

Olfaction: Establishing Normality and Ensuring Safety

Richard L Doty MA PhD FAAN

*Perelman School of Medicine
University of Pennsylvania
Philadelphia, PA 19104*

*Sensonics International
Haddon Heights, NJ 08035*



"Smell" in The Lady & the Unicorn Tapestries, c. 1500, Musee de Cluny, Paris

Disclosures: Dr. Doty is a consultant to Merck Pharmaceuticals, the Michael J. Fox Foundation for Parkinson's Research, and Johnson & Johnson. He receives royalties from Cambridge University Press, Elsevier, Johns Hopkins University Press, McGraw-Hill, and John Wiley & Sons, Inc. He is President and major shareholder of Sensonics International, the largest manufacturer and distributor of smell and taste tests in the world.

Goals of Today's Presentation:

1. Briefly review the anatomy and physiology of the olfactory system
2. Provide a basic overview of how the ability to smell is quantitatively tested in academia, medicine, and industry, including the natural gas industry to establish a “normal” sense of smell
3. Give examples of factors known to impact the ability to smell, notably warning agents added to natural gas, including sex, age, individual differences, long-term exposures, and viruses such as COVID-19

Under 49 CFR § 192.625, the U.S. federal pipeline safety regulation, all combustible gas in a distribution line must be odorized so that it is readily detectable by a person with a **normal sense of smell** at a concentration in air equal to one-fifth of the lower explosive limit (LEL)

A Normal Ability to Smell is Important Not Only for Safety, but for Everyday Life

- **Flavor** and Palatability of Foods and Beverages
- **Esthetics & Quality of Life** (seashore, flowers, perfumes, baking cookies, enjoyment)
- **Communication** (mother/infant interactions, personal identification, hygiene)
- **Mortality** (older anosmics 3X more likely to die over half-decade than non-anosmics)
- **Occupational tool** (e.g., cooks, firefighters, plumbers, wine merchants, food and drug specialists, chemical plant workers, policemen, etc.)
- **Health Surveillance and Early Diagnosis** (hyposmia is a 'preclinical' sign of such diseases as Alzheimer's and Parkinson's and can be among the first signs of viral infections such as COVID-19)
- **Safety** (warning of spoiled foods, toxins, polluted air, smoke/fire, gas leaks)

Safety: Today's Main Issue

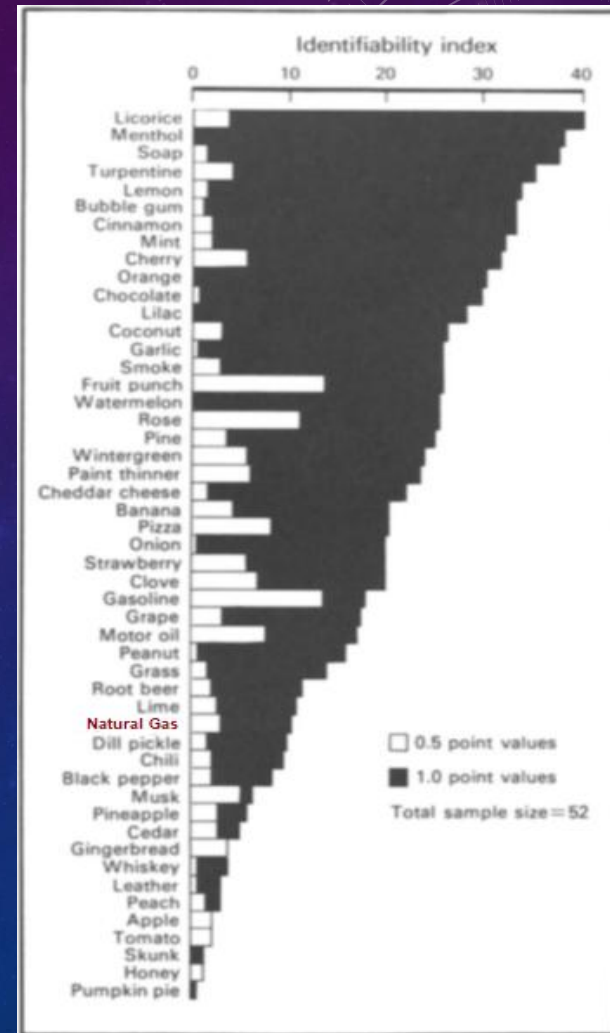
- **A disproportionate number of elderly die in fires and gas explosions, in part because of compromised ability to smell**
- **Over 50% of those 65-80 years of age have some degree of smell dysfunction, with 15% being anosmic; over the age of 80 years, > 80% have such dysfunction, with 25% being anosmic**
- **Anosmics are barred from enlistment and retention in the US Armed Forces, reflecting the importance of smell in the operation of complex machinery, detection of dangers in confined spaces (e.g., tanks, submarines, aircraft), and the detection of toxic gases in the battlefield.**

How easy is it for healthy people to identify the smell of odorized natural gas?

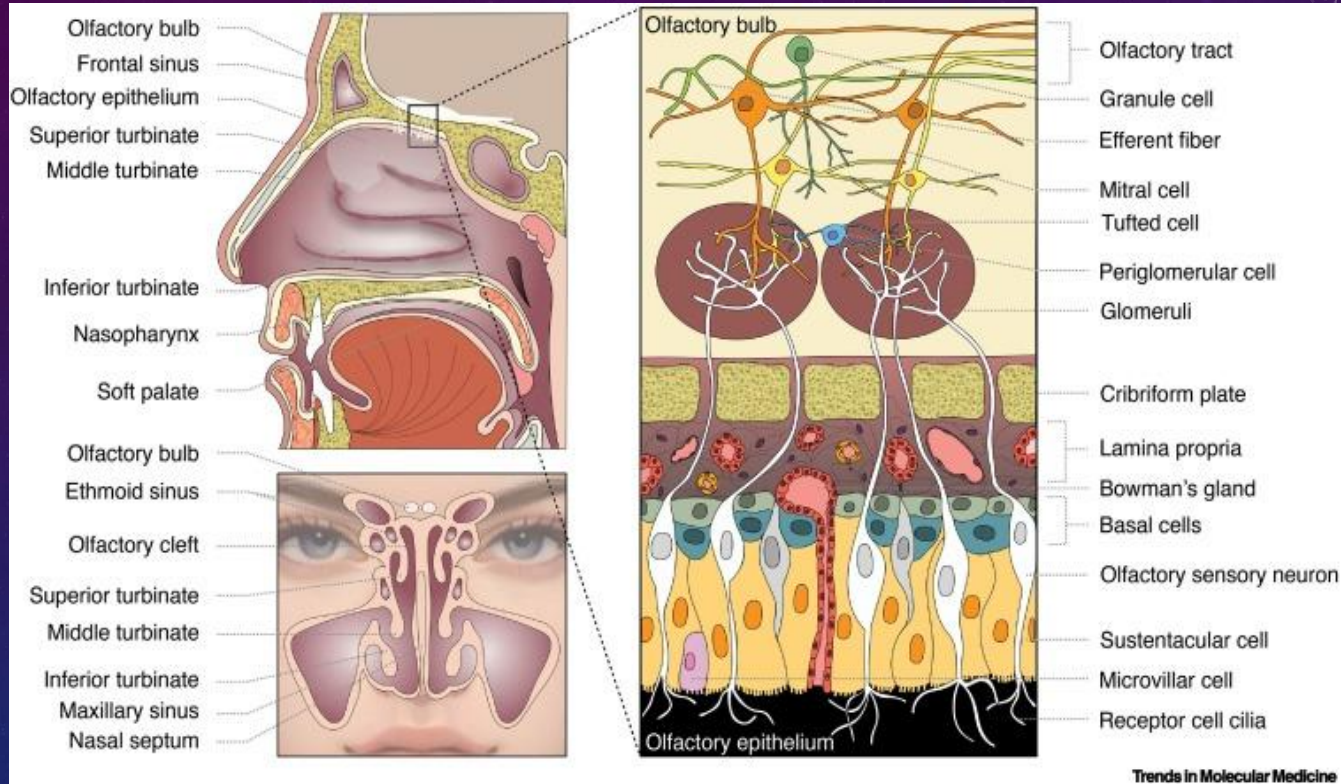
- Identifying odors without cuing is difficult for most people
- Mercaptans are very difficult to recognize
- Of 52 adults asked to smell and name 50 odorants, the ability to name “Natural gas” ranked 35th. **Only 15% correctly identified the odor.**

From Doty RL, Shaman, P. & Dann, M. *Physiology & Behavior* 32:489-502, 1984.

A point was given for correct responses (i.e., the name given by its manufacture such as licorice for licorice) and ½ point for less specific “near” responses (e.g., candy for licorice). The sum of the points across the 52 subjects was the “identifiability index”.

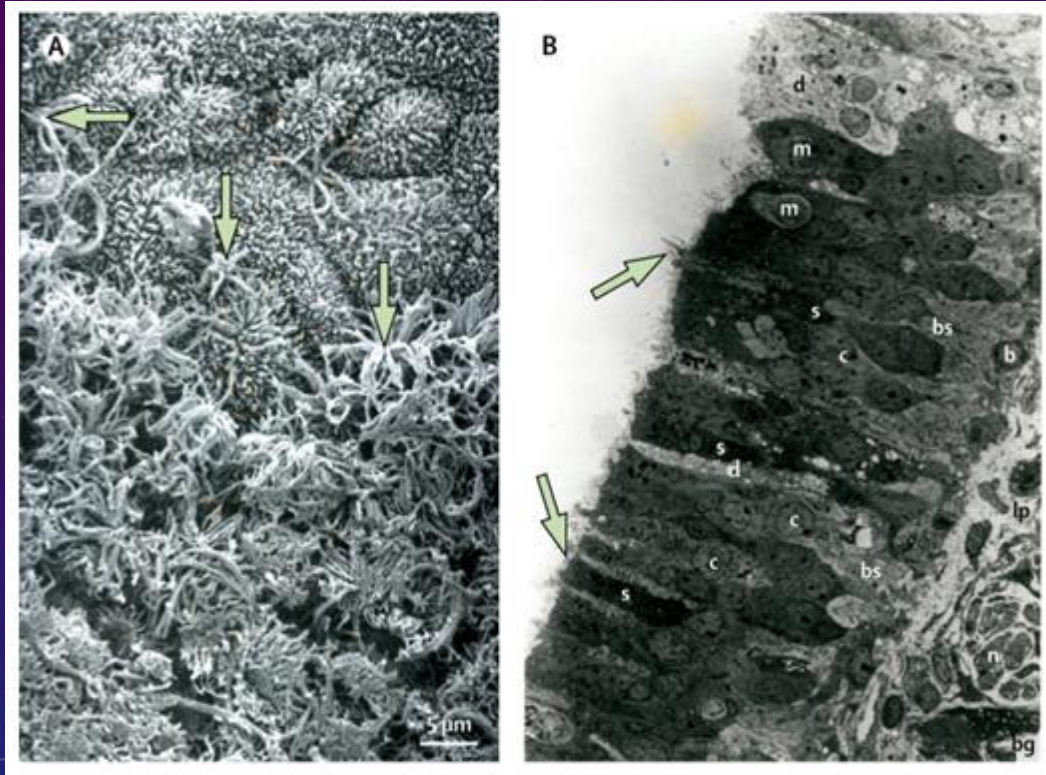


Basic Anatomy of the “Peripheral” Olfactory System



From: Doty, R.L. *Trends in Molecular Medicine* 2022 28(9): 781-794.

