Hypothalamus: Lecture 2

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- Examples of hypothalamic functions:
  - Temperature regulation/fever
  - Suprachiasmatic n. and circadian rhythms
  - Energy balance

The hypothalamus coordinates homeostasis and appetitive functions via integration of :

- Endocrine system
- Autonomic function
- Motivated behaviors

Thermoregulation

- Thermostat in preoptic area normally set to 98.6º-- only few º latitude either way regardless of the individual
- Heat sensitive and cold sensitive neurons in medial preoptic area respond to changes in temperature due to exercise or ambient temperature
- Peripheral information (skin temperature) via spinal pain/temperature medial lemniscal pathways
  core body temperature conveyed via vagus

MPOA is the primary center for temperature homeostasis. The "Set point" or thermostat is maintained in the MPOA, which generally inhibits thermogenesis.

One secondary center is the Posterior Hypothalamic n. (PH). The PH activates shivering and sympathetic activity, so it is heat generating.

Limited control of sweat glands and blood vessel dilation take place as local spinal reflexes.

Hypothalamus and homeostasis-- an example-- thermoregulation

The environment is too cold.

Endocrine mechanisms for heat conservation

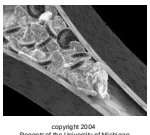
Short term:
Increase in sympathetic outflow
Increased adrenal stress hormones
Increased heat conservation

Long term:
Increase thyroid hormone production
Increased metabolic rate
Increased sympathetic activation of brown fat

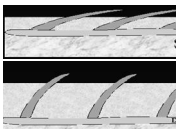
Autonomic mechanisms for coordinating thermoregulation

heat conservation

Stop sweating



Peripheral vasoconstriction



Piloerection

Coordination of thermoregulation by the hypothalamus

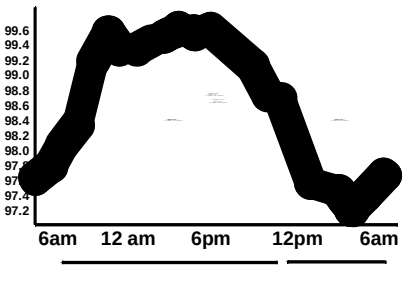
Motivated behavioral mechanisms of heat conservation in response To cold

Add Clothing

Huddle

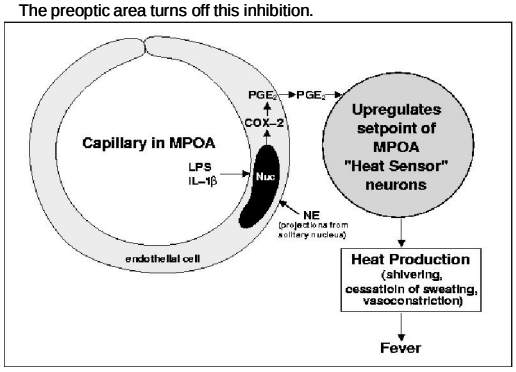
Ingest warm Fluid or food.

	Heat conservation	Heat dissipation
Endocrine	Increase TRH Increase CRF/ACTH/cort	Decreased TRH Decrease adrenal activation
Autonomic	Peripheral vasoconstriction Piloerection Shivering Decreased sweating Epinephrine release from adrenal medulla	Peripheral vasodilation Increase sweating Decrease sympathetic activation
Behavioral	Increased appetite Find shelter, build a fire, put on more clothes, ingest warm substances, huddle	Decrease appetite Find shade, A/C remove clothes ingest cool substances

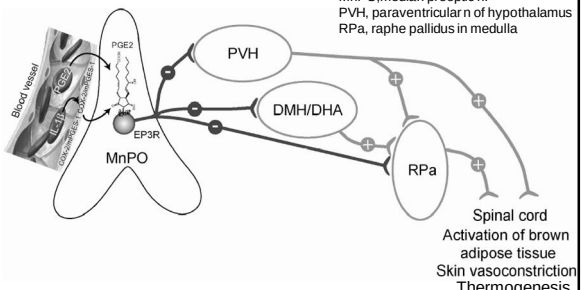


Body temperature fluctuates daily and with age.

Preoptic area: Fever production initiated in median preoptic area. Thermogenesis normally is tonically inhibited. The preoptic area turns off this inhibition.



