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Olfaction

- The most ancient of distal senses
  - In nearly all air-, water-, and land-dwelling creatures
- Determines flavor of foods and beverages
- Significant role in nutrition, safety, and in the maintenance of quality of life
- 2.7 million (1.4%) adults in the U.S. alone with olfactory dysfunction

"I sense a hint of oak and butterscotch"

- Many depend upon smell for livelihood or safety:
  - Cooks
  - Homemakers
  - Firefighters
  - Plumbers
  - Wine merchants
  - Perfumers
  - Cosmetic retailers
  - Chemical Plant Workers

The Sense of Smell

- Often downplayed
- Vital to our everyday existence
  - Stop and smell the roses
  - Has the milk expired?
- Essential in our ability to taste
- Occasionally the first sign of other disorders
- Rarely tested

Definitions

- Total Anosmia: inability to smell all odorants on both sides of the nose
- Partial Anosmia: inability to smell certain odorants
- Specific Anosmia: lack of ability to smell one or a few odorants
- Hyperosmia: abnormally acute smell function and often interpreted as hypersensitivity to odors
- Dysosmia: distorted or perverted smell perception

Definitions

- Parosmi … quality of an olfactory …
- Phantos … absence of an olfactory …
- Olfactory … cognize odor sensatio … essing, languag … n intact
- Presbyo … aging

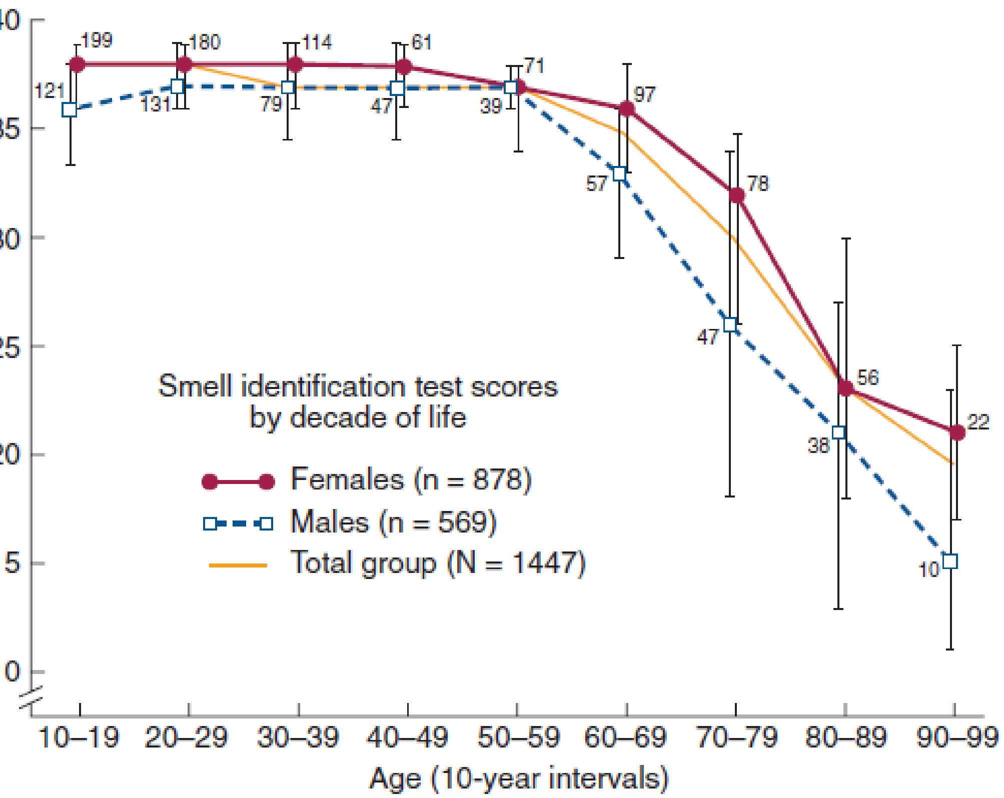
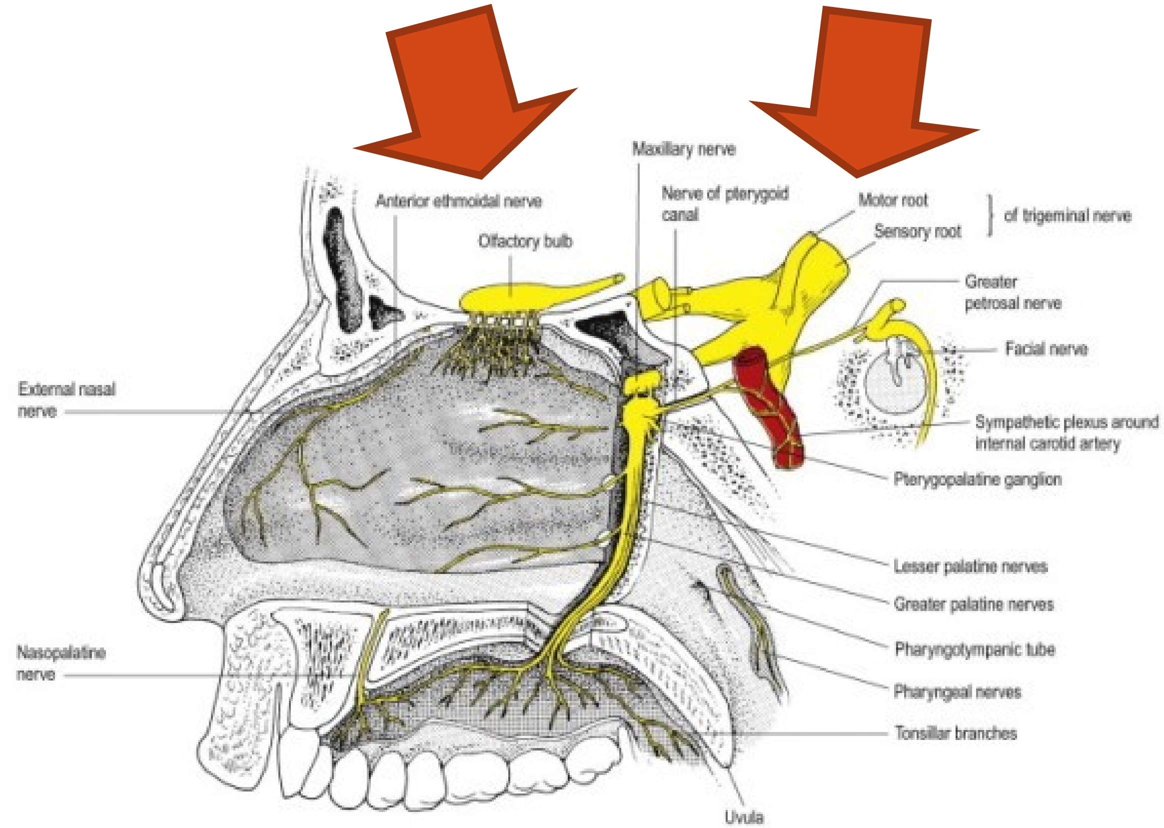


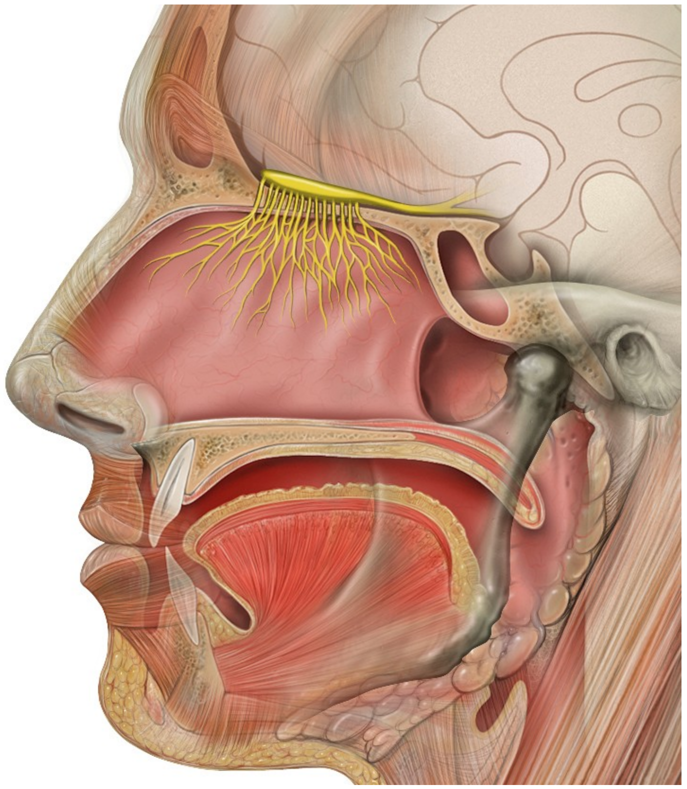
Figure 41-13. Relationship between the University of Pennsylvania Smell Identification Test scores, age, and gender in a large heterogeneous group of subjects. *(From Doty RL, Shaman P, Dann M. Development of the University of Pennsylvania Smell Identification Test: a standardized microencapsulated test of olfactory function.* Physiol Behav. *1984;32:489.)*

Nasal Anatomy and Olfaction

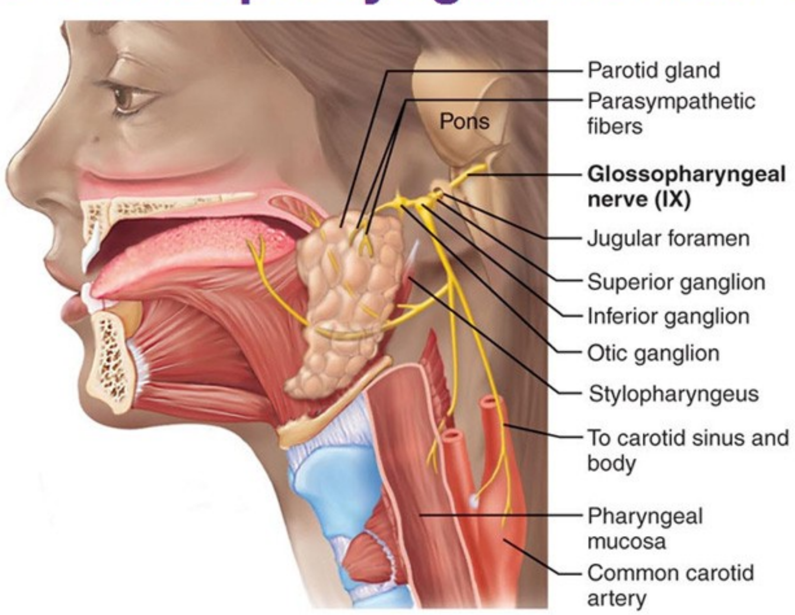
- Odor reception is a result of input from:
  - Olfactory Nerve (CN I)
  - Trigeminal Nerve (CN V)
  - Glossopharyngeal Nerve (CN IX)
  - Vagus Nerve (CN X)