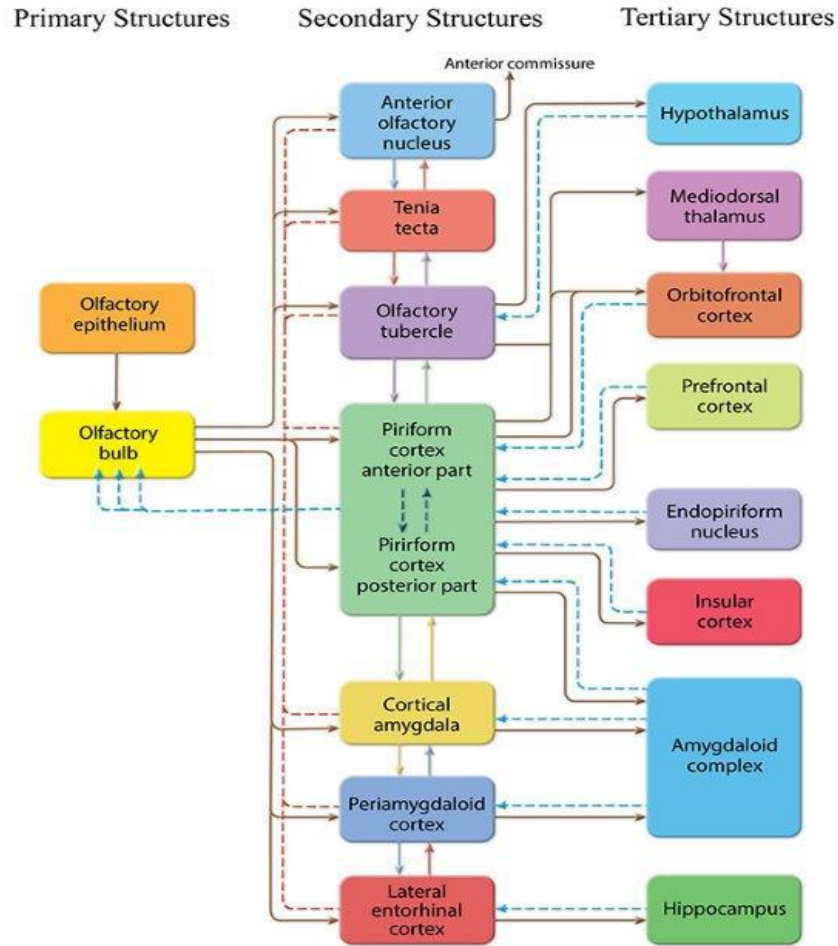
Olfactory Neuroepithelium



- A. Transition area from respiratory (top) to olfactory (bottom) epithelium. Arrows indicate ciliated dendritic knobs of olfactory receptor cells
- B. Cross section of the olfactory epithelium. Arrows indicate dendritic knobs. s: supporting cell; c: cell body of olfactory receptor cell; b: basal cell; m: microvillar cell; lp: lamina propria; n: bundle of axons from receptor cells.

From: B Menco and E Morrison (Chapter 2 in R.L. Doty (Ed), Handbook of Olfaction and Gustation: Marcel Dekker, 1995, 3rd Edition.

Basic Anatomy of the “Central” Olfactory Structures



How is the Sense of Smell Measured? What is a “Normal Sense of Smell”



TYPES OF OLFACTORY TESTS

Psychophysical Tests

- Odor Identification
- Odor Detection
- Odor/Discrimination/Memory

Electrophysiological Tests

- Electro-olfactogram
- Event-Related Potential

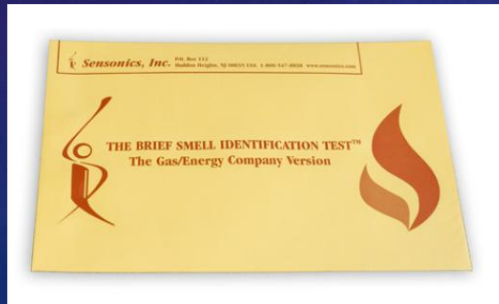
Psychophysiological Tests

- Cardiovascular Changes
- Inhalation Changes

Odor Identification

The background is a gradient of deep blue and purple, speckled with small white dots. On the right side, there is a large, semi-circular scale with numerical markings from 0 to 210. Several white geometric elements are scattered across the image, including concentric circles, arcs, and dashed lines, some of which have small arrows indicating a direction or path.

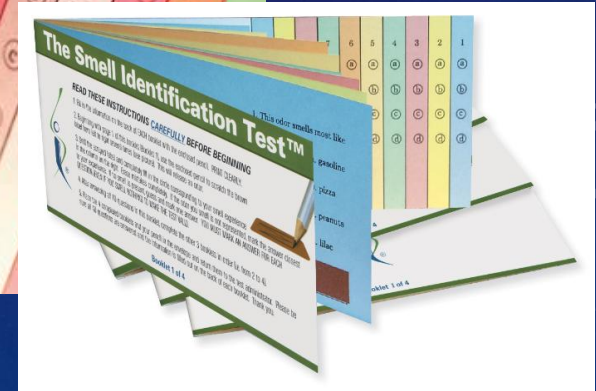
Brief Odor Identification Screening Tests used by the Natural Gas Industry



Photos Courtesy of Sensonics® International
(www.smelltest.com)

University of Pennsylvania Smell Identification Test (UPSIT)

- First practical test for accurately assessing smell function
- Most widely used olfactory test in the world (translated into over 60 languages)
- Self-administered in 15 min.
- Test-retest reliability = 0.94
- Forced-choice
- Norms based upon > 10,000 persons
- Categorizes dysfunction into mild, moderate, severe and total categories
- Percentile Ranks for 5-year age categories
- Detects malingering



Photos courtesy of Sensonics International
(www.smelltest.com)

UPSIT Normative Data

Age of Examinee

Test Score

	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	>85
40	99	99	99	99	99	99	99	99	99	99	99	99	99	99	99	99	99
39	98	96	82	79	88	80	82	84	87	89	89	95	97	98	99	99	99
38	94	74	60	59	59	60	70	85	73	80	88	91	96	98	99	99	99
37	92	57	40	32	40	37	42	39	49	69	51	66	76	86	87	94	98
36	84	42	23	29	27	21	28	26	22	44	34	53	68	77	81	92	95
35	71	31	14	07	16	16	18	17	16	33	28	38	59	70	73	89	92
34	64	23	09	06	09	11	10	15	06	25	23	29	44	63	69	85	90
33	58	16	07	05	05	07	05	11	06	17	18	21	39	55	57	80	86
32	55	10	06	06	06	06	06	10	05	14	14	18	30	44	50	75	86
31	42	07	05	05	05	05	05	07	05	09	13	15	26	39	49	69	82
30	39	06	05	05	05	05	05	05	05	06	13	14	19	34	42	66	76
29	35	05	05	05	05	05	05	05	05	05	13	13	18	29	38	62	72
28	31	05	05	05	05	05	05	05	05	10	10	16	24	37	60	68	68
27	30	05	05	05	05	05	05	05	05	10	09	16	21	34	54	65	65
26	24	05	05	05	05	05	05	05	05	10	06	15	17	31	46	62	62
25	23	05	05	05	05	05	05	05	05	09	05	14	17	29	46	58	58
24	20	05	05	05	05	05	05	05	05	06	05	11	16	29	41	57	57
23	17	05	05	05	05	05	05	05	05	05	05	10	16	26	38	49	49
22	16	05	05	05	05	05	05	05	05	05	05	08	14	24	33	44	44
21	15	05	05	05	05	05	05	05	05	05	05	08	14	21	31	40	40
20	14	05	05	05	05	05	05	05	05	05	05	08	11	21	28	38	38
19	11	05	05	05	05	05	05	05	05	05	05	07	10	19	23	28	28
18	10	05	05	05	05	05	05	05	05	05	05	05	09	16	22	26	26
17	08	05	05	05	05	05	05	05	05	05	05	05	09	16	17	23	23
16	08	05	05	05	05	05	05	05	05	05	05	05	09	11	16	18	18
15	06	05	05	05	05	05	05	05	05	05	05	05	07	09	14	15	15
14	05	05	05	05	05	05	05	05	05	05	05	05	06	08	14	12	12
13	05	05	05	05	05	05	05	05	05	05	05	05	05	08	11	11	11
12	05	05	05	05	05	05	05	05	05	05	05	05	05	05	09	08	08
11	05	05	05	05	05	05	05	05	05	05	05	05	05	05	05	06	06
10	05	05	05	05	05	05	05	05	05	05	05	05	05	05	05	05	05
9	05	05	05	05	05	05	05	05	05	05	05	05	05	05	05	05	05
8	05	05	05	05	05	05	05	05	05	05	05	05	05	05	05	05	05
7	05	05	05	05	05	05	05	05	05	05	05	05	05	05	05	05	05
6	05	05	05	05	05	05	05	05	05	05	05	05	05	05	05	05	05
5	05	05	05	05	05	05	05	05	05	05	05	05	05	05	05	05	05
4	05	05	05	05	05	05	05	05	05	05	05	05	05	05	05	05	05
3	05	05	05	05	05	05	05	05	05	05	05	05	05	05	05	05	05
2	05	05	05	05	05	05	05	05	05	05	05	05	05	05	05	05	05
1	05	05	05	05	05	05	05	05	05	05	05	05	05	05	05	05	05
0	05	05	05	05	05	05	05	05	05	05	05	05	05	05	05	05	05
N=	132	134	212	232	213	174	153	92	90	81	79	80	88	87	77	87	98

