La riabilitazione olfattiva quale componente della riabilitazione multisensoriale nei pazienti con malattia neurodegenerativa: la nostra esperienza

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Conflitti di interesse: nessuno

SIONG 2025…

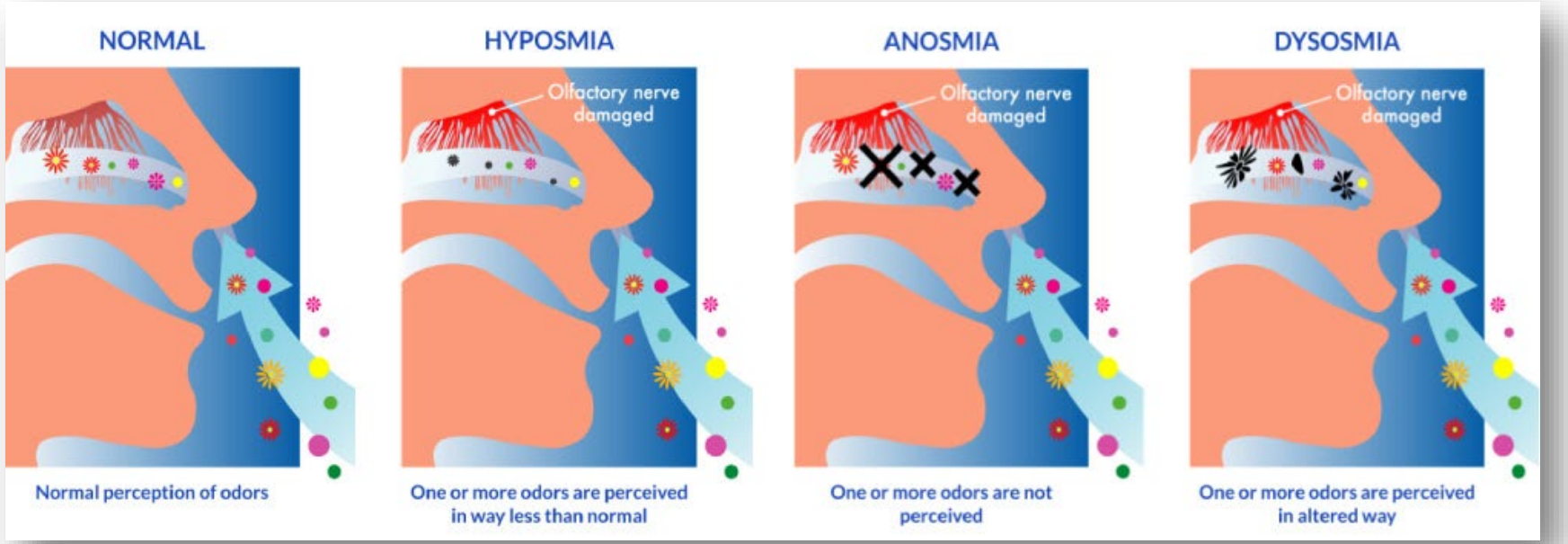
L'olfatto può essere considerato un biomarcatore clinico delle malattie neurodegenerative e con quali applicazioni cliniche?

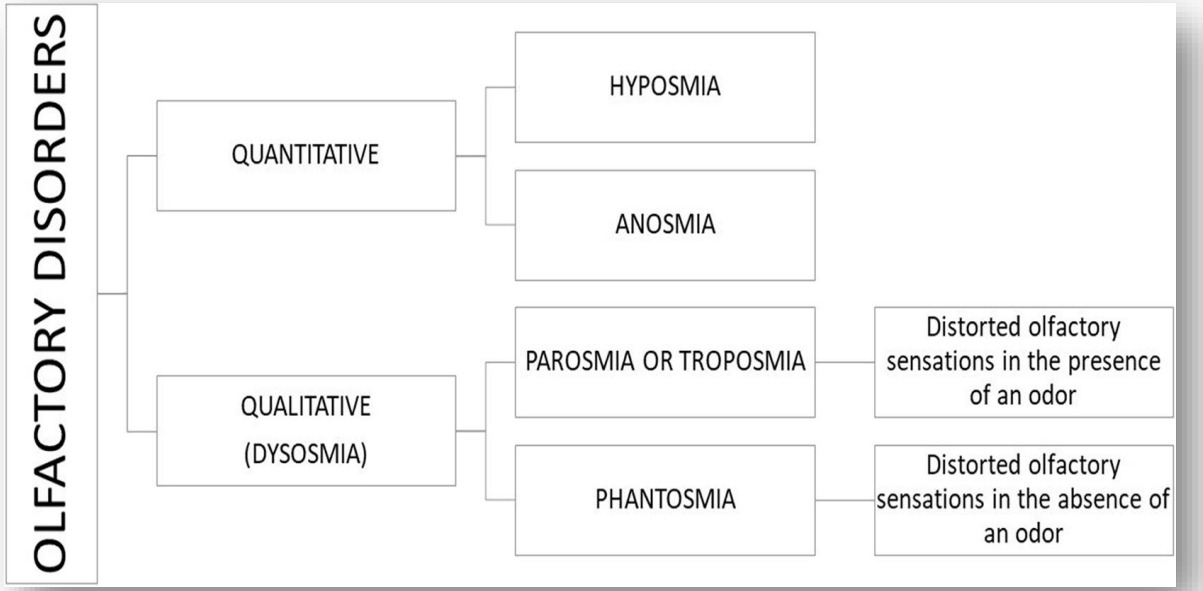
Il deficit del sistema olfattivo può avere un ruolo fisiopatologico nella evoluzione della malattia neurodegenerativa?

La riabilitazione olfattiva (in ambito multisensoriale?) può associarsi alla stimolazione cognitiva per modificare l'andamento delle malattie neurodegenerative?

Table 1. Definitions of terminology used in olfactory research/practice.

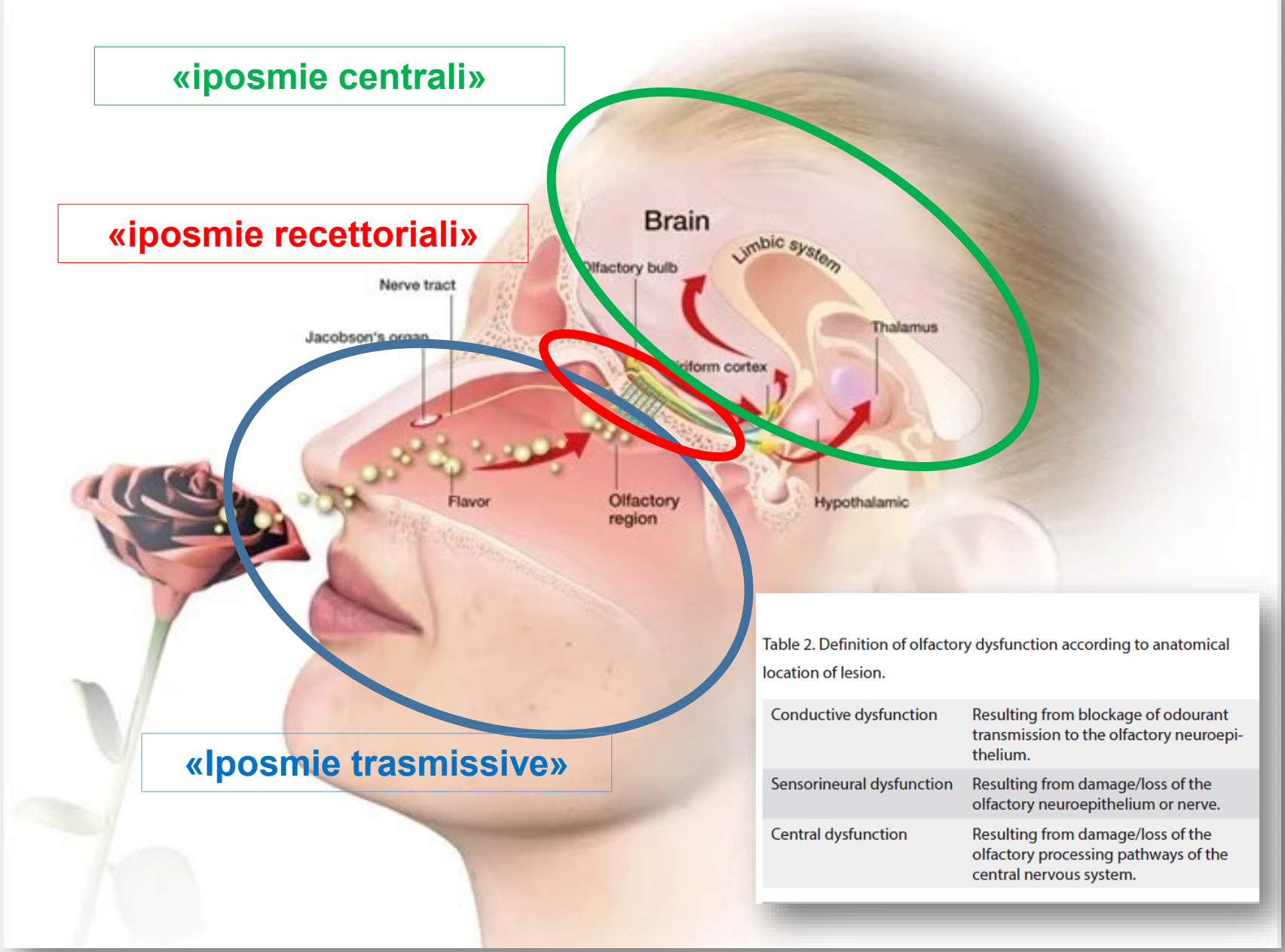
Normosmia	Quantitatively normal olfactory function
Hyposmia (or 'microsmia')	Quantitatively reduced olfactory function.
Anosmia	Quantitatively reduced olfaction to the extent that the sense of smell is not useful in daily life
Specific Anosmia (or 'partial anosmia')	Quantitatively reduced ability to smell a specific odour despite preserved ability to smell the vast majority of other odours.
Hyperosmia	Quantitatively increased ability to smell odours (>90th percentile of scores in an olfactory test)
Olfactory intolerance	Qualitative olfactory dysfunction where individuals, without odor distortions, complain of a subjectively enhanced sense of smell and are intolerant of everyday odors
Parosmia	Qualitative dysfunction in the presence of an odourant (i.e., distorted perception of an odour stimulus).
Phantosmia	Qualitative dysfunction in the absence of an odourant (i.e., an odourant is perceived without concurrent stimulus, an 'olfactory hallucination').





«iposmie centrali»

«iposmie recettoriali»



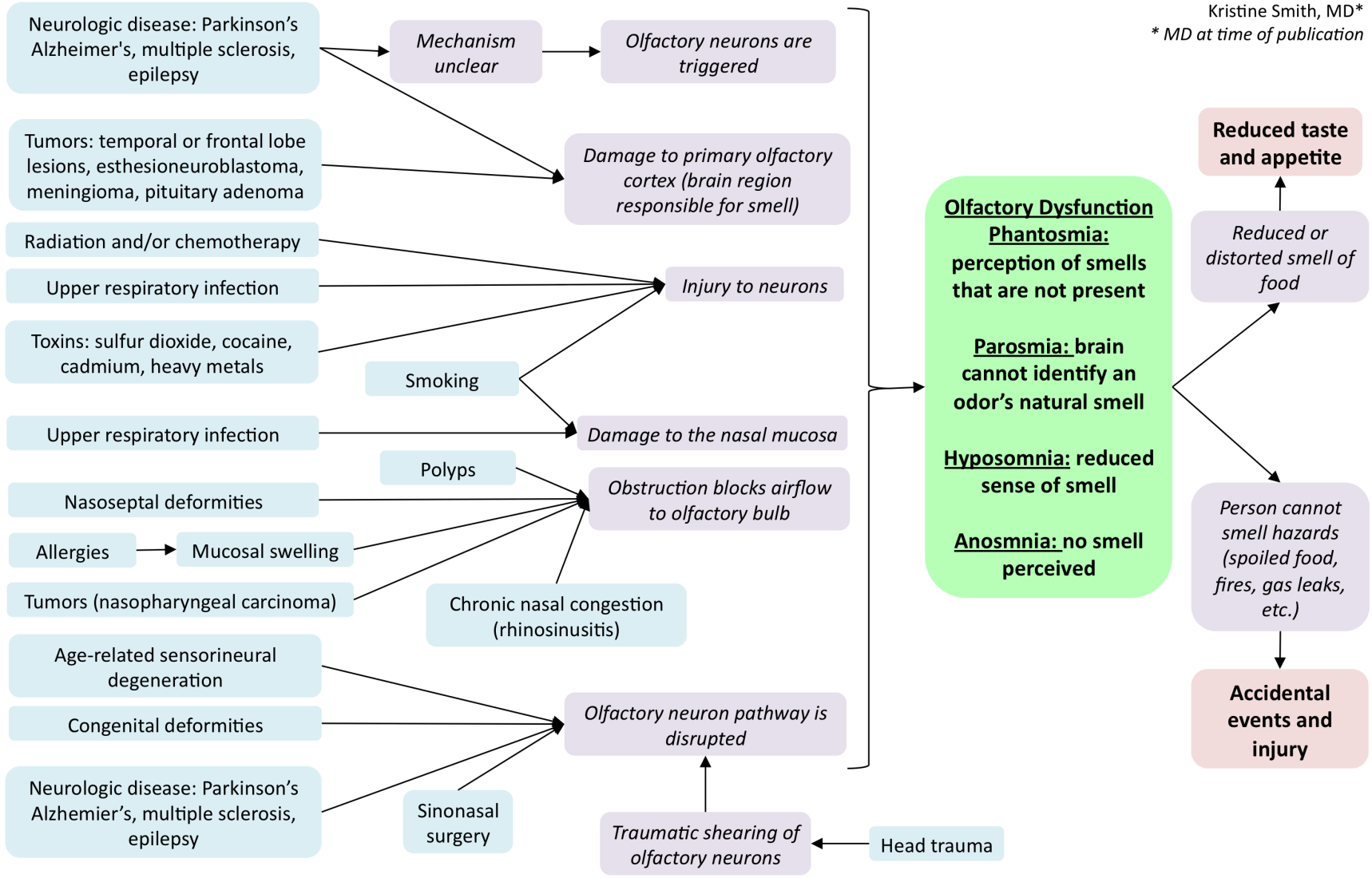
«Iposmie trasmissive»

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.

Olfactory Dysfunction: *Pathogenesis and clinical findings*

Authors:
Emma Holmes
Reviewers:
Stephanie Cote
Kristine Smith, MD*
** MD at time of publication*



Legend: Pathophysiology | Mechanism | Sign/Symptom/Lab Finding | Complications

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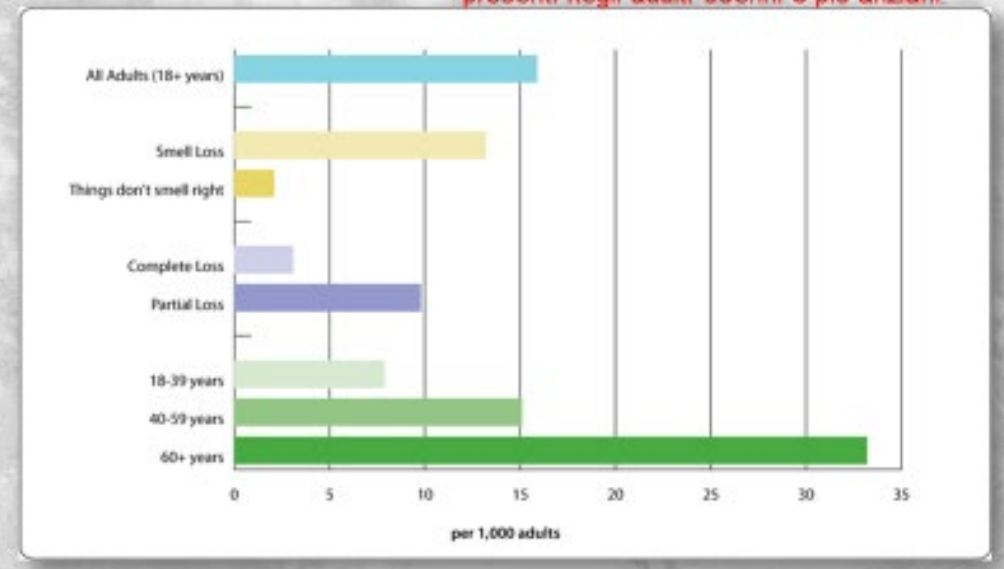
ANNALS OF THE NEW YORK ACADEMY OF SCIENCES

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.