DMH/DHA,dorsomedial hypothalamus
dorsal hypothalamic area
MnPO,median preoptic n.
PVH, paraventricular n of hypothalamus
RPa, raphe pallidus in medulla



Il-1beta increases Cyclooxygenase 2 which produces PGE2.
This activates EP3R, turning off tonic inhibition of thermogenesis.
The increased temperature activates immune system, kills bacteria.
Raphe Pallidus: activates shivering, thermogenesis by brown fat
(Aches and pains due to increased thermogenesis in muscle)

Adapted from Nature Neuroscience 2007

Sickness behavior: an adaptive, coordinated neuroimmune response.

Behavioral components:

- Sleep
- Food aversion
- Social isolation
- Fatigue/malaise
- Hypersensitivity to light, sound

Hyperalgesia (aches and pains due to thermogenic response of muscles)

Fever

Clinical notes:

Patients with spinal cord injury have limited abilities to thermoregulate, other than behaviorally.

Heat stroke is not a form of fever.

Chronic sickness behavior can trigger depression, based on activation of the hypothalamus.

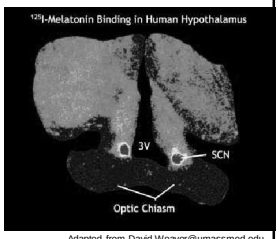
From edenspirit.com

Circadian rhythms and the brain's "Clocks"

Rhythms are:
Circadian- around the day
Menstrual– monthly
Circannual-- around the year (seasonal)

Suprachiasmatic n. is the master clock.

Neurons have natural 24 h oscillations
Oscillations are entrained by light
Receives direct information from retina

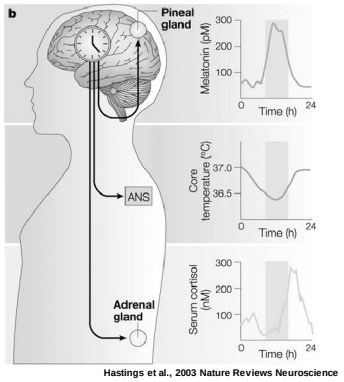


Adapted from David.Weaver@umassmed.edu

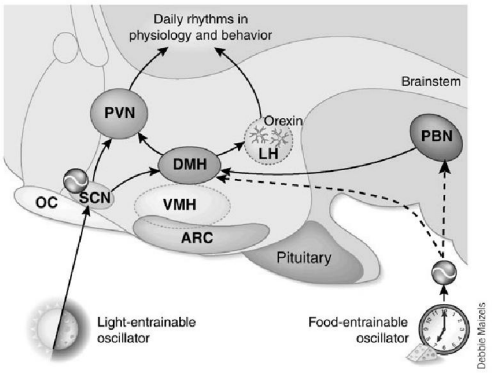
Dorsomedial n. = 2º clock

Entrained by feeding schedule
communicates reciprocally with the SCN

SCN regulation of circadian rhythms

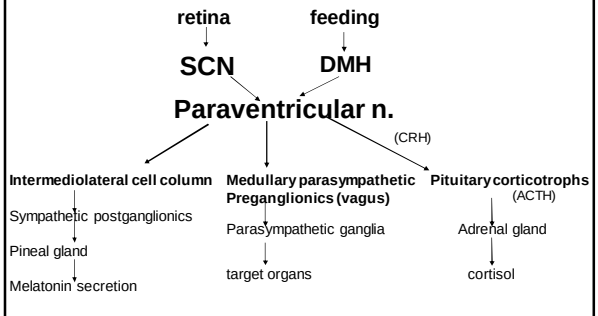


Hastings et al., 2003 Nature Reviews Neuroscience



Nature Neuroscience 9, 300 - 302 (2006)
Erik D Herzog & Louis J Muglia

Humoral and neural connections maintain temporal homeostasis.



Clinical notes on circadian/circannual rhythms:

Jet lag

Shift work (that means you)

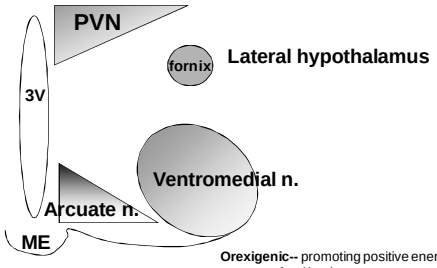
These can result in disturbances of GI tract, menstrual cycle, sleep, and altered stress responses.

Seasonal affective disorder

Hypothalamic regulation of energy balance

- Complex
- Set point is individual
- Set point may change over time (contrast with temperature)
- Small changes in nutrient intake and energy use can have marked effects on body weight
- Energy use is modified by behavior, endocrine and autonomic systems
- Obesity, anorexia, cachexia (wasting), eating disorders,
- Pubertal onset, maintenance of menstrual cycles

Energy balance: key regions in the hypothalamus



Cartoon of 1/2 coronal section tuberal zone; dorsal is up.