ANOSMIA

SEVERE MICROSMIA

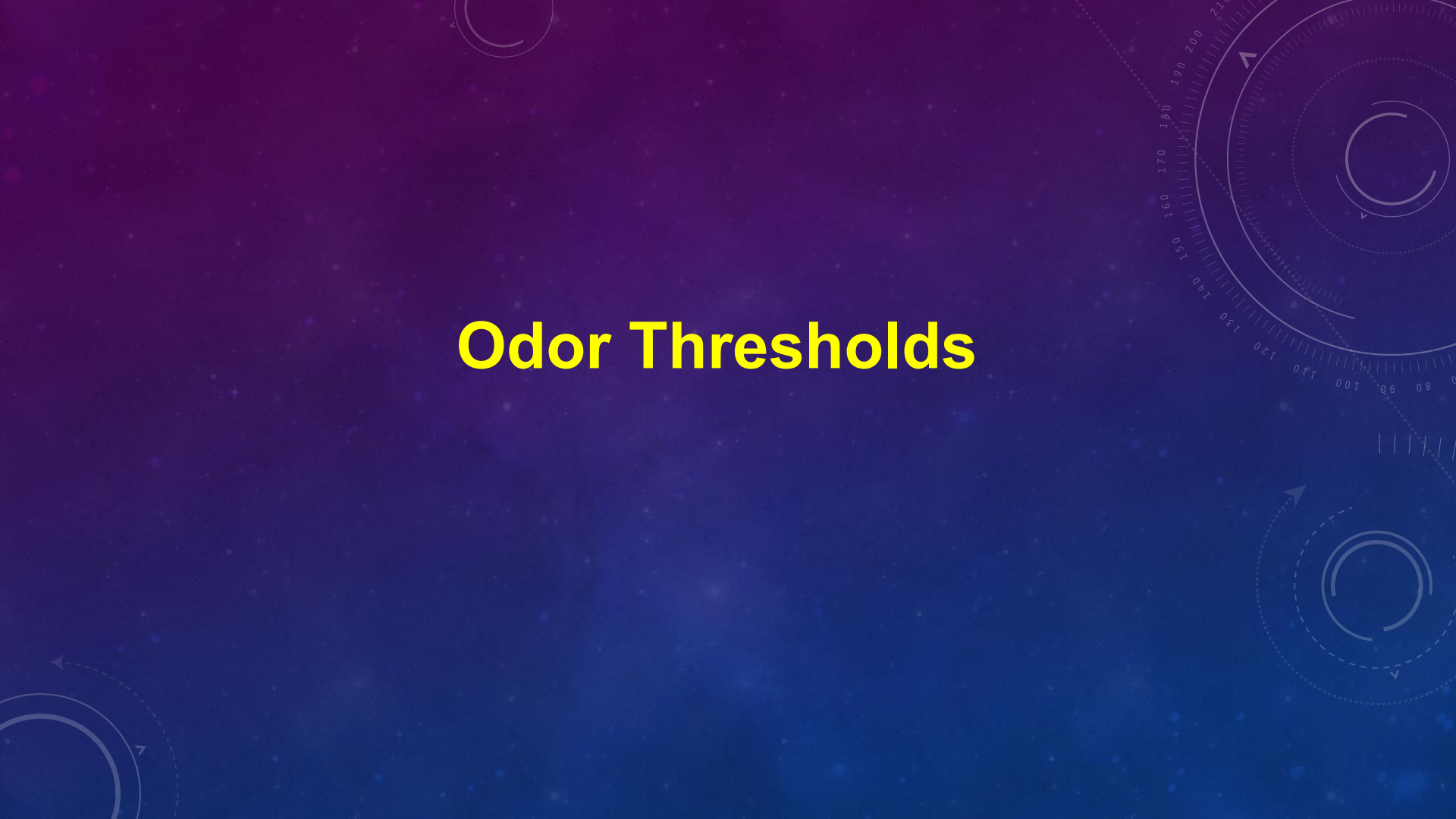
MODERATE MICROSMIA

MILD MICROSMIA

NORMOSMIA

PROBABLE MALINGERING

Odor Thresholds

The background is a dark blue gradient with faint, stylized technical diagrams. In the top right, there is a circular gauge with a scale from 0 to 210 and a needle pointing towards 180. In the bottom right, there are concentric dashed circles with arrows indicating a clockwise direction. In the bottom left, there are solid concentric circles with an arrow indicating a counter-clockwise direction. The overall aesthetic is technical and scientific.

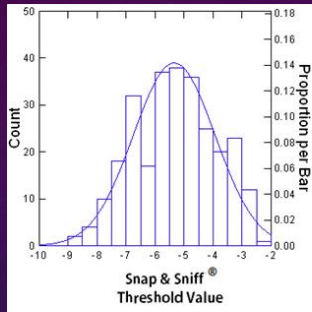
Odor Detection Threshold:

The lowest concentration of an odorant that can be reliably detected without the odor quality being present (“something more than nothing”)

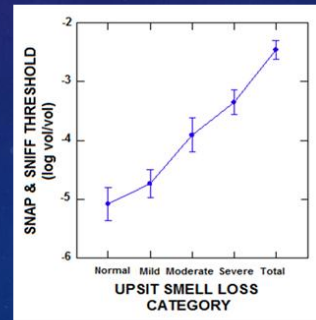
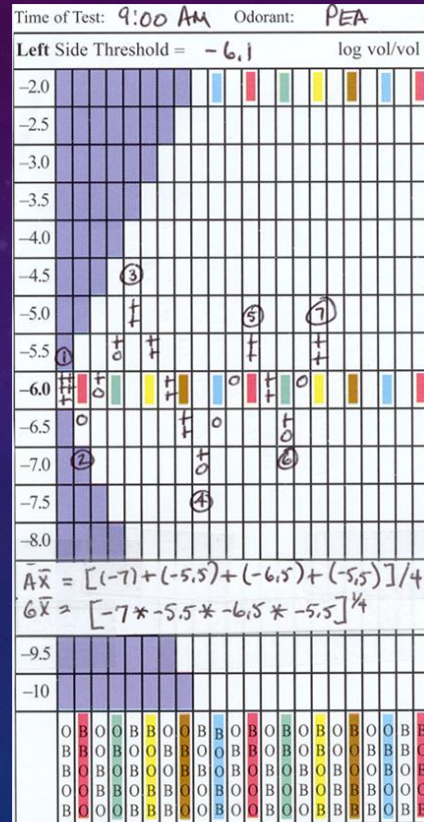
Odor Identification Threshold:

The lowest concentration of an odorant that can be reliably identified (“I smell a rose odor”)

Snap & Sniff® Odor Detection Threshold Test (Phenyl Ethyl Alcohol Odorant)



99 th Percentile	-8.219
95 th Percentile	-7.750
90 th Percentile	-7.125
80 th Percentile	-6.750
75 th Percentile	-6.500
70 th Percentile	-6.125
60 th Percentile	-5.656
50 th Percentile	-5.250
40 th Percentile	-5.000
30 th Percentile	-4.625
25 th Percentile	-4.250
20 th Percentile	-4.000
10 th Percentile	-3.375
5 th Percentile	-3.156
1 st Percentile	-2.625



**Relationships Among
Olfactory Test Scores:
What do Olfactory
Tests Really Measure?**

High Correlations between Odor Identification and Detection Threshold Tests

Study	Year	Age (SD)	N	Group	UPSIT vs:	r	
Doty et al.	1984	42.4 (18.9)	64	Healthy	PEA Threshold	0.89	0.001
Cain & Rabin	1989	77 (70-90)	50	Clinic	Butanol Threshold	0.92- 0.96	0.001
Doty et al	1994	45.8 (20.2)	97	Healthy	Butanol Threshold	0.41	0.001
	"	"	"	Healthy	T&T Threshold	0.41	0.001
	"	"	"	Healthy	PEMEC Threshold	0.49	0.001
	"	"	"	Healthy	PEA Threshold	0.63	0.001
Tourbier et al	2007	59.7 (16.2)	132	Clinic	PEA threshold	0.84	0.001
Doty et al	2019	58.0 (16.1)	736	Clinic	PEA Threshold	0.65	0.001

Reliability and Validity of Psychophysical Olfactory Tests



Reliability of Forced-Choice Odor Identification Tests Generally Related to Test Length

Test	Test Length	Reliability
<i>UPSIT*</i>	40 items	0.94
<i>UPSIT fraction*</i>	30 items	0.90
<i>UPSIT fraction*</i>	20 items	0.86
<i>Scandinavian Odor ID test**</i>	16 items	0.79
<i>Sniffin' Sticks ID***</i>	16 items	0.73
<i>B-SIT****</i>	12 items	0.73
<i>UPSIT fraction*</i>	10 items	0.75

*Doty et al., *Percept. Psychophys.* 45:381-384, 1989; **Nordin et al, *Acta Otolaryngol.* 118:226-234, 1998; ***Hummel et al., *Chem. Senses* 22:39-52, 1997; ****Doty et al., *Laryngoscope* 106:353-356, 1996.