2,5% della popolazione generale
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.

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DOI: 10.1002/evan.22030

REVIEW ARTICLE

Evolutionary Anthropology WILEY
ISSUES, NEWS, AND REVIEWS

Smell throughout the life course

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

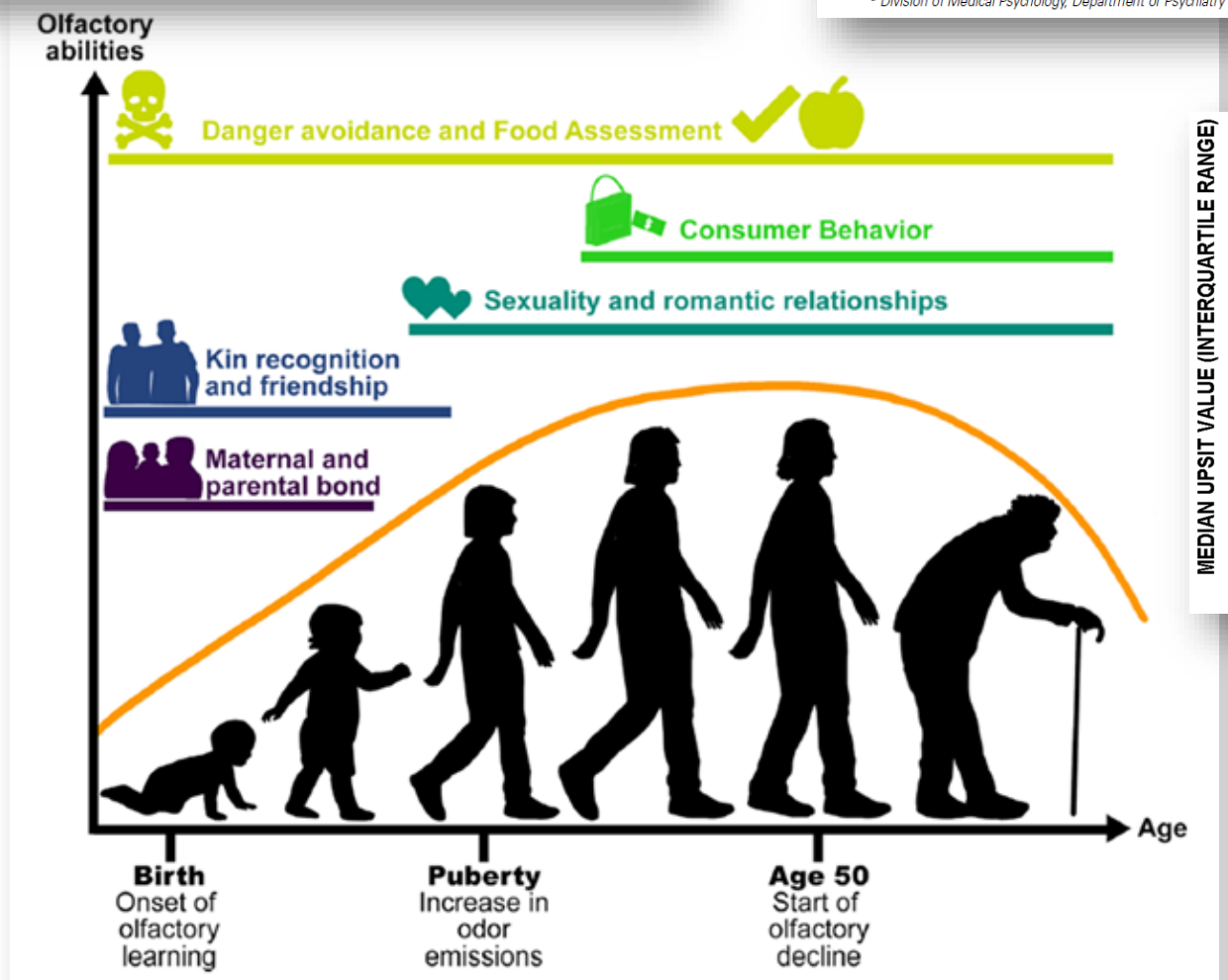
frontiers in PSYCHOLOGY

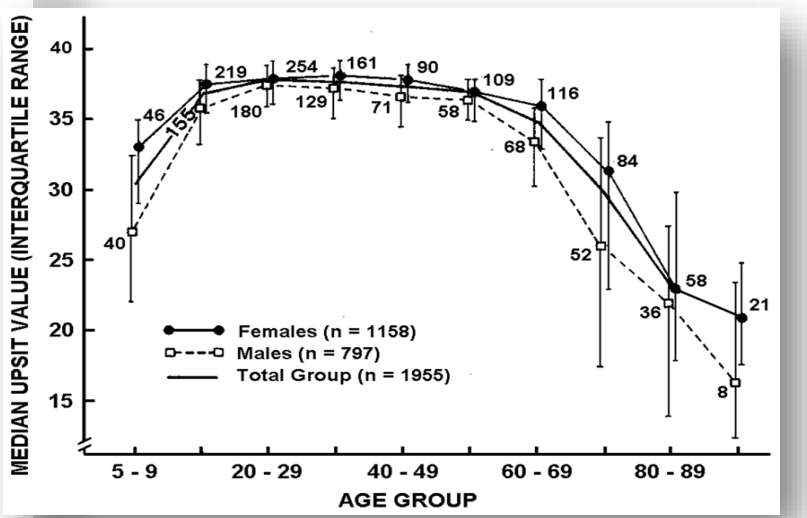
REVIEW ARTICLE
published: 07 February 2014
doi: 10.3389/fpsyg.2014.00020

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





Research

JAMA Otolaryngology–Head & Neck Surgery | Original Investigation Published Online: October 22, 2020

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.

Smell and Taste Disorders in Primary Care

Dillon J. Savard, MD, David Grant Medical Center, Travis Air Force Base, California; Uniformed Services University of the Health Sciences, Bethesda, Maryland
Francesca G. Ursua, MD, University of Nebraska Medical Center, Omaha, Nebraska
Heidi L. Gaddey, MD, Christie Clinic, Champaign, Illinois; Carle Foundation Hospital Family Medicine Residency Program, Urbana, Illinois

Am Fam Physician. 2023;108(3):240-248

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.

Review > Dtsch Arztebl Int. 2013 Jan;110(1-2):1-7, e1. doi: 10.3238/arztebl.2013.0001. Epub 2013 Jan 7.

Olfactory dysfunction: common in later life and early warning of neurodegenerative disease

Karl-Bernd Hüttenbrink [1], Thomas Hummel, Daniela Berg, Thomas Gasser, Antje Hähner

TABLE 3

Relative severity of olfactory dysfunction in neurodegenerative diseases

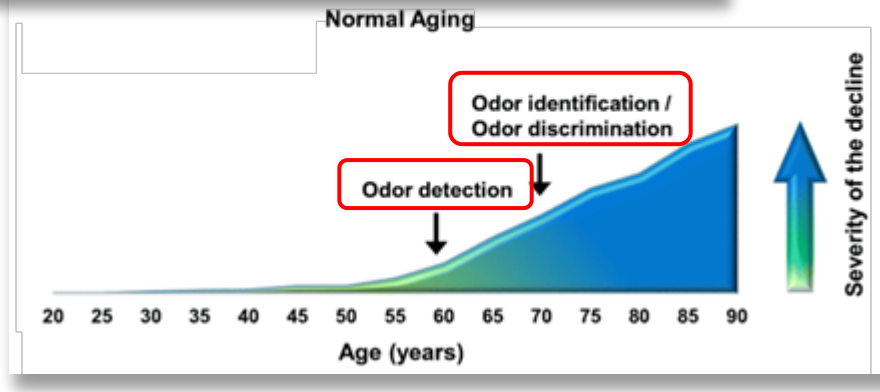
Disease	Relative restriction of olfactory function
Idiopathic Parkinson disease, Alzheimer dementia, Lewy body dementia, PARK 8	+ + +
Multisystemic atrophy, Huntington disease	+ +
Motor neuron diseases, Friedreich ataxia, spinocerebellar ataxia type 2, progressive supranuclear ophthalmoplegia, PARK 1	+
Corticobasal degeneration, spinocerebellar ataxia type 3, PARK 2	+ / 0

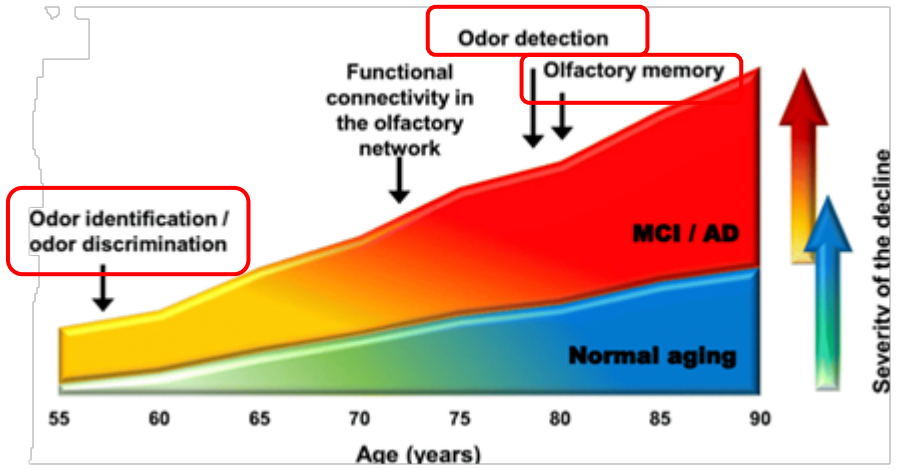
+++... severe loss of olfactory function; 0/(+)... no or only discrete loss of olfactory function. Most of the data are based on studies of small numbers of patients. PARK 1 and 2 = gene loc

Olfactory impairment in men and mice related to aging and amyloid-induced pathology

Wen-Yu Tzeng [1] · Katherine Figarella [1] · Olga Garaschuk [1]

Received: 26 October 2020 / Revised: 7 January 2021 / Accepted: 28 January 2021 / Published online: 20 February 2021





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*

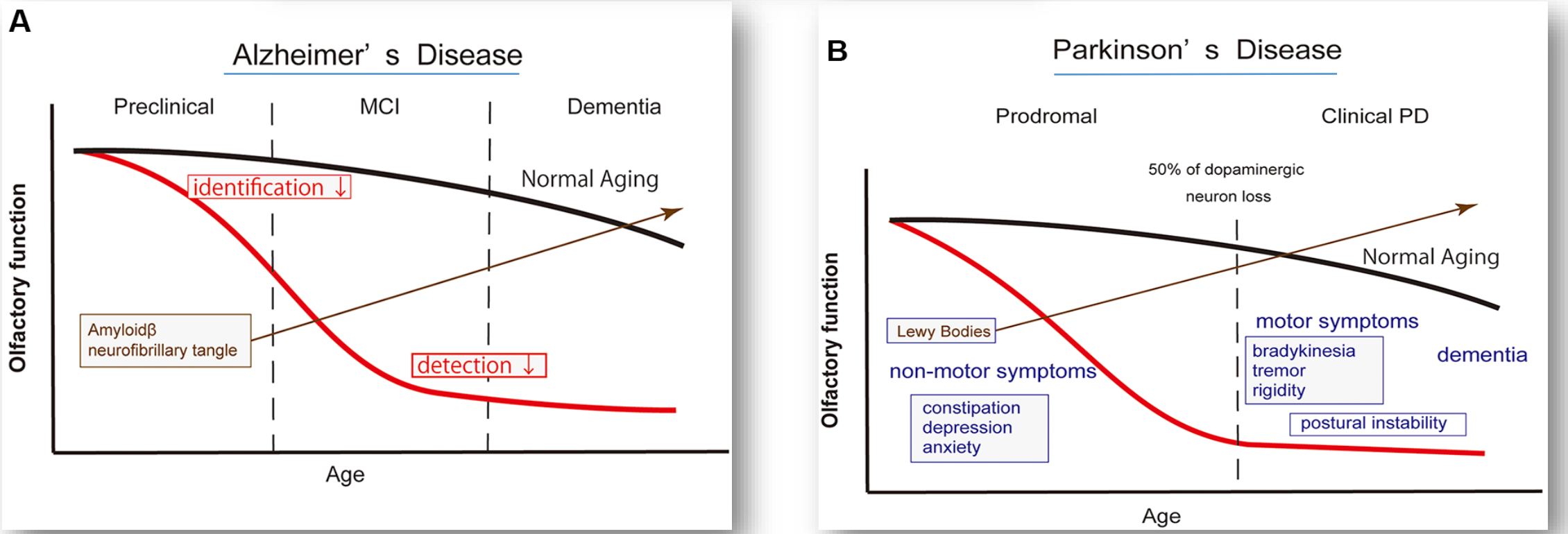


FIGURE 3 | Schematic drawing illustrating the olfactory dysfunction and time course of Alzheimer's disease (AD) and Parkinson's disease (PD). In both neurodegenerative diseases, the emergence of olfactory dysfunction precedes their definite diagnosis. The red and black lines in the drawing indicate the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

The Lancet Commissions

Dementia prevention, intervention, and care: 2024 report of the *Lancet* standing Commission

Gill Livingston, Jonathan Huntley, Kathy Y Liu, Sergi G Costafreda, Geir Selbæk, Suvarna Alladi, David Ames, Sube Banerjee, Alistair Burns, Carol Brayne, Nick C Fox, Cleusa P Ferri, Laura N Gitlin, Robert Howard, Helen C Kales, Mika Kivimäki, Eric B Larson, Noeline Nakasujja, Kenneth Rockwood, Quincy Samus, Kokoro Shirai, Archana Singh-Manoux, Lon S Schneider, Sebastian Walsh, Yao Yao, Andrew Sommerlad, Naaheed Mukadam**

Lancet 2024; 404: 572–628

incidence. Evidence is increasing and is now stronger than before that tackling the many risk factors for dementia that we modelled previously (ie, less education, hearing loss, hypertension, smoking, obesity, depression, physical inactivity, diabetes, excessive alcohol consumption [ie, >21 UK units, equivalent to >12 US units], traumatic brain injury [TBI], air pollution, and social isolation) reduces the risk of developing dementia. In this report, we add the new compelling evidence that untreated vision loss and high LDL cholesterol are risk factors for dementia.

The evidence that treating hearing loss decreases the risk of dementia is now stronger than when our previous Commission report was published. Use of hearing aids appears to be particularly effective in people with hearing loss and additional risk factors for dementia. New evidence also suggests that treating depression and smoking cessation might both reduce dementia risk.

