The Sensory Brain: The Brain and Smell

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The Significance of Olfaction¹

- Phylogenetically, the oldest sensory system
- First means of communication between organisms
  - Direct toward food/mates & away from threats
- Olfactory receptor gene family largest in mammal genome: 1% of genes
- Olfactory repertoire of each species unique to genetic makeup
- Dysfunction in humans linked to:
  - Depression & decreased quality of life
  - Poor nutrition & obesity
  - Neurodegenerative disorders
  - Shortened lifespan

The Evolution of Olfaction

1. **Fish**: Odor-detection is water-soluble
   - Have retained the most olfactory receptor gene lineages
   - Long evolutionary lifespan due to diversity in olfactory organs

2. **Amphibians**: Detect odorants in water & on land
   - Genetic radiation 200 million years ago
   - Led to detection of millions of odors in vertebrates

3. **Mammals**: only species to use nose for odor detection
   - High variation between individuals, sexes, and cultures

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Mammalian Olfaction

- Olfactory receptor (OR) genes vary greatly between species
- Fewer OR genes in higher primates—rely more on vision
  - Mice, cows, possums: 1000-1200 genes
  - Humans: close to 400 OR genes
    - Nearly the same for chimpanzees
  - African elephants: nearly 2000 genes!
- Dynamic changes in OR genes
  - Hundreds of gains and losses during mammalian evolution

Nimura et al, 2014
Human Sense of Smell

• Olfactory genes influenced by individual olfactory experiences
  • i.e. 60% of humans can smell androstenone (steroid in sweat & urine)
    • Androstenone: first pheromone identified in mammals (boars)
  • Non-smellers can become sensitive to odor with repeated exposure

• Humans’ sense of smell not as sensitive as animals’
  • Smell receptors: 10 million in humans vs. 10 billion in dogs
  • In humans, 10% difference in aroma magnitude to tell change
  • But human smell more sensitive than previously believed

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Culture and Smell

- Western societies give priority to sight
  - Analytical, concerned with structure & appearance
  - Historically, cultures that value smell seen as “primitive”
- Smell perception varies by culture and geographic location
  - In Ethiopia, Dassanetch tribe smell based on cattle-herding season
    - Dry season smells smoky, wet season smells fresh and fragrant
  - The Suya culture in Brazil, characterize men as “pleasantly bland-smelling” and women as “unpleasantly strong-smelling”
    - Reflects culture’s value of men over women
  - In a subregion of Oceania, the Melanesian people use scents of mint and ginger in “love magic” potion

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The Neurobiology of Olfaction
The Transduction Process of Olfaction¹

• Odor Detection

1. Olfactory receptors (OR) bind to odorants in environment
2. OR activate electrical impulses in epithelium, send signals to neuron
3. Signals relayed in the glomeruli - the synapse of the olfactory nerve
4. Info from signals processed in olfactory bulb
5. Info transmitted to olfactory (piriform) cortex for odor perception

The Transduction Process of Olfaction\textsuperscript{3}, cont.

**Odor Perception**

1. Olfactory bulb connects directly to piriform (olfactory) cortex via olfactory nerve (1\textsuperscript{st} cranial nerve)

2. Olfactory info processed in piriform cortex
   - Other senses processed by thalamus
   - Piriform cortex part of **limbic system**

3. Odors recognized in frontal cortex after processed in limbic system
   - Orbitofrontal (OFC) & anterior cingulate (ACC) cortices

Human Olfactory Processing: The Limbic System

• Limbic system
  • Brain center that stores memories and processes primal emotions:
    • Amygdala: emotional processing
    • Hippocampus: memory storage
    • Hypothalamus: regulate basic functions
  • Explains how olfaction induces memories and emotions
  • Olfactory info processed in limbic system before recognized in OFC
    • Explains why mammals react to odors prior to thinking about them

Olfaction Explored Thru Neuroimaging
Olfactory Processing & the Amygdala

• Functional magnetic resonance imaging (fMRI) of human brains show amygdala processing of odors
  • Processes odors related to positive & negative emotions\textsuperscript{6}
  • NOT activated by neutral odors, \textit{even if odor is strong}
  • Amygdala processes odors that elicit emotions

• Limbic system processing of odors is state-dependent\textsuperscript{7}
  • Limbic system response enhanced if anxiety induced when perceiving odors, \textit{even if odor initially perceived as neutral}
  • Response correlated with magnitude of anxiety


Olfaction and Emotional Processing

- Olfactory perception associated with emotion
  - Reminders of personal experiences
- In fMRI study, emotional potency of odor-evoked memories correlated with amygdala activation
  - Personally meaningful odor induced higher amygdala activation than other sensory cues
  - Provides neuroimaging evidence of emotional potency of odors evoked by strong memories

Activation for experimental odor in the amygdala. The white outline denotes the region of interest (ROI) on the left, including hippocampus and the amygdala.