Reversal #1 0.453 0.453

Reversal #2 0.595

Reversal #3 0.674

Reversal #4 0.647

Reversal #5 0.731

Reversal #6 0.641

Reversal #7 0.675

Reversal #1 + #2 0.657 0.657

Reversal #2 + #3 0.665

Reversal #3 + #4 0.764

Reversal #4 + #5 0.705

Reversal #5 + #6 0.767

Reversal #6 + #7 0.673

Reversal #1 + #2 + #3 0.692 0.692

Reversal #2 + #3 + #4 0.771

Reversal #3 + #4 + #5 0.774

Reversal #4 + #5 + #6 0.756

Reversal #5 + #6 + #7 0.753

Reversal #1 + #2 + #3 + #4 0.776 0.776

Reversal #2 + #3 + #4 + #5 0.793

Reversal #3 + #4 + #5 + #6 0.807

Reversal #4 + #5 + #6 + #7 0.762

Reversal #1 + #2 + #3 + #4 + #5 0.793 0.793

Reversal #2 + #3 + #4 + #5 + #6 0.827

Reversal #3 + #4 + #5 + #6 + #7 0.811

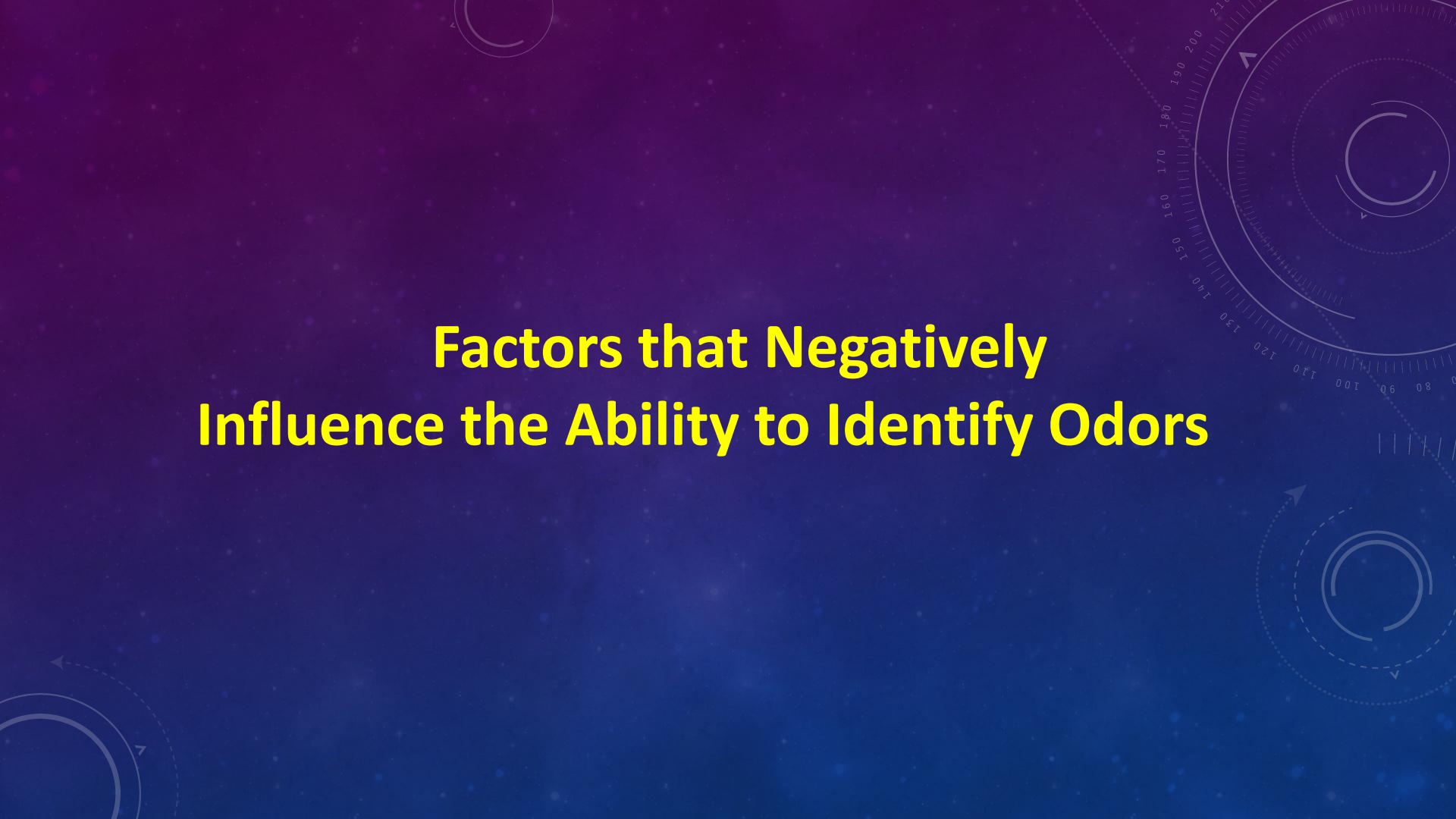
Reversal #1 + #2 + #3 + #4 + #5 + #6 0.832

Reversal #2 + #3 + #4 + #5 + #6 + #7 0.834

Reversal #1 + #2 + #3 + #4 + #5 + #6 + #7 0.845 0.845

The Reliability of a Threshold Test Increases as the Number of Reversals Increase

From: Doty et al., A study of the test-Retest reliability of 10 olfactory tests. Chemical Senses 20: 645-656, 1995.

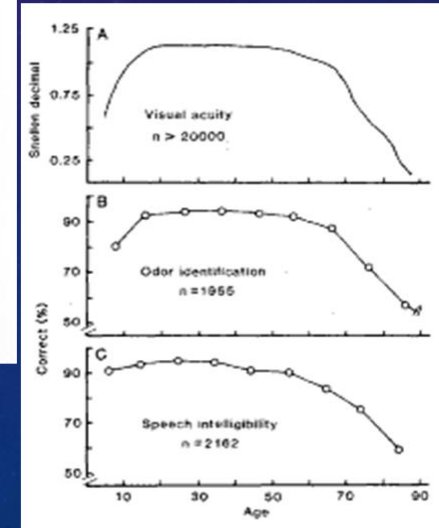
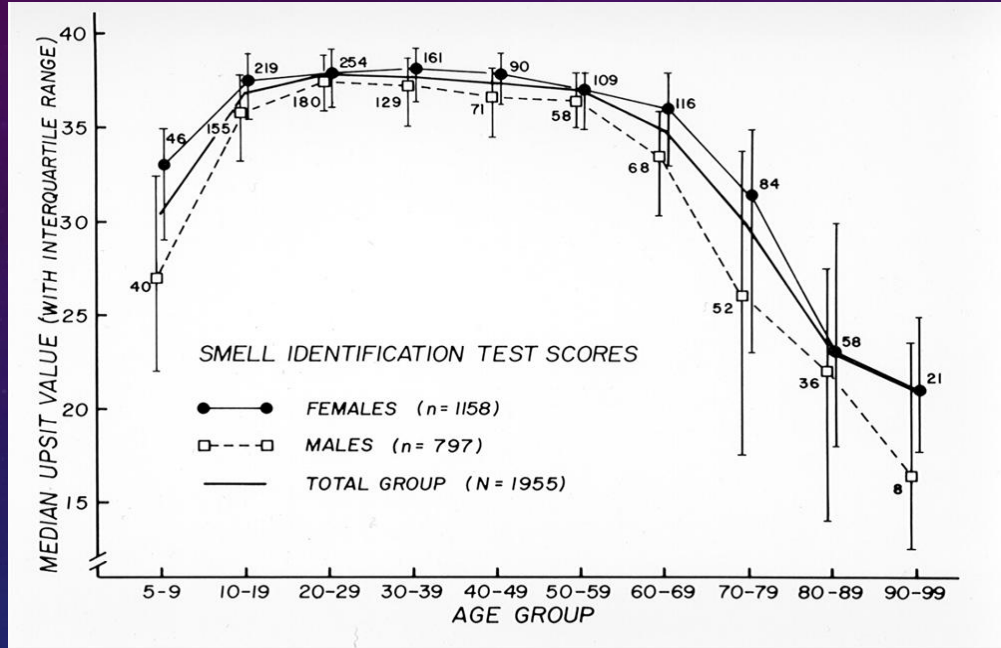


Factors that Negatively Influence the Ability to Identify Odors

AGE

Association of Age and Sex with Smell Ability

Doty, R.L., Shaman, P., Applebaum, S.L., Giberson, R., Sikorski, L. & Rosenberg, L. *Science* 226:1441-1443, 1984.





SMOKING

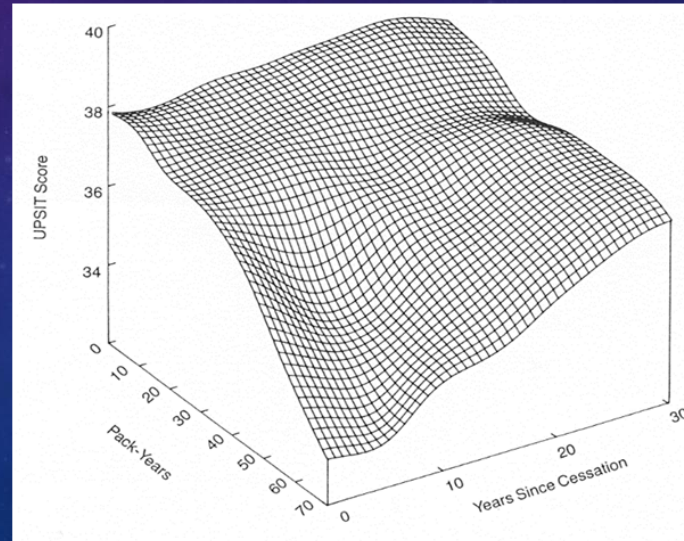
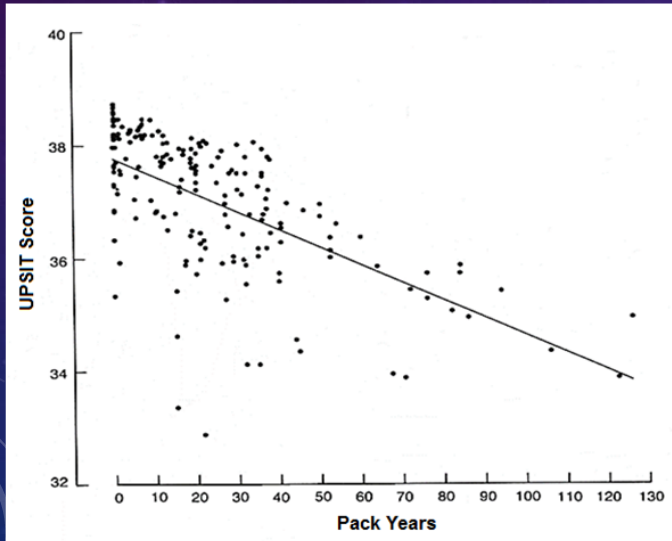
Dose-related Effects of Cigarette Smoking on Olfactory Function

Frye, R.E., Schwartz, B.S. & Doty, R.L. *JAMA* 263:1233-1236, 1990.

Goal: To establish the effects of cigarette smoking on smell function

Design: UPSIT administered to 638 subjects for whom detailed smoking histories were available.

Results: Dose-related changes in smell function found in both current and previous smokers. Improvement in previous smokers related to time since cessation of smoking. Current smokers twice as likely to have an olfactory deficit than never smokers.