Several mechanisms have been hypothesised to explain how hearing loss might increase dementia risk. Psychosocial factors, such as loneliness, depression, and social isolation, might be involved. Other mechanisms include reduced cognitive reserve from decreased environmental stimuli, increased cognitive resources needed for listening, and an interaction of these risks with brain pathology.[99] A causal link between hearing loss and dementia is supported by longer exposure to hearing loss being associated with higher dementia risk, with maximum risk in people who were diagnosed with hearing loss for more than 25 years.[100] Another postulated mechanism is common cardiovascular pathology, whereby vascular disease affects the cochlea or the ascending pathway, causing hearing loss, and the medial-temporal lobe, causing dementia. This mechanism would suggest that confounding by cardiovascular health status or risks would substantially account for the association between hearing loss and dementia risk, which has not been shown in meta-analyses.[99]

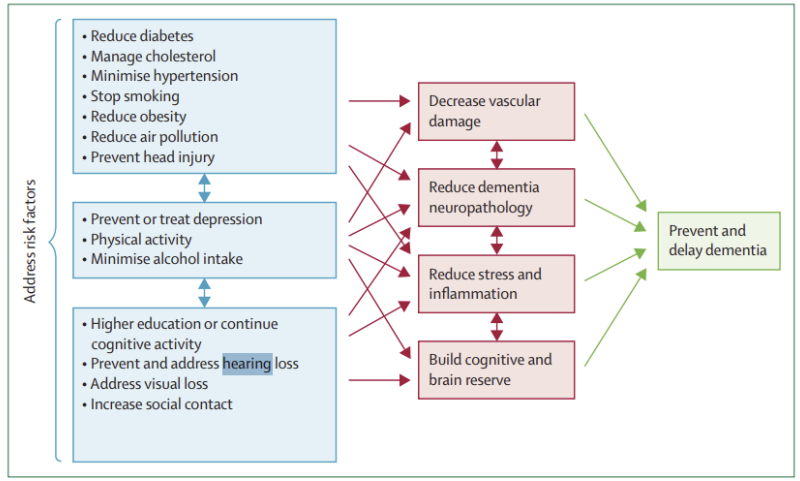


Figure 2: **Possible brain mechanisms for enhancing or maintaining cognitive reserve and risk reduction of potentially modifiable risk factors in dementia**

We previously discussed the evidence that hearing aid use is protective against dementia and reduces cognitive deterioration rates after beginning hearing aid use.[2] Since then, a systematic review and meta-analysis of eight cohort studies with 126 903 participants, followed up for 2–25 years, reported that people with hearing loss who used hearing aids had a significantly lower risk of cognitive decline (HR 0·81, 0·76–0·87; I^2=0%) and dementia (0·83, 0·77–0·90; I^2=0%; four studies) than those who did not use assistive devices (figure 5).[103]

JAMA Network Click to view article >

JAMA Otolaryngol Head Neck Surg. 2017 Dec 7;144(2):115–126. doi: 10.1001/jamaoto.2017.2513

Association of Age-Related Hearing Loss With Cognitive Function, Cognitive Impairment, and Dementia

A Systematic Review and Meta-analysis

David G Loughrey [1,2,✉], Michelle E Kelly [1,3], George A Kelley [4], Sabina Brennan [1], Brian A Lawlor [1,2,5]

Findings

In this systematic review and meta-analysis of 36 epidemiologic studies and 20 264 unique participants, age-related hearing loss was significantly associated with decline in all main cognitive domains and with increased risk for cognitive impairment and incident dementia. Increased risks for Alzheimer disease and vascular dementia were nonsignificant.

Meaning

Age-related hearing loss is a possible biomarker and modifiable risk factor for cognitive decline, cognitive impairment, and dementia.

Conclusions and Relevance

Age-related hearing loss is a possible biomarker and modifiable risk factor for cognitive decline, cognitive impairment, and dementia. Additional research and randomized clinical trials are warranted to examine implications of treatment for cognition and to explore possible causal mechanisms underlying this relationship.

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Innov Aging. 2024 Dec 31;8(Suppl 1):19. doi: 10.1093/geroni/igae098.0057

EFFECT OF HEARING INTERVENTION ON OLDER ADULTS AT RISK OF COGNITIVE DECLINE: ACHIEVE RANDOMIZED TRIAL

James Pike [1]

The Aging and Cognitive Health Evaluation in Elders (ACHIEVE, Clinicaltrials.gov Identifier: NCT03243422) randomized trial investigated the effect of a hearing intervention versus a health education control on 3-year cognitive change among dementia-free older adults with untreated hearing loss. Participants were recruited from the Atherosclerosis Risk in Communities (ARIC) study (n=238) or de novo from the community (n=739). The hearing intervention slowed cognitive decline by 48% in ARIC participants, but not in healthy de novo volunteers. A possible explanation for this difference is that the cognitive benefits of the hearing intervention could be observed only for individuals at increased risk for cognitive decline. To evaluate whether risk of cognitive decline moderated the effect of the hearing intervention, we used a sample of dementia-free ARIC participants (N=2,692) who did not participate in ACHIEVE to develop a model that explained 80.7% of the variance in cognitive decline over a 6-year period. The model was applied to baseline measures of ACHIEVE participants (N=977) to calculate their predicted risk of cognitive decline. The covariate-adjusted, intention-to-treat effect of the hearing intervention on 3-year cognitive change was examined in a mixed effects model that included a three-way interaction between time, randomization, and predicted risk of cognitive decline. Among participants in the top quartile of risk, cognitive decline in the hearing intervention group was 58.1% (95% CI 31.4%-90.9%) slower than the control group. The results suggest the effect of a hearing intervention on 3-year cognitive change was greatest among individuals at higher risk of cognitive decline.

alzheimer's association | Alzheimer's & Dementia | Translational Research & Clinical Interventions

Alzheimers Dement (N Y). 2022 Feb 22;8(1):e12248. doi: 10.1002/trc2.12248

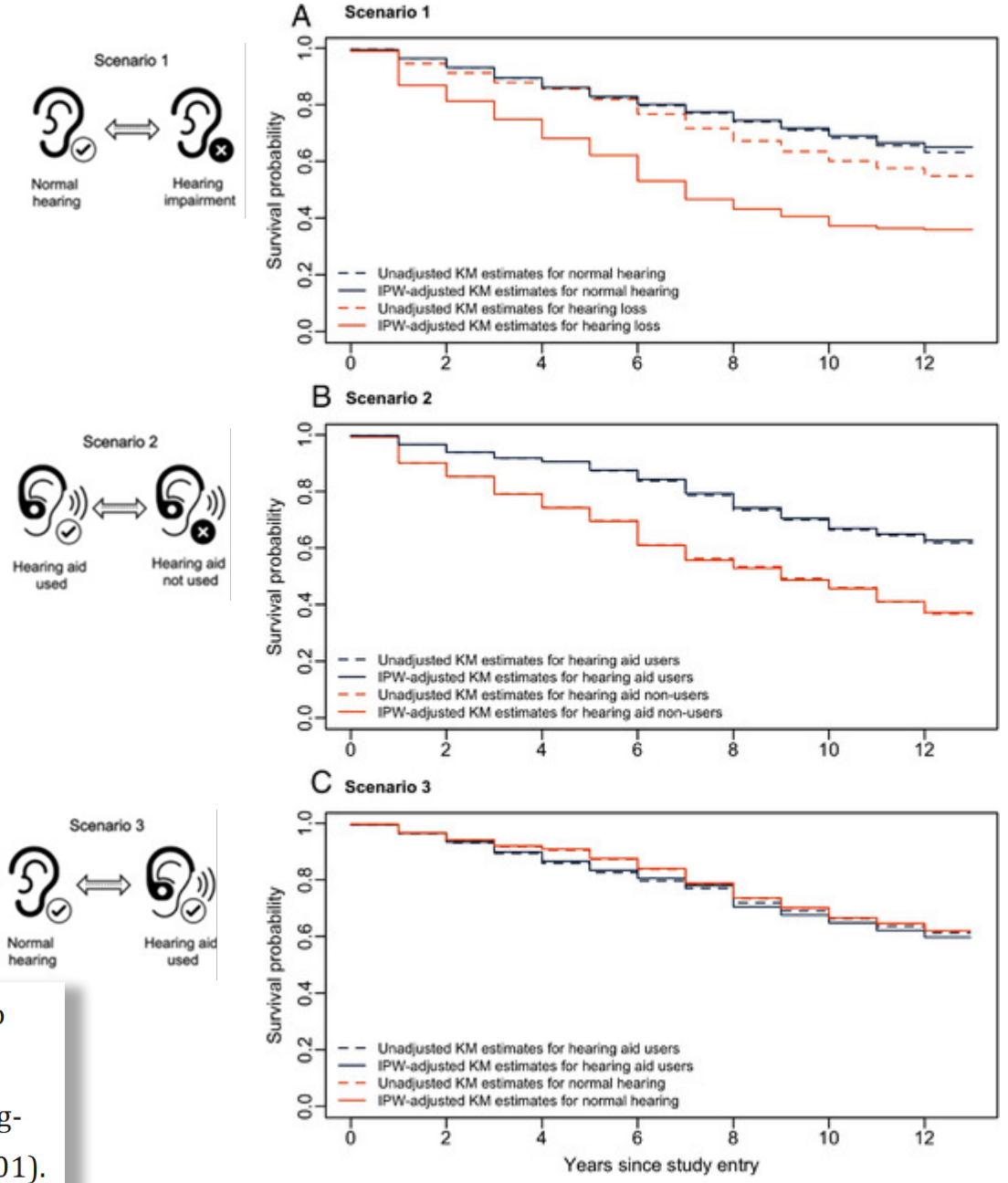
The impact of hearing impairment and hearing aid use on progression to mild cognitive impairment in cognitively healthy adults: An observational cohort study

Magda Bucholc [1,✉], Sarah Bauermeister [2], Daman Kaur [3], Paula L McClean [3], Stephen Todd [4]

HIGHLIGHTS

- Hearing loss is associated with higher risk of mild cognitive impairment (MCI).
- Hearing loss is associated with accelerated cognitive decline.
- Hearing aid use is associated with lower risk of MCI and slower cognitive decline.
- People with normal hearing and hearing aid users have similar risk of MCI.
- Quality audiology screening might prove an effective dementia prevention strategy.

Hearing impairment was associated with increased risk of MCI (standardized hazard ratio [HR] 2.58, 95% confidence interval [CI: 1.73 to 3.84], $P = .004$) and an accelerated rate of cognitive decline ($P < .001$). Hearing aid users were less likely to develop MCI than hearing-impaired individuals who did not use a hearing aid (HR 0.47, 95% CI [0.29 to 0.74], $P = .001$).



Treatment of olfactory dysfunction

Despite considerable efforts within both the clinical and research communities, long-term, effective treatments for OD largely remain elusive [473–478]. The current literature base is limited by lack of high-level evidence (e.g., from large-scale randomised control trials), likely due to historical lack of funding, insufficient study participants, and inherent methodological and/or hypothesis driven differences that prevent generalisation of results. However, the devastating impact of the COVID-19 pandemic has focused efforts and attracted funding towards PIOD. The whole arena of OD will likely benefit from such ongoing work.

Treatment strategies for postviral olfactory dysfunction: A systematic review

Samuel N. Helman, M.D.,[1] Jonah Adler, B.A.,[2] Aria Jafari, M.D.,
Jackson R. Vuncannon, M.D.,[4] Ashley C. Cozart, B.S.,[5] Sarah K.
Merin E. Kuruvilla, M.D.,[6] and Joshua M. Levy, M.D., M.P.H.[4]

ALLERGY AND ASTHMA PROCEEDINGS
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Table 4 Medical and procedural treatments and associated recommendations

Therapy	Level of Evidence Summary[23]	Recommendation
Medical Regimen		
Alpha-lipoic acid	C	No recommendation
Caroverine	B	No recommendation
Corticosteroids (systemic)	B	Recommend against
Corticosteroids (topical)	B	Option
Ginkgo biloba	C	No recommendation
Topical insulin	C	No recommendation
Minocycline	B	No recommendation
Sodium citrate (topical)	B	Option
Theophylline (topical)	C	No recommendation
Vitamin A	B	Option
Vitamin B	C	No recommendation
Zinc sulfate	B	Recommend against
Procedural regimen		
Olfactory training	B	Strongly recommend
Traditional Chinese acupuncture	B	Option

Olfactory training for patients with olfactory loss after upper respiratory tract infections

Rhinology | Published: 06 October 2013
Volume 271, pages 1557–1562, (2014) Cit

Abstract Olfactory training consisting of daily suprathreshold odor exposure over 12 weeks seems to improve olfactory function. It is unknown if a longer period of training might be more effective. A prospective non-randomized clinical study was performed including 39 patients with olfactory loss after an upper respiratory tract infection (URTI) of less than 24 months duration. Patients exposed themselves with suprathreshold concentrations of four odors (rose, eucalyptus, lemon, cloves) applied in ''Sniffin' Sticks'' felt-tip pens over 32 weeks. Olfactory function was performed before (T1), after 16 weeks (T2), and 32 weeks of training (T3) using the 'the Sniffin' Sticks test kit calculating the TDI score (Threshold, Discrimination, Identification). The mean TDI score showed a non-significant trend of improvement at T2, and was significantly increased at T3 ($p = 0.021$). Overall, 31 patients (79 %) showed an increased TDI score at T3. The increase of TDI from T1 to T3 was 4.6 ± 5.1. Age, gender, duration and initial severity of olfactory loss had no influence on the improvement (all $p > 0.05$). Only patients with a D score lower than the median value of 8 showed a significantly higher increase of the D score at T3 ($p = 0.004$). The present study confirmed that olfactory training improves olfactory function in patients with olfactory loss after URTI. A longer duration of training over 32 weeks seems to increase the effectiveness in comparison to a 12-week period. This was tested in a completed German multicenter trial to be published soon containing a control group to include the effect of a spontaneous recovery after URTI.

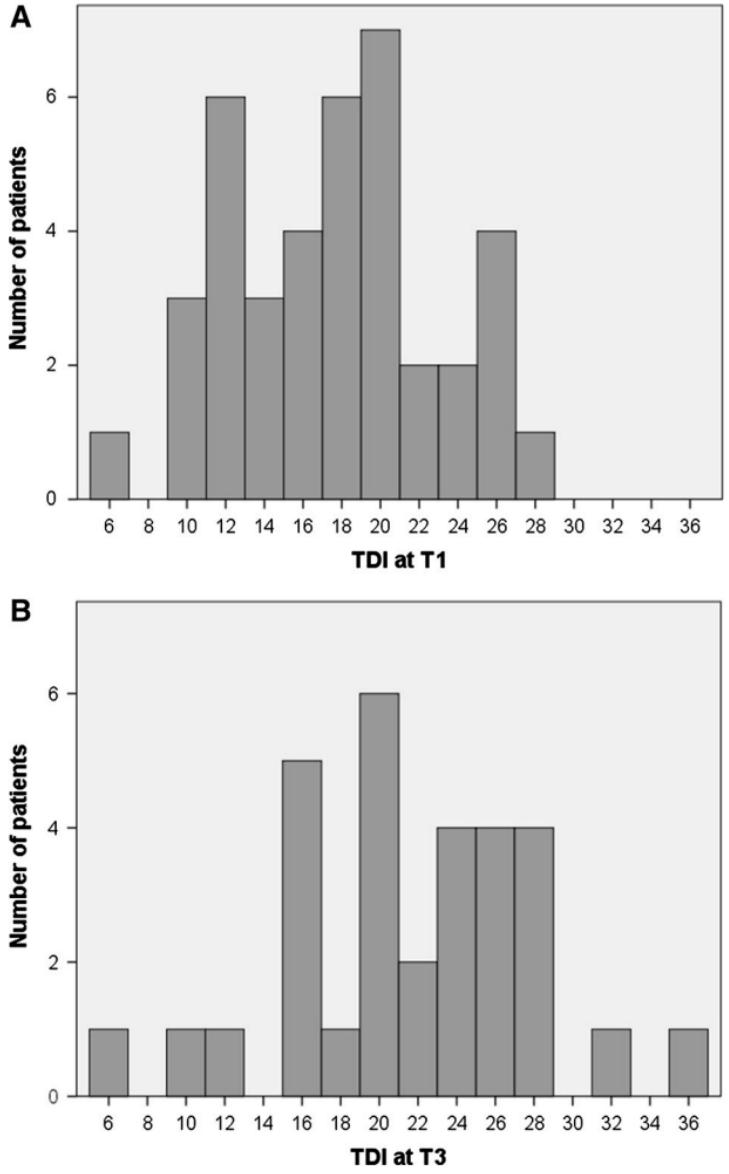

Fig. 1 Effect of olfactory training on TDI scores. **a** at T1 (baseline), **b** at T3 (after 32 weeks of training)

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olfactory training

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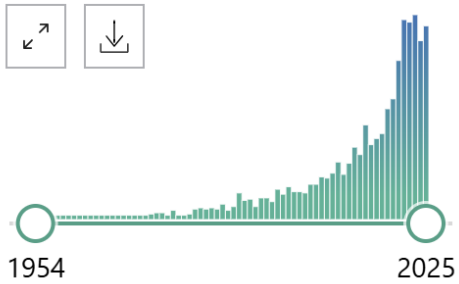
RESULTS BY YEAR



1 Cite

Olfactory training - Thirteen years of research reviewed.

Pieniak M, Oleszkiewicz A, Avaro V, Calegari F, Hummel T.

Neurosci Biobehav Rev. 2022 Oct;141:104853. doi: 10.1016/j.neubiorev.2022.104853. Epub 2022 Sep 5.

PMID: 36064146 **Free article.** Review.