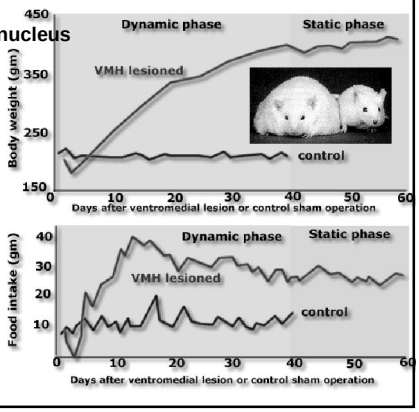
Orexigenic-- promoting positive energy balance
food intake
energy conservation

Anorexigenic-- promoting negative energy balance
inhibit food intake
promote energy consumption

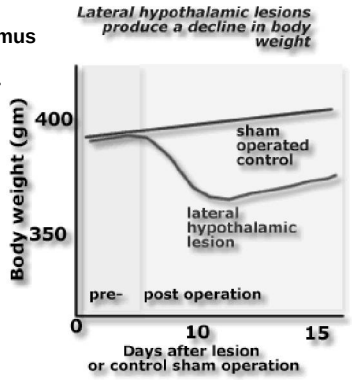
The ventromedial nucleus is often called the satiety center.

(Satiety= state of being full.)

This idea isn't entirely accurate, but the idea persists.



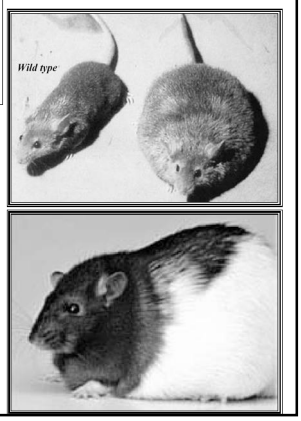
The lateral hypothalamus Is often called the "feeding center"-- again, not exactly accurate.



Genetic obesity due to recessive, spontaneous single locus point mutations.

ob/ob mouse:
Leptin deficient

fa/fa rat:
Leptin receptor deficient



Peripheral signals to hypothalamus re: energy balance--

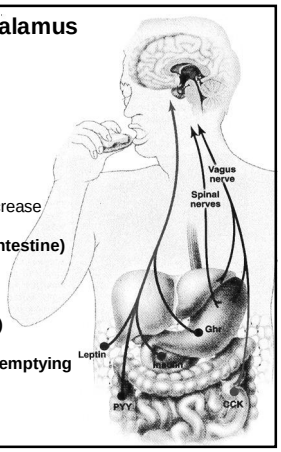
Adipokines:
Hormones from white adipose tissue
Leptin (satiety signal)

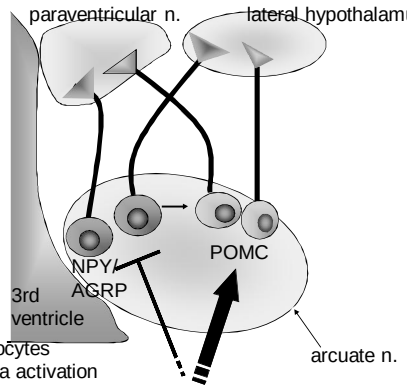
GI signals:
Ghrelin (hunger signal; levels increase with time since last meal**)**
CCK (satiety signal from small intestine)
PYY (satiety signal from colon)

Insulin (pancreas), glucose, IGF-1 (liver)

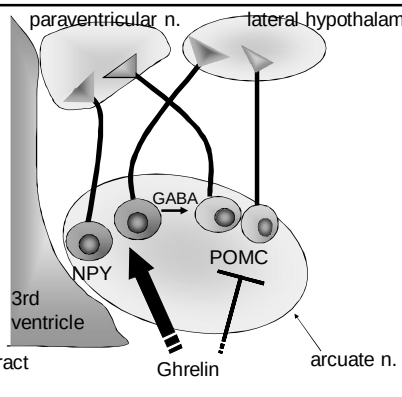
Vagal afferents convey gastric fullness/emptying

Many more satiety signals than hunger signals





Leptin, from adipocytes inhibits feeding via activation of POMC.
Turns off Neuropeptide Y and AGRP (agouti related peptide).



Ghrelin from GI tract promotes feeding
via activation of NPY and AGRP neurons.
Ghrelin and NPY turn off POMC.