AIR POLLUTION



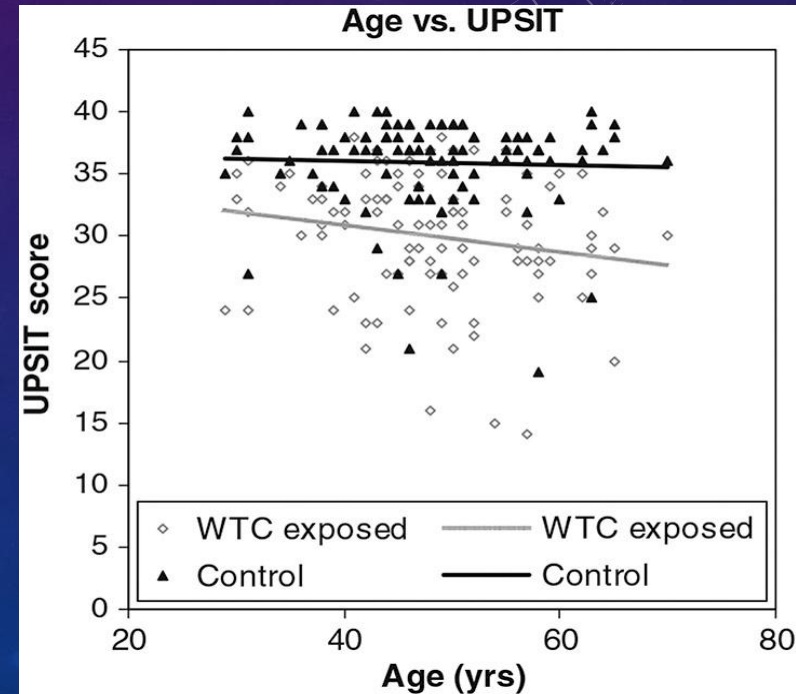
Relatively Brief Effects of Air Pollution can Produce Smell Dysfunction: UPSIT scores of Workers at the Post-9/11 World Trade Center Site

Exposure requirements: (a) Onsite for 4 hrs on September 11-14 or (b) ≥ 24 hrs during Sept, or (c) ≥ 80 hours from Sept to Dec 2001

99 Exposed Ss; 99 Matched Controls

Respective mean (SD) UPSIT scores = **30.05** (5.08) & **35.94** (3.76); $p = 0.003$

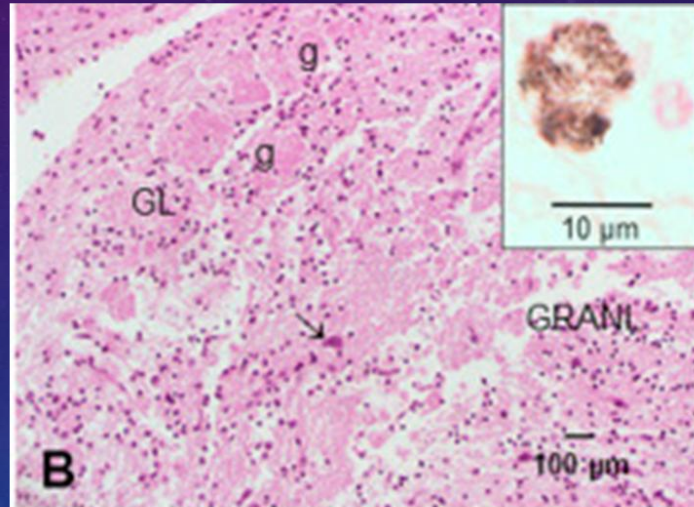
15% Exposed had severe Microsmia; only 3% anosmia



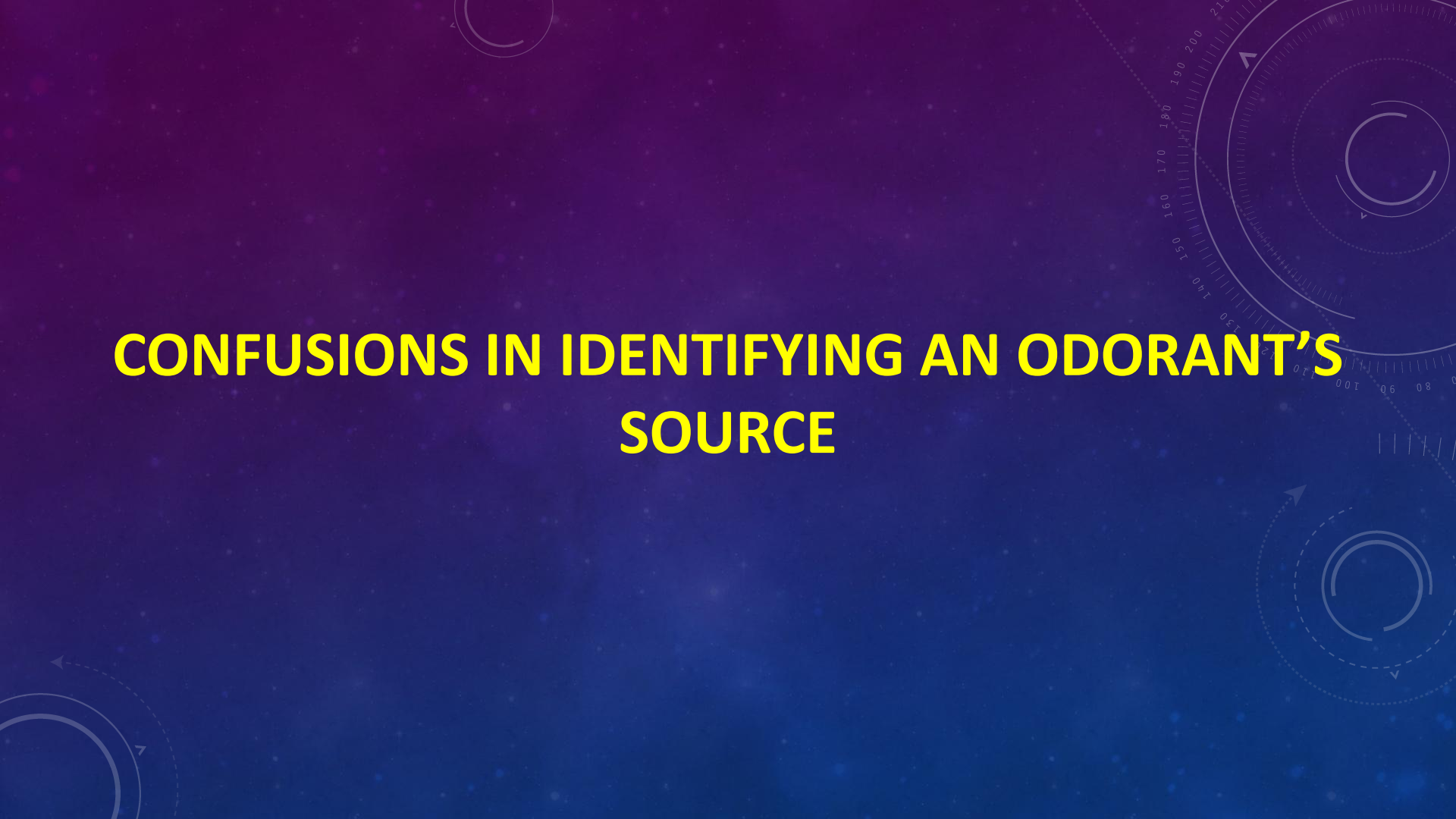
Air pollution (AP) is a risk factor for several neurodegenerative diseases [e.g., Alzheimer's disease]

Decreased smell function occurs in highly polluted areas

- AD- and PD-related pathology found in 179 autopsied olfactory bulbs (OBs) of children and young adults (11 months to 40 years old; mean & median age: 26 yrs) living in highly polluted regions of Mexico City.
- APOE4 carriers were 6-13 x more likely than APOE3 carriers to exhibit OB vascular amyloid, neuronal amyloid accumulation, α -synuclein aggregates, hTau neurofibrillary tangles, and neurites
- Serendipitous finding: APOE4 carriers 4.57 x more likely than non-carriers to die by suicide



Olfactory bulb section of a 2-year old boy chronically exposed to Mexico City pollution. Focal disorganization with isolated mitral cell neurons (arrow). Insert: Abundant particulate matter present in isolated olfactory tract cells. g = glomerulus; GL = glomerular layer; GRANL = granule cell layer.



CONFUSIONS IN IDENTIFYING AN ODORANT'S SOURCE

Sources of Odorants are Commonly Confused

Examples:

- 1. Mercaptan is also found in sewer gas¹ and its odor can be misidentified as skunk odor, dead mice and rats, and other sources.**
- 2. Mercaptan thresholds vary markedly among individuals. For example, for methyl mercaptan, the threshold values in a study of 34 subjects varied by 24-fold (0.14 to 3.4 ppm).²**

1. Sivret EC et al., 2016, Prioritisation of odorants emitted from sewers using odour activity values. Water Research, 88, 306-321.

2. Wily FB. 1969, Variation in recognition odor threshold of a panel. Journal of the Air Pollution Control Association. 19: 96-100

Odor Adaptation:

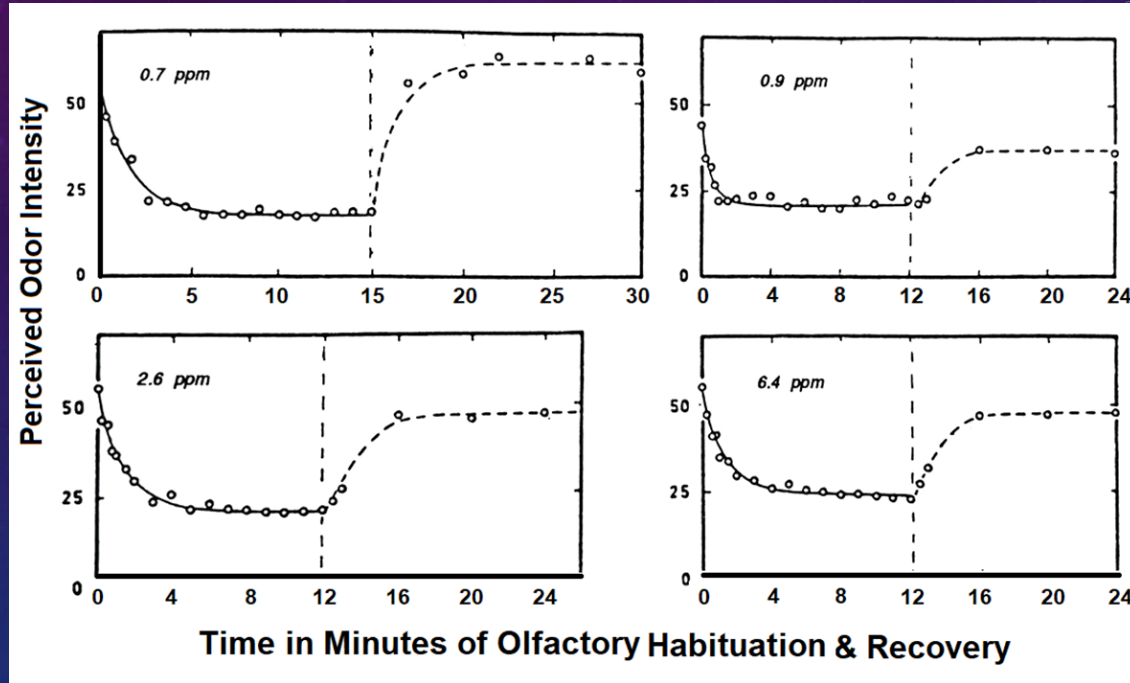
A decrement in smell sensitivity due to repeated stimulation which adapts (tires out) olfactory receptors and associated nerves