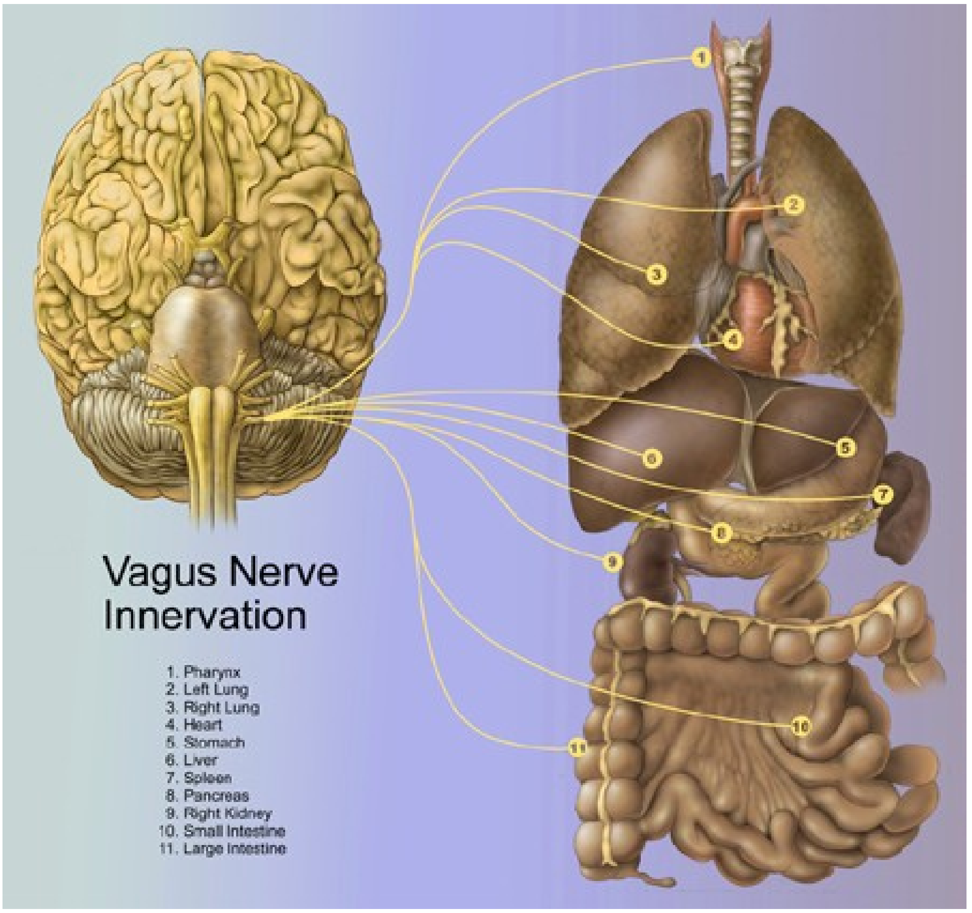
Nasal Anatomy





The Glossopharyngeal Nerves -IX



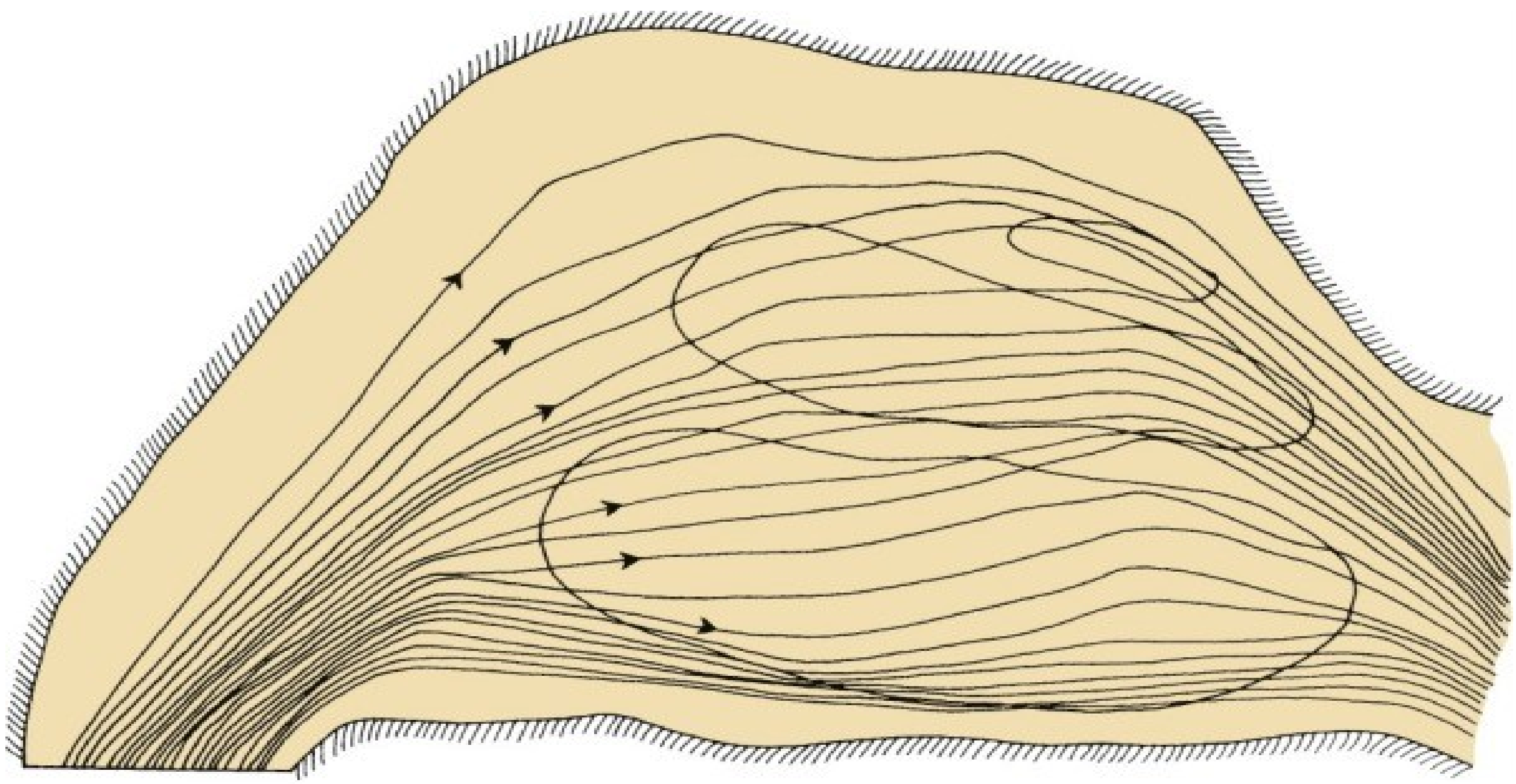


Olfactory Nerve Stimulation

- Requires odorant’s molecules reaching the olfactory mucosa at the top of the nasal cavity
- Olfaction requires some type of nasal airflow
- Orthonasal flow: airflow toward the olfactory epithelium on inhalation
- Retronasal flow: during eating, stimulates olfactory receptors and contributes greatly to the flavor of food

Physiologic Airflow of the Nasal Passages

- 50% of the total airflow passes through the middle meatus
- 35 % of total airflow passes through the inferior meatus
- 15% of total airflow passes through the olfactory region



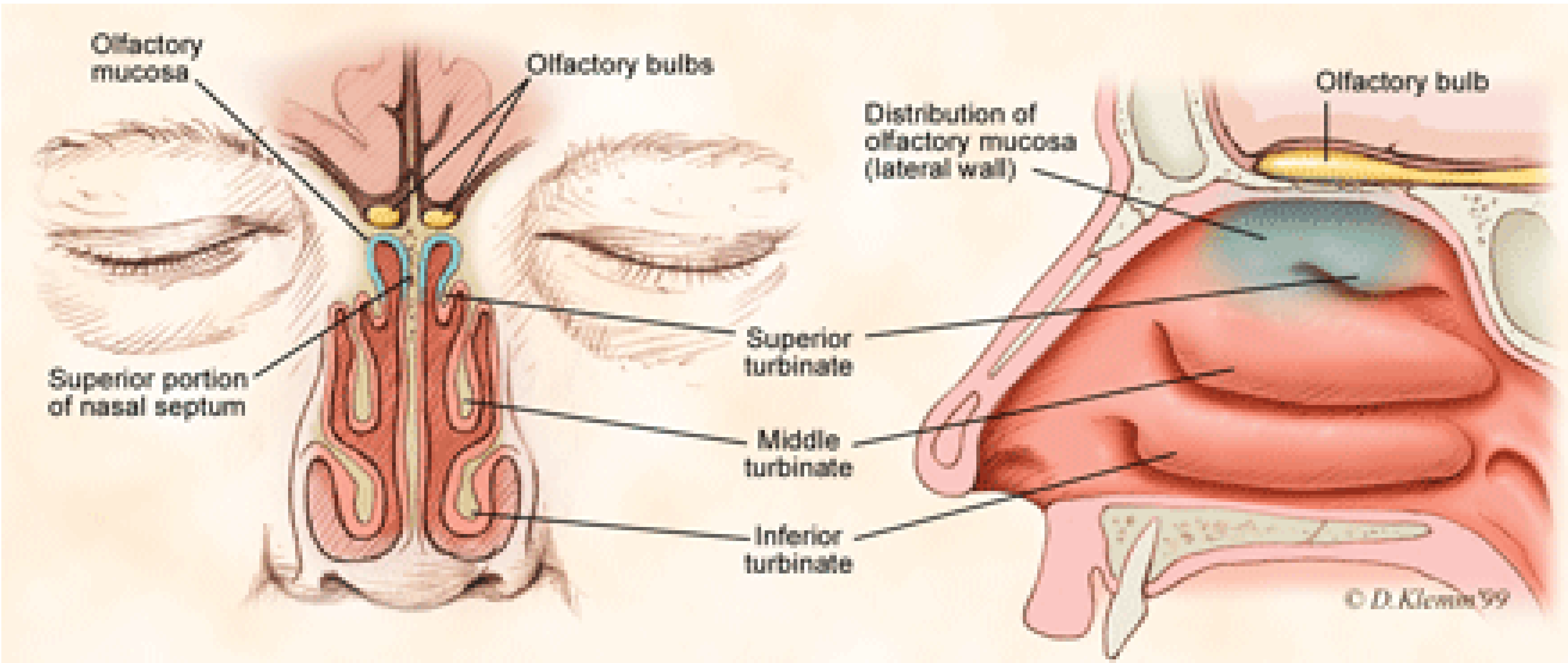
Why do we sniff?