Clinical notes on energy homeostasis

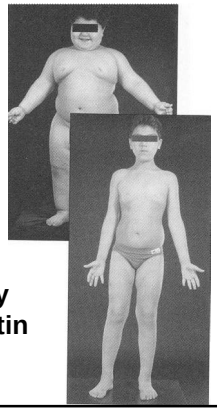
Obesity-- genetic, environmental (the thrifty gene)

Cachexia-- associated with specific illnesses

Anorexia/bulimia

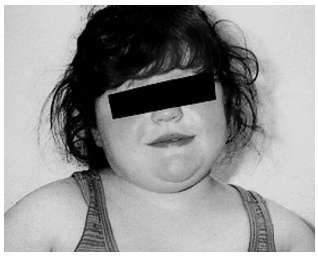
Set point for body weight can change due to physiologic condition, behavior, age or illness.

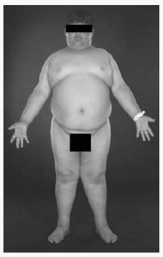
Leptin deficient boy



Same boy Post Leptin therapy

3 year old girl with human POMC deficiency






9 year old with MC4R mutation **16 year old brother**

The MC4Rmutation accounts for about 6% of severe childhood Obesity and is the most common monogenic obesity disorder yet identified.

MC4R expressing neurons in PVN regulate appetite but not the autonomic regulation of body weight.

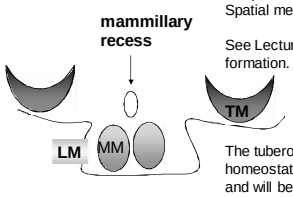
Adapted from
New England Journal of Medicine
(2003) 348: 1085-95

Studies from families and patients with single locus mutations important--

Show that body weight and appetite are controlled at multiple different levels and not just a matter of character and will power.

Also provide possible pharmacologic tools.

But body weight regulation is complex; controlled by many different neurotransmitters, neuropeptides, and receptors.



Cartoon of hypothalamus, at mammillary level base of the diencephalon

Why are't we discussing the Mammillary nuclei (medial, MM; lateral, LM) Of the hypothalamus?

These receive massive input from hippocampal formation and send unilateral, collateral projections to: anterior thalamus, midbrain tegmentum, and reticular nuclei associated with cerebellum
Unique: highly restricted inputs/outputs
Spatial memory/position of head in space.

See Lectures on Limbic system, hippocampal formation.

The tuberomammillary nucleus (TM)does have homeostatic functions related to arousal and sleep and will be discussed in the lecture on sleep.

Limbic System

E.J. Neafsey, Ph.D.
Loyola University Chicago Stritch School of Medicine

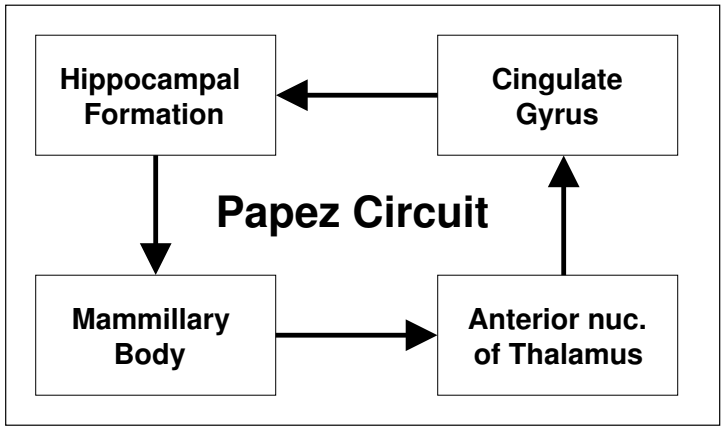
Outline

1. History and Overview of Limbic System Concept
2. Hippocampus
3. Septal nuclei
4. Amygdala
5. Olfactory system
6. Limbic Cortex

History of Limbic System Concept

Papez Circuit ➜ Limbic System

- In 1937 James Papez proposed a complex circuit in the brain as the *CNS substrate for emotional experience*