Odor Habituation:

A decrement in smell sensitivity due to repeated stimulation which can include odor adaptation as well as cognitive influences on smell perception (e.g., attention)

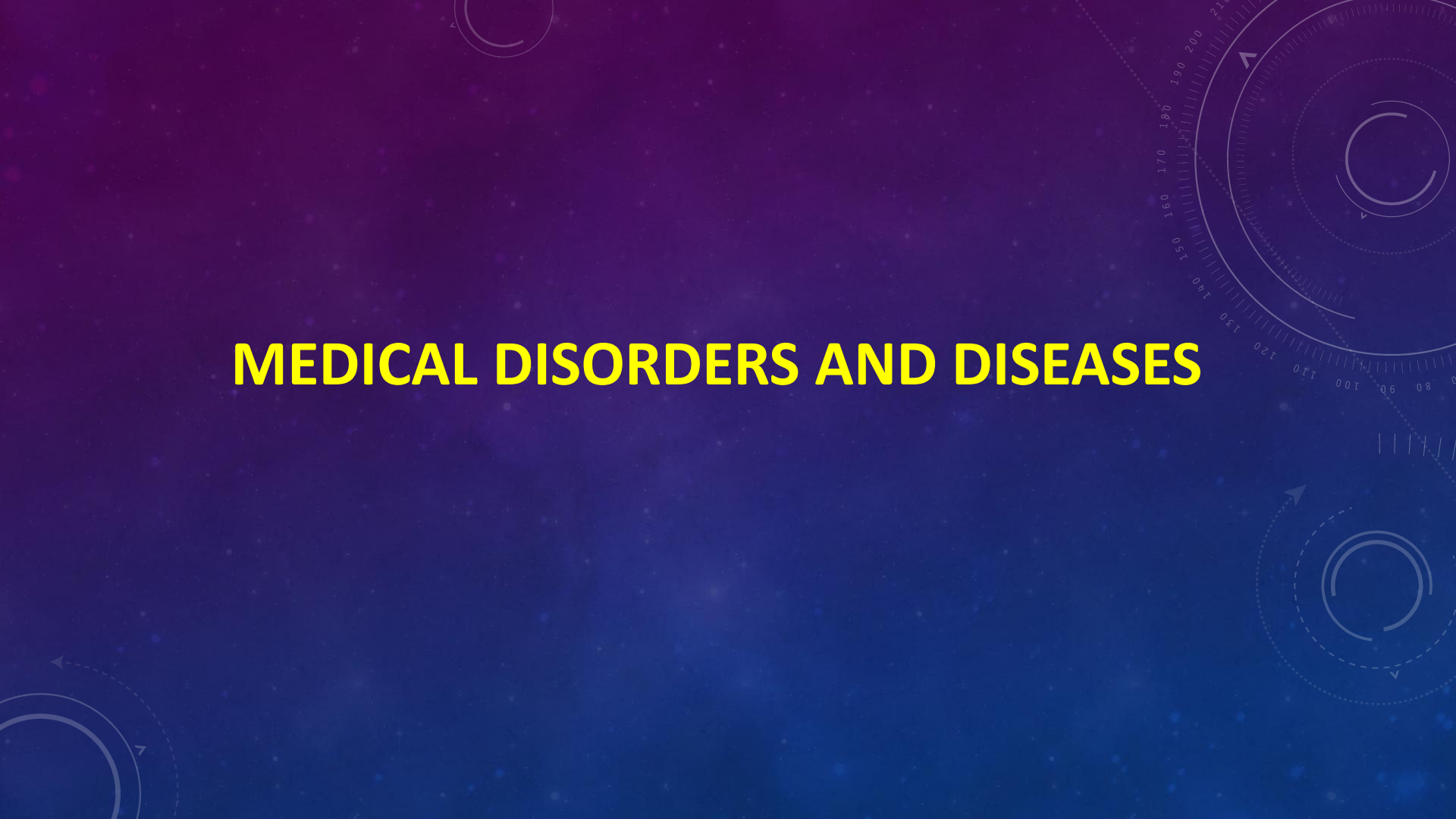
Significant Adaptation/Habituation to Odorants Occurs within 5 Minutes.

This can lead to the false belief that the odorant is disappearing



Odor: Hydrogen Sulfide; From: Ekman et al., *Scand. J. Psychol.*, 1967, 8, 177-186.

MEDICAL DISORDERS AND DISEASES

The background is a gradient of deep blue and purple, speckled with white dots. It features several white circular elements: a large dotted circle with a solid inner circle and a dashed arrow in the top right; a smaller solid circle with a dashed arrow in the bottom right; and a partial dotted circle with a solid inner circle in the top left. A faint dotted grid is also visible in the upper right quadrant.

Common Causes of Olfactory Dysfunction

- ▶ Acquired immune deficiency syndrome
- ▶ Adenoid hypertrophy
- ▶ Addison's disease
- ▶ Age-related physiological changes
- ▶ Alzheimer's disease
- ▶ Amyotrophic lateral sclerosis
- ▶ Attention deficit/hyper-reactivity disorder
- ▶ Auto-Immune Diseases (most)
- ▶ Chronic alcoholism
- ▶ Cystic Fibrosis
- ▶ Depression
- ▶ Diabetes
- ▶ Down's syndrome
- ▶ Epilepsy
- ▶ Essential tremor
- ▶ Hanson's disease
- ▶ Head trauma*
- ▶ Hypothyroidism
- ▶ Huntington's disease
- ▶ Iatrogenesis
- ▶ Kallmann's syndrome
- ▶ Kidney disease
- ▶ Korsakoff's psychosis
- ▶ Liver disease
- ▶ Lyme disease
- ▶ MPTP-induced parkinsonism
- ▶ Multi-infarct dementia
- ▶ Neoplasms, Cranial/Nasal
- ▶ Multiple Sclerosis
- ▶ Myasthenia Gravis
- ▶ Panic disorder
- ▶ Parkinson's disease
- ▶ Parkinson's dementia complex of Guam
- ▶ Pick's disease
- ▶ Progressive supranuclear palsy
- ▶ Restless leg syndrome
- ▶ Rhinosinusitis/Polyposis*
- ▶ Schizophrenia
- ▶ Seasonal Affective Disorder
- ▶ Sjögren's Syndrome
- ▶ Stroke
- ▶ Turner's syndrome
- ▶ Toxic Chemical Exposure, including Smoking
- ▶ Viruses, e.g. , Common Cold, Influenza, SARS-CoV-2

Blue: Indicates little or no dysfunction or apparent hypersensitivity

Green: Indicates neurodegenerative diseases with smell dysfunction

Red: Indicates highest frequency of clinical presentations to the Smell & Taste Center

VIRUSES

The background is a gradient of deep blue and purple, speckled with white dots of varying sizes. Faint, stylized circular patterns are visible in the corners, including a large circular scale with numerical markings (0, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 210) and arrows in the top right, and a dashed circular arrow in the bottom right.

Seasonal Variations in Post-Viral Olfactory Disorders (PVODs) Presenting to Penn's Smell and Taste Center (1980-2018)

