4%) con un problema olfattivo e 1,1 milione di adulti (0,6%) con problemi gustativi. Quando, invece, i problemi dell'olfatto e del gusto erano associati, 3,2 milioni (1,65%) di adulti segnalavano un problema chemiosensitivo cronico. I tassi di prevalenza aumentavano esponenzialmente con l'età, con quasi il 40% di tutti i problemi (1,5 milioni) presenti negli adulti 65enni o più anziani.



Alterazioni olfatto
25% dopo i 50 anni
40% dopo i 60 anni

Original Contribution

November 13, 2002

Prevalence of Olfactory Impairment in Older Adults

Table 2. Prevalence of Olfactory Impairment by Age and Sex*

	Women		Men		Total	
Age, y	No. at Risk	Prevalence, % (95% CI)	No. at Risk	Prevalence, % (95% CI)	No. at Risk	Prevalence, % (95% CI)
53-59	319	3.8 (1.7-5.9)	214	9.1 (5.5-12.8)	560	6.1 (4.1-8.1)
60-69	463	11.2 (8.4-14.1)	385	24.7 (20.4-29.0)	848	17.3 (14.8-19.9)
70-79	429	20.8 (16.9-24.6)	315	40.6 (35.2-46.1)	744	29.2 (25.9-32.5)
80-97	234	59.4 (53.1-65.7)	105	69.5 (60.7-78.3)	339	62.5 (57.4-67.7)
All ages	1445	20.2 (18.1-22.3)	1046	30.4 (27.6-33.2)	2491	24.5 (22.8-26.2)

*CI indicates confidence interval.

This is the first large population-based study to our knowledge to report the prevalence of olfactory impairment measured by testing. The prevalence of measured olfactory impairment in this study of older persons was quite high (24.5% overall), and impairment increased with advancing age in both men and women. According to the 2000 census, there are approximately 60 million Americans aged 55 years or older.14 Thus, we estimate that approximately 14 million older adults in the United States have olfactory impairment.

Causes and classification of olfactory dysfunction

- Post infectious olfactory dysfunction (PIOD)
  - o COVID-19-associated PIOD (C19OD)
  - o Non-COVID-19-associated PIOD
- Olfactory dysfunction secondary to sinonasal disease
- Post-traumatic olfactory dysfunction (PTOD)
- Olfactory dysfunction associated with neurological disease
- Olfactory dysfunction associated with exposure to drugs/ toxins
- Congenital olfactory dysfunction
- Olfactory dysfunction associated with aging (presbyosmia)
- Other possible causes: iatrogenic - complications (e.g., sinonasal and skull base surgery), iatrogenic - consequence (e.g., laryngectomy), tumours, multiple systemic co-morbi-dities
- Idiopathic olfactory dysfunction

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DOI: 10.1002/evan.22030

REVIEW ARTICLE

Evolutionary Anthropology WILEY

Smell throughout the life course

Alice C. Poirier[1] | Amanda D. Melin[1,2,3]

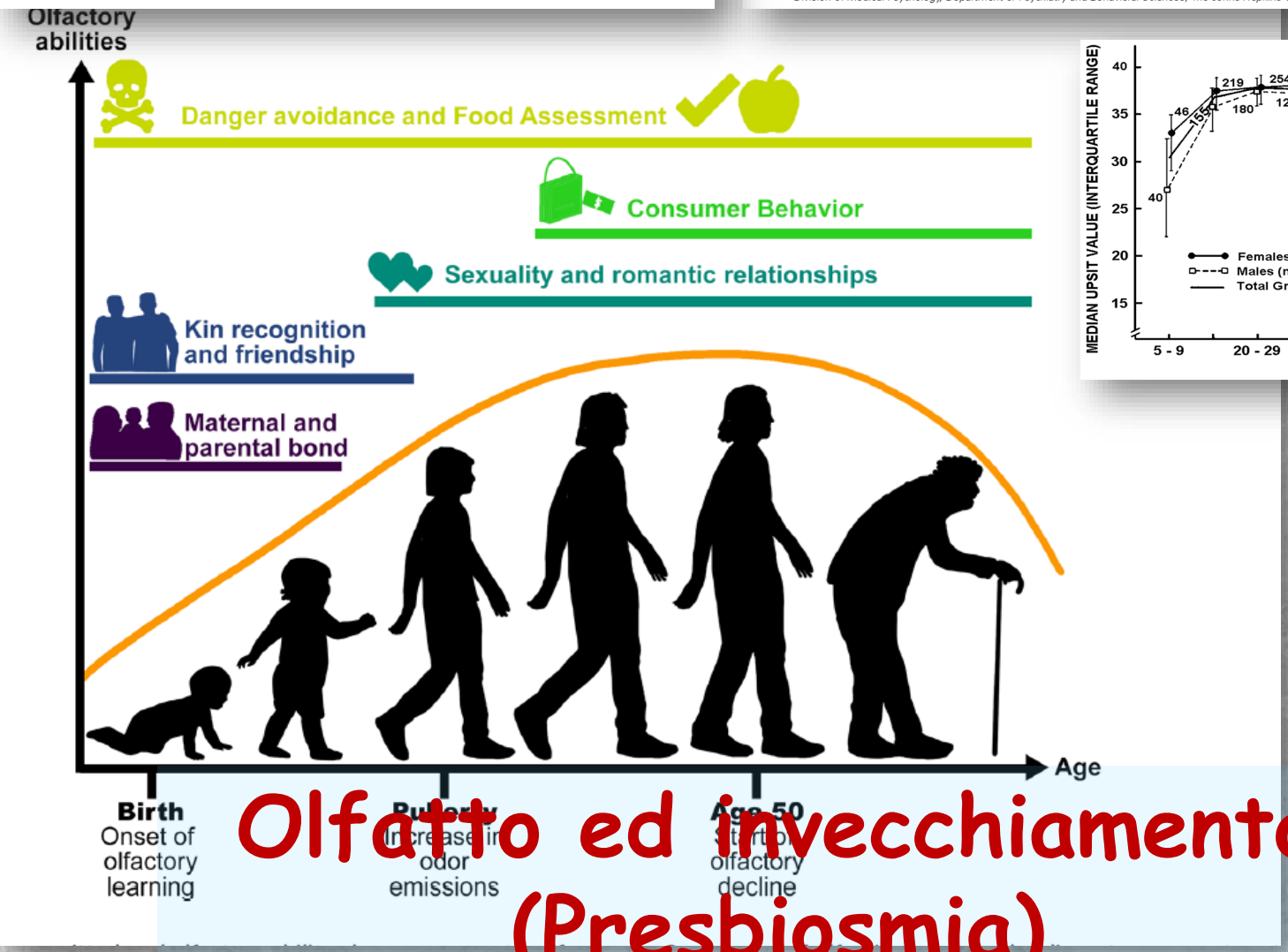
frontiers in PSYCHOLOGY

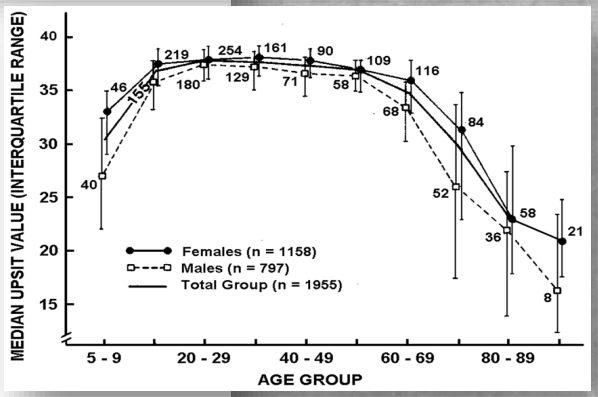
REVIEW ARTICLE
published: 07 February 2014
doi: 10.3389/fpsyg.2014.00020

The influences of age on olfaction: a review

Richard L. Doty[1] and Vidyulata Kamath[1,2]*

[1] Department of Otorhinolaryngology: Head and Neck Surgery, Smell and Taste Center, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA
[2] Division of Medical Psychology, Department of Psychiatry and Behavioral Sciences, The Johns Hopkins University School of Medicine, Baltimore, MD, USA