- *Current research does not support such a lofty role for this circuitry*

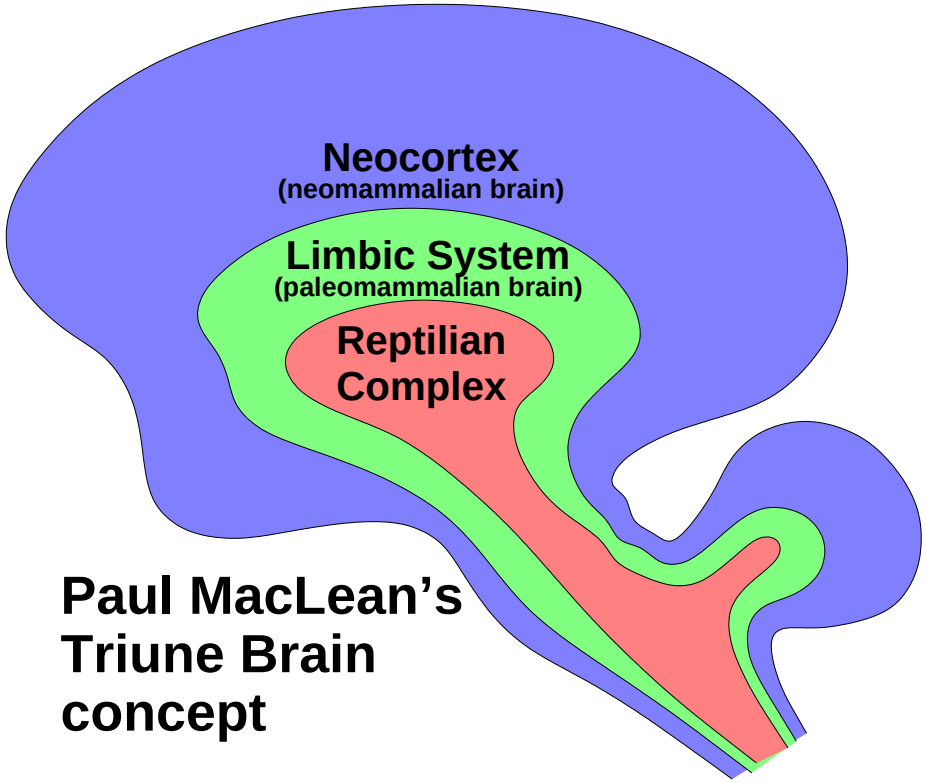
- Instead, much of the circuitry appears related to coding spatial location, at least in rats, where "place cells" are found in the hippocampus, "direction cells" in the subiculum, "grid cells" in the entorhinal cortex, and "head direction cells" in the mammillary bodies and anterior thalamus. A significant afferent input to this system comes from the vestibular nuclei, which is relayed to the mammillary bodies by the dorsal tegmental nucleus, located in the pons medial to the locus ceruleus.

- However, his idea laid groundwork for concept of a "limbic system"

Papez J. A proposed mechanism for emotion. *Arch Neurol Psychiatr* 38:725–743, 1937

MacLean's Triune Brain and the Limbic System

- In 1952 Paul MacLean proposed the term "limbic system" for the older, paleomammalian component of his "triune brain."



Today "Limbic System" refers to a set of brain structures that are important for: Self- and Species-Preservation Behaviors

Dr. DonCarlos referred to these behaviors as "motivated behaviors" in her discussion of the hypothalamus.

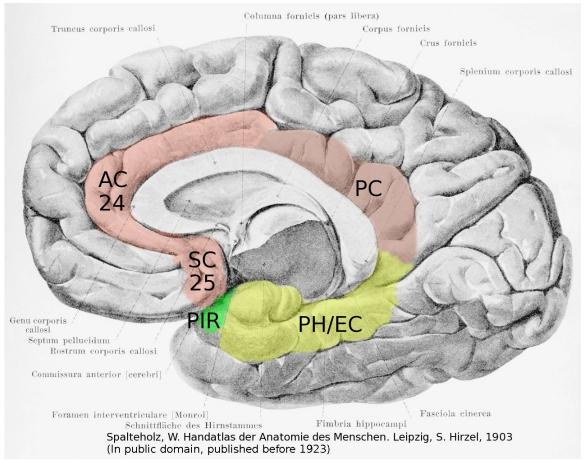
- Olfactory sensory processing
- Neuroendocrine and autonomic regulation
- Reproduction
- Aggression
- Memory
- Emotion and motivation