The sense of smell is interrelated with psychosocial functioning. **Olfactory** disorders often decrease quality of life but treatment options for people with **olfactory** loss are limited. Additionally, **olfactory** loss accompanies and precedes psychiatric and neurod ...

Otolaryngol Head Neck Surg. 2021 Jan;164(1):82-86. doi: 10.1177/0194599820943530. Epub 2020 Jul 14.

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

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

Randomized Controlled Trial. Eur Rev Med Pharmacol Sci. 2021 Jun;25(11):4156-4162. doi: 10.26355/eurrev_202106_26059.

Randomized clinical trial "olfactory dysfunction after COVID-19: olfactory rehabilitation therapy vs. intervention treatment with Palmitoylethanolamide and Luteolin": preliminary results

L D'Ascanio [1], F Vitelli, C Cingolani, M Maranzano, M J Brenner, A Di Stadio

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OTORINOLARINGOIATRIA

RIABILITAZIONE OLFATTIVA POST-COVID 19

Cosa serve:

- Quattro vasetti di vetro con coperchi 30 ml
- Un po' di carta per acquerelli e forbici
- Oli essenziali (rosa, limone, chiodi di garofano, eucalipto)
- Etichette adesive

Indicazioni:

Ritaglia quattro dischetti di carta per acquerello che i adattano al fondo dei barattoli. Metti un disco su ogni barattolo. Aggiungi alcune gocce degli oli essenziali a ciascuno dei vasetti. Tappa i vasetti e conserva le tue bottigliette di oli essenziali nel frigorifero (durano almeno 4-5 mesi). Assicurati di porre un'etichetta sia sui vasetti sia sui coperchi.

Timing della riabilitazione olfattiva:

Pratica lo smell training almeno 2 volte al giorno (al mattino e alla sera) per 10 minuti consecutivi tutti i giorni.

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

RHINOLOGY

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]

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]

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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2001

Current Neuropharmacology, 2022, 20, 2001-2012

BENTHAM SCIENCE

CLINICAL TRIAL STUDY

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], Federica Vitelli[2], Giuseppe Spriano[7,8], Marco De Vincentiis[9], Angelo Camaioni[10], Ignazio La Mantia[1], Fabio Ferreli[7,8] and Michael J. Brenner[11,#]

RHINOLOGY
Official Journal of the European and International Societies
VOLUME 61 | SUPPLEMENT 33 | OCTOBER 2023

POSITION PAPER ON OLFACTORY DISFUNCTION: 2023

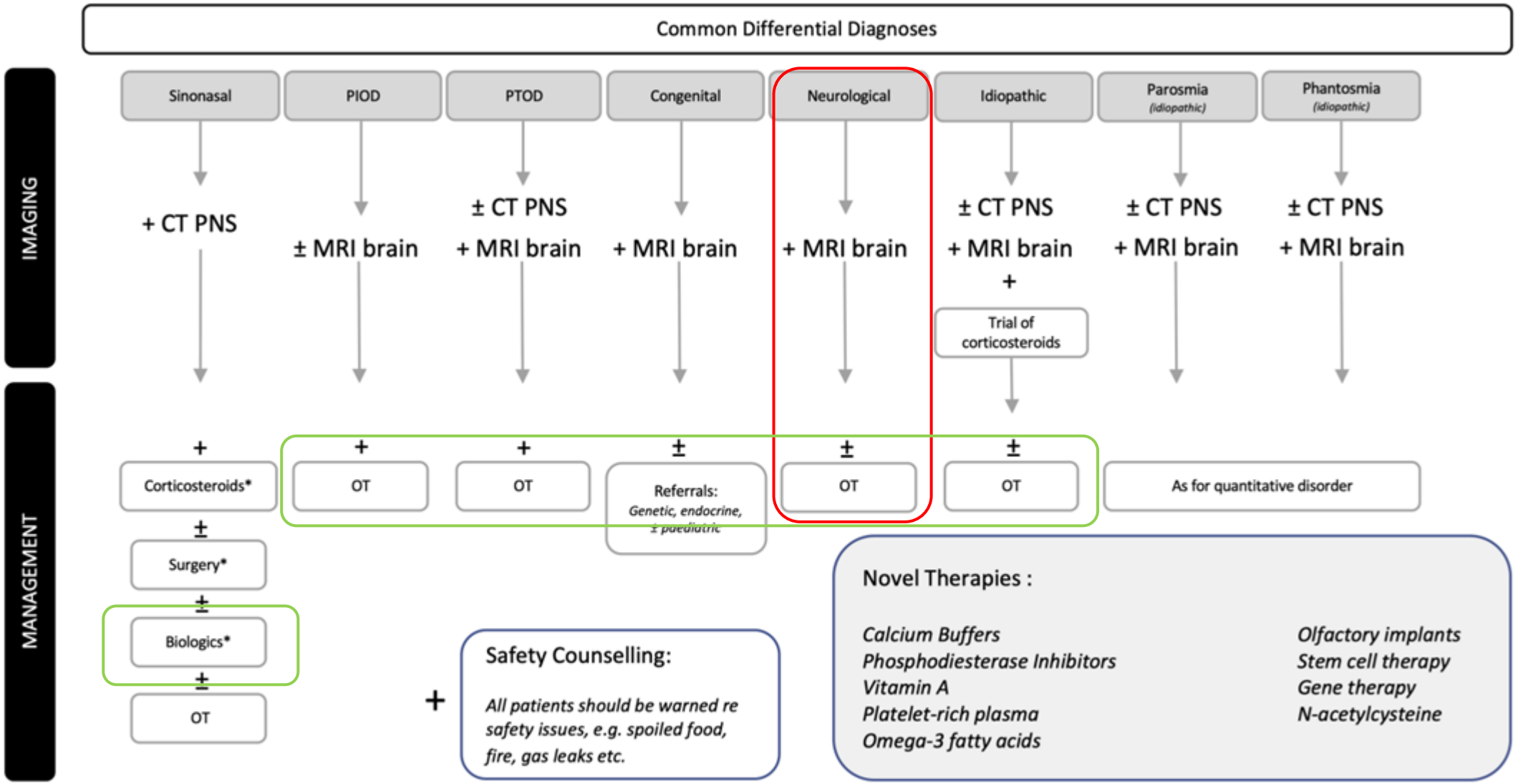


Figure 4. Summary flowchart showing suggested approach to assessment and management of olfactory dysfunction. Please see relevant sections for more detail. *Use according to existing CRS guidelines.

The Laryngoscope
© 2009 The American Laryngological, Rhinological and Otological Society, Inc.

2009

Effects of Olfactory Training in Patients with Olfactory Loss

Thomas Hummel, MD; Karo Rissom; Jens Reden, MD; Aantje Hähner, MD; Mark Weidenbecher, MD; Karl-Bernd Hüttenbrink, MD

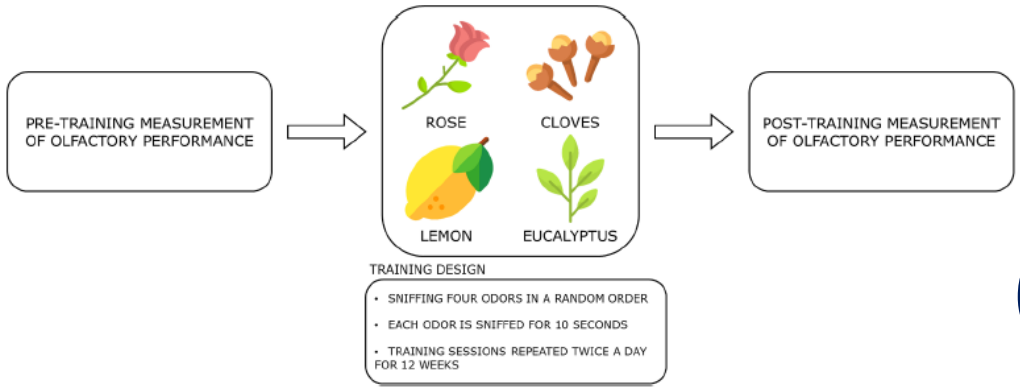
Abstract

Objectives: Olfactory function is known to be modulated by repeated exposure to odors. The aim of this investigation was whether patients with olfactory loss would benefit from "Training" with odors in terms of an improvement of their general olfactory function. It was hypothesized that olfactory Training should produce both an improved sensitivity towards the odors used in the Training process and an overall increase of olfactory function.

Study design: The prospective study was performed in patients with olfactory dysfunction.

Methods: One group of patients performed the Training (n = 40), whereas another part did not (n = 16). Exclusion criteria for patients were sinunasal disease. Olfactory training was performed over a period of 12 weeks. Patients exposed themselves twice daily to four intense odors (phenyl ethyl alcohol: rose, eucalyptol: eucalyptus, citronellal: lemon, and eugenol: cloves). Olfactory testing was performed before and after training using the "Sniffin' Sticks" (thresholds for phenyl ethyl alcohol, tests for odor discrimination and odor identification) in addition to threshold tests for the odors used in the training process.

Results: Compared to baseline, training patients experienced an increase in their olfactory function, which was observed for the Sniffin' Sticks test score and for thresholds for the odors used in the training process. In contrast, olfactory function was unchanged in patients who did not perform olfactory training. The present results indicate that the structured, short-term exposure to selected odors may increase olfactory sensitivity.



OT

Fig. 1. The original procedure of the olfactory training proposed by Hummel et al. (2009). The first study was conducted among patients with post-infectious, post-traumatic, or idiopathic olfactory loss but more recent studies are also including healthy populations and assess not only olfactory but also cognitive and emotional functioning. Note: All icons made by Freepik from www.flaticon.com.

Classical Olfactory Training (OT) was defined as the regimen described by Hummel et al, which involves **twice-daily exposure to a set of 4 odors**, including rose, eucalyptus, lemon, and cloves, from media such as brown jars or markers. Patients typically smell each odorant for 10 seconds or longer, rotating through each until they have finished the entire set.

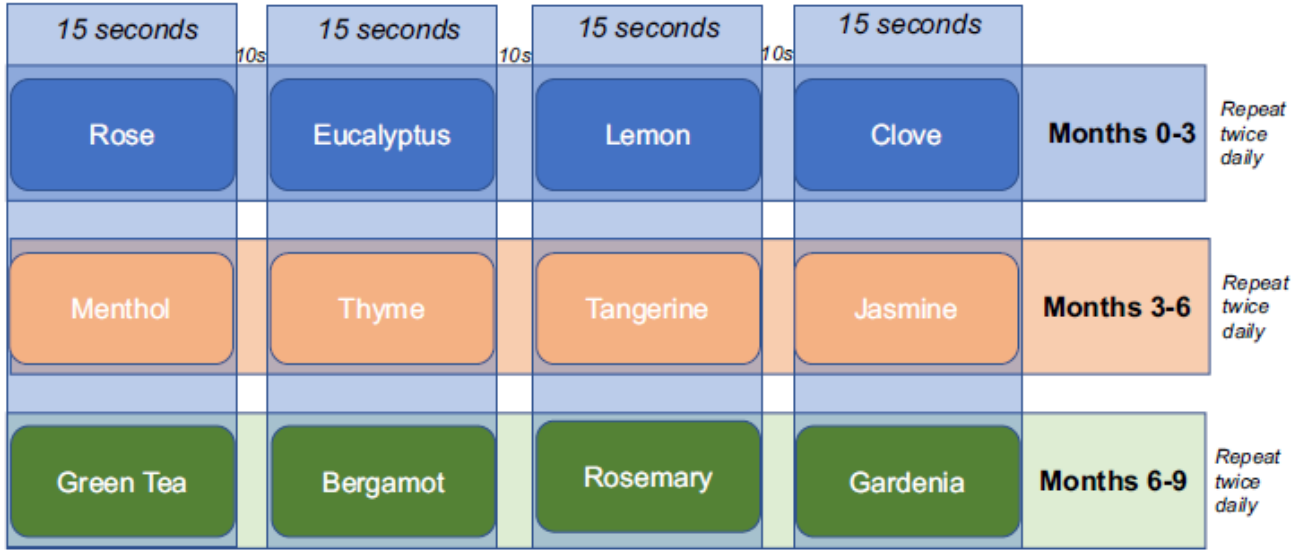


Fig. 1 Olfactory Training Paradigm, adopted by the authors (adapted from Altundag et al. [30]) Caption: A set of four odorants as described below are selected every three months for olfactory training. Each odorant is smelled for 15 seconds, with a 10 second rest between odorants. The set of odorants are smelled twice daily

MOT

Modified Olfactory Training

To stimulate more and different olfactory receptors in the MOT group, periodically changing the training odors

Olfactory training (OT)

The exact underlying mechanism for improvement following smell training is unknown. However, evidence suggests some degree of plasticity both at peripheral and central levels. In rats, there is increased electrophysiological activity at the level of the OE following training in an odour identification task [588]. Similarly, in humans, EOG responses to PEA and H2S were recorded more frequently in patients (PIOD and idiopathic OD) following a course of standard OT, suggesting either some modification at the level of the OR (e.g. upregulation), or increase in functional OSN population [589]. Increased OB volume has also been demonstrated in healthy participants after a period of OT (interestingly, there were increases in bilateral OB volume despite monorhinal OT) [590]. Following excitotoxic OB ablation in rats, OT has been associated with increased subventricular zone neurogenesis and OB dopaminergic interneurons [229,591]. Structural changes in grey matter volume and cortical thickness upstream of the OB have also been demonstrated after OT in humans [592]. Finally, OT appears to cause alterations in functional connectivity [593].

Given the low associated cost and established safety profile of OT, it is an attractive treatment modality, which can be employed with relative impunity.

Meta-Analysis > Am J Rhinol Allergy. 2023 Jul;37(4):495-501. doi: 10.1177/19458924221150977. Epub 2023 Jan 12.

The Efficacy of Olfactory Training as a Treatment for Olfactory Disorders Caused by Coronavirus Disease-2019: A Systematic Review and Meta-Analysis

Se Hwan Hwang [1], Sung Won Kim [2], Mohammed Abdullah Basurrah [3], Do Hyun Kim [2]

Abstract

Background: There have been reports investigating the use of olfactory training in olfactory dysfunction after COVID-19.

Objective: We evaluated the effect of olfactory training on the olfactory dysfunction of patients infected with COVID-19.

Methods: We searched PubMed, EMBASE, the Web of Science, the Cochrane database, SCOPUS, and Google Scholar up to May 2022. We retrieved studies that compared the extents of olfactory dysfunction before and after olfactory training. We performed a subgroup analysis by the duration of olfactory dysfunction.

Results: The olfactory score after olfactory training (standard mean difference [SMD] = 1.0830, 95% confidence interval [CI] [0.6416; 1.5245], $P < .0001$, $I^2 = 90.4\%$) was higher than that before training. The olfactory dysfunction rate differed significantly (OR = 0.0232, 95% CI [0.0052; 0.1044], $P < .0001$, $I^2 = 63.1\%$) before and after olfactory training. On subgroup analysis, although patients with both acute (onset < 30 days prior) and chronic (onset > 30 days prior) olfactory dysfunction evidenced clinically significant improvements, training during acute dysfunction (compared to acute dysfunction) increased the olfactory score to a greater extent (SMD = 1.7779, 95% CI [1.0077; 2.5481] vs 0.6928 [0.2143; 1.1712], $P = 0.0190$). Moreover, as a result of subgroup analysis by dividing the included studies into2 using 2-month training period as standard, there was no statistically significant difference in the effect of the training period in the included study.

Conclusion: Olfactory training improved olfactory disorders caused by COVID-19. Such training was effective in both the acute and chronic phases.

Received January 14, 2013; **Accepted** March 13, 2013; **Published** April 17, 2013

PLOS ONE

Olfactory Training in Patients with Parkinson's Disease

Antje Haehner[1]*, Clara Tosch[1], Martin Wolz[2,4], Lisa Klingelhoefer[2], Mareike Fauser[2], Alexander Storch[2], Heinz Reichmann[3], Thomas Hummel[1]

1 Smell & Taste Clinic, Department of Otorhinolaryngology, University of Dresden Medical School, Dresden, Germany, **2** Division of Neurodegenerative Diseases, Department of Neurology, Dresden University of Technology, Dresden, Germany, **3** Department of Neurology, University of Dresden Medical School, Dresden, Germany, **4** Department of Neurology, Elblandkliniken Meissen, Meissen, Germany

Results: Compared to baseline, trained PD patients experienced a significant increase in their olfactory function, which was observed for the Sniffin' Sticks test score and for thresholds for the odors used in the training process. Olfactory function was unchanged in PD patients who did not perform olfactory training.