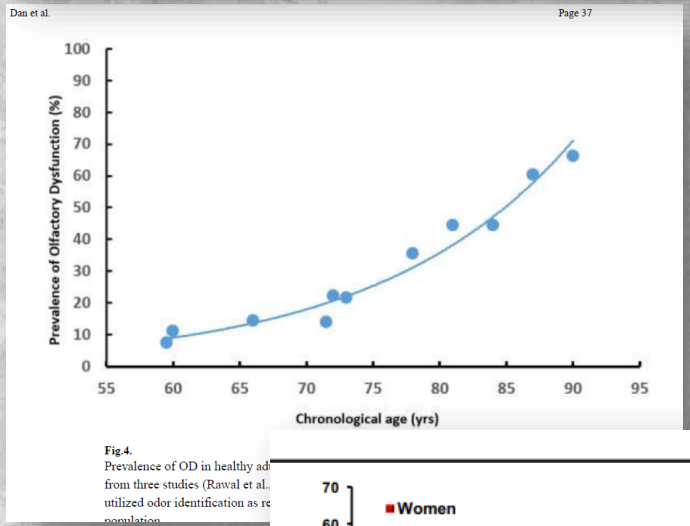
Olfatto ed invecchiamento (Presbiosmia)

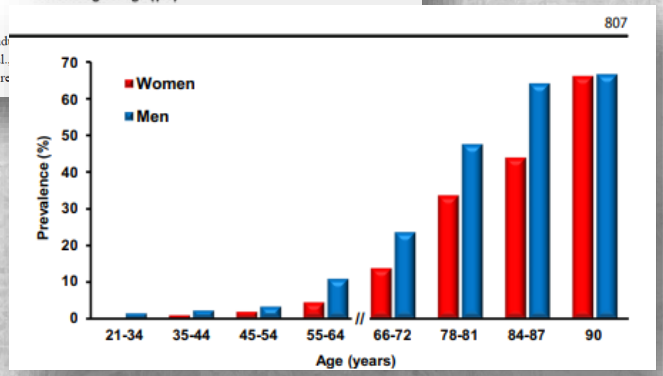
National Institute on Deafness and Other Communication Disorders

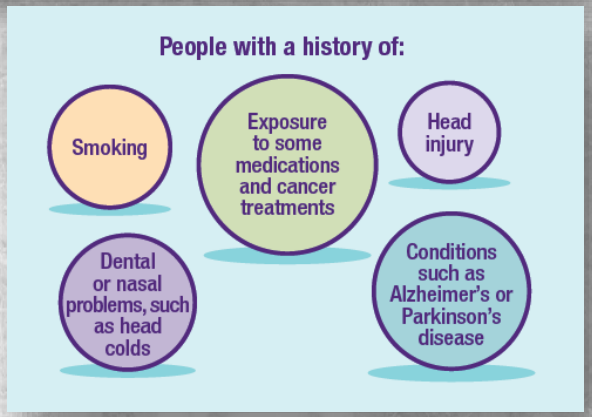
https://www.nidcd.nih.gov

https://twitter.com/nidcd

Sources:
Smell Disorders: https://www.nidcd.nih.gov/health/smell-disorders
U.S. National Health and Nutrition Examination Survey. Analyses reported in *Chemical Senses* in 2016, *JAMA Otolaryngology—Head & Neck Surgery* in 2018, and *Reviews in Endocrine and Metabolic Disorders* in 2016.







Multiple factors contribute to age-related olfactory sensory loss, including nasal engorgement, cumulative damage of the olfactory epithelium from environmental insults, a reduction in mucosal metabolizing enzymes, sensory loss of receptor cells to odorants, and changes in neurotransmitter and neuromodulator systems. In addition, structural and functional abnormalities of the olfactory epithelium, olfactory bulb, central olfactory cortex, and basic olfactory circuitry, which are related to the neuronal expression of aberrant proteins in these areas, may result in olfactory sensory impairment in aging and neurodegenerative diseases

Special Issue: Our Unique Sense of Smell

i-PERCEPTION

Olfaction and Aging: A Review of the Current State of Research and Future Directions

i-Perception
2021, Vol. 12(3), 1–24

DOI: 10.1177/20416695211020331
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Nutrition and Health

Malnutrition is a major concern regarding the aging population, in particular among the institutionalized aging persons. Between 3% and 10% of independently living aging adults and 25% to 60% of institutionalized aging adults suffer from malnutrition. The problem is particularly common in nursing homes, with prevalence rates of up to 85% (Saletti et al., 2000; Swedish National Food Administration, 1998; Vellas et al., 2001). Malnutrition among aging adults can largely be attributed to aging-related anorexia, which is due to various social, psychological, and biological factors that include disease (Brownie, 2006; Donini et al., 2003).

Recent study, using longitudinal data, strengthens the associations by showing that olfactory impairment in aging persons, at least among women, might be a contributing factor to poor diet quality (Gopinath et al., 2016). Furthermore, B. J. Rolls and McDermott (1991) demonstrated diminished sensory-specific satiety in old age, which may contribute to the decreased dietary variation with age, and Kremer et al. (2014) showed that those with diminished olfaction more often report eating the same meal within a week. There is also a considerable risk among aging adults to ingest spoiled food. It has, for example, been suggested that aging adults are less likely than young adults to reject foods with unpleasant odors (Pelchat, 2000). The unawareness of age-related olfactory loss (e.g., Nordin et al., 1995; Seubert et al., 2017) may aggravate the risk of ingesting spoiled food as these persons are less likely to take precautions to avoid eating such food.

How should these risks be mitigated? Early work by Schiffman et al. demonstrated that anorexia in the aging population may remit when foods are amplified by additional flavoring to compensate for diminished chemosensory function, resulting in increased preference for and intake of food, increased salivation, and improved immunological status and grip strength (Schiffman, 1998; Schiffman & Miletic, 1999; Schiffman & Warwick, 1988, 1993).

Special Issue: Our Unique Sense of Smell

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SAGE

Cognition and Dementia

Olfactory deficits are a common feature of the normal aging processes but may also reflect unique patterns of cognitive brain changes in aging. To date, several studies have shown that olfactory deficits often coincide with or even precede impairments in nonolfactory cognitive tests (Djordjevic et al., 2008; Dulay & Murphy, 2002; Swan & Camelli, 2002; Wilson et al., 2006). Correlations between olfactory and cognitive deficits in aging adults are unlikely to arise simply due to the semantic memory components in the olfactory identification task. In fact, word knowledge is typically retained in old age, whereas odor identification declines

Prospective studies show that performance in odor identification could predict future decline in general cognition (Conti et al., 2013; Graves et al., 1999) or executive functioning (Schubert et al., 2013), and effects persist even after controlling for vocabulary, a nonolfactory control task where synonyms are matched (Olofsson, Larsson et al., 2020; Olofsson et al., 2009). These previous findings have recently been confirmed by a large-scale population-based study of middle-aged and aging participants (Tebrugge et al., 2018). Here, **participants with olfactory deficits performed significantly worse on a large variety of cognitive subtests, such as verbal memory and fluency, problem solving, visuo-spatial abilities, speed of processing, and inhibition.**

ARTICLE OPEN ACCESS

Impaired olfaction is associated with cognitive decline and neurodegeneration in the brain

Christina S. Dintica, MSc, Anna Marseglia, PhD, Debora Rizzuto, PhD, Rui Wang, PhD, Janina Seubert, PhD, Konstantinos Arfanakis, PhD, David A. Bennett, MD,* and Weili Xu, MD, PhD*