Limbic System Components

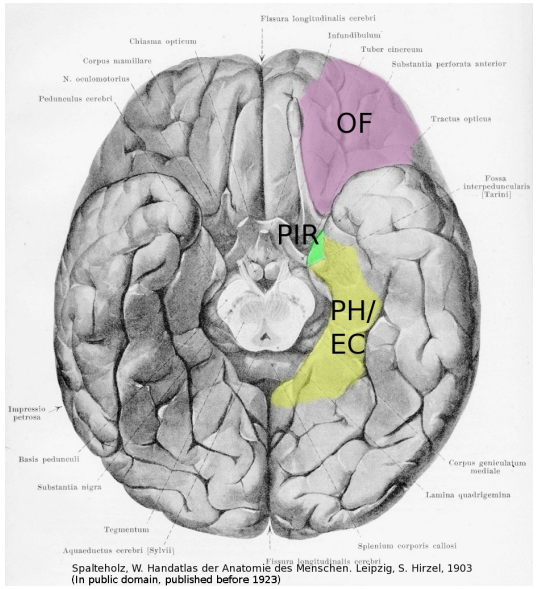
- Olfactory bulb
- Piriform olfactory cortex
- Hypothalamus
- Amygdala
- Hippocampal formation
- Anterior nucleus of thalamus
- Septal nuclei
- Limbic ring of neocortex (insular, orbitofrontal, subcallosal, anterior and posterior cingulate, and parahippocampal-entorhinal cortex)
- Ventral striatum (nucleus accumbens)

The limbic system used to be called the "rhinencephalon" (nose brain) because of its prominent olfactory inputs.

Limbic Ring of Cortex



Spalteholz, W. Handatlas der Anatomie des Menschen. Leipzig, S. Hirzel, 1903
(In public domain, published before 1923)



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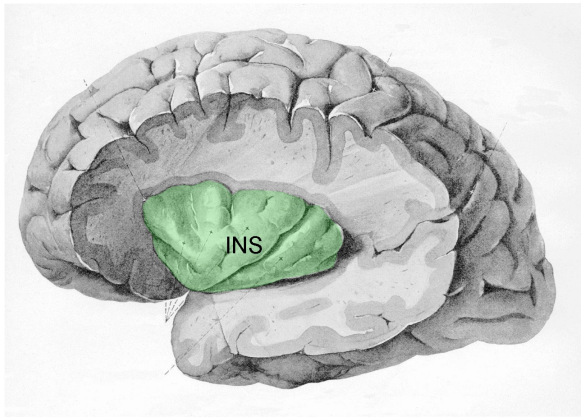
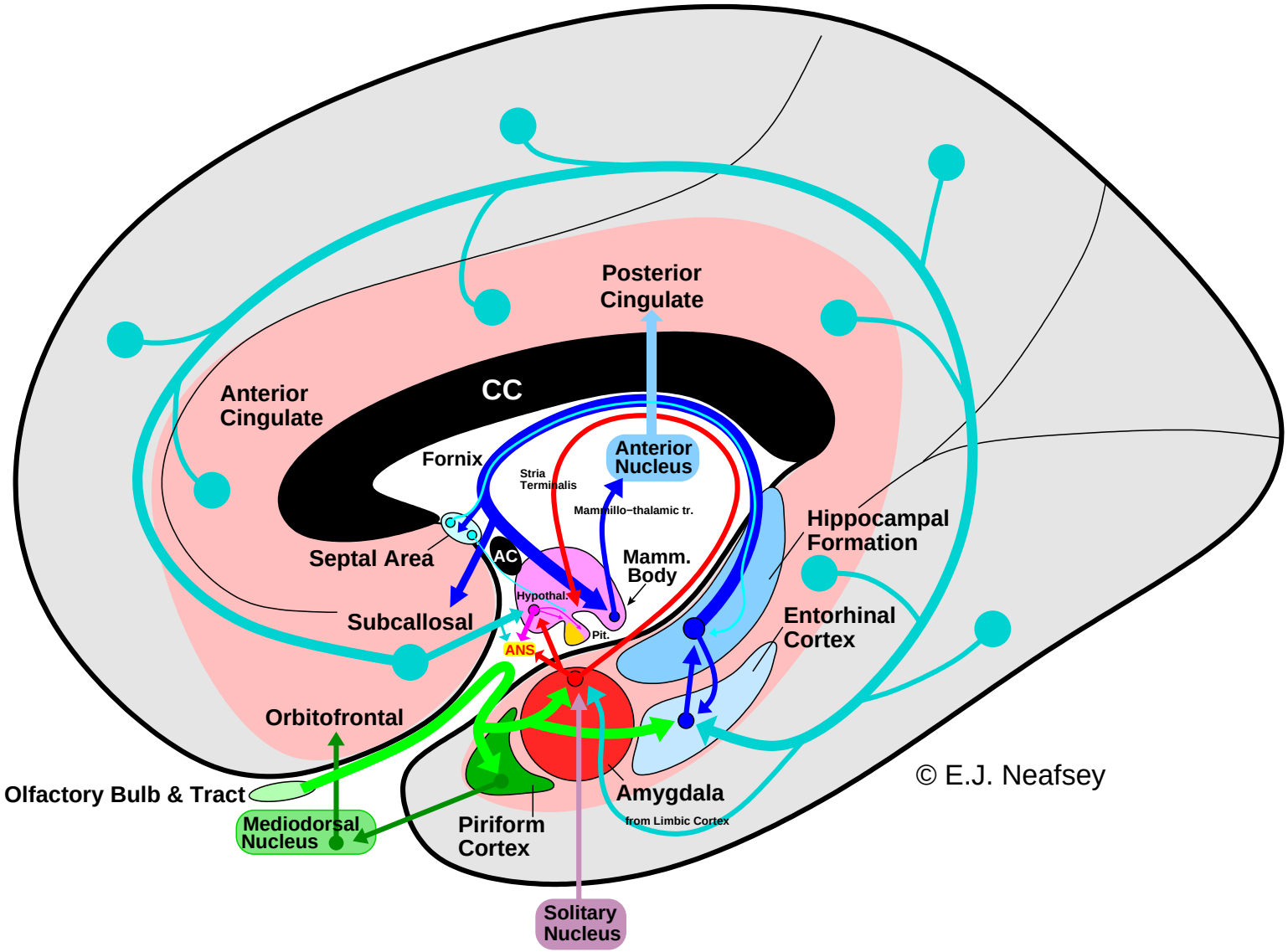