Conclusion: The present results indicate that olfactory training may increase olfactory sensitivity in PD patients.

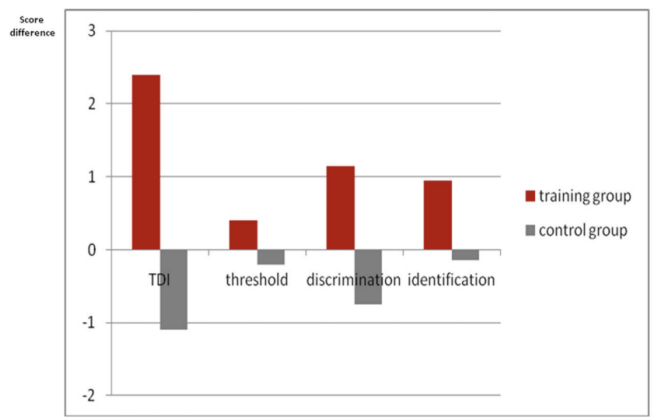


Figure 3. Change of olfactory function after 12 weeks as expressed by the TDI score (comprehensive score of threshold, discrimination, and identification abilities) in the training group compared to controls without training.
doi:10.1371/journal.pone.0061680.g003

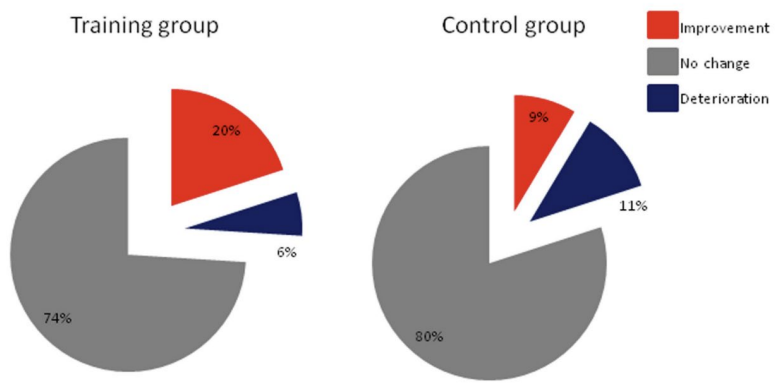


Figure 4. Change of olfactory function of more than 5.5 points in the TDI score (individual improvement).
doi:10.1371/journal.pone.0061680.g004

JOURNAL OF THE AMERICAN GERIATRICS SOCIETY

Letters to the Editor

Preventing Olfactory Deterioration: Olfactory Training May Be of Help in Older People

Valentin A. Schriever MD, Sarah Lehmann MD, Judith Prange MD, Thomas Hummel MD

First published: 12 February 2014 | https://doi.org/10.1111/jgs.12669 | Citations: 61

CONCLUSION

Although no significant improvement in olfactory function was observed, olfactory training seems to prevent olfactory deterioration that occurs with age.

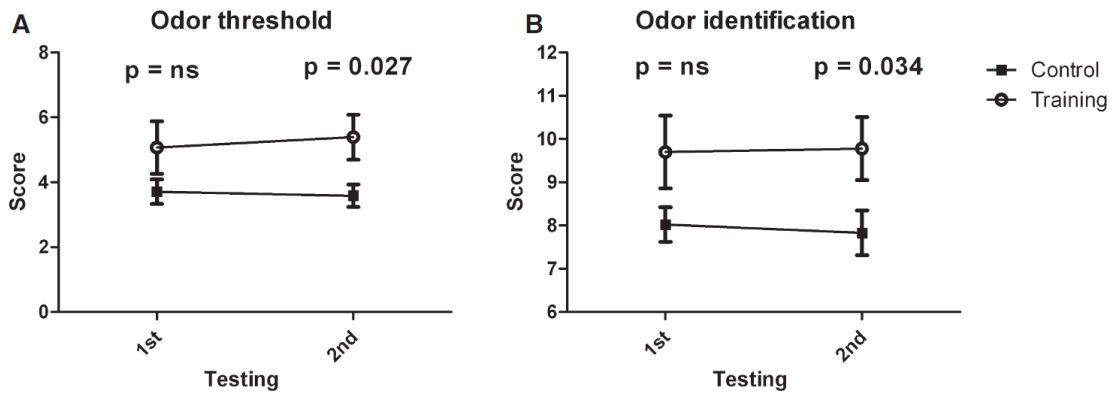


Figure 1. Olfactory training prevents deterioration of olfactory function. Olfactory test scores of the training (n = 23) and control (n = 48) groups for odor (A) threshold and (B) identification are shown. Mean scores and standard errors are plotted from both testing sessions (before and after training). Only participants who followed the olfactory training protocol as instructed were included in the training group. Scores were significantly different between the two groups for odor threshold and odor identification from the second but not the first testing session.

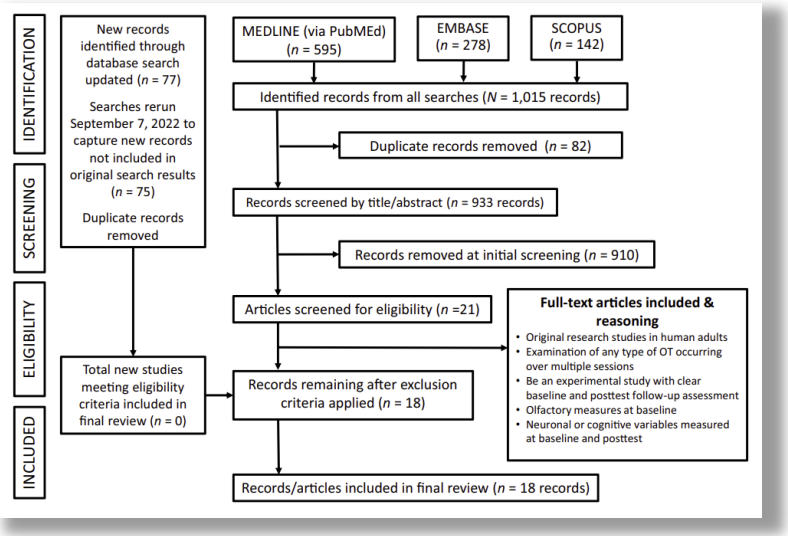
Neuropsychology Review
https://doi.org/10.1007/s11065-022-09573-0

REVIEW

Does Olfactory Training Improve Brain Function and Cognition? A Systematic Review

David E. Vance[1] · Victor A. Del Bene[2] · Vidyulata Kamath[3] · Jennifer Sandson Frank[1] · Rebecca Billings[4] · Do-Yeon Cho[5] · Jun Y. Byun[1] · Alexandra Jacob[6] · Joseph N. Anderson[7] · Kristina Visscher[8] · Kristen Triebel[7] · Karli M. Martin[7] · Wei Li[9] · Frank Puga[1] · Pariya L. Fazeli[1]

Received: 2 April 2022 / Accepted: 1 December 2022



In our review of OT studies, we found that OT improved olfaction over baseline performance in those with and without olfaction loss. In general, this olfactory improvement was associated with improved cognition and changes in neurological structures and connections. Specifically,

Abstract

Olfactory training (OT), or smell training,consists of repeated exposure to odorants over time with the intended neuroplastic effect of improving or remediating olfactory functioning. Declines in olfaction parallel declines in cognition in various pathological conditions and aging. Research suggests a dynamic neural connection exists between olfaction and cognition. Thus, if OT can improve olfaction, could OT also improve cognition and support brain function? To answer this question, we conducted a systematic review of the literature to determine whether there is evidence that OT translates to improved cognition or altered brain morphology and connectivity that supports cognition. Across three databases (MEDLINE, Scopus, & Embase), 18 articles were identified in this systematic review. Overall, the reviewed studies provided emerging evidence that OT is associated with improved global cognition, and in particular, verbal fluency and verbal learning/memory. OT is also associated with increases in the volume/size of olfactory-related brain regions, including the olfactory bulb and hippocampus, and altered functional connectivity. Interestingly, these positive effects were not limited to patients with smell loss (i.e., hyposmia & anosmia) but normosmic (i.e., normal ability to smell) participants benefitted as well. Implications for practice and research are provided.

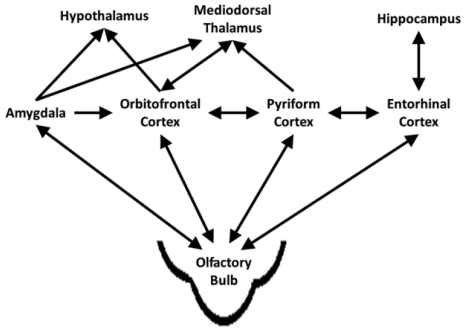


Fig. 1 Overview of olfactory training and olfactory system connections

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Randomized Controlled Trial > Behav Neurosci. 2021 Dec;135(6):732-740.

doi: 10.1037/bne0000478. Epub 2021 Jun 10.

Beyond olfaction: Beneficial effects of olfactory training extend to aging-related cognitive decline

A Oleszkiewicz [1], A Abriat [2], G Doelz [1], E Azema [2], T Hummel [1]

Abstract

Studies on olfactory training (OT) outcomes have mostly been limited to olfactory performance, while direct neural connections between olfactory system and amygdala–hippocampal complex allow expecting OT to have psychological effects. To address this hypothesis, we examined olfactory, cognitive and emotional effects of OT in the group of 68 subjects aged between 50 and 88 years (M_{age} = 62.8 ± 8.9 years; 28 males) who are likely to experience an age-related decline in olfactory and cognitive performance. We diversified stimuli used in the OT to verify whether odor mixtures result in more effective activation of olfactory receptor neurons than single molecule odors. Subjects were randomly assigned to one of the experimental conditions: (a) simple OT utilizing single-molecule odors; (b) mixtures OT using odor mixtures; (c) control group without OT. Results indicate beneficent effects of the simple OT on cognitive assessment, cognitive decline symptoms, and olfactory sensitivity. OT can be adapted from otorhinolaryngological practice to successfully serve neurocognitive research and in supporting the cognitive-related aging process. (PsycInfo Database Record (c) 2025 APA, all rights reserved)

Innovation in Aging, 2024, **8**, igae044
https://doi.org/10.1093/geroni/igae044
Advance access publication 30 May 2024
Scholarly Review

Aging and Olfactory Training: A Scoping Review

Megan Loughnane, PhD[1,*], Victoria Tischler, PhD[1], Reem Khalid Saifeldeen,[1] and Emily Kontaris, MSc[2]

[1]School of Psychology, University of Surrey, Guildford, UK.
[2]Health and Well-Being Centre of Excellence, Givaudan UK Limited, Ashford, UK.

*Address correspondence to: Megan Loughnane, PhD. E-mail: m.loughnane@surrey.ac.uk

Decision Editor: Steven M. Albert, PhD, MS, FGSA

Abstract

Background and Objectives: Decreased olfactory function commonly occurs alongside the aging process. Research suggests olfactory training (OT) has the potential to improve olfactory and cognitive function in individuals with and without olfactory dysfunction. The degree to which these benefits extend into older age and among those with cognitive impairment (i.e., people with dementia and mild cognitive impairment) is less clear. The purpose of the current review was to investigate the extent to which OT affects olfactory function, cognition, and well-being among older people.

Research Design and Methods: A scoping review of the literature was conducted in PubMed, Embase, EbscoHost, and SCOPUS. Articles were considered eligible for original research studies with human populations, included adults aged 55 and older, performed any type of OT, and included a form of olfactory testing. The data from the included studies were synthesized and presented narratively.

Results: A total of 23 studies were included. The results suggest that OT provides multiple benefits to older adults, including those with cognitive impairment. Particularly, OT was associated with measurable changes in olfactory function, improved cognitive function, specifically semantic verbal fluency and working memory, reduced depressive symptoms, and protection from cognitive decline.

Discussion and Implications: The findings suggest that benefits from OT extend beyond changes in olfactory function and include improved cognitive function, amelioration of depressive symptoms, and protection from cognitive decline. Future research is needed across specific participant groups, including those with differentiated types of dementia, to investigate the olfactory and cognitive benefits of OT.

Randomized Controlled Trial > J Alzheimers Dis. 2022;85(2):745-754. doi: 10.3233/JAD-215257.

The Effect of Olfactory Training on Olfaction, Cognition, and Brain Function in Patients with Mild Cognitive Impairment

Ben Chen [1 2], Melanie Espin [1], Robert Haussmann [3], Claudia Matthes [3], Markus Donix [3 4], Thomas Hummel [1], Antje Haehner [1]

Conclusion: OT was found to have a limited effect on olfaction and cognition in patients with MCI compared to a non-OT condition but increased their functional response to odors in frontal area.

Randomized Controlled Trial > J Alzheimers Dis. 2022;88(2):743-755. doi: 10.3233/JAD-220248.

Training with Odors Impacts Hippocampal Thickness in Patients with Mild Cognitive Impairment

Antje Haehner [1], Ben Chen [2 1], Melanie Espin [1], Robert Haussmann [3], Claudia Matthes [3], Dmitriy Desser [1], Lorenz Loessner [3], Moritz D Brandt [4 5], Markus Donix [3 5], Thomas Hummel [1]

Conclusion: Olfactory training was associated with an increase in cortical thickness of the hippocampus but not olfactory bulb volume in patients with MCI. Olfactory training may serve as an early intervention of preventing hippocampal atrophy.

Psychiatria Polska

Can olfactory training support improvement of cognitive functioning in patients with mild cognitive impairment?

Agnieszka Mydlikowska-Śmigórska [1], Krzysztof Śmigórski [2], Dorota Szcześniak [3], Joanna Rymaszewska [3]

Psychiatr Pol 2022;56(2):405-416

> Geriatr Gerontol Int. 2022 Jan;22(1):5-11. doi: 10.1111/ggi.14287. Epub 2021 Nov 8.

Effect of intensive olfactory training for cognitive function in patients with dementia

Hyegyeong Cha [1], Sisook Kim [1], Hansong Kim [2], Gaeyoung Kim [3], Kyum-Yil Kwon [4]

Results: Baseline characteristics were not different between the two groups. The IOT group showed significant improvements in depression, attention, memory and language functions, but not global cognition, frontal executive, or visuospatial functions compared with the control group.

Conclusion: This study shows the ability of IOT to alleviate depression and improve some cognitive functions in patients with dementia. These results suggest that IOT may be an effective non-pharmacological approach for improving the symptoms of dementia. Geriatr Gerontol Int 2022; 22: 5-11.

Recapitulation

The results suggest lack of expected therapeutic effects of olfactory training. However, assuming that such effects do not occur is premature. Having analyzed the strong and weak points of the applied methodology, the authors point out that further research in this area is necessary. Empirical reports and theoretical analysis suggesting the possibility of neuropsychological rehabilitation of cognitive functions by means of olfactory stimulation are a strong argument to do so.

Ear, Nose & Throat Journal
OnlineFirst

https://doi.org/10.1177/01455613251384121

Sage Journals

Review

Effects of Olfactory Training on Olfactory and Cognitive Function: A Systematic Review

Yangzi Tan, MD[1,2], Xiangxian Liu, MD[1,2], Yankun Li, MD[1], Xiaolu Liu, MD, PhD[3], Yali Du, MD, PhD[1], Danhua Zhao, MD, PhD[4], and Dawei Wu, MD, PhD[1]

Conclusion

Accumulating evidence supports the view of OT as a multimodal neurotherapeutic intervention that modulates the chemosensory-cognitive axis through distinct neurobiological pathways, particularly in cognitively-normal populations. OT elicits improvements in olfactory function across diverse populations, including individuals with olfactory dysfunction and healthy adults. Cognitive performance is also enhanced following OT, with notable gains observed in global cognition, language abilities, verbal learning, and working memory. Although classical OT yielded a limited improvement in cognitively-impaired individuals, intensive protocols demonstrated potential to slow cognitive decline. Furthermore, neuroimaging studies consistently showed that OT increases volume in several cognition-related brain regions and promotes neuronal reorganization, suggesting a potential mechanism for OT-mediated olfactory recovery and cognitive improvement. Importantly, our structured evidence synthesis enhances the reliability of these conclusions and provides a robust foundation for future clinical applications.