- Effects of a rapid change in flow velocity on the in vivo airflow pattern remains unknown
- Scherer and colleagues found percentage and velocity of airflow to the olfactory region are similar for various steady-state airflow rates in the physiologic range
- Sniffing remains an almost universally performed maneuver when presented with an olfactory stimulus
- Sniff may allow trigeminal nerve to alert olfactory neurons that an odorant is coming
- Our natural sniff seems to be the optimal for our nasal anatomy

Olfactory Anatomy

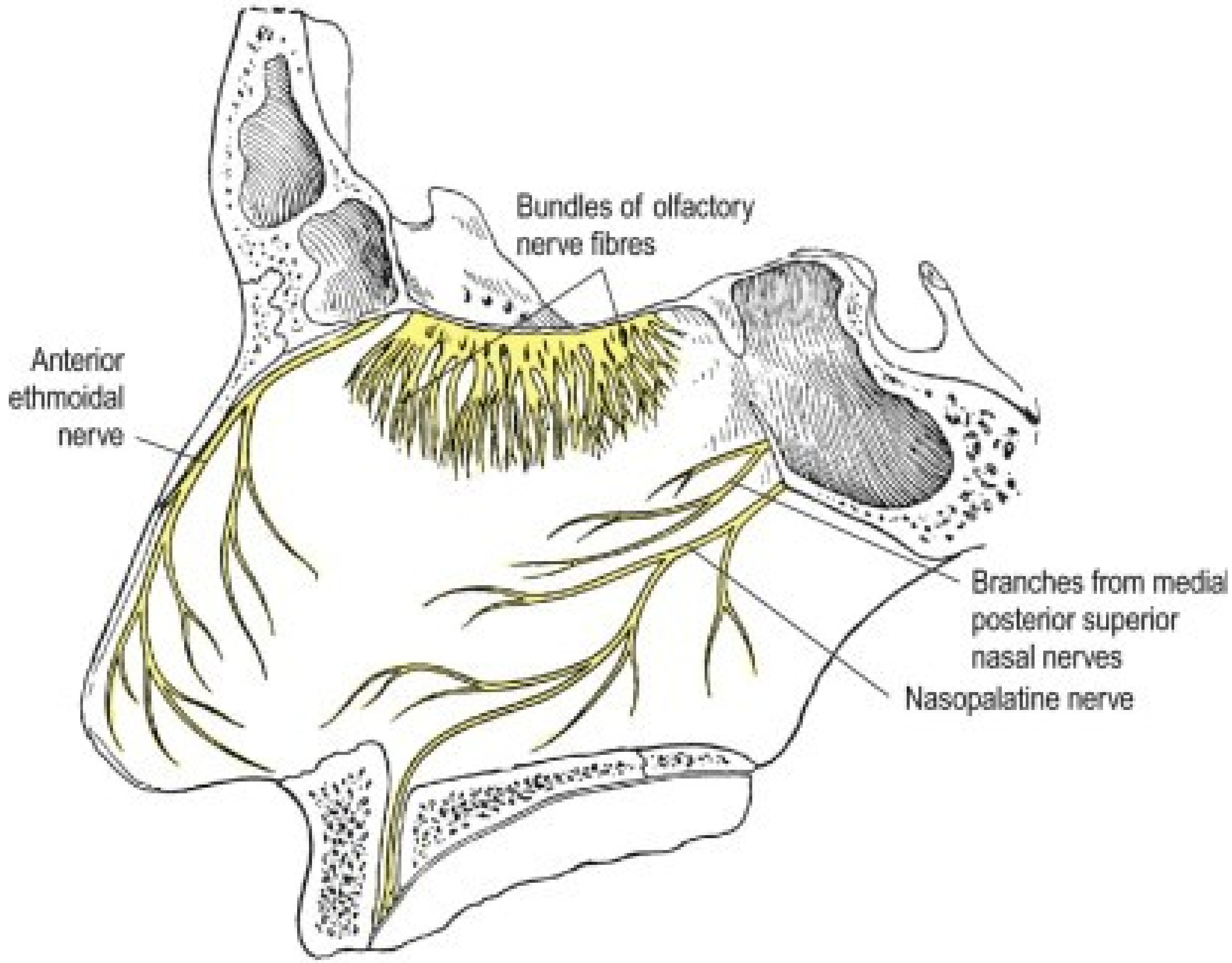
- Olfactory molecules must pass through the tall but narrow nasal passageways
- Olfactory epithelium is wet, has variable thickness, and aerodynamically “rough”
  - Schneider and Wolf observed olfactory ability to be best when epithelium is moderately congested, wet, and red
- Olfactory ability seems to improve with narrowed nasal chambers
- Nasal cycle does not have any effect on olfactory ability

Olfactory Anatomy



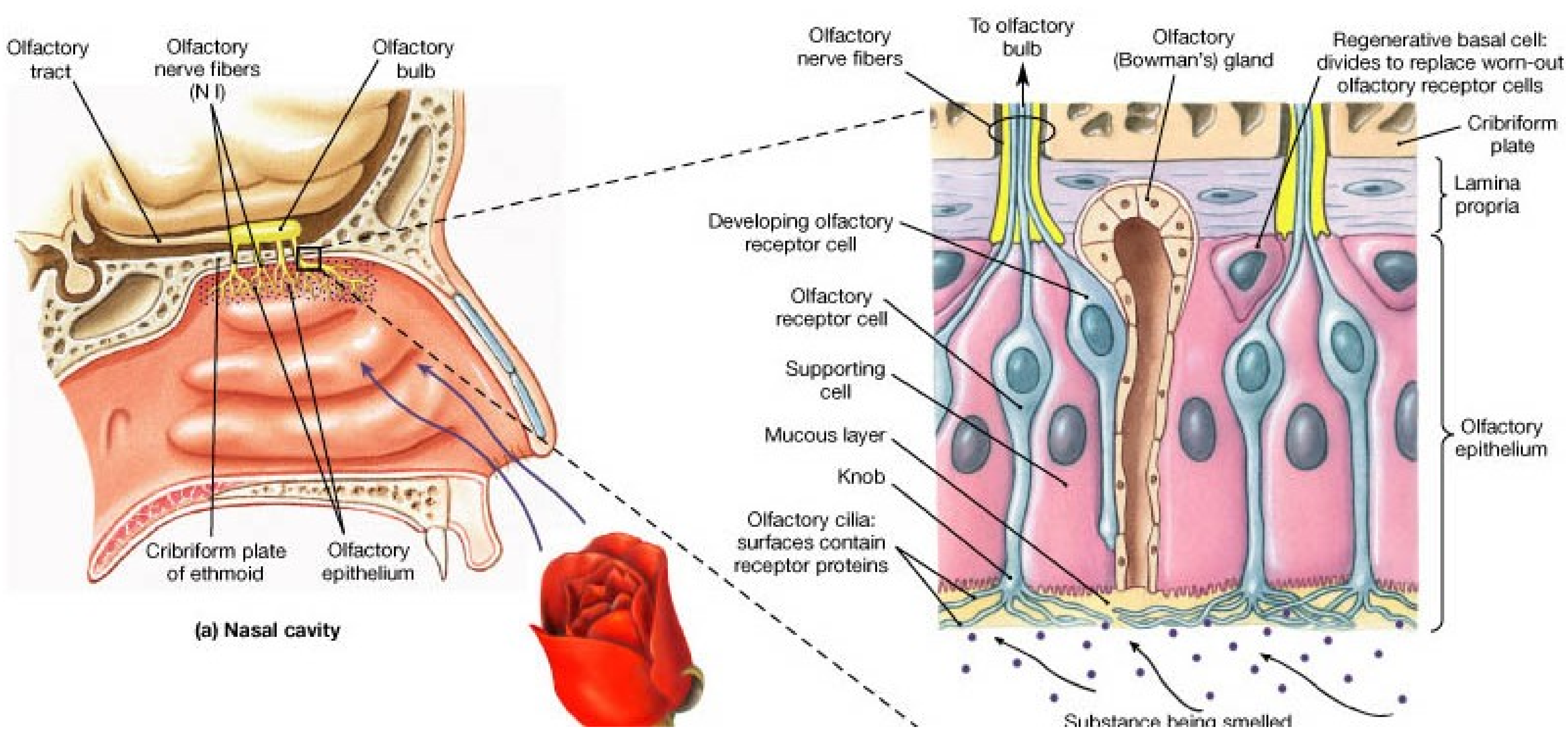
Source: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine, 18th Edition*: www.accessmedicine.com

Olfactory Anatomy



Absorption of Molecules

- Mucus-lined walls absorb molecules from the air stream and increase their travel time through the nasal passageways
- This may influence the spectrum of chemicals reaching the olfactory cleft
- Absorption of molecules may separate/sort odorants before reaching the olfactory mucosa
  - Highly absorbable chemicals may have minimal or no odor as they never reach the olfactory cleft