- "Limbic" means "pertaining to a border or margin" and refers to cortex and structures at medial edge or limit of the cerebral hemisphere.

- Broca termed this cortex the "Limbic Lobe." It is composed of the subcallosal (SC), anterior cingulate (AC), posterior cingulate (PC), and parahippocampal-entorhinal (PH/EC) regions of cortex; the more lateral orbitofrontal cortex (OF) and insular cortex are also functionally part of the limbic cortex.

Limbic System Diagram

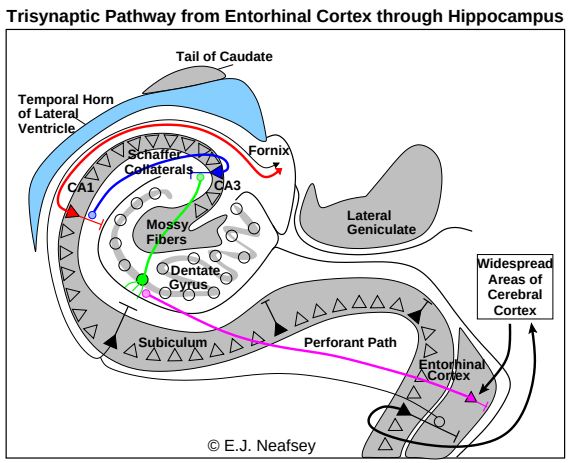
medial view of hemisphere

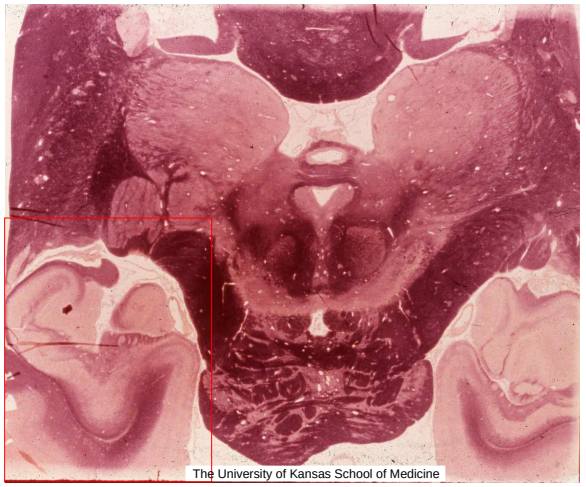


Note convergence of limbic system on hypothalamus, which controls ANS, pituitary, and "self- and species-preservation behaviors" such as feeding, drinking, mating, reproduction, aggression, etc.

(Can you find the Papez circuit?)

Hippocampal Formation





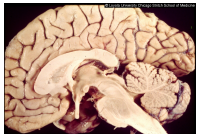
- Allocortical (three layer) cortex folded under medial aspect of temporal lobe where it forms medial wall of lateral ventricle

- Components
  - *Subiculum (adjacent to the entorhinal cortex)*
  - *CA1-CA4 pyramidal cell regions (CA = cornu ammonis)*
  - *Dentate gyrus (granule cells)*


Ammon

- Trisynaptic pathway: entorhinal → dentate gyrus → CA3 → CA1

Hippocampal Connections



Hippocampal Formation:

Entorhinal cortex relays information from wide areas of *cerebral cortex* into hippocampus; this input begins the "trisynaptic circuit."