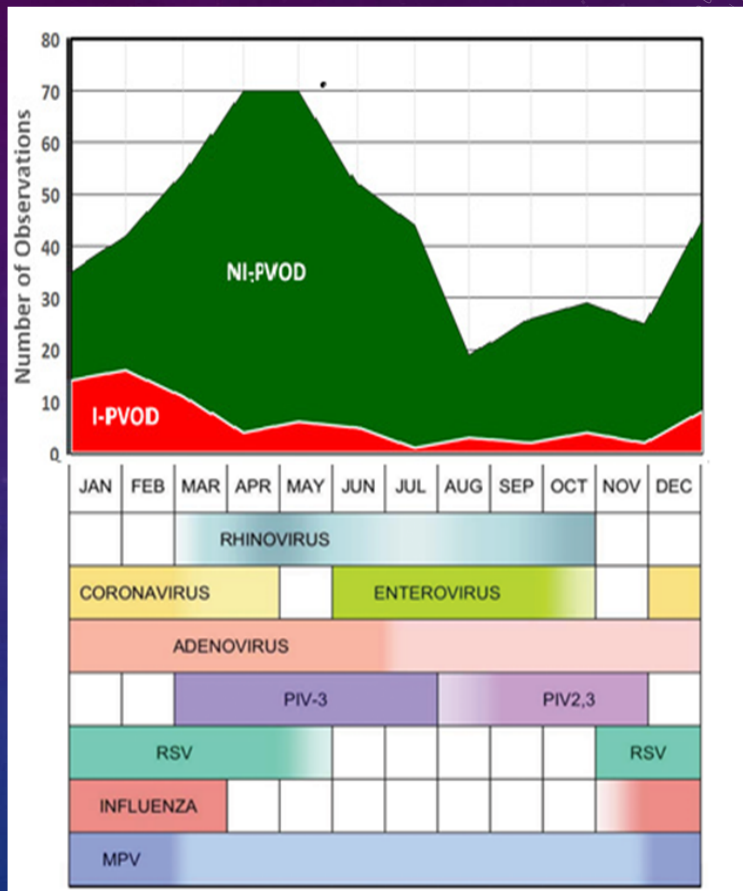
NI-PVOD: Non-influenza

I-PVOD: Influenza

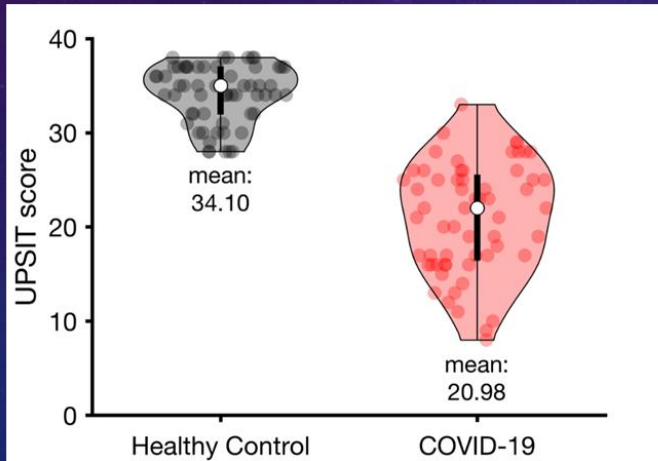
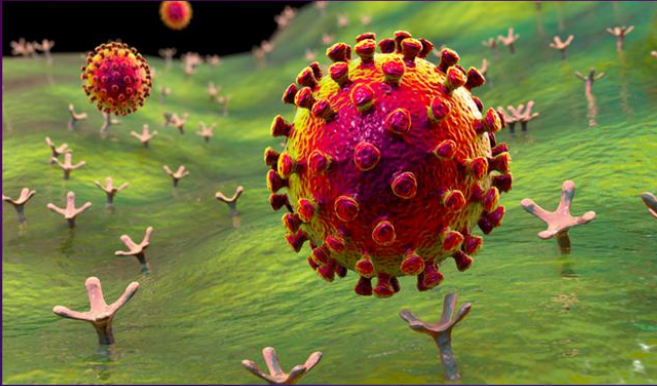
RSV: respiratory syncytial virus

PIV: parainfluenza virus

MPV: metapneumovirus

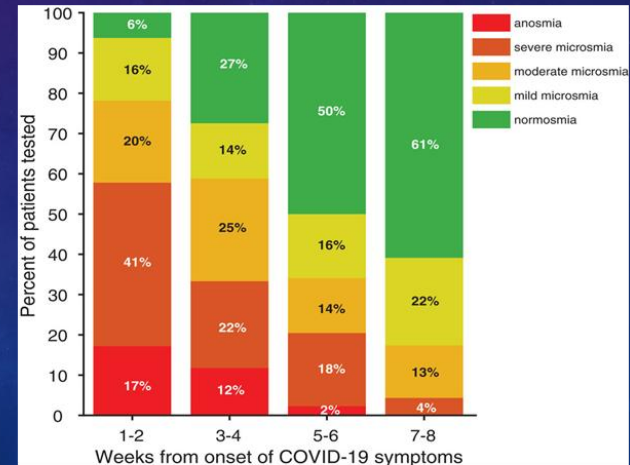


Smell Dysfunction: A Biomarker for COVID-19



Moein, et al. (2020a) *IFAR*, 10, 944-950

- 59/60 COVID-19 patients exhibited some smell dysfunction in acute phase
 - 25% anosmic, 33% severely microsmic, 27% moderate microsmic, 13% mild microsmic, 2% normosmic
- Only 35% of patients aware of dysfunction before testing
- Two-thirds regained normal function by 7-8 weeks after initial symptoms



Moein et al. (2020b) *IFAR*, 10, 1127-1135

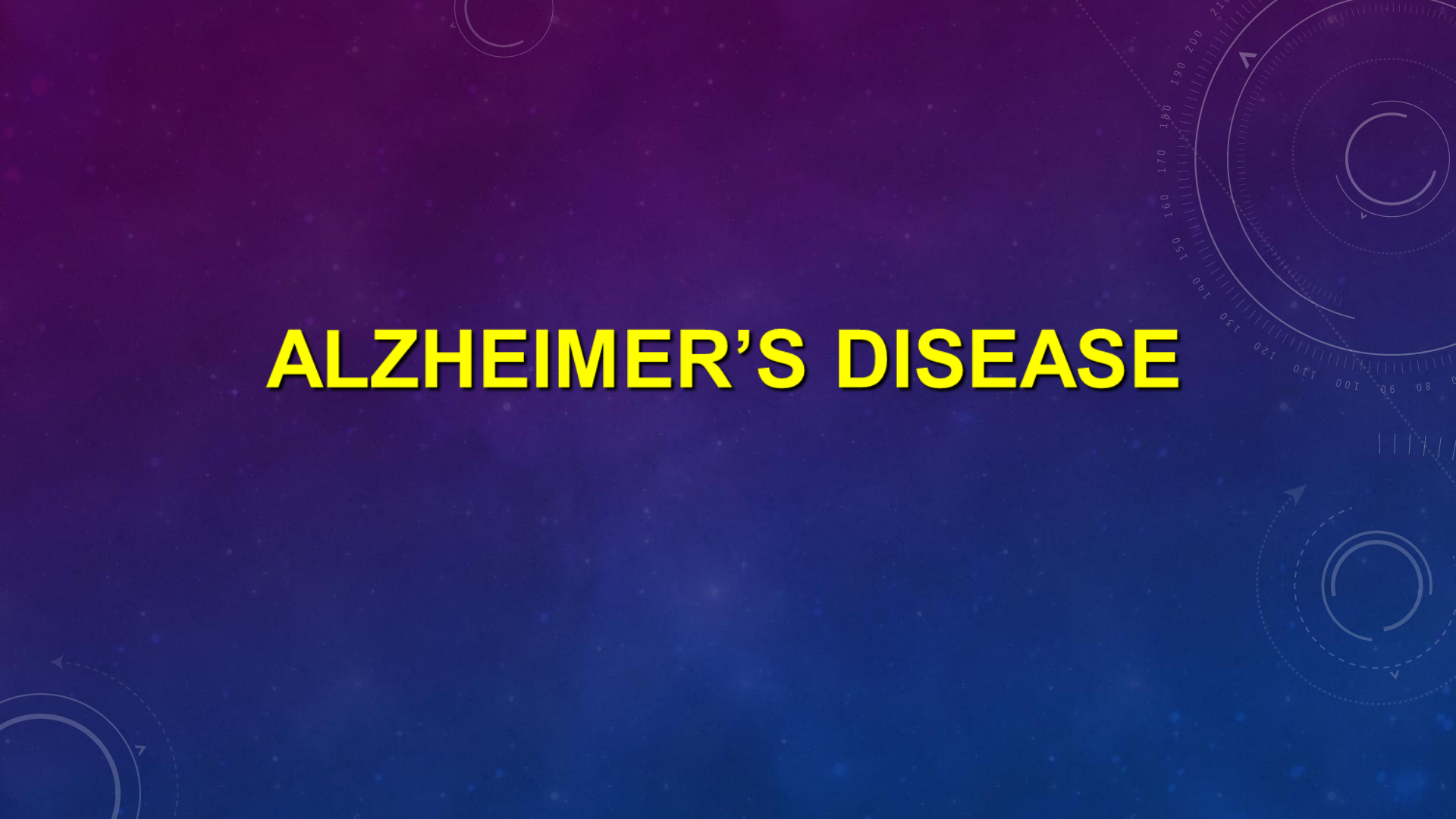
A Year After COVID-19 infection, a Significant Number of Persons Continue to Experience Some Smell, but not Taste, Loss

OLFACTION (UPSIT)	Normosmia	Mild to Moderate Loss	Severe to Total Loss
No COVID-19 History (n = 434)	79.0 %	18.2 %	2.8 %
Omicron Variant (n = 214)	75.2 %	20.1 %	4.7 %
Delta Variant (n = 32)	71.9 %	21.9 %	6.2 %
Alpha Variant (n = 42)	52.4 %	23.8 %	23.8 %
Original Variant (n = 52)	59.6 %	26.9 %	13.5 %

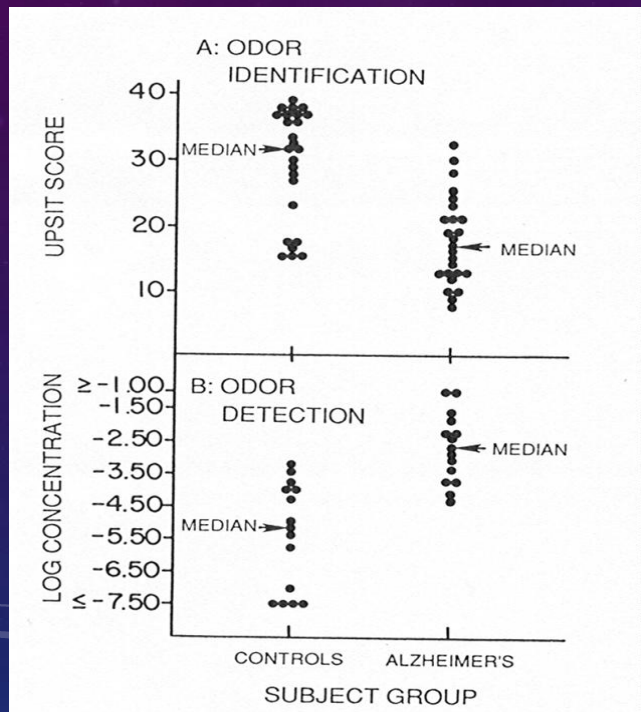
TASTE (WETT)	No Infection	Original	Alpha	Delta	Omicron	P value
Sample size:	434	52	42	32	214	
Sucrose:	4.77	4.56	4.69	4.41	4.71	0.85
Citric Acid:	5.30	5.09	5.86	5.56	5.55	0.23
NaCl:	5.36	4.83	5.63	5.40	5.52	0.30
Caffeine:	4.50	4.52	3.99	3.63	4.53	0.30
MSG:	3.09	2.77	2.99	2.20	2.80	0.23
Total Test Score:	33.39	32.97	33.43	32.22	33.82	0.91

From: Sharett, R., Moein, S.T., Khan, R., Doty, R.L. Long-Term Taste and Smell Outcomes After COVID-19. JAMA Network Open. 2024;Apr 1:7(4):e247818.

ALZHEIMER'S DISEASE

The background features a gradient from dark blue at the bottom to deep purple at the top, speckled with white stars. Faint, stylized circular patterns with arrows are visible in the corners, suggesting a scientific or medical theme.