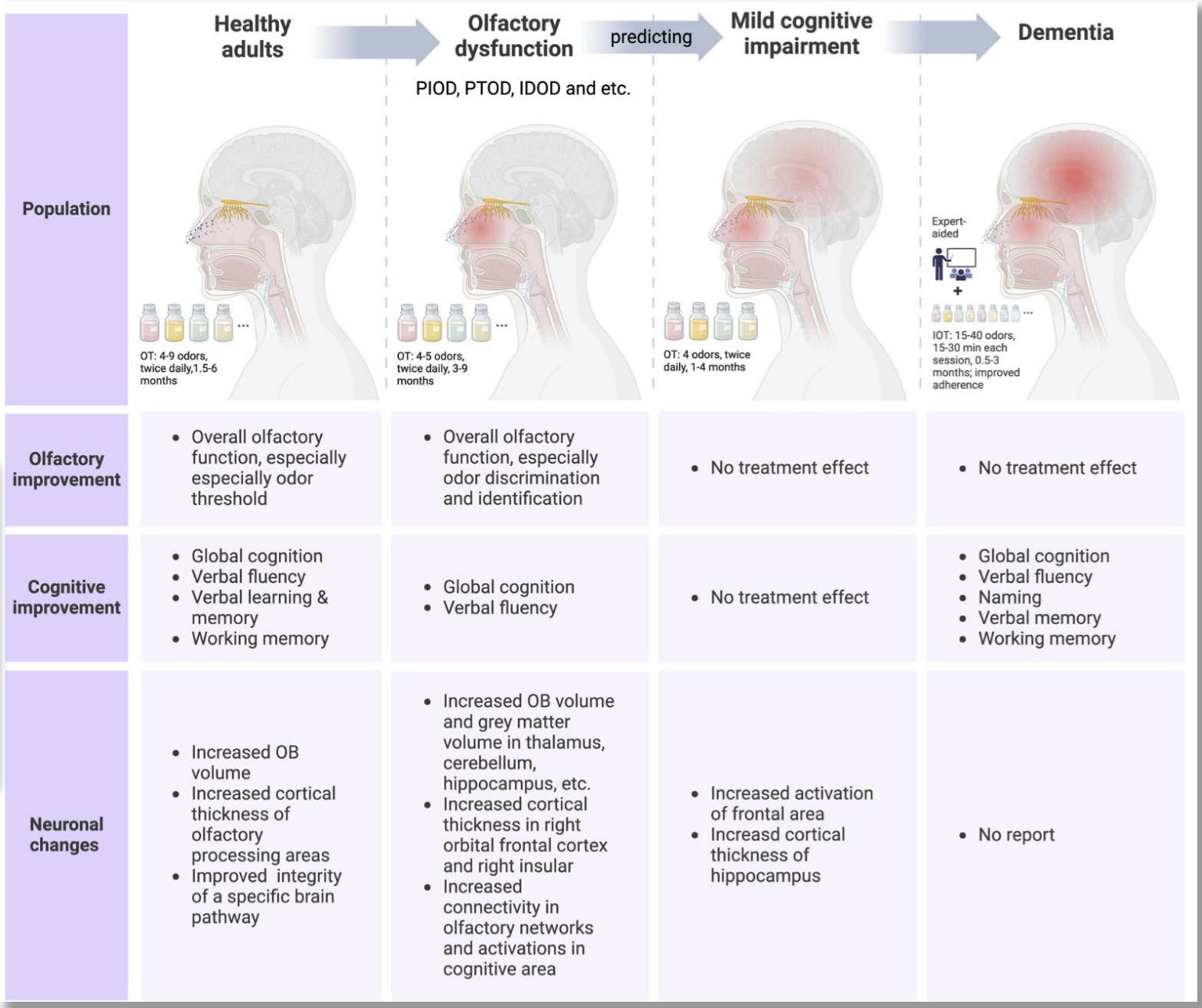


Figure 5. Effects of OT on olfaction and cognition across different populations. The review involved 3 distinct populations: healthy adults, individuals with olfactory dysfunction, and individuals with cognitive impairment, including MCI and dementia. These 3 populations align with specific stages along the trajectory of cognitive impairment: Healthy adults may develop olfactory dysfunction, which can be predictive of progression to MCI, and MCI may eventually progress to dementia. The efficacy of OT as a potential intervention was investigated across different stages of cognitive decline. The olfactory, cognitive, and neuronal outcomes of OT were separately summarized in the figure. IDOD, idiopathic olfactory dysfunction; IOT, intensive olfactory training; OB, olfactory bulb; OT, olfactory training; PIOD, postinfectious olfactory dysfunction; PTOD, posttraumatic olfactory dysfunction.

Il nostro studio

PAZIENTI AFFETTI DA DISTURBO NEURODEGENERATIVO (DNM, DNL, MCI, disturbo soggettivo di memoria)

1.VALUTAZIONE NEUROPSICOLOGICA

2. VALUTAZIONE OTORINOLARINGOIATRICA
Olfattometria
Audiometria tonale e vocale

OBIETTIVI

C’è correlazione fra declino cognitivo e deficit olfattivo?

C’è correlazione fra deficit uditivo e deficit olfattivo?

La riabilitazione olfattiva può rallentare il declino cognitivo?

E se sì, la riabilitazione olfattiva e la stimolazione uditiva/protesizzazione acustica possono avere un effetto sinergico sul declino cognitivo?

1. VALUTAZIONE NEUROPSICOLOGICA: strumenti e metodi

È un processo clinico per l'analisi del funzionamento cognitivo, comportamentale ed emotivo con l'**obiettivo** di identificare alterazioni associate a patologie neurologiche, disturbi neuropsichiatrici e sviluppo atipico.

Rilevanza Clinica nell'Adulto e Anziano: Fondamentale per la diagnosi differenziale tra:

- Invecchiamento fisiologico;
- Mild Cognitive Impairment (MCI);
- Malattie neurodegenerative.

Screening cognitivo:

- Mini Mental State Examination (MMSE);
- Montreal Cognitive Assessment (MoCA)

Funzioni esecutive e frontali:

- Frontal Assessment Battery (FAB)

Memoria e attenzione:

- Digit Span;
- Corsi Block Test;
- Matrici Attentive

Velocità di elaborazione:

- Symbol Digit Modalities Test

Abilità visuospaziali:

- Disegno dell'Orologio (CDT)

Valutazione Funzionale e Qualità di Vita:

- Funzionamento quotidiano:
  - Activities of Daily Living (ADL)
  - Instrumental Activities of Daily Living (IADL)
- Qualità della vita:
  - World Health Organization Quality Of Life (WHOQOL-Bref)

LA STIMOLAZIONE COGNITIVA

Approccio non farmacologico centrato sull'attivazione delle funzioni cognitive attraverso esercizi specifici, strategie metacognitive e attività strutturate**.** Si fonda sul principio della **neuroplasticità**, ovvero la capacità del cervello di riorganizzarsi e creare nuove connessioni neuronali in risposta all'esperienza e all'esercizio cognitivo.

Benefici: in soggetti con MCI produce miglioramenti nelle prestazioni mnestiche, nelle funzioni esecutive, nella velocità di elaborazione, nell'attenzione, nell'intelligenza fluida e nella percezione soggettiva dell'efficienza cognitiva, ma anche sul benessere psicologico e sul funzionamento sociale.

Obiettivi: integrare la stimolazione cognitiva con la riabilitazione olfattiva (olfactory training) come coadiuvante nella gestione di MCI con deficit olfattivo.

STIMOLAZIONE COGNITIVA: PROVE DI EFFICACIA

Meta-Analysis > Ageing Res Rev. 2024 Jun:97:102312. doi: 10.1016/j.arr.2024.102312. Epub 2024 Apr 16.

Effectiveness of Cognitive Stimulation Therapy (CST) for mild to moderate dementia: A systematic literature review and meta-analysis of randomised control trials using the original CST protocol

Roopal Desai [1], Wing Gi Leung [2], Caroline Fearn [2], Amber John [2], Joshua Stott [2], Aimee Spector [2]

Review > J Clin Med. 2025 Oct 13;14(20):7225. doi: 10.3390/jcm14207225.

Cognitive Stimulation in Older Adults with Dementia: A Systematic Review

María Jiménez-Palomares [1], Olga Montero-Barrero [2], Elisa María Garrido-Ardila [1], Alicia Gibello-Rufo [3], Blanca González-Sánchez [1], Juan Rodríguez-Mansilla [1]

> Altern Ther Health Med. 2023 Oct;29(7):74-79.

A Systematic Review and Evaluation of Non-Pharmacological Interventions for Elderly Patients with Mild Cognitive Impairment

Huan Xue, Yang Li, Zhuojun Xu

Review > Biomedicines. 2025 Jan 9;13(1):149. doi: 10.3390/biomedicines13010149.

Multisensory Stimulation in Rehabilitation of Dementia: A Systematic Review

Andrea Calderone [1], Angela Marra [2], Rosaria De Luca [2], Desirèe Latella [2], Francesco Corallo [2], Angelo Quartarone [2], Francesco Tomaiuolo [1], Rocco Salvatore Calabrò [2]

Meta-Analysis > Geroscience. 2025 Feb;47(1):409-444. doi: 10.1007/s11357-024-01400-z. Epub 2024 Nov 1.

The efficacy of cognitive stimulation, cognitive training, and cognitive rehabilitation for people living with dementia: a systematic review and meta-analysis

Alice Paggetti [# 1], Ylenia Druda [# 2], Francesco Sciancalepore [1 3], Francesco Della Gatta [4], Antonio Ancidoni [1], Nicoletta Locuratolo [1], Paola Piscopo [5], Luca Vignatelli [6], Luciano Sagliocca [7], Antonio Guaita [8], Piero Secreto [9], Andrea Stracciari [10], Paola Caffarra [11], Nicola Vanacore [1], Elisa Fabrizi [12], Eleonora Lacorte [1]; Italian Dementia Guideline Working Group

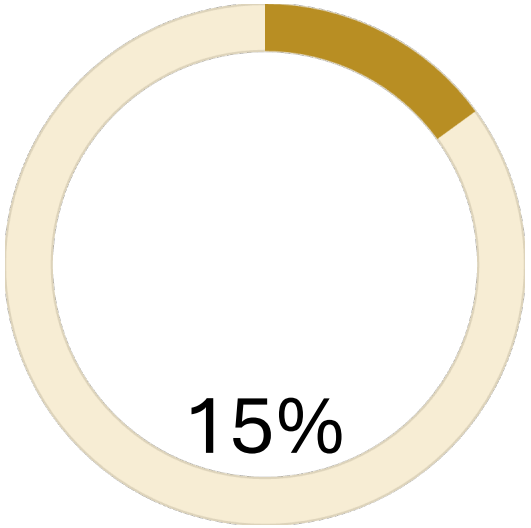
5(6):e090767. doi: 10.1136/bmjopen-2024-090767.

Effectiveness of cognitive stimulation for individuals with mild cognitive impairment: a systematic review and meta-analysis

Lu Hua Chen [1 2 3], Oi Ling Lee [4], Yan Wing Lee [4], Shu Ting Ng [4], Sum Yi Eugenia Ngai [4], Yat Hei Zita Pau [4], Tongyu Ma [4], Hon-Lam Joseph Yuen [5]

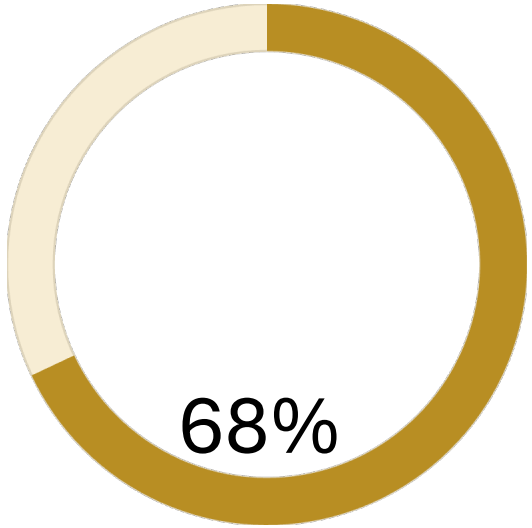
Numerose evidenze suggeriscono che la stimolazione cognitiva e multisensoriale sia efficace nel **migliorare le funzioni cognitive**. I risultati di revisioni sistematiche e meta-analisi condotte nel corso degli anni, così come studi più recenti, evidenziano **benefici significativi**. In particolare, questo approccio può contribuire a **rallentare il declino cognitivo** e a **migliorare la qualità della vita**, soprattutto se applicato attraverso **protocolli strutturati e monitorati**.

BENEFICI MULTIDOMINIO DELLA STIMOLAZIONE COGNITIVA



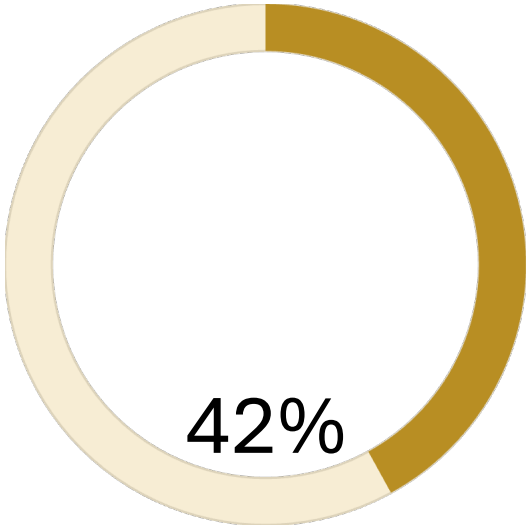
Miglioramento IADL

Incremento delle attività strumentali della vita quotidiana dopo un anno di intervento.



Qualità di Vita

Aumento della soddisfazione esistenziale e del benessere soggettivo percepito



Riduzione Sintomi

Diminuzione significativa dei sintomi depressivi e miglioramento dell'umore

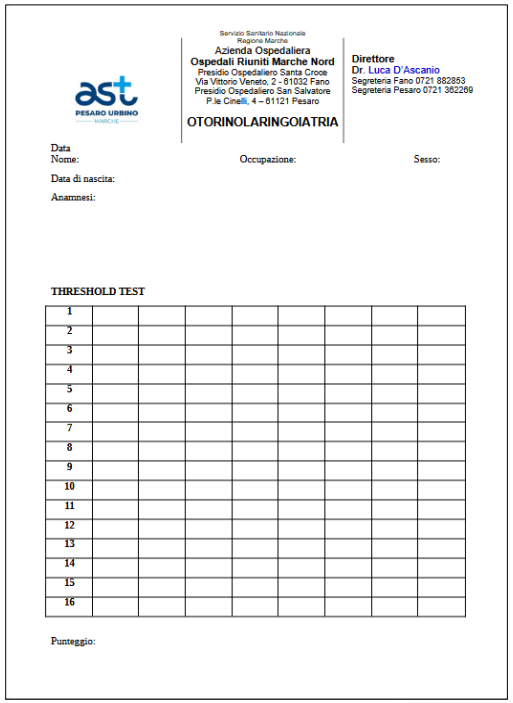
Una revisione sistematica su 15 trial RCT ha documentato che gli interventi di stimolazione cognitiva ottengono effetti significativi non solo sulle funzioni cognitive, ma anche su qualità della vita, comunicazione e interazione sociale. Gli interventi più efficaci sono quelli **multidominio**, che combinano esercizi su differenti funzioni cognitive con tecniche di compensazione e strategie metacognitive.

Il Progetto e il Protocollo CST

La **Cognitive Stimulation Therapy** (CST) è il protocollo riabilitativo di riferimento per questo intervento (*Spector, 2007*) poichè ha dimostrato efficacia nel produrre benefici cognitivi, migliorare la qualità della vita e incrementare la partecipazione sociale in persone con demenza lieve-moderata.

- **Durata:** 7 settimane per il ciclo base, con sessioni bisettimanali da 60 minuti. Possibilità di mantenimento fino a 6 mesi.
- **Setting**: Piccoli gruppi di 4-5 persone con MCI presso l'Ambulatorio di Neuropsicologia dell'Ospedale Santa Croce di Fano.
- **Monitoraggio**: Valutazione baseline completa antecedente l'avvio del training cognitivo; Valutazione post-intervento a un mese dalla conclusione del training; Follow-up a 6 mesi.
- **Materiali**: Schede cartacee, supporti digitali, immagini e oggetti concreti per esercizi sui diversi domini cognitivi (memoria, attenzione, linguaggio, fuzioni esecutive).