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Cross-modal Recognition Memory\textsuperscript{10}

- Cross-modal: interaction of at least two sensory modalities
- Episodic memory: retrieve memory for events
  - Relies on reactivation of multiple senses, i.e. recalling a beach vacation
  - Previously thought that retrieval was modality-specific
- When visual and olfactory information is presented together, retrieval may occur if presented with only one sensory cue
  - Based on fMRI activation of the hippocampus & olfactory (piriform) cortex during retrieval

The Temporal Pole & Emotional Processing

• Temporal pole (TP): tip of temporal lobe; connected to amygdala & OFC
  • Sends/receives connections to sensory systems, including olfactory cortex
  • Studies suggest involvement in multimodal perception

• TP dysfunction associated with socio-emotional disorders
  • i.e. Kluver-Bucy syndrome: social withdrawal, blunted affect, reduced fear, hypersexuality

• Parts of the TP receive olfactory input
  • Brain scan evidence shows it responds to emotional odor stimuli

• TP often resected in cases of severe epilepsy
  • Common effects: anosmia (inability to smell) and olfactory hallucinations

Olfaction in Daily Life
Olfaction & Emotional Functioning

• Chemosensory (via human natural sweat) signals individual identity, familiarity, & genetic relatedness
• Signals have access to emotion due to anatomical overlap
• Much variation in human chemosensory & socioemotional functioning
• Zhou & Chen (2009) demonstrated that variance in emotional functioning and odor recognition are related
  • Participants who were better able to identify roommates’ olfactory cues scored higher on measures identifying others’ emotions & facial expressions
  • Depicts association between emotional functioning and odor recognition

The “Proust Phenomenon”

- Marcel Proust (1871-1922)
  - French novelist, first described the neuroscience of memory & olfaction
- “Proust phenomenon”
  - Odor-evoked memories more emotional than those elicited by other senses
  - Potent reminders of autobiographical experiences
  - Indicated by self-report and physiological responses (i.e. heart rate)
  - First described by Marcel Proust in *Swann’s Way* (1919):
    - “...and as soon as I had recognized the taste of madeleine... immediately the old grey house upon the street, where her room was, rose up like a stage set ... and with the house the town, from morning to night and in all weathers, the Square where I used to be sent before lunch, the streets along which I used to run errands, the country roads we took when it was fine.”

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Gender Differences in Olfactory Ability

- Research shows gender differences
  - Women (of reproductive age) > Men
  - Women better at odor identification & detecting low odor concentrations
  - Women become sensitive to odors faster than men do
- Women’s smell sensitivity greatest during ovulation
- Olfactory brain structures differ between sexes
  - In size & architecture
- Differences in newborns: within days of birth, baby girls turn to novel smells more than baby boys

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Pheromones & Sexual Attraction

- **Pheromones**
  - Chemicals secreted in bodily fluids believed to influence behavior of opposite sex, i.e. sexual interest

- **Human sex pheromone has not been identified (yet)**
  - Research may have overemphasized effect of pheromones on humans
  - “Male-effect” pheromone in male goats: induces ovulation in females

- **For women judging men, body odor powerful in judging attractiveness**
  - Suggests odor cues may be at least as important as visual cues

- **Foster (2009): sight more important than smell**
  - Olfaction still important, but more so for fertile women

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The Industry of Smell
Marketing Olfaction

- Marketers use power of olfaction to boost sales
  - Hershey’s outlet in Times Square vents chocolate smell into air
  - At least half of Las Vegas casinos have corporate “scent systems”
- Scents affect mood and behavior
  - Shoppers more likely to help around pleasant scents, i.e. cookies
- The “congruency” problem: scent must match context
  - Women’s clothing sales rose with feminine, vanilla scent, & men’s sales dropped; vice versa in presence of spicy, masculine scent
- Gender-appropriate scent = $55 spent
- Gender-inappropriate scent = $23 spent
- Bottom line: meaning counts more than mood

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The Perfume Industry

- Eugene Rimmel created 1st mass-marketed perfume in mid-1800’s
  - Gave away scented fans/almanacs
  - Precursor to scented perfume ads in magazines
- ScentStrip sampler in magazine first used by Giorgio in May, 1983 issue of Vogue
  - Sales boomed, but readers complained magazine “reeked of perfume”
  - Allure magazine claims that 85% of readers try scent strips immediately
- Scents also marketed to hide unpleasant odors