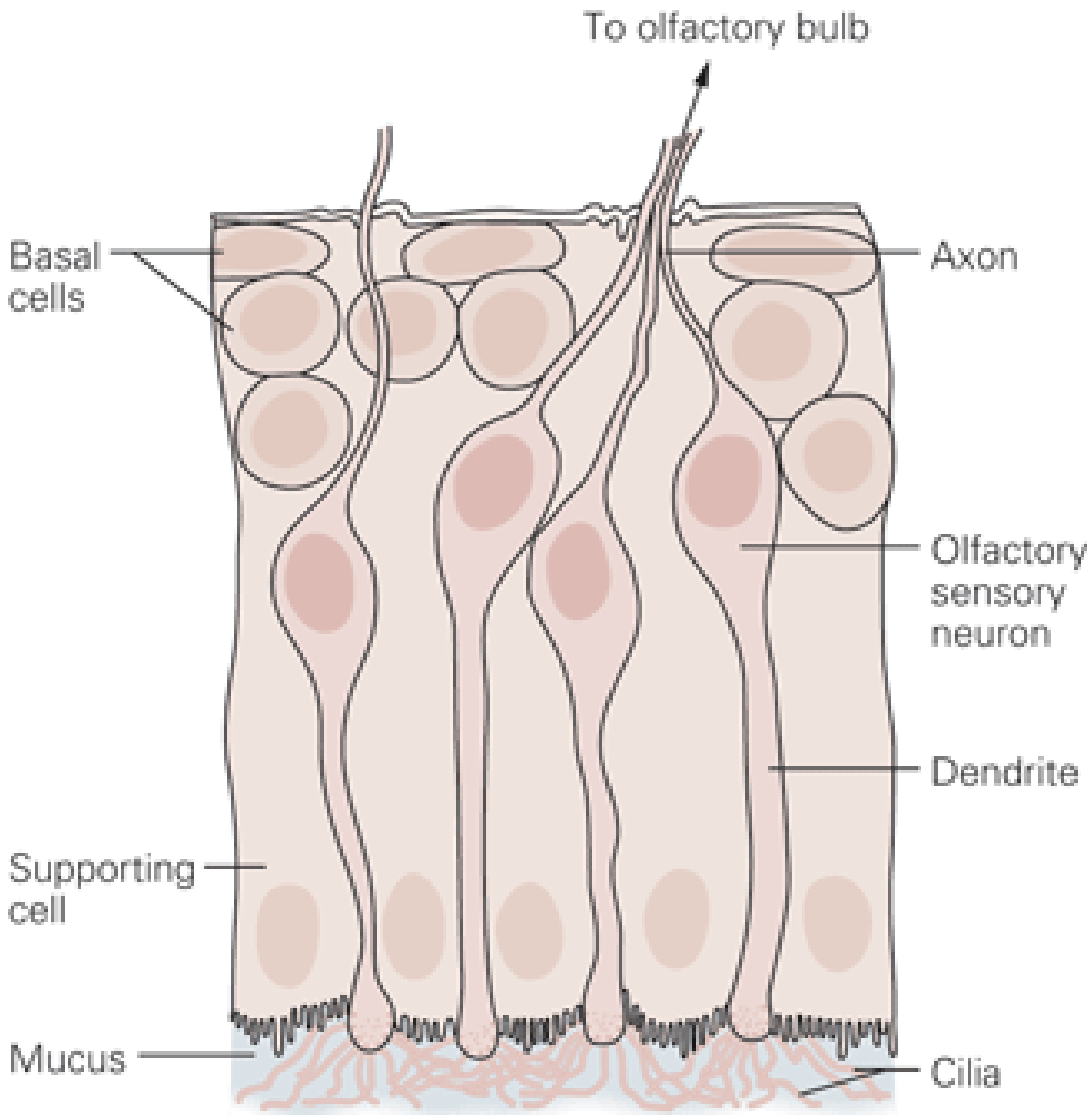
Olfactory Mucus

- When odorant molecules reach olfactory region, must interact with mucus overlying the receptor cells
- Produced by Bowman’s glands and adjacent respiratory mucosa (goblet cells)
- Partitioning of odorant’s molecules between air phase and mucus phase important in reaching olfactory epithelium
- Must be soluble in mucus but not too strongly captured to interact with the receptors
- Adrenergic, cholinergic, and peptidergic agents change the properties of mucus overlying the olfactory receptors

Olfactory Mucus

- In the olfactory mucus-epithelial system, clearing odorants is equally as important as absorption
- Olfactory mucus may exert a differential role in deactivating, removing, or desorbing odorants from the olfactory area

Olfactory Epithelium



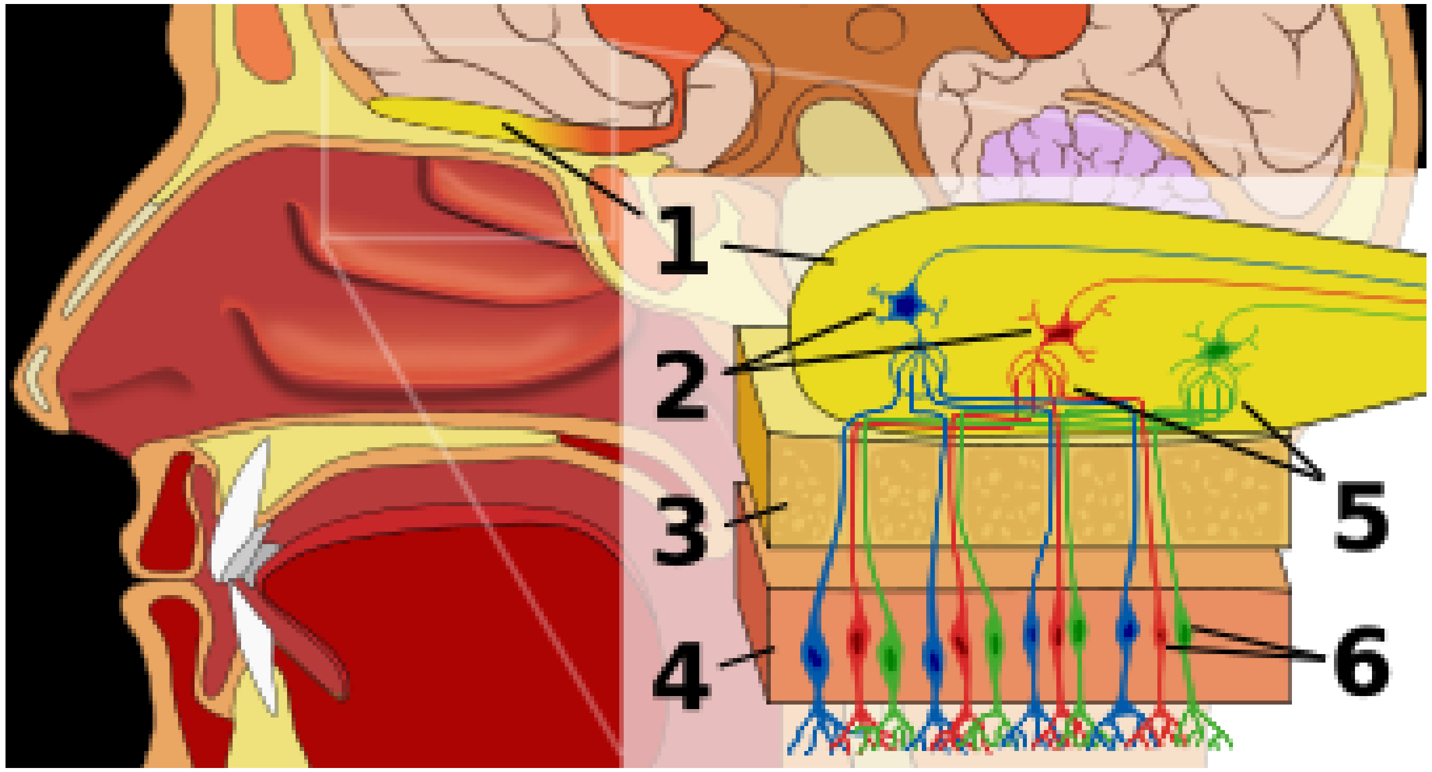
Source: Barrett KE, Barman SM, Boitano S, Brooks H: *Ganong's Review of Medical Physiology, 23rd Edition*: http://www.accessmedicine.com

Olfactory Epithelium

- Olfactory sensory neurons protected in a 1-mm-wide crevice of the posterosuperior nose
- Covers roughly 1 cm^2 on each side
- Neuroepithelium is pseudostratified columnar epithelium
- Neurons exposed to the outside world through their dendrites and cilia
- Axons of these neurons synapse at the base of the brain in the olfactory bulb
- As least six morphologically and biochemically distinct cell types

Olfactory Neuroepithelium

- Bipolar receptor cell: projects from the nasal cavity into the brain without an intervening synapse



Olfactory Receptor Cell

- Each receptor cell expresses a single odorant receptor gene
- > 1,000 different types of receptor cells present within the olfactory epithelium
- Olfactory receptor genes account for ~1% of all expressed genes of the human genome
  - Largest known vertebrate gene family
- Receptors not randomly distributed but confined to one of several nonoverlapping striplike zones
- Each cell is responsive to a wide, but circumscribed, range of stimuli
- Olfactory receptor proteins linked to stimulatory guanine nucleotide-binding protein G_{olf}

Olfactory Receptor Cell

- Derived from ectoderm
- First-order neurons, can regenerate after they are damaged
- Glial-type cells that ensheathe olfactory neurons support axonal growth of both olfactory and nonolfactory neurons
  - Interest as potential agents for reversing spinal cord injuries and demyelinating disease