2. VALUTAZIONE OTORINOLARINGOIATRICA: strumenti e metodi



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

ast PESARO URBINO MARCHE

OTORINOLARINGOIATRIA

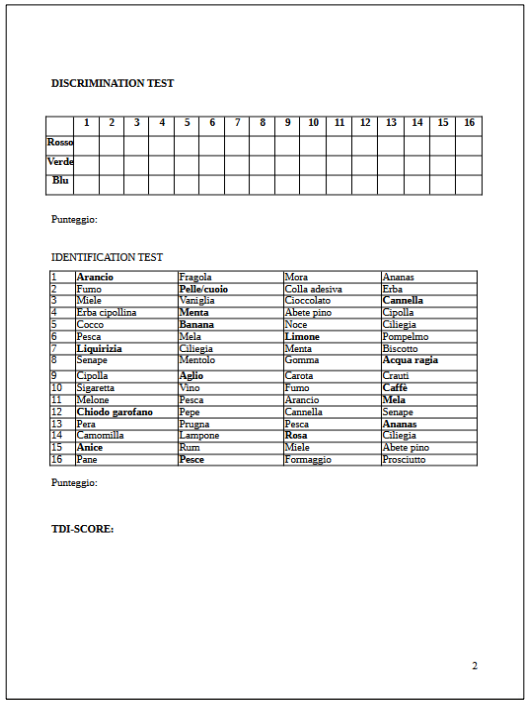
Direttore
Dr. Luca D'Ascanio
Segreteria Fano 0721 882853
Segreteria Pesaro 0721 362269

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:

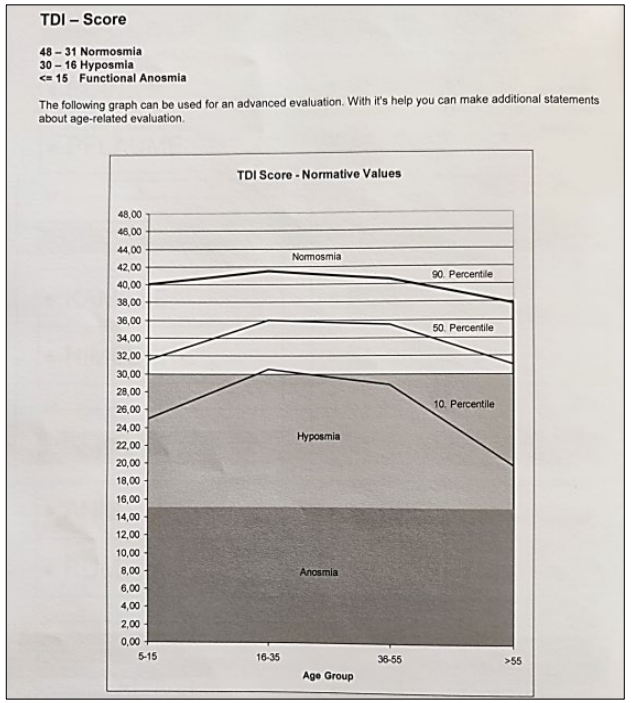
IDENTIFICATION TEST

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	Melone	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:

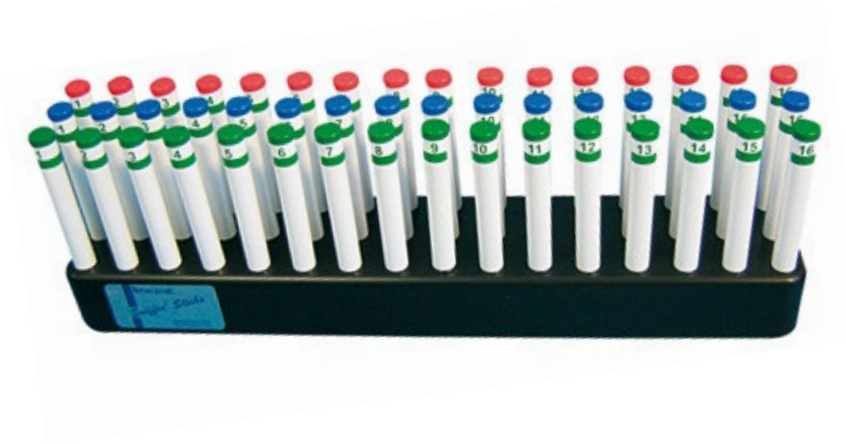
2



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.



RIBILITAZIONE OLFATTIVA

Servizio Sanitario Nazionale
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Azienda Sanitaria Territoriale
Pesaro Urbino AST

OTORINOLARINGOIATRIA

Direttore U.O.C.
Dr. Luca D'Ascanio

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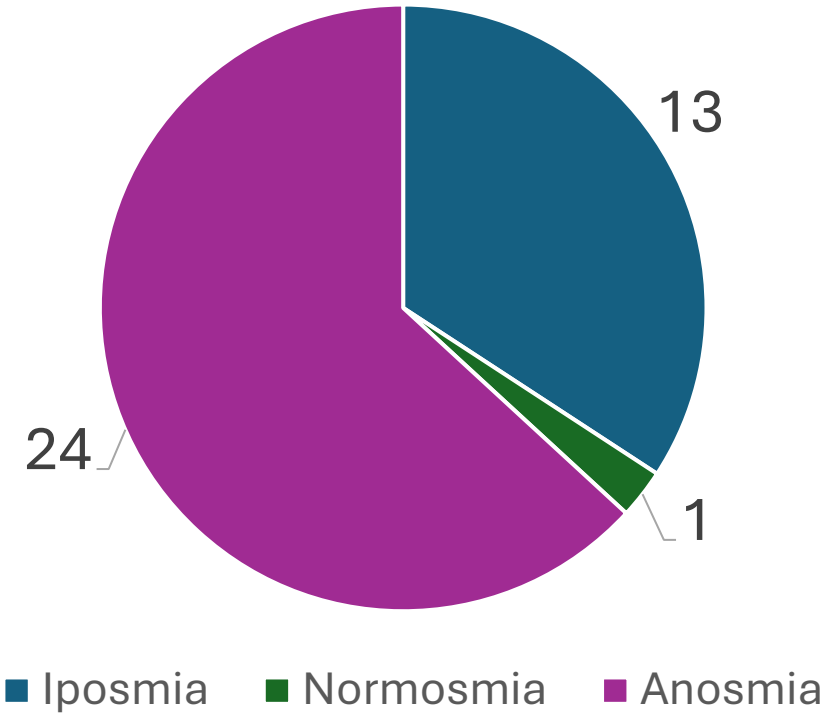
ESERCIZI PER LA RIABILITAZIONE DELL'OLFATTO

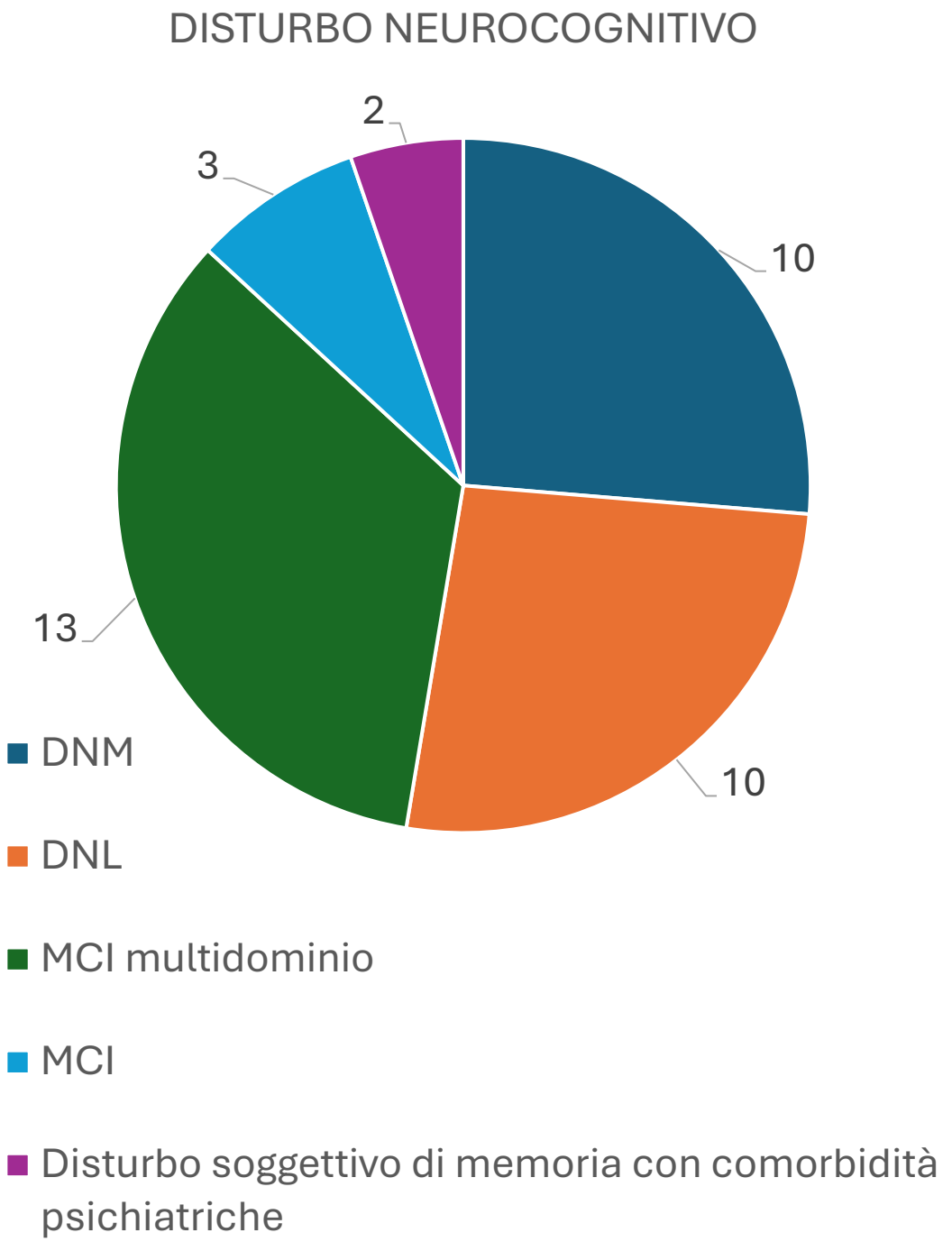
COME PRATICARE IL TRAINING OLFATTIVO

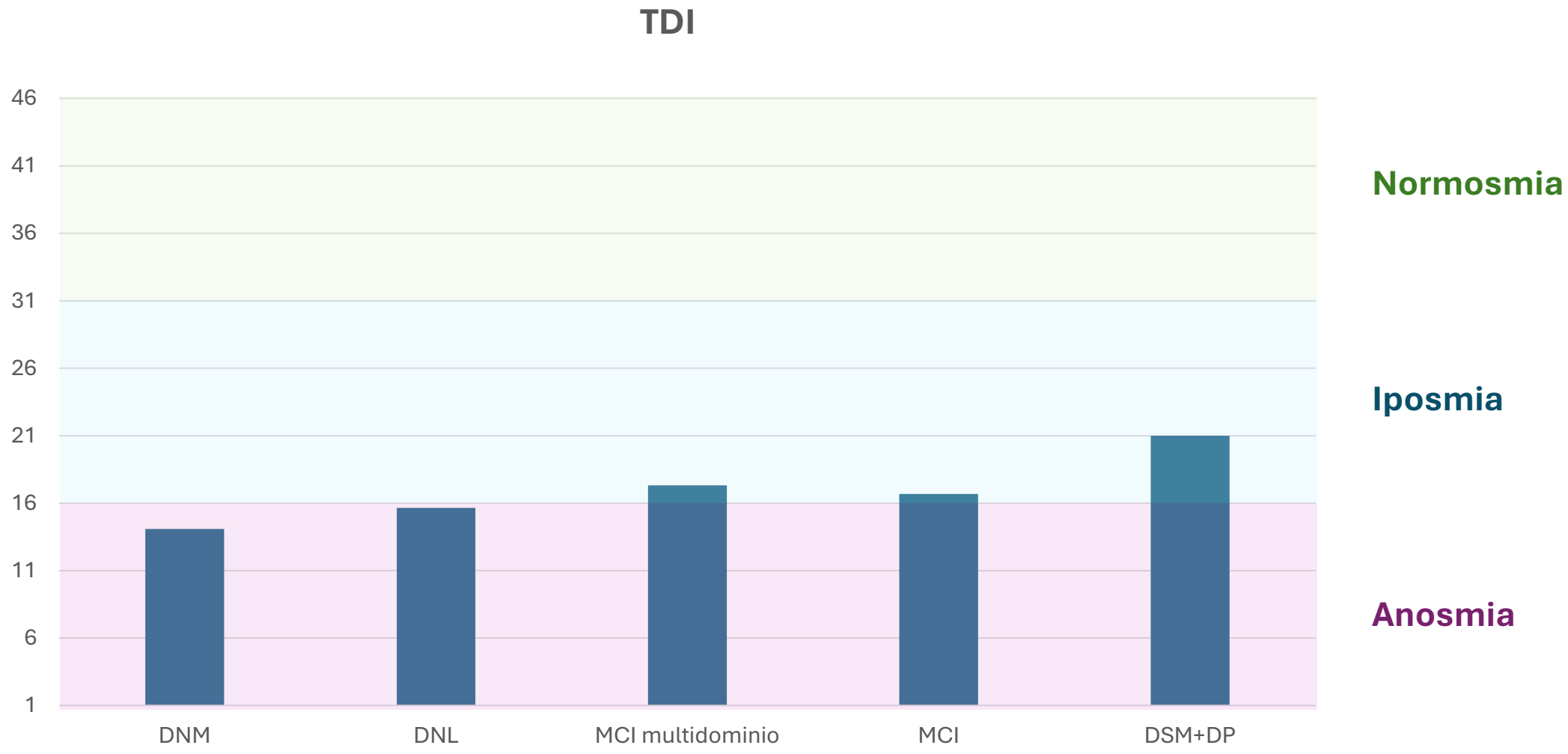
1. Usi i quattro oli essenziali (contenuti in piccoli barattoli di vetro richiudibili con cotone imbevuto), seguendo l'ordine numerico da 1 a 4.
2. Scelga un ambiente tranquillo della casa, privo di distrazioni, dove potersi sedere comodamente e concentrarsi sugli odori.
3. Annusi la prima fragranza inspirando lentamente per circa 15 secondi, cercando di focalizzarsi e di collegare l'odore a un'immagine, un suono oppure un colore.
4. Attenda circa 30 secondi prima di passare all'essenza successiva, mantenendo una respirazione regolare.
5. Una volta a settimana annoti le sue sensazioni in un diario, così da tenere traccia di eventuali miglioramenti o variazioni.
6. Ripeta questo esercizio ogni giorno, due volte al giorno (ad esempio al mattino e alla sera) per almeno quattro mesi. Non si scoraggi se all'inizio fatica a percepire o distinguere gli odori: il cervello può richiedere tempo per riapprendere il riconoscimento corretto. In alcuni casi il recupero potrebbe non essere completo, ma è comunque utile tentare. L'olfatto, infatti, è una capacità che può migliorare con un allenamento costante.