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The Allure of Perfume

• Using sex in the perfume industry
  • Ads suggest one will become desirable & attractive
  • “Wearable pheromones” guarantee sexual success
• Gender differences in attraction ratings
  • Women rated men wearing Axe spray as significantly more attractive
  • BUT, women did not smell the men; ratings based on videos
  • Axe spray → men’s increased confidence → higher ratings by women
• Mate selection
  • Fertile women sexually attracted based on scent: natural or cologne
  • Biologically “unsuitable” man wearing cologne can trick woman
  • Men not influenced by women’s body odor in this manner

The Cultural Significance of Chanel Nº 5

- Created in 1921 by Gabrielle “Coco” Chanel
- Best-selling & arguably, most iconic fragrance
- The austere bottle design is unchanged from its debut
- Coco herself starred in its first campaign, in 1937
- Official perfume launch was on the fifth day and fifth month of 1921
- Artists Salvador Dali & Andy Warhol painted the bottle

http://inside.chanel.com/en/no5
The Healing Power of Scent: Aromatherapy
Introduction to Aromatherapy

• Aromatherapy
  • Using essential oils to enhance psychological and physical well-being\(^\text{24}\)
  • Essential oils may be toxic or cause allergic reactions
  • Studies provide evidence of benefits, but many findings still mixed

• Perfumer Mandy Aftel, identified five landmark scents\(^\text{25}\):
  1. **Cinnamon**: spicy scent; linked to risk & discovery
  2. **Mint**: quintessential American; linked to home & the familiar
  3. **Frankincense**: deeply aromatic; spiritual & out-of-body experience
  4. **Ambergris**: animal essence; linked to unusual, strange experience
  5. **Jasmine**: floral fragrance; yearning for beauty & evanescence

\(^{24}\)www.naha.org
Effects on Sleep

• Study explored ten scents for possible effects on sleep in rats:
  • Clove, jasmine, lavender, lemon, peppermint, pine, rose, sandalwood, valerian, & ylang-ylang

• Valerian and rose inhalation significantly prolonged sleeping time
  • But only valerian demonstrated changes in EEG brain waves
  • Valerian enhances GABA activity

• Lemon inhalation significantly shortened sleeping time
  • May worsen insomnia symptoms

Immuno-stimulating Effects

• **Eucalyptus oil:** antimicrobial effects against viruses, tuberculosis, & MRSA\textsuperscript{27}
  • Stimulates immune system & anti-inflammatory
  • Improves respiratory problems such as bronchitis & COPD
  • Can offset toxicity of some chemotherapy agents
  • But uncertain if it may decrease chemotherapy benefit

• **Turmeric oil:** significant anti-inflammatory effects\textsuperscript{28}
  • May delay, prevent, or treat chronic diseases, i.e. cancer, diabetes, & cardiovascular pulmonary diseases
  • Can scavenge free radicals in body, increase carcinogen detoxification, and act as cancer-preventing agent


Olfactory Pathology
Anosmia

• Anosmia: the inability to perceive odor; loss of smell
  • Occurs with a frequency of less than 5%\textsuperscript{34}
  • Incidence rises to 24% in ages 53-97
  • No known treatment or cure
  • Associated with:\textsuperscript{35}
    • Parkinson’s disease
    • Alzheimer’s disease
    • Depression
    • Severe head injuries
    • Epilepsy
    • Multiple sclerosis (MS)


Olfactory Impairment & Quality of Life

- Decreased quality of life after diagnosis in 77% of patients\textsuperscript{36}
- One third rate mood, ability to enjoy food, and social interactions as fair to poor\textsuperscript{37}
  - Half of patients willing to spend 20% of income to treat disorder
- Negatively affects mood, eating behaviors, and safety\textsuperscript{34}
  - Concerns regarding inability to detect gas leaks, spoiled food, etc.
- Younger patients (≤ age 40) report fewer difficulties
- Women report more difficulties than men
  - Suggests that olfaction more important to women

Olfactory Impairment & Depression

- Depression shown to alter ability to perceive odors
  - Overlap in brain structures involved in emotional processing & olfaction
- Depressed patients differ in emotional evaluation of odors
  - Respond more to unpleasant odors than pleasant odors
  - Rated negative odor (butyric acid) as more unpleasant than controls
  - No differences in rating of positive odor (vanilla)
  - Reflection of depressed patients’ negative thinking

Olfactory Impairment & Cognitive Decline

• Dementia
  • Broad category of brain diseases (includes Alzheimer’s disease)
  • Decreased ability to think and remember, affects daily functioning

• Alzheimer’s disease (AD)
  • Progressive, degenerative disease that attacks the brain
  • Impairs thinking, memory, and behavior