Olfactory Cilia

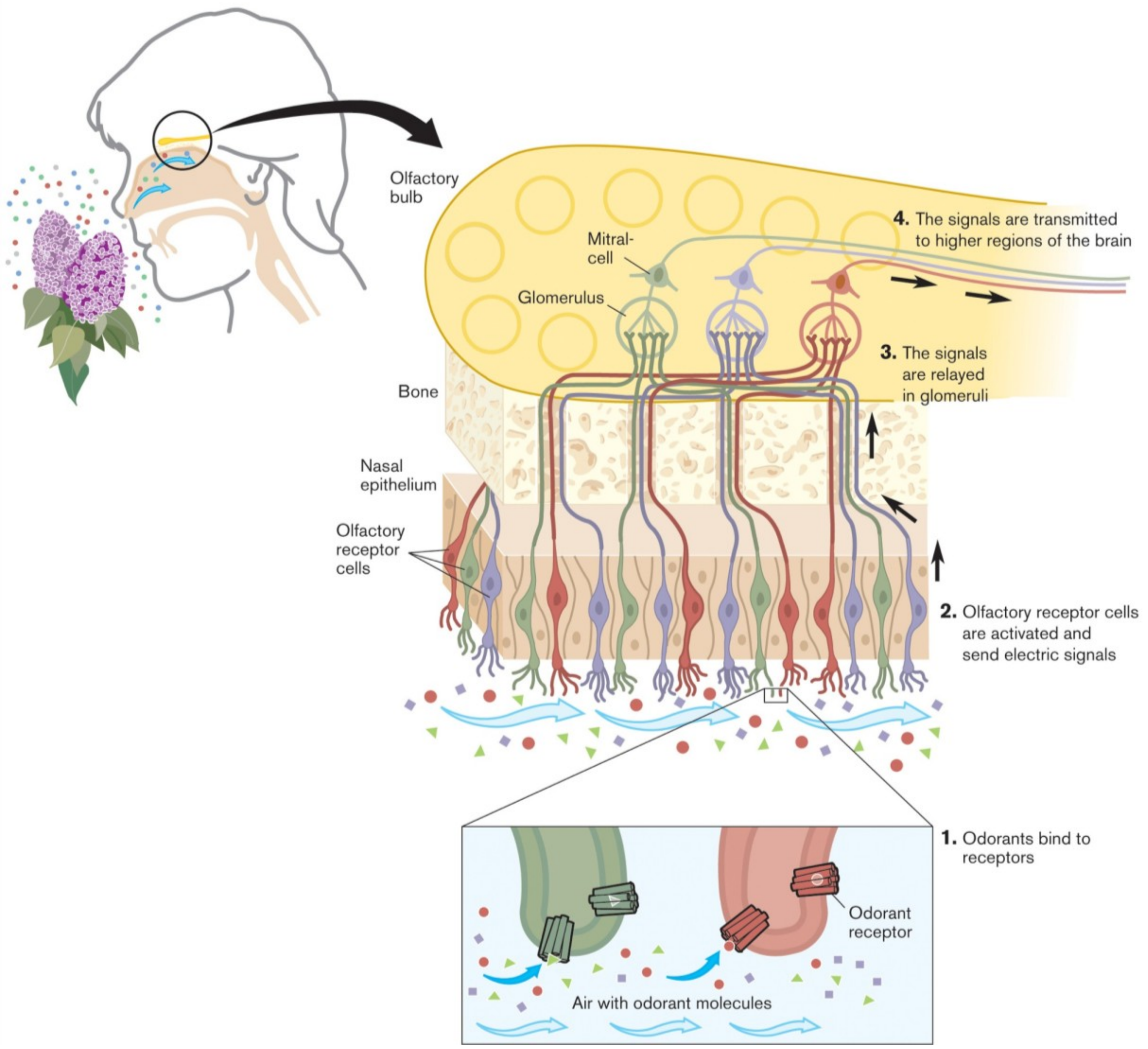
- Cilia differ from respiratory epithelium in being much longer, lacking dynein arms (lacking motility)
- Surface area of cilia exceeds 22 cm^2 in humans
  - Exceeds 700 cm^2 in German Shepherd dog

Olfactory Epithelium

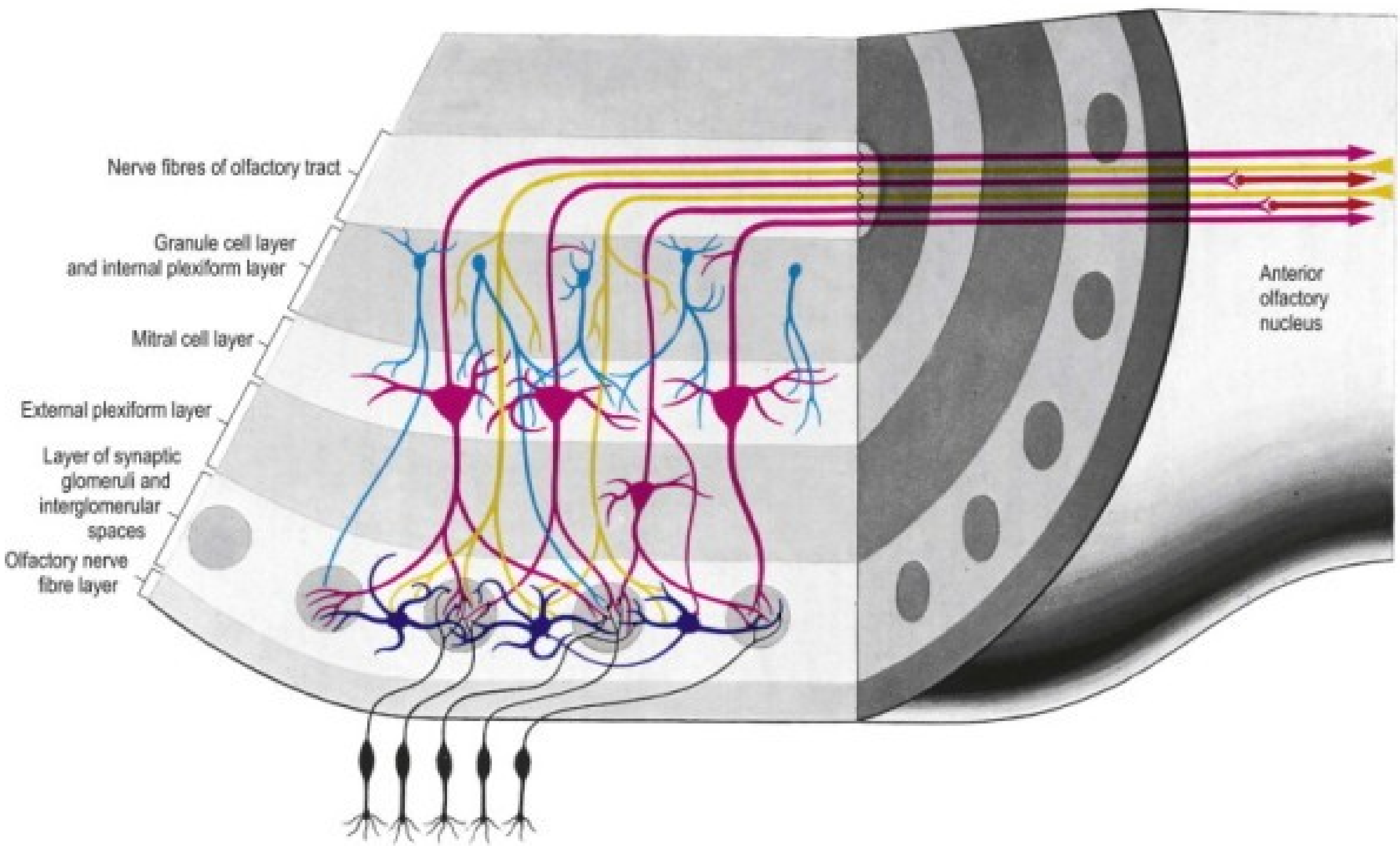
- Supporting or sustentacular cell: contain microvilli and insulate the biopolar receptor cells and help to regulate composition of the mucus
  - Involved in deactivating odorants and assisting in protecting epithelium from foreign agents
- Microvillar cells: poorly understood cells located at the epithelial surface
- Fourth cell type lines the Bowman’s glands and ducts
- Horizontal (dark) and Globose (light) basal cells: located near the basement membrane from which the other cell types arise

Olfactory Bulb

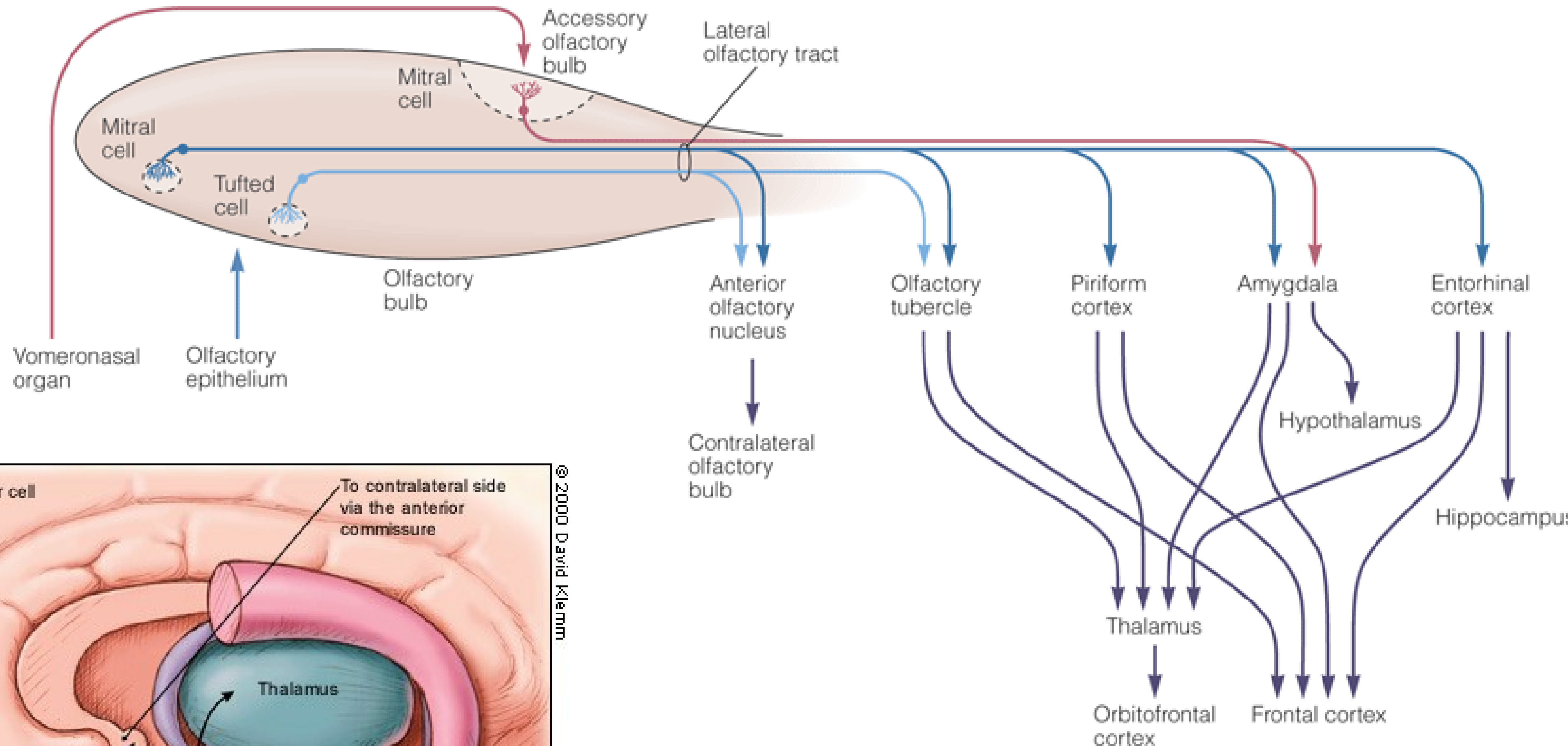
- Lies in base of frontal cortex in anterior fossa
- First relay station in olfactory pathway
- Synapses and their postsynaptic partners form dense aggregates of neutrophil called glomeruli
- Given region of the bulb receives its most dense input from a particular region of the mucosa, inputs to a particular region of the bulb converge from many receptor cells distributed throughout a certain zone of the mucosa
- Excitatory and inhibitory influences narrow the neural stimulus
- Olfactory bulb specialized to narrow the spatial pattern of glomerular activation by an odorant or mixture of odorants