Correspondence

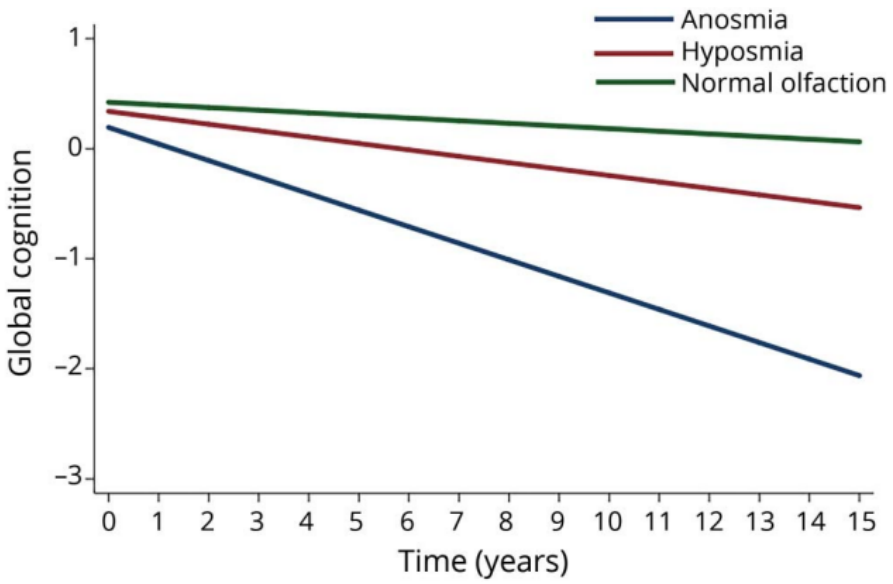
Neurology® 2019;92:e700-e709. doi:10.1212/WNL.0000000000006919

Conclusion:

Impaired olfaction predicts faster cognitive decline and might indicate neurodegeneration in the brain among dementia-free older adults.

In this sample of dementia-free older adults, we report a longitudinal association between worse scores on baseline odor identification testing and cognitive decline, and a crosssectional association between odor identification and volumes in structures of the medial temporal lobe as well as the fusiform gyrus. Future research should further investigate the potential for odor identification tests to serve as cost-effective screening tools for accelerated cognitive decline that may progress to dementia.

Figure 2 Predicted trajectory of global cognitive decline by olfaction categories



Lines represent β coefficients from linear mixed-effects model adjusted for age, sex, education, practice effects, and *APOE* ε4 allele, with normal olfaction as reference group. Green line: normal olfaction (B-SIT score men 10.25–12, women 10.5–12); red line: hyposmia (B-SIT score men 6–10, women 6–10.25); and blue line: anosmia (B-SIT <6). B-SIT = Brief Smell Identification Test.

According to some studies, the risk of future cognitive decline in aging individuals with olfactory loss depends on the ApoE gene; a plasma protein involved in lipid transport, and located on chromosome 19, carrying the three possible alleles e2, e3, and e4. The gene is expressed in the central nervous system (CNS), including the olfactory bulb and the olfactory epithelium (Nathan et al., 2007; Struble et al., 1999), and is believed to play a role in neuronal regenerative processes as well as in the development of Alzheimer's disease (AD). Aging ApoE e4 carriers with no sign of dementia have a diminished olfactory ability relative to noncarriers (Graves et al., 1999; Larsson et al., 2016; Olofsson et al., 2010), and in the e4 carrier group, olfactory deficits are more strongly indicative of generalized cognitive decline in the coming years (Olofsson, Larsson et al., 2020; Olofsson et al., 2009). Aging adults with an e4 allele also show a diminished electrophysiological brain activity in response to odors (Green et al., 2013). Despite some inconsistency in the literature (Handley et al., 2006), impaired odor identification has been observed in cognitively impaired aging e4-carriers without dementia (Murphy et al., 1998). Longitudinal data suggest that aging e4-carriers show larger-than-normal decline in odor identification performance (Calhoun-Haney & Murphy, 2005; Josefsson et al., 2017). The accelerated decline concurs with declining episodic memory abilities (Josefsson et al., 2017). The main interpretation of these findings is that in the e4 carriers, olfactory dysfunction is predominantly caused by early, still preclinical AD pathology which accumulates in the mediotemporal lobe (Olofsson et al.,2016).

Research

JAMA Otolaryngology–Head & Neck Surgery | Original Investigation

Association Between Olfactory Dysfunction and Mortality in US Adults

Janet S. Choi, MD, MPH; Sophie S. Jang, MS; Jeehong Kim, MD; Kevin Hur, MD; Elisabeth Ference, MD; Bozena Wrobel, MD

Our study findings suggest olfactory dysfunction as independently associated with mortality has clinical implications for physical, mental, and cognitive health, especially among older adults. Adults with olfactory dysfunction are expected to be prone to malnutrition, because these individuals may have decreased appetite and ability to enjoy food, thereby leading to poor food intake.[1,50] Olfactory dysfunction may also prevent adults from recognizing life-threatening situations, such as a gas leak or a fire.[5] Olfactory dysfunction is known to be associated with poorer quality of life and higher prevalence of depressive symptoms.[3,25,50] In addition to olfactory dysfunction being suggestive of accelerated brain aging, it has been found to be an early factor associated with development of Alzheimer and Parkinson disease.[51,52] Detection of olfactory dysfunction, especially among older adults, suggests that further workup for malnutrition, depression, and neurodegenerative disease may be needed. Adults with known olfactory dysfunction should be more cautious of life-threatening situations because they are unable to smell danger signals in the household environment.[53]

Conclusions

Objectively measured olfactory dysfunction is associated with an increased risk of 5-year all-cause mortality among older (≥65 years) but not middle-aged (40-64 years) US adults.

Olfactory dysfunction was identified as independently associated with mortality after accounting for demographics, medical comorbidities, depression, and cognitive functioning

Age-Related Olfactory Dysfunction: Epidemiology, Pathophysiology, and Clinical Management

Kenji Kondo, Shu Kikuta, Rumi Ueha, Keigo Suzukawa and Tatsuya Yamasoba*

Department of Otolaryngology—Head and Neck Surgery, Graduate School of Medicine and Faculty of Medicine, The University of Tokyo, Tokyo, Japan

frontiers in Aging Neuroscience

REVIEW
published: 07 July 2020
doi: 10.3389/fnagi.2020.00208

MANAGEMENT STRATEGIES FOR AGE-RELATED OLFACTORY DYSFUNCTION

The prevention of olfaction dysfunction may lead to happier and more successful aging. In the case of olfactory impairment, clinical management may help patients to overcome the difficulties associated with their impairment. Although, several drugs have been tested for the treatment of age-related sensorineural olfactory dysfunction including zinc, vitamins, and herbal medicines, no evidence-based medicine has been established to improve age-related olfactory dysfunction (Miwa et al., 2019).

Recently, olfactory training has been reported to be useful for the treatment of sensorineural olfactory disorders (Hummel et al., 2009; Damm et al., 2014). The original method reported by Hummel et al. (2009) required patients to expose themselves twice daily to four odors [phenyl ethyl alcohol (PEA): rose, eucalyptol: eucalyptus, citronellal: lemon, and eugenol: cloves]. Olfactory training has been reported to improve age-related olfactory loss (Birte-Antina et al., 2018), although further studies are warranted to confirm the efficacy.

Intranasal administration of drugs has also been extensively studied as a treatment of central nervous system diseases, because the olfactory mucosa may be used as a route to deliver drugs to the intracranial space bypassing the blood-brain barrier (Chapman et al., 2013). The provision of daily-life advice, especially to guarantee patient safety and the appreciation of food is also important to manage age-related olfactory impairment. With olfactory deterioration, patients tend to fail the detection of hazardous odors, such as gas leakage and fire smoke odors. In a family of an elderly couple, possibly none can detect such hazardous odors. For such patients, the use of odor detection machines is recommended (Miwa et al., 2001). Patients may also fail to notice the smell of spoiled food. In such a situation, it is recommended to pay attention to food conditions by checking the expiration date label, especially in the summertime.

Another problem to be addressed is malnutrition due to olfactory impairment. It is reported that the addition of flavor to the food may increase appetite and improve the nutritional condition (Schiffman and Warwick, 1993). Conversely, patients with a neural disorder such as postviral and traumatic olfactory dysfunction, frequently experience parosmia, which causes food such as fish, oily food, some vegetables and fruits, and fermented goods to have unpleasant odors during the recovery period. Therefore, adequate food choices while cooking are important to maintain the joy of the meals.