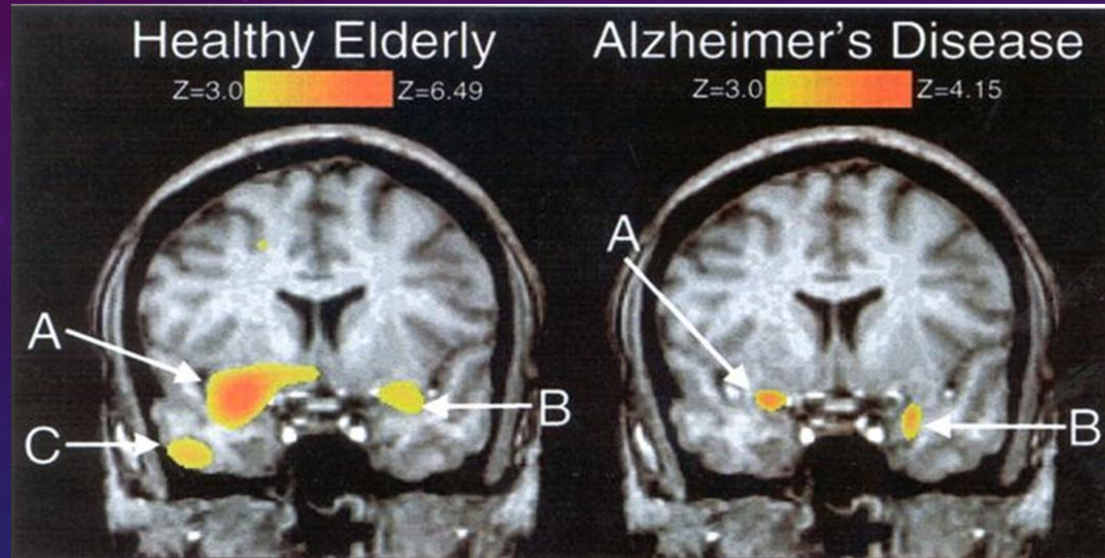
UPSIT AND Smell Threshold Scores both Significantly Altered in Early AD



- **Average UPSIT scores differ by ~ 14 points between AD & control subjects**
- **Despite overlapping distributions, 95% of AD cases have lower function scores than age-matched controls**
- **Not true that AD associated only with "higher order" olfactory deficits**

From: Doty, Reyes & Gregor (1987) Presence of both odor identification and detection deficits in Alzheimer's disease. Brain Res. Bull. 18: 597-600.
Copyright © 1987 Pergamon Journals, Ltd.

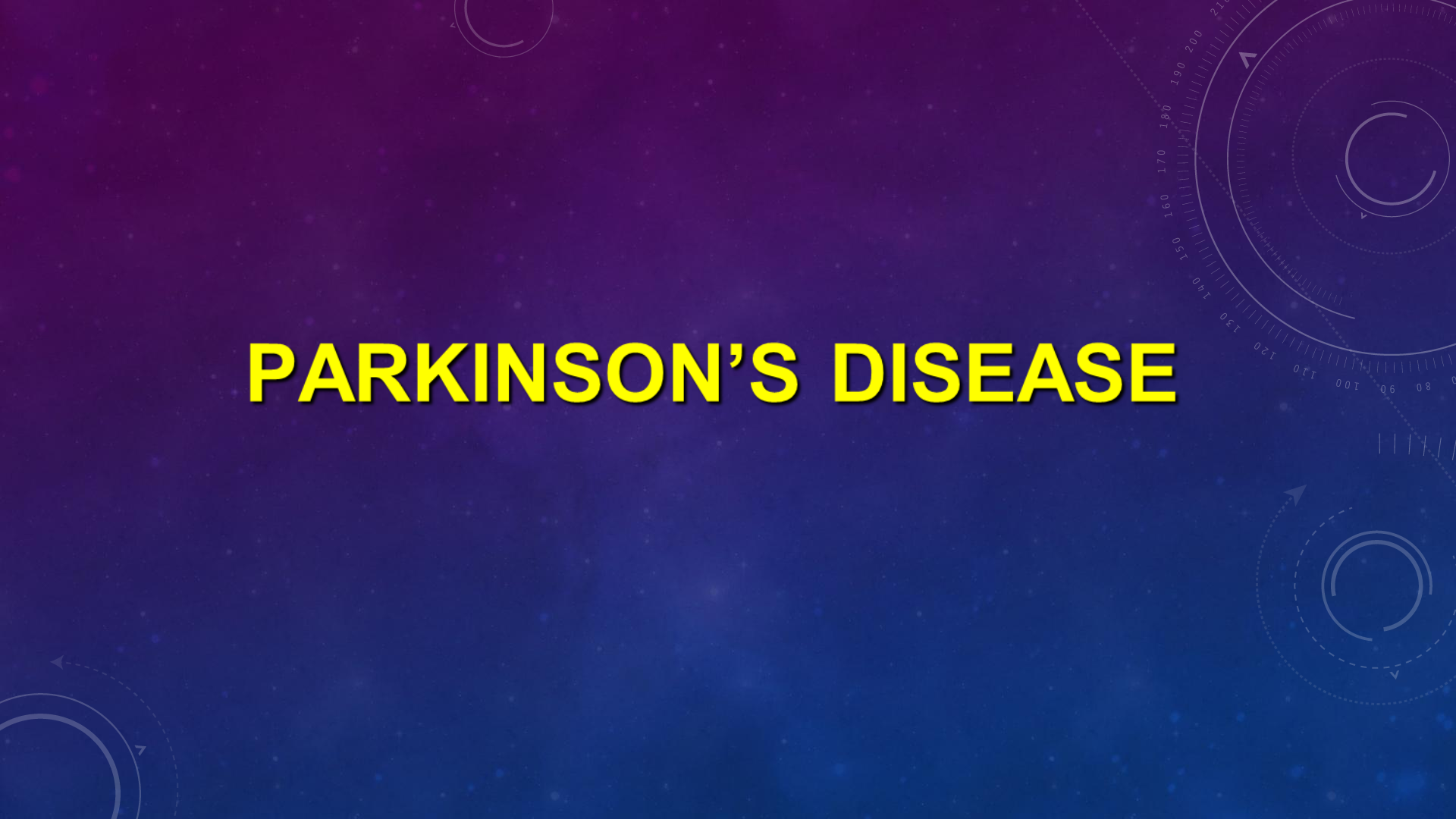
Alzheimer's Disease: Mesotemporal Decrement in Odor-induced PET Activation



A: Right frontotemporal junction (piriform area); B: Left piriform area; C: Right anterior ventral temporal lobe (Brodmann 20). N = 7, UPSIT = 32.4; PEA = -5.5

A: 7 mm anterior to frontotemporal junction; B: left amygdala-uncus. N = 6. UPSIT = 18.7; PEA = -5.1

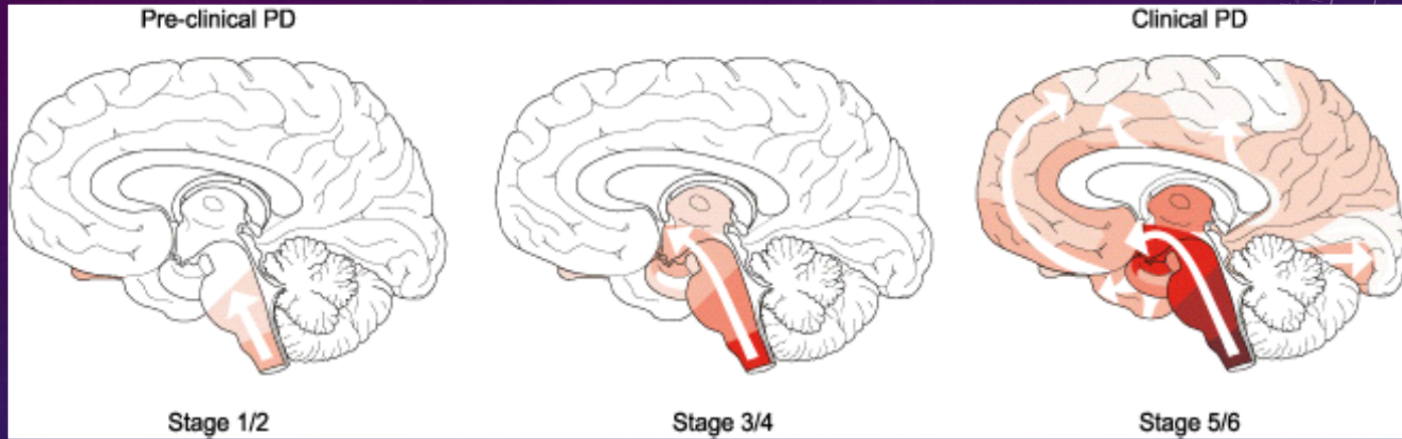
PARKINSON'S DISEASE

The background is a gradient of deep blue and purple, speckled with white dots. Faint, stylized circular patterns and lines are visible, particularly on the right side, suggesting a technical or scientific theme.

Olfactory Dysfunction in Parkinson's Disease

- > 90% of PD patients have demonstrable olfactory loss on the UPSIT and STT
- Olfactory loss is more prevalent than some cardinal motor signs of PD (e.g., tremor)
- PD-related olfactory dysfunction unrelated to disease stage, motoric, or other signs of PD
- Olfactory loss indistinguishable in terms of frequency or magnitude from that of AD
- Olfactory loss unresponsive to anti-PD medications

PD-related Lewy Body Pathology Appears to Evolve in Predictable Stages (Braak et al).



Stage 1: Lewy bodies (LB) form within in the olfactory bulb and dorsal motor nucleus of the vagus and glossopharyngeal nerves

Stages 2 & 3: LB pathology expands into additional brain stem nuclei (e.g., locus coeruleus and substantia nigra) and then into the amygdala.

In Stages 4 to 6, the pathology extends into the cerebral cortex. Clinical symptoms arise during Stages 4 to 6 when the pathology involves significant regions of the substantia nigra and related brain areas.

Summary and Conclusions

Under 49 CFR § 192.625, the U.S. federal pipeline safety regulation, all combustible gas in a distribution line must be odorized so that it is readily detectable by a person with a normal sense of smell

- **Olfaction is important beyond safety**
- **Normality is not a simple concept and is defined by measurement**
- **Numerous factors impact the ability to smell: age, sex, disease states, viral infections (e.g., COVID-19)**
- **Simple smell tests are useful for screening employees in the energy sector to be certain that they can detect odorized natural gas**

Thank you for your attention



Smell you around!!!