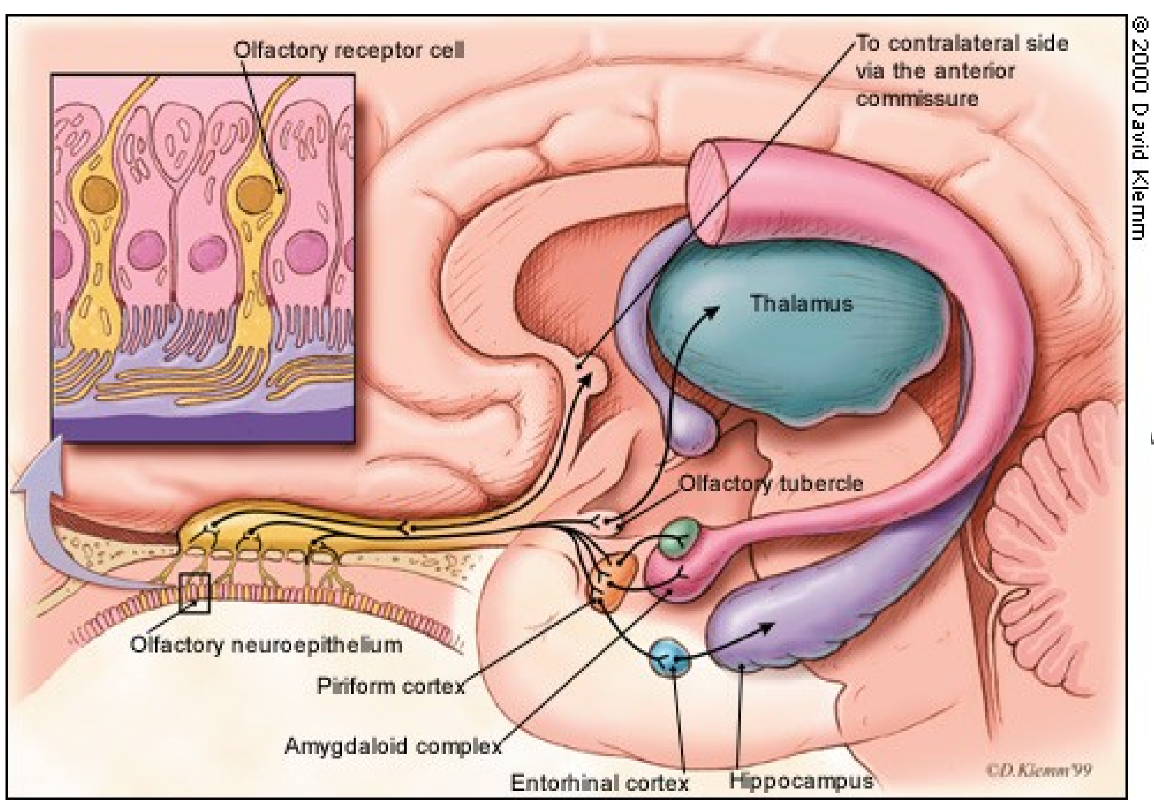


Olfactory Bulb



Olfactory connections to the Brain





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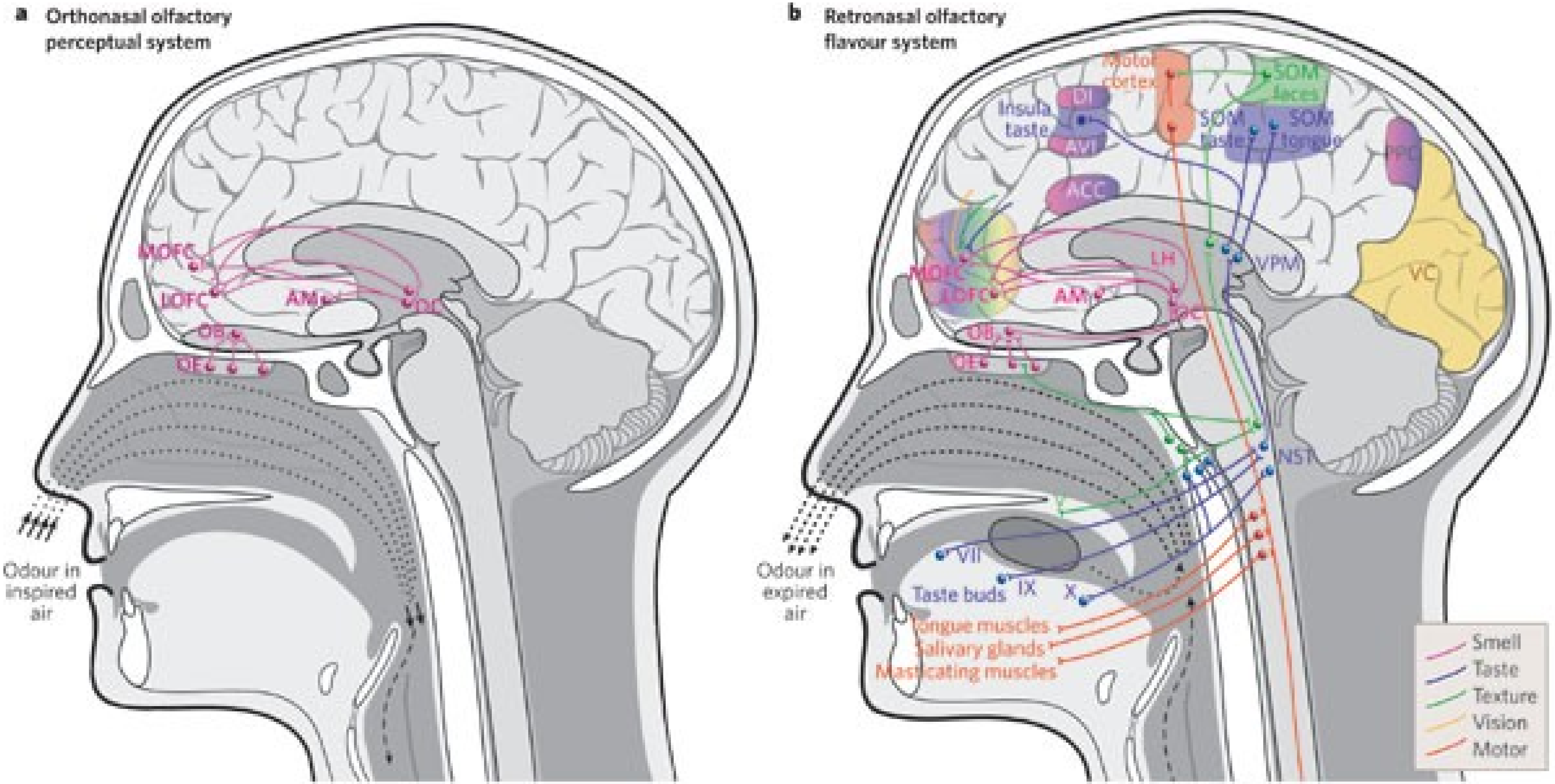
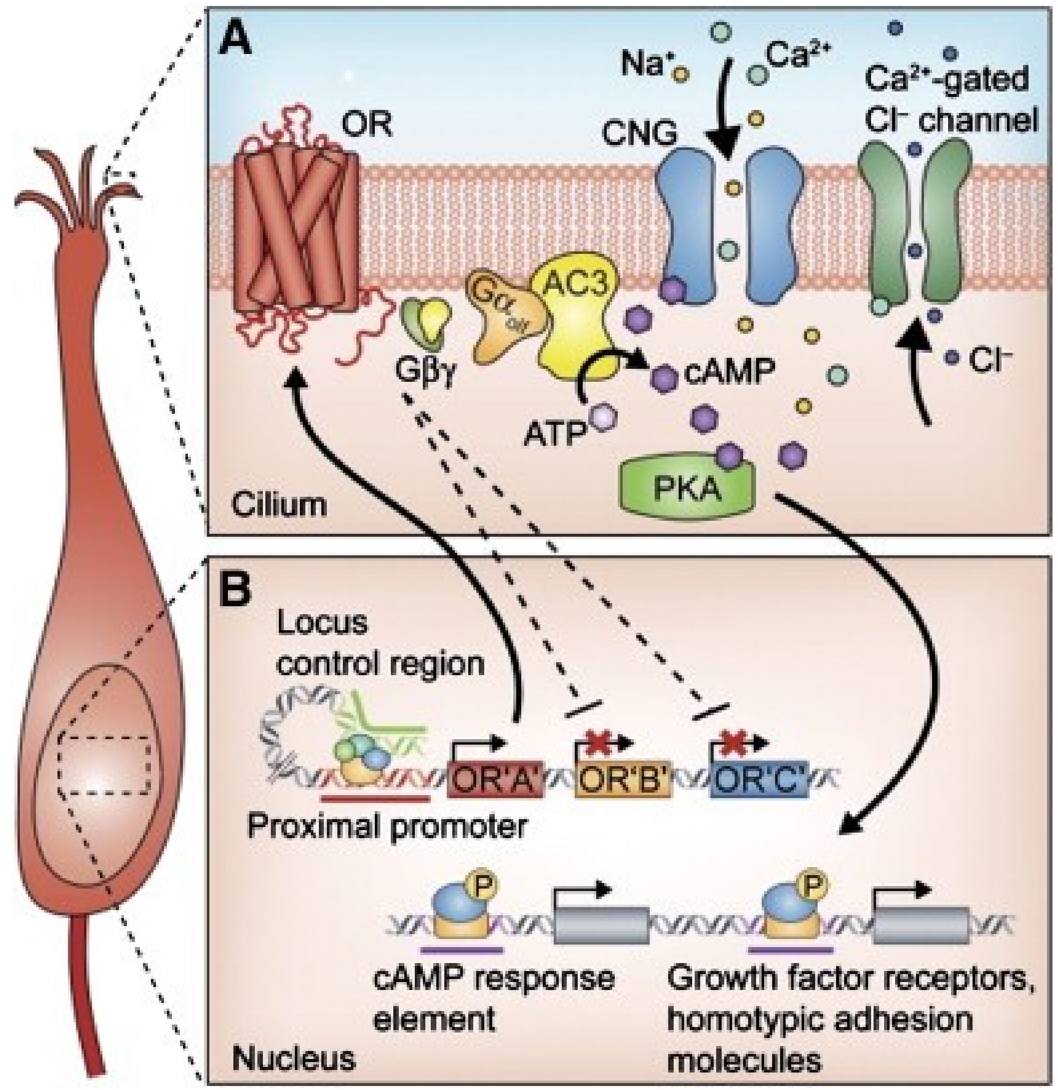
Olfactory Connections