Olfatto ed malattie neurodegenerative

TABLE 3

Relative severity of olfactory dysfunction in neurodegenerative diseases

Disease	Relative restriction of olfactory function
Idiopathic Parkinson disease, Alzheimer dementia, Lewy body dementia, PARK 8	+ + +
Multisy	
Motor n spinoc supran	
Cortico type 3,	

+++... severe
are based on

unction. Most

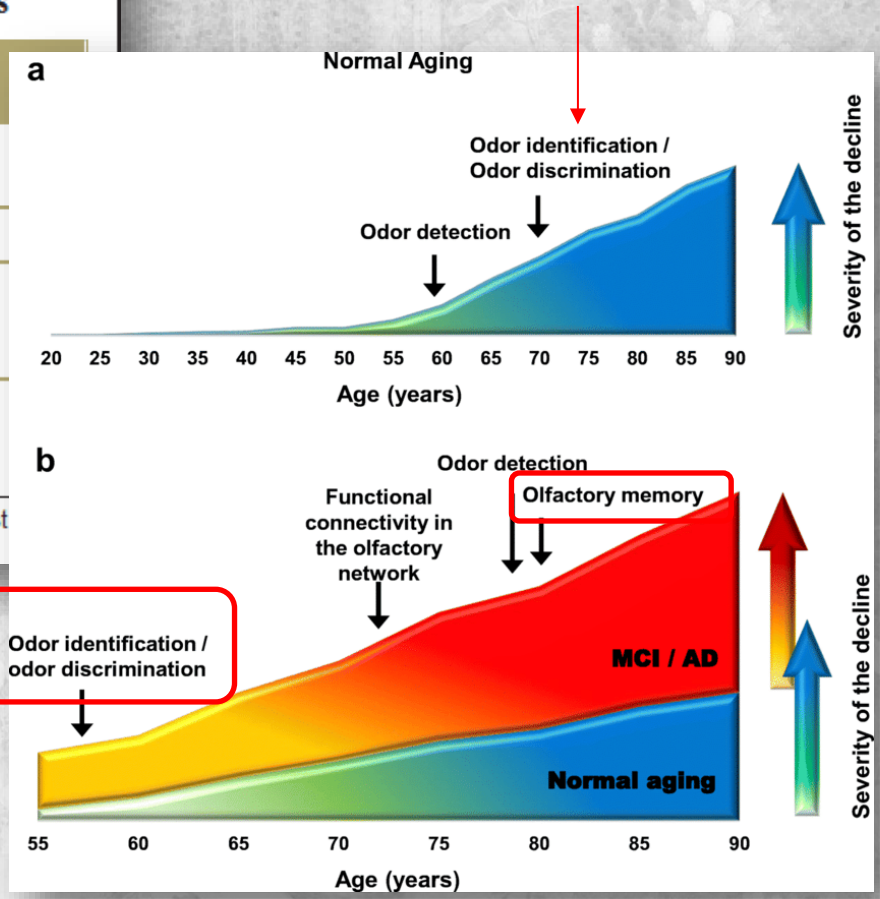
TABLE 6

Neurodegenerative Diseases Associated With Olfactory Dysfunction

Idiopathic Parkinson disease
Alzheimer dementia
Lewy body dementia
Familial Parkinson disease
Multisystemic atrophy
Huntington disease
Wilson disease
Friedreich ataxia
Spinocerebellar ataxia (types 2 and 3)
Creutzfeldt-Jakob disease

Note: Diseases are listed from most severely affected to least severely affected.

Information from reference 10.



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smell and neurodegenerative diseases

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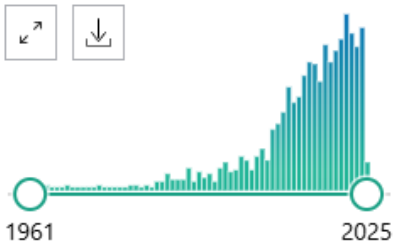
RESULTS BY YEAR



1 Cite Share

Olfactory dysfunction in aging and **neurodegenerative diseases**.

Dan X, Wechter N, Gray S, Mohanty JG, Croteau DL, Bohr VA.

Ageing Res Rev. 2021 Sep;70:101416. doi: 10.1016/j.arr.2021.101416. Epub 2021 Jul 27.

PMID: 34325072 **Free PMC article.** Review.

Alterations in olfactory functions are proposed to be early biomarkers for neurodegeneration. Many **neurodegenerative diseases** are age-related, including two of the most common, Parkinson's disease (PD) and Alzheimer's disease (AD). ...The utility of OD as a biomarke ...

frontiers in Aging Neuroscience

REVIEW
published: 07 July 2020
doi: 10.3389/fnagi.2020.00208

Age-Related Olfactory Dysfunction: Epidemiology, Pathophysiology, and Clinical Management

Kenji Kondo, Shu Kikuta, Rumi Ueha, Keigo Suzukawa and Tatsuya Yamasoba*

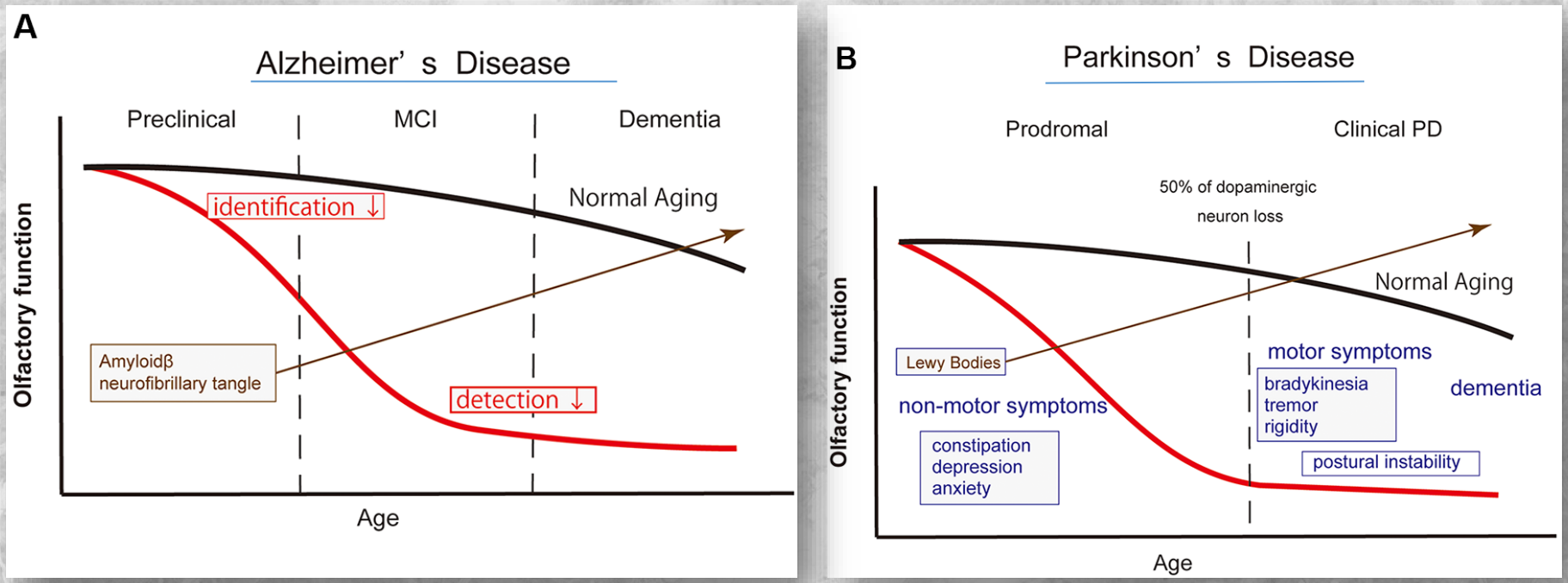


FIGURE 3 | Schematic drawing illustrating the olfactory dysfunction and time course of Alzheimer's disease (AD) and Parkinson's disease (PD). In both neurodegenerative diseases, the emergence of olfactory dysfunction precedes their definite diagnosis. The red and black lines in the drawing indicate the time course of olfactory function in patients and normal elderly individuals, respectively.