RISULTATI

Caratteristiche popolazzione	
N	38
Genere	13 (F) 25 (M)
Età media	71,08 anni

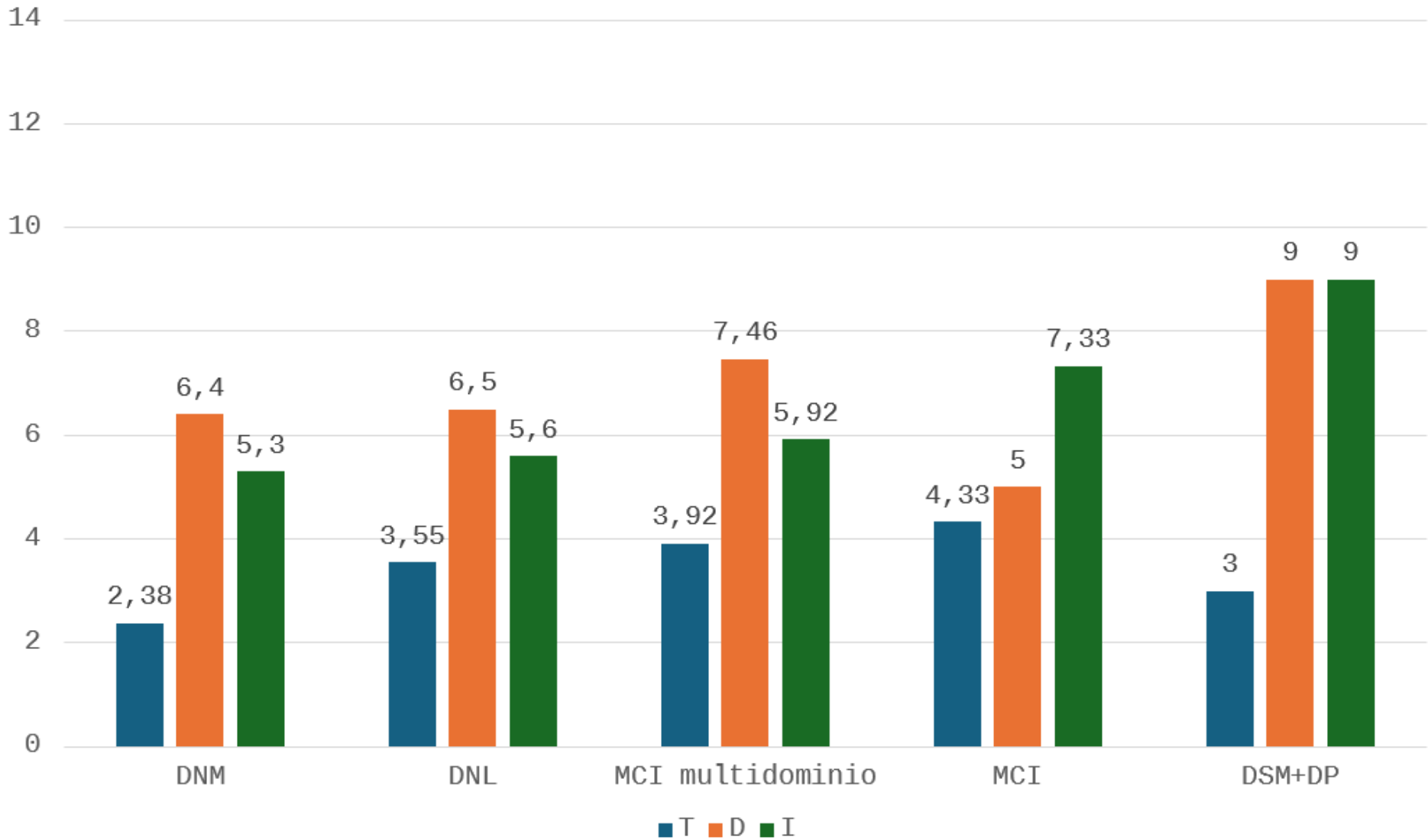






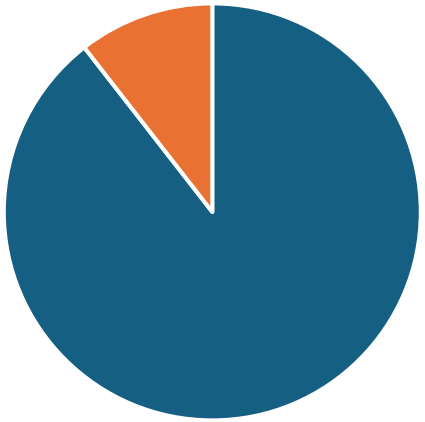
T = threshold (1-16 punti) D = discrimination (0-16 punti) I = Identification (0-16 punti)

T + D + I = TDI (1-48 punti)

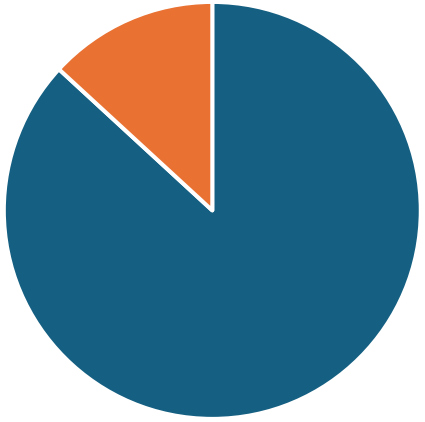


T = threshold (1-16 punti) D = discrimination (0-16 punti) I = Identification (0-16 punti)

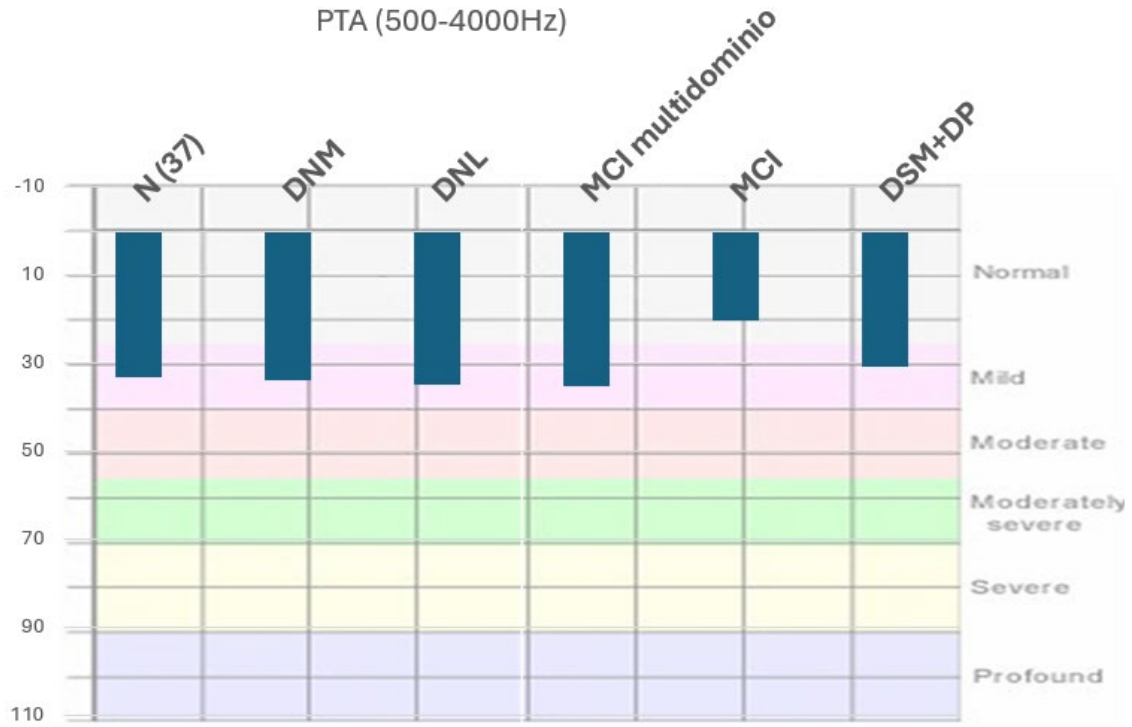
Protesi acustiche



Dissociazione tono-verbale



Popolazione	Età media	PTA (500-4000Hz)	PTA popolazione di riferimento(500-4000Hz)
Tutti (N=37)	71,08 aa	33,29	**21,4 dB** (70-75 aa) [1]
DNM (N=10)	72,06 aa	33,81	**21,4 dB** (70-75 aa) [1]
DNL (N=10)	70 aa	34,88	**21,4 dB** (70-75 aa) [1]
MCI multidominio(N=13)	73,33 aa	35,21	**21,4 dB** (70-75 aa) [1]
MCI (N=3)	59,67 aa	20,21	**13,95 dB** (50-59 aa)[2]
DSM+DP (N=3)	71,5 aa	30,94	**21,4 dB** (70-75 aa) [1]



1. Yang TH, Chen YF, Cheng YF, Wu CS, Chu YC. Establishment of reference audiometric norms for the elderly population: A community-based study on mean and median hearing thresholds. Heliyon. 2024;11(1):e41393. Published 2024 Dec 20. doi:10.1016/j.heliyon.2024.e41393
2. Park HJ, Yoo MH, Baek SY, Kim SW, Cho YS. Normative Hearing Threshold Levels in Koreans with Normal Tympanic Membranes and Estimated Prevalence of Hearing Loss. Clin Exp Otorhinolaryngol. 2017;10(2):129-136. doi:10.21053/ceo.2016.00031

..e il palmitoiletanolamide (PEA)?

biomolecules

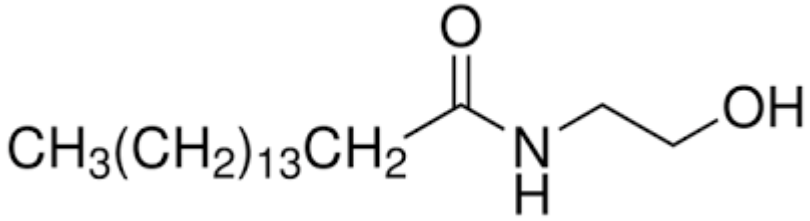
MDPI

Review

Effects of Palmitoylethanolamide on Neurodegenerative Diseases: A Review from Rodents to Humans

Eugenia Landolfo [1], Debora Cutuli [1,2], Laura Petrosini [1,*] and Carlo Caltagirone [1]

Abstract: Palmitoylethanolamide (PEA) stands out among endogenous lipid mediators for its neuroprotective, anti-inflammatory, and analgesic functions. PEA belonging to the N-acetylanolamine class of phospholipids was first isolated from soy lecithin, egg yolk, and peanut flour. It is currently used for the treatment of different types of neuropathic pain, such as fibromyalgia, osteoarthritis, carpal tunnel syndrome, and many other conditions. The properties of PEA, especially of its micronized or ultra-micronized forms maximizing bioavailability and efficacy, have sparked a series of innovative research to evaluate its possible application as therapeutic agent for neurodegenerative diseases. Neurodegenerative diseases are widespread throughout the world, and although they are numerous and different, they share common patterns of conditions that result from progressive damage to the brain areas involved in mobility, muscle coordination and strength, mood, and cognition. The present review is aimed at illustrating in vitro and in vivo research, as well as human studies, using PEA treatment, alone or in combination with other compounds, in the presence of neurodegeneration. Namely, attention has been paid to the effects of PEA in counteracting neuroinflammatory conditions and in slowing down the progression of diseases, such as Alzheimer's disease, Parkinson's disease, Huntington's disease, Frontotemporal dementia, Amyotrophic Lateral Sclerosis, and Multiple Sclerosis. Literature research demonstrated the efficacy of PEA in addressing the damage typical of major neurodegenerative diseases.



10. Conclusions

Taken together, the results reported here strongly suggest that by activating multifactorial pharmacological targets and different cellular mediators, PEA could play a promising protective role in counteracting neuroinflammation related to major neurodegenerative diseases. Despite the fact that a simplistic extrapolation of data from the animal model to human condition should be avoided, the results of both preclinical and clinical studies propose PEA as a potential therapeutic agent against neurodegeneration. Mentioned studies emphasize that PEA, especially in its ultra-micronized form, significantly impacts on the progression of some neurodegenerative diseases, acting on specific symptoms and when the pathology is at an early stage. In the final analysis, there is still much to be investigated regarding the effect of PEA, alone or in combination with other compounds, both at the preclinical level and, especially, on subjects with PD, MS, ALS, and FTD. More controversial and less clear is its role in HD. Given the numerous preclinical results regarding the efficacy of PEA in in vitro studies of AD, it would be very interesting to investigate how effective this compound really could be in AD and MCI patients.

Review > Biomedicines. 2023 Aug 3;11(8):2189. doi: 10.3390/biomedicines11082189.

Efficacy of Palmitoylethanolamide and Luteolin Association on Post-Covid Olfactory Dysfunction: A Systematic Review and Meta-Analysis of Clinical Studies

Anna Paola Capra [1], Alessio Ardizzone [1], Lelio Crupi [1], Fabrizio Calapai [1 2], Michela Campolo [1], Salvatore Cuzzocrea [1], Emanuela Esposito [1]

Abstract

Post-Covid Olfactory Dysfunction (PCOD) is characterized by olfactory abnormalities, hyposmia, and anosmia, which are among the most often enduring symptoms in individuals who have recovered from SARS-CoV-2 infection. This disorder has been reported to persist in subsets of patients well after 12 months following infection, significantly affecting their quality of life. Despite the high prevalence of PCOD among patients who suffered from SARS-CoV-2 infection, specific therapeutic strategies are still limited. Among these, emerging evidence seems to indicate the administration of CoUltraPEALut, a combination of micronized Palmitoylethanolamide (PEA), an endogenous fatty acid amide, and Luteolin, a natural antioxidant flavonoid, as a viable therapy, especially when given as an adjuvant to olfactory training. Based on the above, a systematic review and a meta-analysis of the literature were conducted, with the aim of evaluating the efficacy of CoUltraPEALut as an addition to olfactory training (OT), in treating PCOD symptoms. Pubmed (MEDLINE), Embase (OVID), and Web of Science scientific databases were screened from the inception until 31 May 2023, and a total of 407 articles were recovered; only five of these studies (441 total patients between treated and control groups) were included in the systematic review. CoUltraPEALut demonstrated significant efficacy in the overall recovery of the olfactory function, compared to the conventional therapy, suggesting that it could represent a possible future adjuvant treatment for PCOD.

Randomized Controlled Trial > Eur Rev Med Pharmacol Sci. 2021 Jun;25(11):4156-4162.

doi: 10.26355/eurrev_202106_26059.

Randomized clinical trial "olfactory dysfunction after COVID-19: olfactory rehabilitation therapy vs. intervention treatment with Palmitoylethanolamide and Luteolin": preliminary results

L D'Ascanio [1], F Vitelli, C Cingolani, M Maranzano, M J Brenner, A Di Stadio

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Current Neuropharmacology, 2022, *20*, 2001-2012

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], Federica Vitelli[2], Giuseppe Spriano[7,8], Marco De Vincentiis[9], Angelo Camaioni[10], Ignazio La Mantia[1], Fabio Ferreli[7,8] and Michael J. Brenner[11,#]

...or

...hed therapy vs. 36.8% receiving olfactory training with placebo, 40% receiving twice daily um-PEA–LUT alone, and 41.6% receiving once daily um-PEA–LUT alone ($p < 0.00001$). Patients receiving treatment with um-PEA–LUT alone demonstrated subclinical improvement (< 3 point odor identification improvement) more often than patients receiving olfactory training with placebo ($p < 0.0001$.)

Conclusions

Olfactory training plus once daily um-PEA–LUT resulted in greater olfactory recovery than either therapy alone in patients with long-term olfactory function due to COVID-19.

Springer

Eur Arch Otorhinolaryngol. 2023 Jun 28;280(11):4949–4961. doi: 10.1007/s00405-023-08085-8

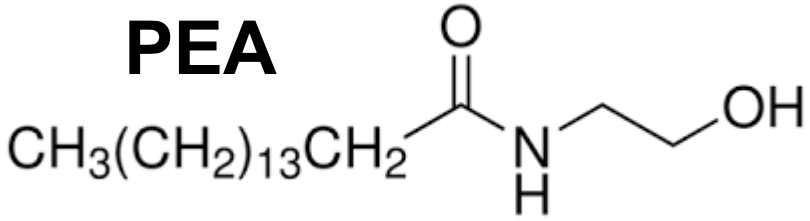
Treatment of COVID-19 olfactory dysfunction with olfactory training, palmitoylethanolamide with luteolin, or combined therapy: a blinded controlled multicenter randomized trial

Arianna Di Stadio [1,✉], Salvatore Gallina [2], Salvatore Cocuzza [1], Pietro De Luca [3], Angelo Ingrassia [2], Simone Oliva [2], Federico Sireci [2], Angelo Camaioni [3], Fabio Ferreli [4], Giuseppe Mercante [4], Francesca Gaino [4], Gian Marco Pace [4], Ignazio La Mantia [1], Michael J Brenner [5]

Il nostro studio

PAZIENTI AFFETTI DA DISTURBO NEURODEGENERATIVO (DNM, DNL, MCI, disturbo soggettivo di memoria)

PEA



FOLLOW – UP PROLUNGATO (5 anni)

Grazie!!!

ast
PESARO URBINO
MARCHE