Olfactory Transduction

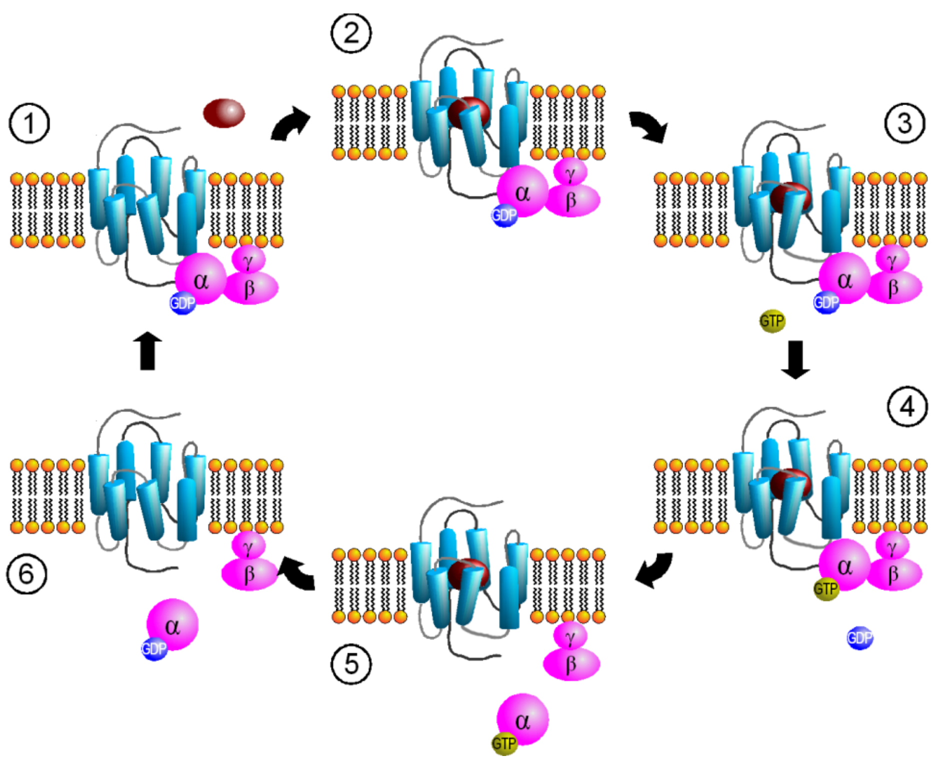
- Olfactory Binding Proteins: bind and solubilize the hydrophobic odorant molecules into hydrophilic olfactory mucus
  - Increases concentration into the surrounding environment as much as 1,000 to 10,000 times more than their concentration in ambient air
  - May also act to remove odorant molecules from the region of the receptor cell

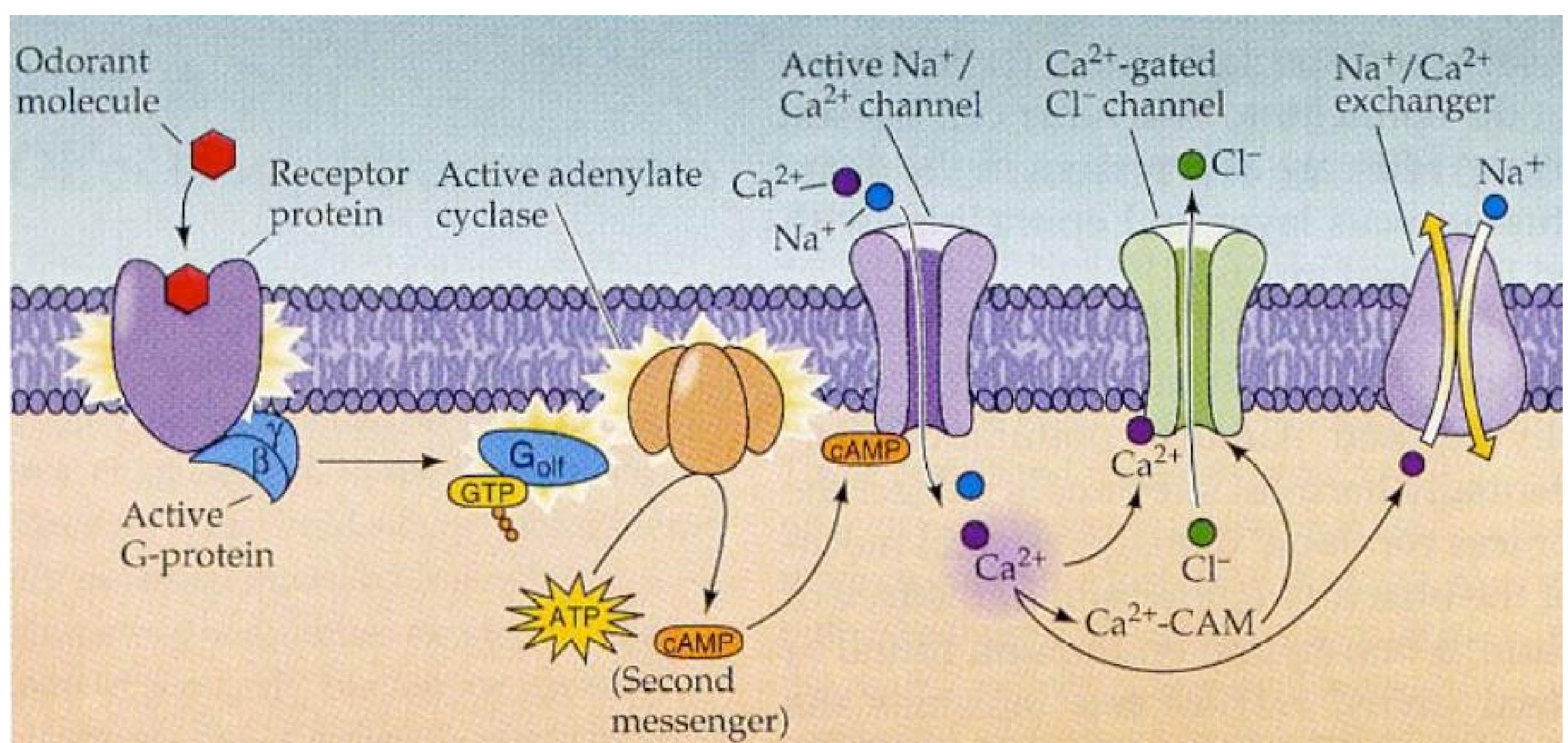
Olfactory Transduction



Olfactory Transduction

- cAMP and IP3 are primary signaling pathways mediating olfactory transduction
- G_{olf} : Guanine-nucleotide binding protein exclusively localized to the olfactory epithelilum
- cAMP binds to Na, Ca ion channel depolarizing the cell creating an action potential





Olfactory Odor Map

- Mouse model shows their olfactory epithelium is roughly divided into four zones
- Group of different olfactory receptor subtypes confined within the designated zone
- Clinical evidence exists for receptor specificity of odorants
  - Loss of specific odor receptor genes creates an inability to perceive particular odorants

Olfactory Cognition

- We understand odors largely on experience; develop our own hedonic code within cultural restraints
- Studies show odor memory can last at least 1 year while visual memory lasts only a few months
  - Odor memory is facilitated by bilateral nasal stimulation, one study suggests patients with one-sided nasal obstruction may form poorer odor memories
- Macfarlane examined 30 newborns and 30 women
  - Women underwent washing of one breast and babies were placed in prone position between their breasts
  - 22 of the 30 newborns selected the unwashed (odorous) breast

Clinical Evaluation of Olfaction

- An evaluation of 750 patients with chemosensory dysfunction, demonstrated that most patients presented with both smell and taste loss, few (<5%) have identifiable whole-mouth gustatory deficits
  - Taste: true gustation
  - Flavor: olfactory-derived sensations from foods
- Whole-mouth taste function much more resistant to injury than olfactory function largely due to redundancy of innervation
- When CN I is damaged, leaves only sweet, sour, salty, bitter and umami sensation

Physical Examination

- Complete otolaryngologic examination with anterior rhinoscopy and nasal endoscopy
  - Unfortunately, nasal endoscopy is not overly sensitive
  - During endoscopy, examine nasal mucosa for color, surface texture, swelling, inflammation, exudate, ulceration, epithelial metaplasia, erosion, and atrophy
  - Even minor polypoid disease at the olfactory cleft can account for olfactory dysfunction
- Cranial nerve examination
- Optic disc examination to determine presence of increased intracranial pressure

Olfactory Testing

- Essential for multiple factors:
  - Validate patient’s complaint
  - Characterize specific nature of the problem
  - Monitor changes in function over time
  - Detect malingering
  - Establish compensation for permanent disability
- Many patients complaining of anosmia or hyposmia have normal function relative to age and gender
  - 90% of patients with idiopathic Parkinson’s Disease have demonstrable smell loss, yet less than 15% are aware of their problem

Olfactory Testing

- Asking a patient to sniff odors is like testing vision by shining a light in each eye and asking whether the patient can see the light
- No current testing that can distinguish central and peripheral deficits
- Unilateral testing is often warranted
  - Sealing contralateral naris using Microfoam tape and having the patient sniff naturally and exhale through the mouth to prevent retronasal stimulation

Olfactory Testing

- Psychophysical Testing
- Electrophysiologic Testing
- Neuropsychologic Testing

Psychophysical Testing

- UPSIT or Smell Identificiation Test
  - Can be administered in 10 to 15 minutes by most patients
  - 4 booklets of 10 odorants apiece
  - Stimuli embedded into 10- to 50-μm diameter microencapsulated crystals
  - Multiple choice questions with four response alternatives
  - Test is forced-choice, required to choose an answer even if none seems appropriate
  - Chance performance is 10 out of 40 , lower scores can represent avoidance
  - Norms available based on administration to 4,000 people
  - Individuals are ranked relative to age and gender

UPSIT (continued)

- Test can classify individual's function into 6 categories:
  - Normosmia
  - Mild microsmia
  - Moderate microsmia
  - Severe microsmia
  - Anosmia
  - Probable malingering
- Very high reliability, test-retest Pearson r = 0.94