International Journal of *Molecular Sciences*

Int. J. Mol. Sci. **2023**, *24*, 2117

Review

Neurons, Nose, and Neurodegenerative Diseases: Olfactory Function and Cognitive Impairment

Irene Fatuzzo [1], Giovanni Francesco Niccolini [1], Federica Zoccali [1], Luca Cavalcanti [1], Mario Giuseppe Bellizzi [1], Gabriele Riccardi [1], Marco de Vincentiis [1], Marco Fiore, Antonio Minni [1,3] and Christian Barbato [2,*]

In neurology, olfactory impairment is a potential early marker for the onset of neurodegenerative diseases, but the underlying mechanism is poorly understood. The loss of smell is considered a clinical sign of early-stage disease and a marker of the disease's progression and cognitive impairmen. Specific anatomical systems and environmental factors can contribute to olfactory loss associated with neurological diseases, although the direct biological relationship with each disorder remains unsolved and further investigations are needed.

Neuropathology hallmarks

Olfactory mucosa:

- β-amyloid aggregates
- OSN degeneration
- Occlusion of the foramina
- α-synuclein aggregates

Olfactory bulb:

- Reduction in bulb volume
- Tauopathy
- Diffused β-amyloid aggregates
- α-synuclein aggregates
- Increase in DA neurons
- Axonal loss in OT
- NFTs and core plaques

Olfactory cortices:

Tauopathy and α-Synucleinopathy in:

- OT
- AMG
- PC
- EC
- OFC

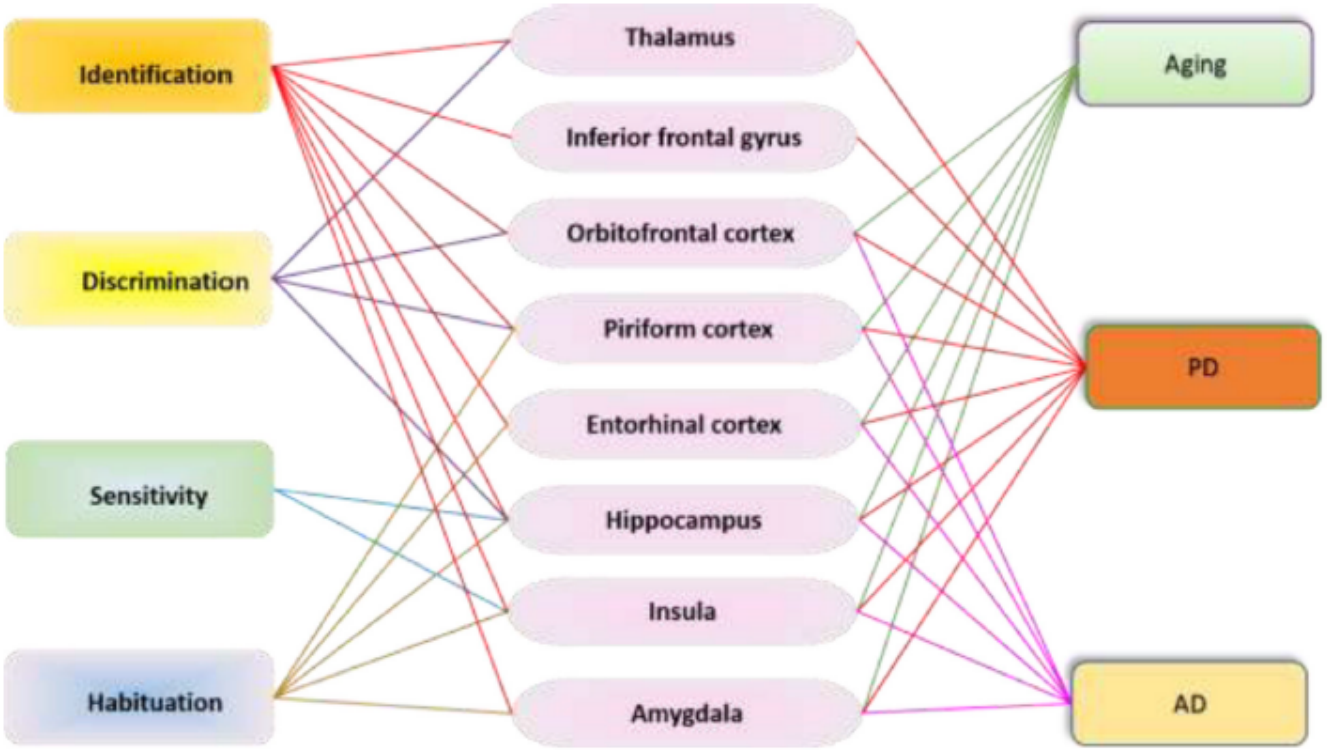


Fig.3.

The interconnection between different olfaction aspects and brain regions and the involvement of these brain region in aging, PD, and AD in human and mammalian animal models. Among the mentioned brain regions involved in olfaction, all are related with PD (Braak et al., 1994; Criaud et al., 2016; Henderson et al., 2000; Jia et al., 2019; Kobayakawa et al., 2017; Liu et al., 2019; Sancandi et al., 2018; Terada et al., 2018) and a majority (orbitofrontal cortex, piriform cortex, entorhinal cortex, hippocampus, insula, and amygdala) are related with AD (DeTure and Dickson, 2019; Saiz-Sanchez et al., 2015) and aging (Churchwell and Yurgelun-Todd, 2013; Gocel and Larson, 2013; Reagh et al., 2018; Resnick et al., 2007; St Jacques et al., 2010).

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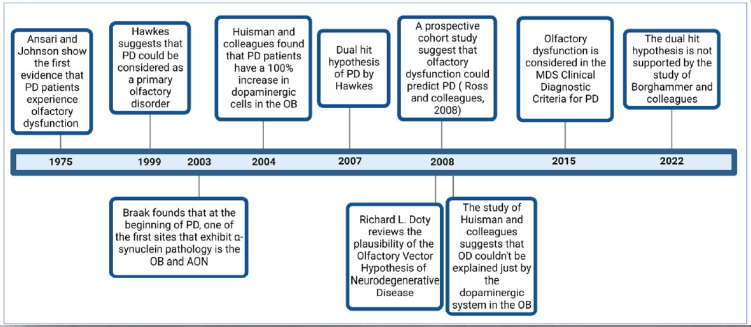
Review

Olfactory Dysfunction in Parkinson's Disease, Its Functional and Neuroanatomical Correlates

Gabriel Torres-Pasillas [1], Donají Chi-Castañeda [2], Porfirio Carrillo-Castilla [3], Gerardo Marín [4], María Elena Hernández-Aguilar [2], Gonzalo Emiliano Aranda-Abreu [2], Jorge Manzo [2] and Luis I. García [2,*]



Up to **90%** of preclinical PD cases showed an olfactory impairment preceding the onset of motor symptoms by decades