• Olfactory impairment early feature in AD\(^{35}\)
  • Impaired olfactory sensitivity and olfactory memory
  • Worsens with disease progression
  • Patients with cognitive decline often do not notice change
  • Relationship not completely understood; still being studied

Olfactory Impairment as a Predictor of Dementia

• Self-reported olfactory impairment predicted dementia diagnosis within 10 years in cognitively healthy adults\textsuperscript{39}
  • Identified ability to smell as “worse than normal”
• In cognitively healthy adults, decreased ability to identify smells predicted more rapid memory decline\textsuperscript{40}
  • 34 people had low smell ID but no cognitive impairment
  • But autopsy still showed higher AD neuropathology
  • Demonstrates odor ID relationship to cognition and neuropathology
• Ability to identify smells correlated with scores on a dementia battery (RBANS) in patients referred for dementia evaluation\textsuperscript{41}

Functional Representation of Olfactory Impairment

• PET scans of odor function in early AD patients & healthy controls
• Used “Sniffin Sticks” test
  • Odor identification (ID): highest difficulty
  • Odor discrimination (DIS): intermediate difficulty
  • Odor threshold (THR): lowest difficulty
• Reduced function in olfactory regions of AD patients
• THR detection
  • Related to unawareness of olfactory deficit
  • Least dependent on higher cognitive functions
• ID activation
• Overlap with pathology in postmortem AD studies

1. ID activation:
   • R prefrontal cortex, orbitofrontal cortex, & parietal cortex
     • Higher-order processing, memory, decision-making, visuospatial

2. DIS activation:
   • L post central gyrus
     • Somatosensory processing

3. THR activation:
   • Thalamus and cerebellum
     • Ancient brain regions
     • Lower-order processing
   • Correlation between activation and odor task to assist in early identification of AD

The Neuropathology of Olfaction

• Olfactory dysfunction in the elderly found to be result of accumulated AD disease pathology\(^{43}\)
  • Elderly participants completed an odor ID test
    • On average participants died 2.2 years later
  • Autopsies analyzed plaques and tangles of deceased participants
  • Revealed robust association between odor ID and tangles in the hippocampus, but not tangles in other areas
  • Results suggest difficulty in odor ID in old age partly due to accumulation of disease pathology in central olfactory regions

Odor Identification and Hippocampus Tangles

Inverse relationship between odor identification and tangles in the hippocampus, with solid circles indicating dementia at the time of olfactory testing and a linear regression line adjusted for age at death, sex, education and time from smell assessment to death.

Anosmia in Traumatic Brain Injury (TBI)

- TBI one of the major causes of olfactory dysfunction\(^{46}\)
  - Incidence of 12.8% at 6-32 months after injury\(^{47}\)
  - Poor olfaction not associated with severity of head injury
- Smell recovery often occurs after several months
- After 1-2 years of anosmia, diagnosis considered final
- Three mechanisms of post-traumatic anosmia:
  1. Shearing or stretching of olfactory nerve during brain movement
     - If stretched, olfaction returns (30%); tearing leads to anosmia\(^{48}\)
  2. Lesion(s) in olfactory center: olfactory bulbs or tracts, primary olfactory cortex, OFC, or insular cortex.
  3. Conductive hypothesis: nasal injury and upper airway obstruction\(^{49}\)

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Case Study of Post-Traumatic Anosmia

- Post-traumatic anosmia w/OFC lesion\(^{46}\)
  - Inability to identify/recognize odors
  - Odor perception intact
  - Right OFC- central processing of smell
  - May lead to “blind smell,” OFC activity but no conscious olfaction\(^{50}\)

- Primary olfactory cortex damage leads to inability to perceive odors

- Damage to OFC $\rightarrow$ inability to identify and recognize odors
  - Multisensory integration in frontal areas
  - Necessary for odor recognition


Factors Affecting Post-Traumatic Anosmia\textsuperscript{49}

- Mood
  - Depressed mood typically associated with olfactory dysfunction
  - But mood is altered regardless of olfactory ability\textsuperscript{51}

- Age
  - Mood & injury not associated with olfactory impairment when age considered

- Anosognosia: lack of awareness of deficit
  - Occurs in 40-44\% of patients with olfactory impairments
  - Systematic olfactory evaluations recommended following TBI

- Lesion
  - Type and location of lesion better indicator than TBI impairment
  - Frontal lesions lead to more impairment than other lesions


Conclusions & Future Directions

• Despite being the most ancient sensory system, there is much to learn about olfaction and its functions

• Olfaction has important relationships with:
  • Mood & emotional functioning
  • Human relationships
  • Memory
  • Cognitive decline and brain injury

• Recent advances in brain imaging shedding light on olfaction’s significance in other areas, particularly Alzheimer’s disease