Electrophysiologic Testing

- 2 procedures are available but application largely experimental
- Odor event-related potentials (OERPs)
- Electro-olfactogram (EOG)

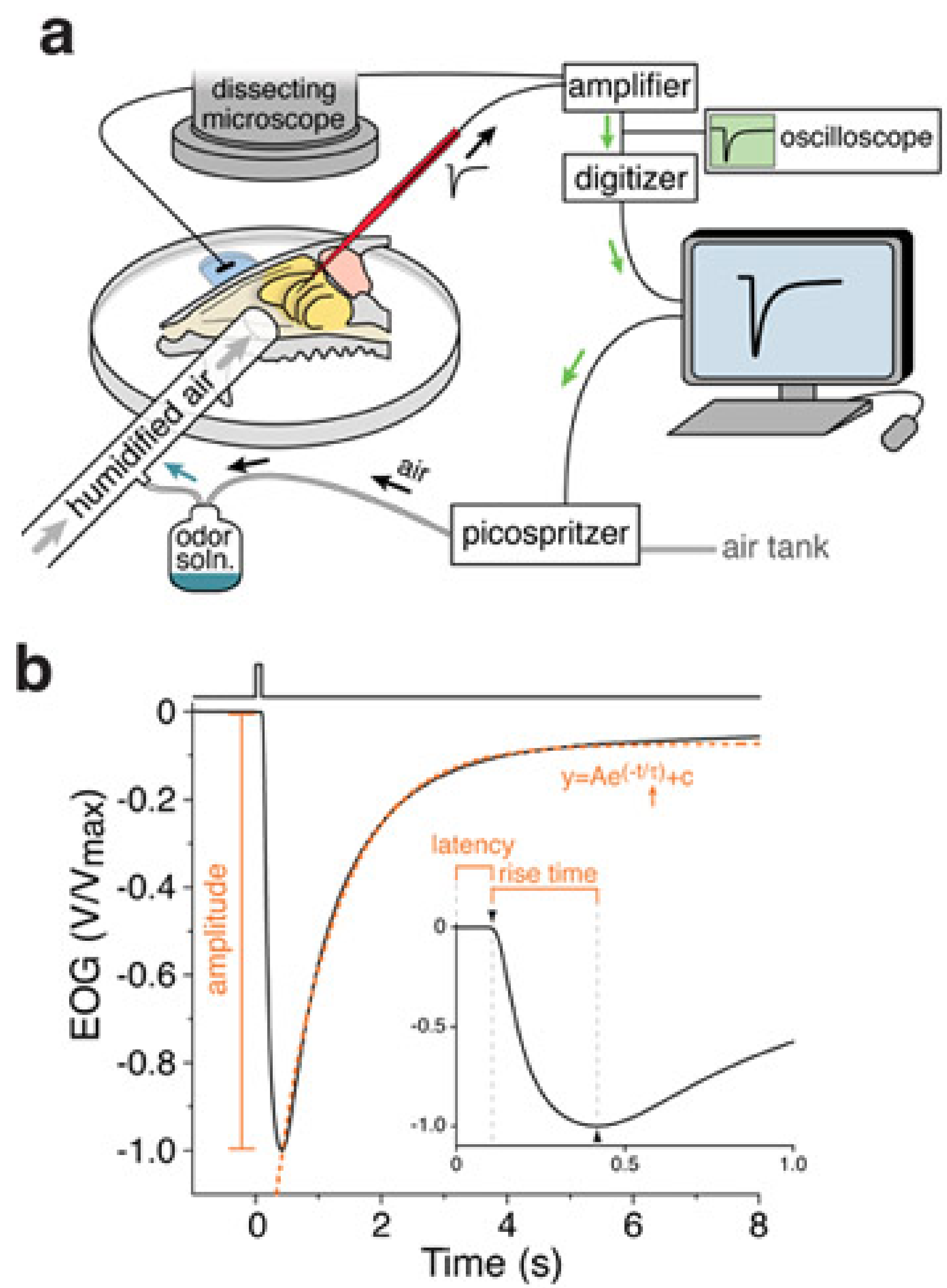
Odor Event-Related Potentials (OERPs)

- Discerning synchronized brain EEG activity recorded on the scalp from overall EEG activity following presentations of odorants
- Stimuli presented in precise manner using equipment that produces stimuli embedded in warm, humidified air stream
- Unable to perform necessary trials and test reliability is suspect
- No inference can be made regarding location of a lesion or deficit
- Can be usefully in detecting malingering

OERP

Electro-olfactogram (EOG)

- Measures electrode placed on the surface of the olfactory epithelium
- Few patients amenable to recordings
- Must place electrode under endoscopic guidance without local anesthesia
  - Can be quite unpleasant and sneezing/mucous discharge common
- Cannot reliably record in many subjects
- Presence of robust EOG does not always represent olfactory functioning

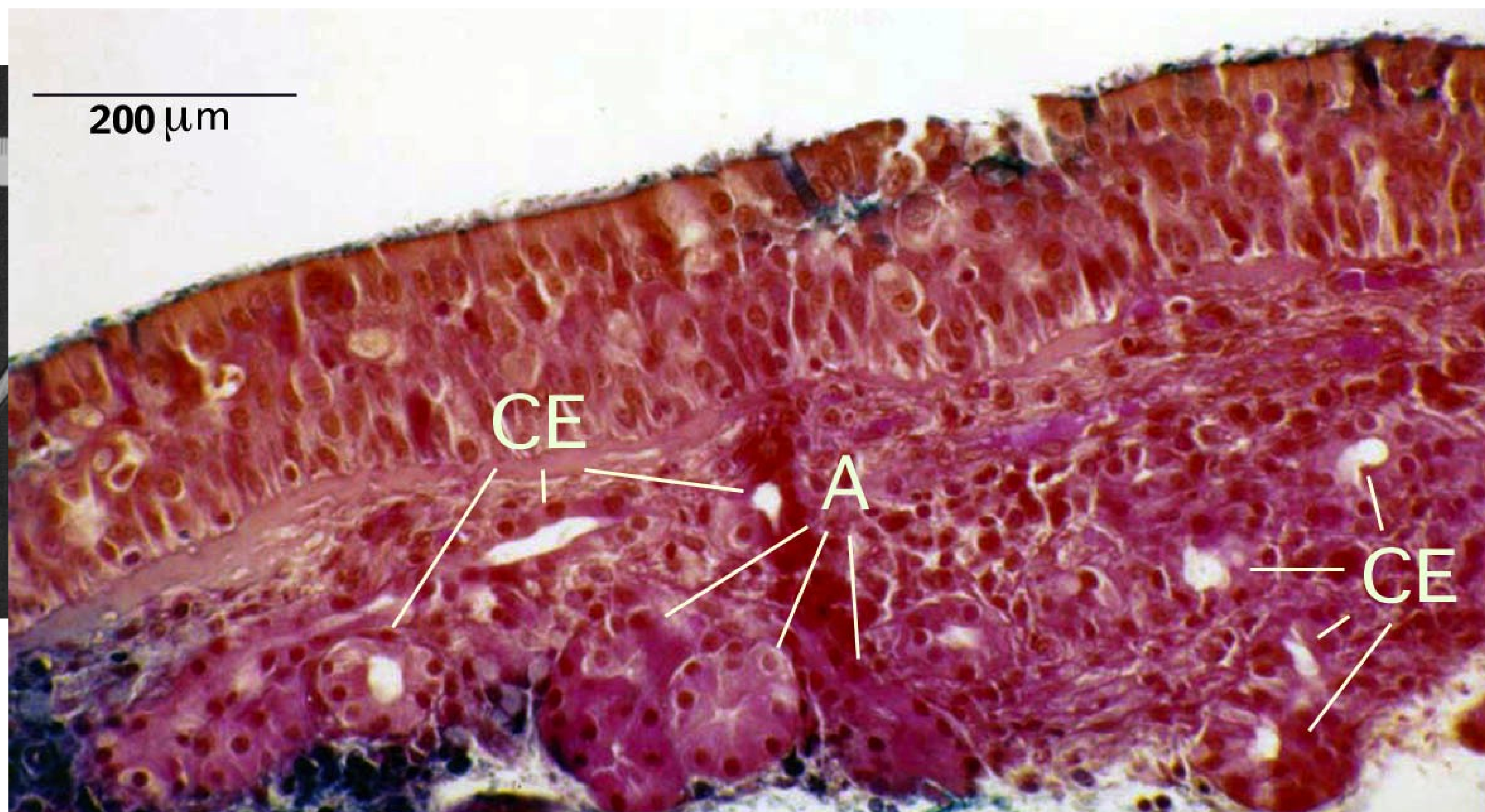


Neuroimaging

- Olfactory dysfunction of idiopathic etiology warrants CT imaging
  - High-resolution CT is most useful and cost-effective screening tool
- MRI: useful in evaluating olfactory bulbs, olfactory tract, and intracranial structures
  - MRI can detect decrements associated with anosmia and patients with schizophrenia

Olfactory Biopsy

- Small amount of superior septal tissue removed by experienced rhinologist
- Multiple biopsies needed to obtain true neuroepithelium



Disorders of Olfaction

- Obstructive Nasal and Sinus Disease
- Upper Respiratory Infection
- Head Trauma
- Aging
- Congenital Dysfunction
- Toxic Exposure
- Neoplasms
- HIV
- Epilepsy and Psychiatric Disorders
- Medications
- Surgery
- Idiopathic Loss

Disorders of Olfaction

Table 41-1

Spectrum of Olfactory Loss as Reported at Four Chemosensory Centers

	Goodspeed and Colleagues (1987)[239]*	Davidson and Colleagues (1987)[226]†	Leopold and Colleagues (1987)[222]‡	Heywood and Costanzo (1986)[169]§
Total no. patients	441	63	198	133
Etiologic category (%):				
Obstructive nasal and sinus disease	30	33	29	20
Post–upper respiratory infection	19	32	15	17
Head trauma	9	10	19	32
Aging	0	0	8	6
Congenital	0	5	8	0
Toxins	1	11	3	0
Miscellaneous	14	10	8	16
Idiopathic	26	0	10	10

*Connecticut Chemosensory Clinical Research Center, Farmington, Connecticut.
†Chemosensory Perception Laboratory, University of California, San Diego.
‡Clinical Olfactory Research Center, SUNY Health Science University, Syracuse, New York.
§Smell and Taste Clinic, Medical College of Virginia, Richmond, Virginia.