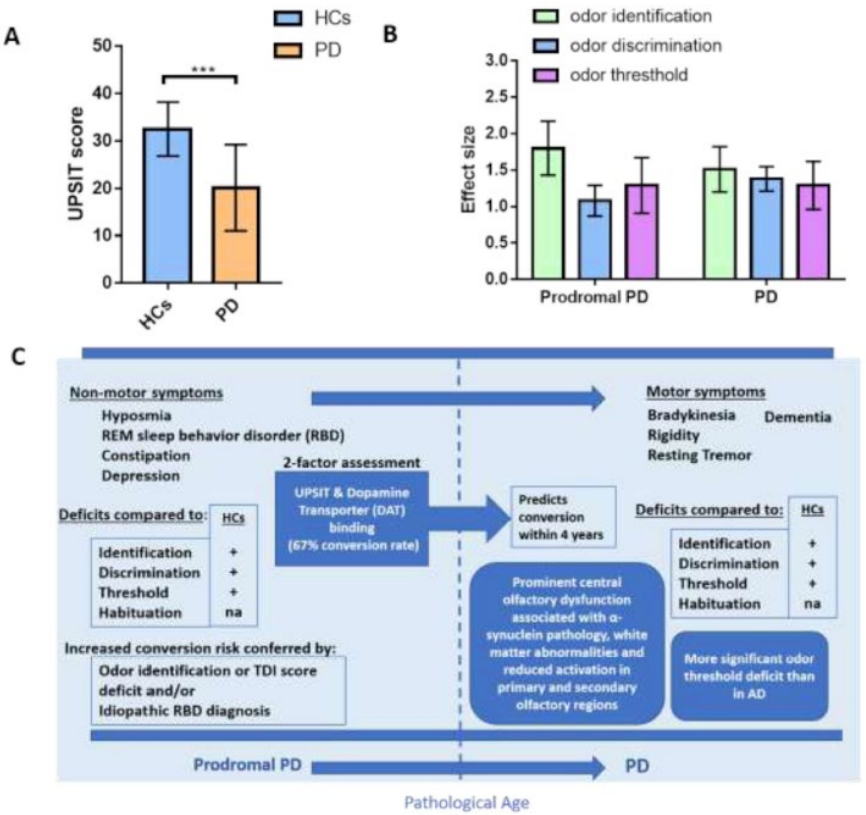


Fig. 5.
OD in PD. (A) Comparison of odor identification ability between healthy control (HC) and PD patients. Graph plotted based on (Chou and Bohnen, 2009). NC (n=44): 59.6±10.8 years; PD (n=44): 59.3±10.1years. (B) Effect sizes for different olfactory domains in prodromal PD and PD (error bars indicate 95% confidence interval). Prior convention has classified effect sizes as small (d=0.2), medium (d=0.5) or large (d≥0.8). Graph plotted based on 2 meta-analyses (Lyu et al., 2021; Rahayel et al., 2012). (C) Infographic profiles of OD in prodromal PD and PD patients.

NeuroSci

MDPI

Review

Olfactory Dysfunction in Parkinson's Disease, Its Functional and Neuroanatomical Correlates

Gabriel Torres-Pasillas [1], Donají Chi-Castañeda [2], Porfirio Carrillo-Castilla [3], Gerardo Marín [4], María Elena Hernández-Aguilar [2], Gonzalo Emiliano Aranda-Abreu [2], Jorge Manzo [2] and Luis I. García [2,*]

9. Future Directions

Some brain structures involved in the olfactory system, such as the OB, amygdala, and hippocampus, have been more widely studied in PD patients with OD. However, other regions have received less attention, including the piriform cortex, so there is a need for further investigation into these brain structures. Furthermore, since certain types of neurons are more susceptible to developing α-synuclein pathology, it is necessary to identify which types of cells are more affected in these structures. It is worth noting that glial cells have not been extensively studied except for a few cases.

In addition to the cardinal motor symptoms of PD, patients also exhibit an impairment in sniffing, which could contribute to OD. This fine motor impairment may implicate the cerebellum. Therefore, further studies on sniffing in PD patients and the role of the cerebellum in OD are necessary.

Considering that the assessment of the olfactory function is simple, non-invasive, and cost-effective, it is ideal for being performed on those individuals already at risk of PD, such as those patients with family members with clinical PD or other non-motor symptoms characteristic of this neurodegenerative disease. Additionally, it is crucial to perform this type of evaluation in patients already diagnosed with PD in order to understand the pathophysiology of this symptom.

10. Conclusions

Scientific evidence shows functional, microstructural, tissue, and morphological alterations in the structures related to the olfactory system, both peripheral and in the primary and secondary olfactory cortex. Furthermore, considering the multiple studies that show alterations in white matter and functional connectivity, and based on the recently proposed SOC model, it appears that a complex network of structures related to the olfactory system may be involved in the pathophysiology of OD in PD.

frontiers | Frontiers in Neuroscience

TYPE Review
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Olfactory deficit: a potential functional marker across the Alzheimer's disease continuum

Dongming Liu[1,2,3†], Jiaming Lu[1,2,3†], Liangpeng Wei[1,2,3], Mei Yao[1,2,3], Huiquan Yang[1,2,3], Pin Lv[1,2,3], Haoyao Wang[1,2,3], Yajing Zhu[1], Zhengyang Zhu[1], Xin Zhang[1,2,3], Jiu Chen[1,2,3*], Qing X. Yang[4*] and Bing Zhang[1,2,3,5,6,7,8*]

Olfactory dysfunction can be seen as a predictor for a conversion from MCI to AD.

In fact, a strong increase of loss of smell predicts a conversion from MCI to AD. Approximately 35% of patients with MCI transitioned to dementia within one year. Other studies have indicated conversion rates of 15% to 24% within two years, or approximately one-third over three years.

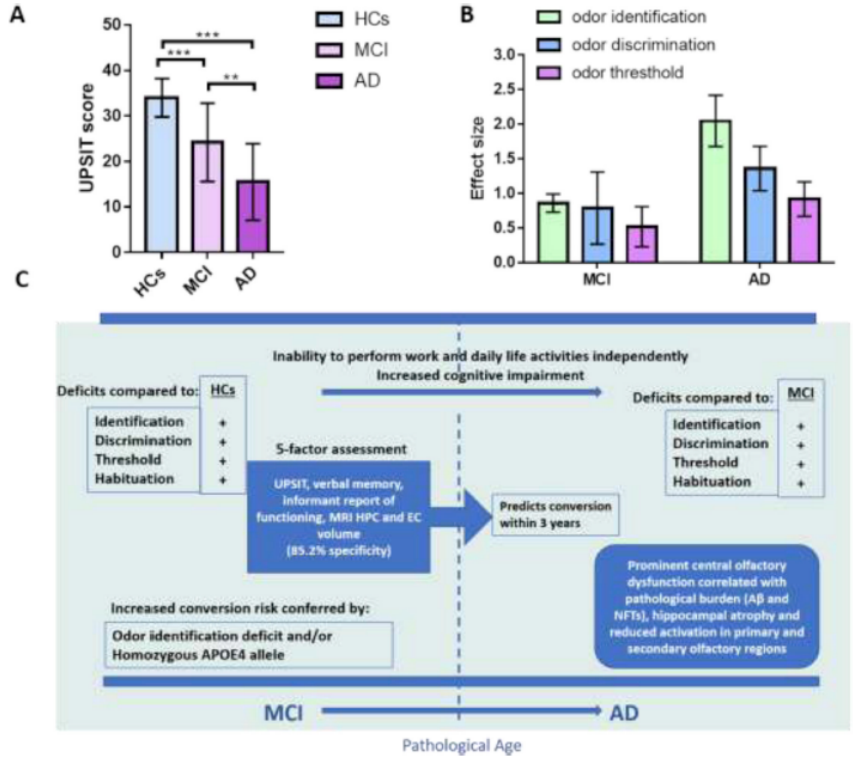


Fig. 6.
OD in AD. (A) Comparison of odor identification ability among NC, MCI, and AD patients. Graph plotted based on Vasavada et al. (Vasavada et al., 2017). NC (n=27): 69.5±10.4, MCI (n=21): 73.2±9.0, AD (n=15): 71.9±11.9. Mean ± SD. ** $P < 0.01$, *** $P < 0.001$. (B) Effect sizes for different olfactory domain deficits in prodromal MCI and AD (error bars indicate 95% confidence interval). Prior convention has classified effect sizes as small (d=0.2), medium (d=0.5) or large (d≥0.8). Graph plotted based on 2 meta-analyses (Rahayel et al., 2012; Roalf et al., 2017). (C) Profiles of OD of MCI and AD patients. HPC: hippocampus; EC: entorhinal cortex.

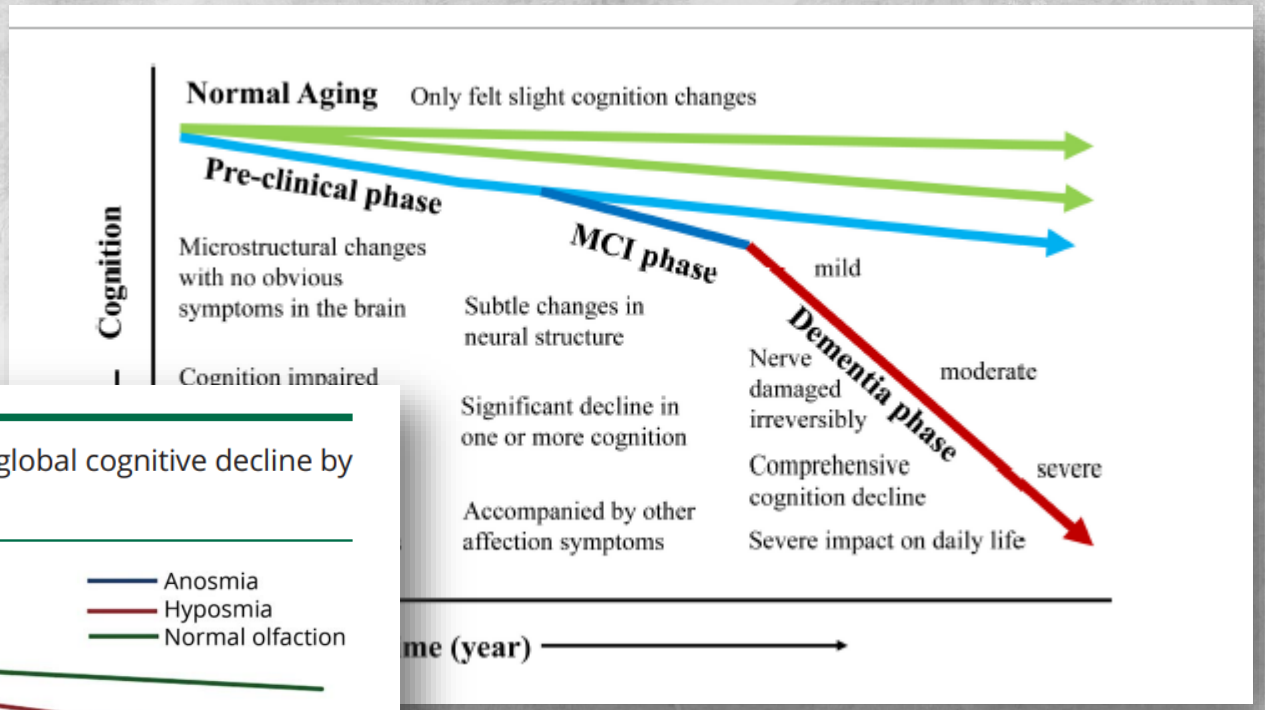
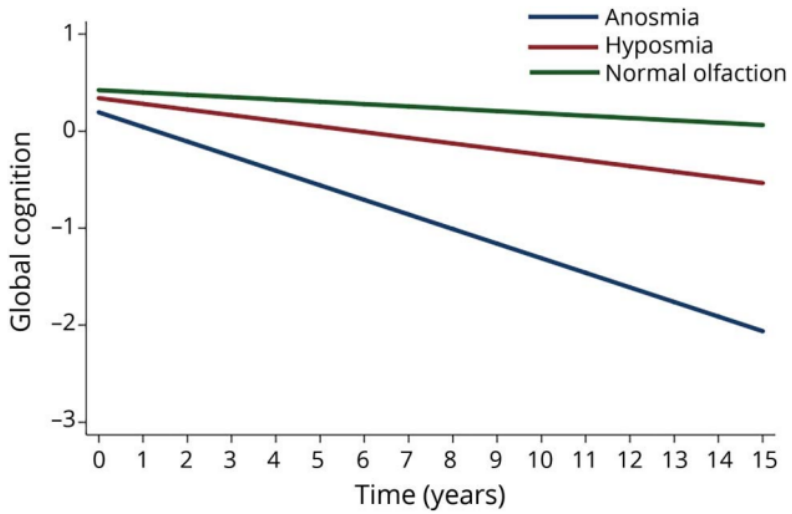


Figure 2 Predicted trajectory of global cognitive decline by olfaction categories



Lines represent β coefficients from linear mixed-effects model adjusted for age, sex, education, practice effects, and *APOE* ε4 allele, with normal olfaction as reference group. Green line: normal olfaction (B-SIT score men 10.25–12, women 10.5–12); red line: hyposmia (B-SIT score men 6–10, women 6–10.25); and blue line: anosmia (B-SIT <6). B-SIT = Brief Smell Identification Test.

5 Conclusion

Accumulating evidence suggests that subtle changes in olfaction may occur years before the appearance of AD classic clinical pathology, and declines in all aspects of olfactory function can herald the onset of the prodromal phase of AD. The olfactory dysfunction is strongly correlated with other markers of the AD prodrome. The olfactory identification function of the subjects has demonstrated a robust ability to distinguish between cognitively normal individuals and those at risk for AD in the populations of AD, MCI, and SCD. Preliminary evaluation of an individual's olfactory function can be based on subjective or objective olfactory behavioral examinations, but the sensitivity and specificity of these examinations require further enhancement. Other olfactory functions, such as odor recognition memory and context odor identification memory, warrant future investigation. Furthermore, current evidence from structural and olfactory functional MRI indicates varying degrees of structural atrophy and odor activation abnormalities (primarily in the POC and hippocampus) in different stages of the AD spectrum. With advancements in the spatiotemporal resolution of functional MRI imaging, olfactory functional MRI may have the potential to elucidate further the neural mechanisms underlying olfactory impairment in AD. Nevertheless, future efforts should focus on mapping the progression of olfactory abnormalities to better assess the contribution of olfactory dysfunction to disease occurrence and progression. More efforts are needed to explain their potential associations with degenerative neuropathological changes, blood, and cerebrospinal fluid biomarkers to improve their sensitivity and specificity in screening preclinical AD.

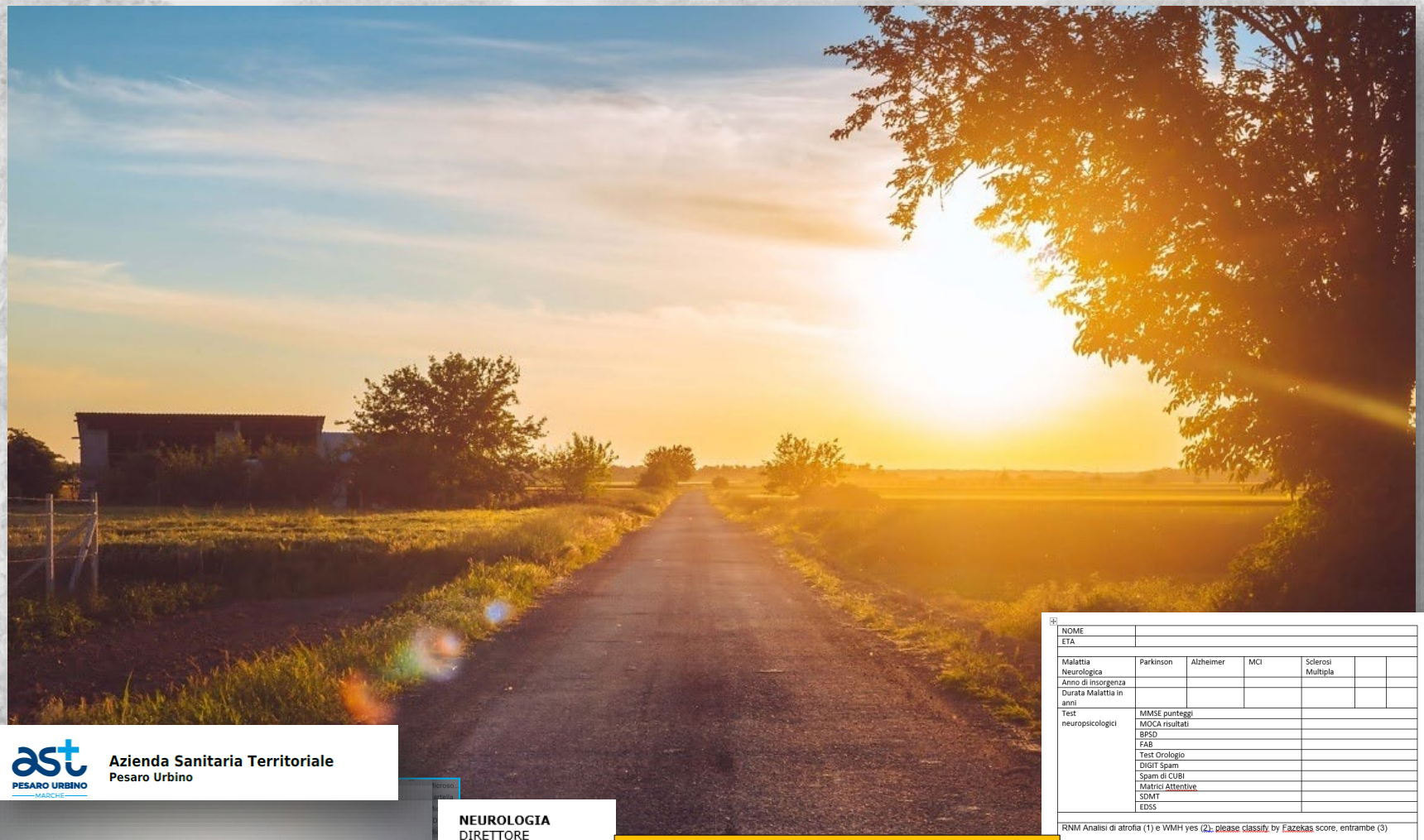
Olfactory deficit: a potential functional marker across the Alzheimer's disease continuum

Dongming Liu[1,2,3†], Jiaming Lu[1,2,3†], Liangpeng Wei[1,2,3], Mei Yao[1,2,3], Huiquan Yang[1,2,3], Pin Lv[1,2,3], Haoyao Wang[1,2,3], Yajing Zhu[1], Zhengyang Zhu[1], Xin Zhang[1,2,3], Jiu Chen[1,2,3*], Qing X. Yang[4*] and Bing Zhang[1,2,3,5,6,7,8*]

L'olfatto può essere considerato un biomarcatore clinico delle malattie neurodegenerative e con quali applicazioni cliniche?

Il deficit del sistema olfattivo può avere un ruolo fisiopatologico nella evoluzione della malattia neurodegenerativa?

il «training olfattivo» può modificare l'andamento delle malattie neurodegerative?



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DIRETTORE
Dr. Luca D'Ascanio

The Brain&Senses study
Impatto dei deficit sensoriali (udito, olfatto ed equilibrio) sulla progressione del declino cognitivo e la qualità della vita nei pazienti over 55.

INTRODUZIONE E RAZIONALI

Differenti studi clinici hanno analizzato come anche un solo deficit sensoriale possa avere un impatto sia sulle capacità cognitive che sulla qualità della vita a tutte le età [ref].
Nello specifico si è studiato come la perdita dell'udito non trattata sia in grado di causare un deterioramento importante nei pazienti con Mild Cognitive Impairment (MCI) aumentando il rischio di sviluppare la malattia di Alzheimer [ref]; gli autori dello studio hanno identificato un re-indirizzamento di alcune aree del cervello, in origine deputate ad altre funzioni, per

Arianna Di Stadio
University of Campania "Luigi Vanvitelli" - Dipartimento di Salute Mentale e Fisica e Medicina Preventiva
MD,PhD
Neuro-Otolaryngologist and Neuroscientist focused on neuroinflammatory and neurodegenerative disorders

Da febbraio 2025
Ad oggi 11 pazienti

NOME							
ETA							
Malattia Neurologica	Parkinson	Alzheimer	MCI	Sclerosi Multipla			
Anno di insorgenza							
Durata Malattia in anni							
Test neuropsicologici	MMSE punteggi						
	MOCA risultati						
	BPSD						
	FAB						
	Test Orologio						
	DIGIT Spam						
	Spam di CUBI						
	Matrici Attentive						
	SDMT						
	EDSS						

RNM Analisi di atrofia (1) e WMH yes (2); please classify by Fazekas score, entrambe (3)

Lobo Frontale (corteccia Orbito-Frontale	Lobo Temporale (area memoria)	Amygdala	Enthorinal Cortex

OLFATTOMETRIA	Threshold	Detection	Identification	TDI	

Endoscopia Nasale						
Otoscopia						
ESAME AUDIOMETRICO	250	500	1000	2000	4000	6000
Dx (rosso)						
SN (blu)						

Audiometria vocale	
Utilizzo protesi acustiche	
Disturbi equilibrio (Vertigini (1), Instabilità/Dizziness (2))	
Utilizzo occhiali esclusa presbiopia, miopia (1), astigmatismo (2), entrambi (3)	

Questionario Qualità della Vita	
Comorbitità	
Trattamenti in corso	

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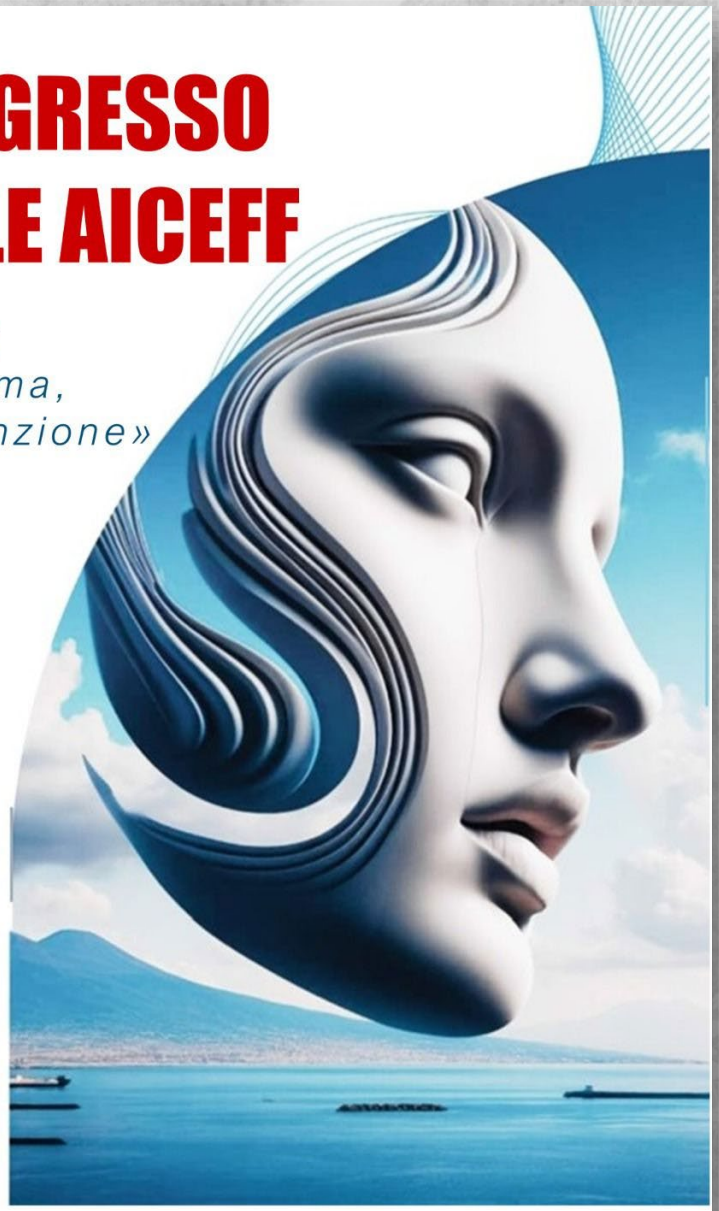

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Jan Brueghel : Il senso dell'olfatto (1616-17). Madrid Museo del Prado
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