Hippocampus also projects back to entorhinal cortex.

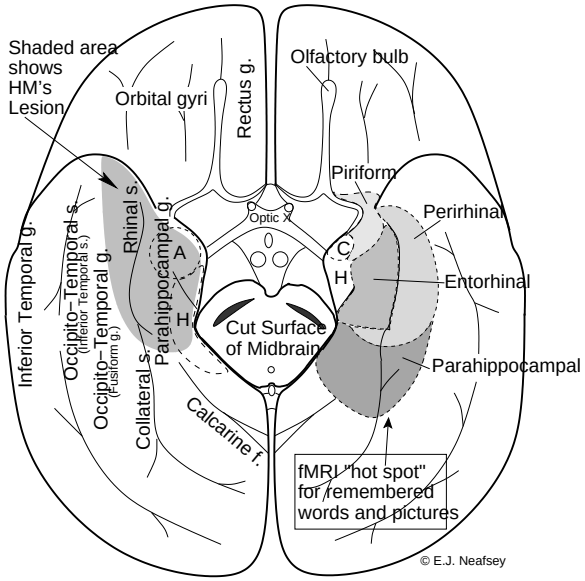
Fornix carries output of hippocampus to *mammillary body*, *septal nuclei*, and *subcallosal cortex*.

Hippocampal Functions I: Patient HM Permanent Anterograde Amnesia

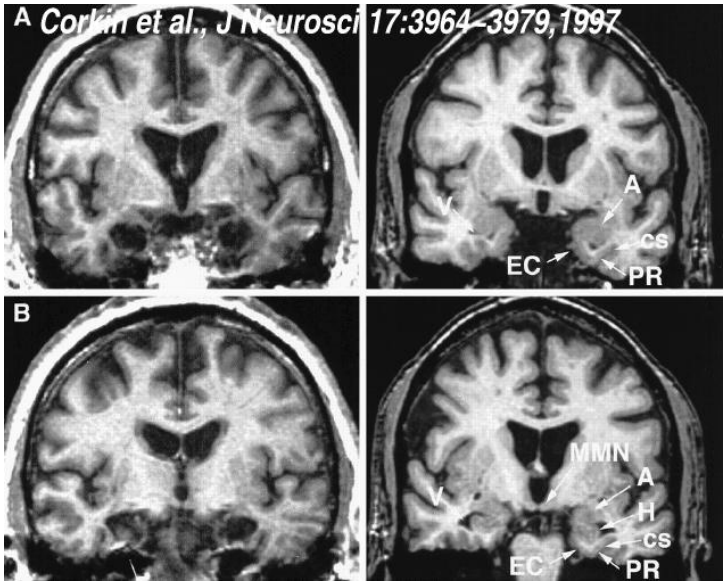
Henry Molaison
1926–2008

HM underwent bilateral medial temporal lobectomy in 1953 to treat complex partial seizures. After surgery he suffered from **permanent anterograde amnesia**, being unable to form any new memories. His amnesia related to **declarative memory**, which refers to statements such as "I had cereal for breakfast this morning." It did not affect his **procedural memory**, which means that if he practiced some skill his performance improved, even if he didn't remember practicing. The amnesia appears to be due to damage to both the hippocampal formation and the adjacent entorhinal/parahippocampal cortex.

HM also suffered from **some retrograde amnesia** (loss of old memories) covering the 11 years prior to his surgery.



HM's lesion was BILATERAL.

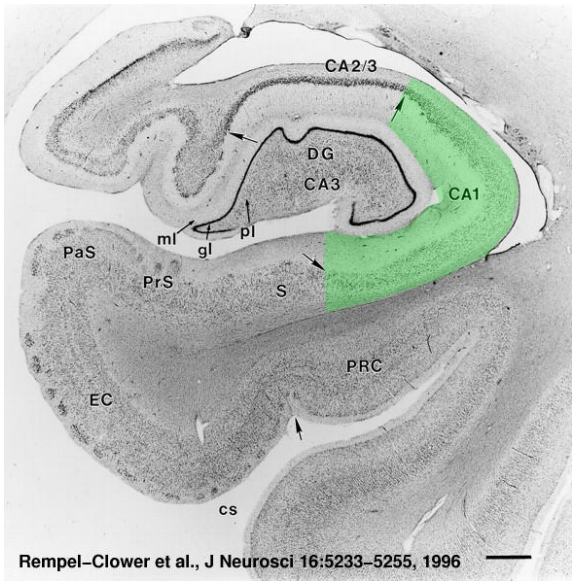


HM's MRI Normal MRI

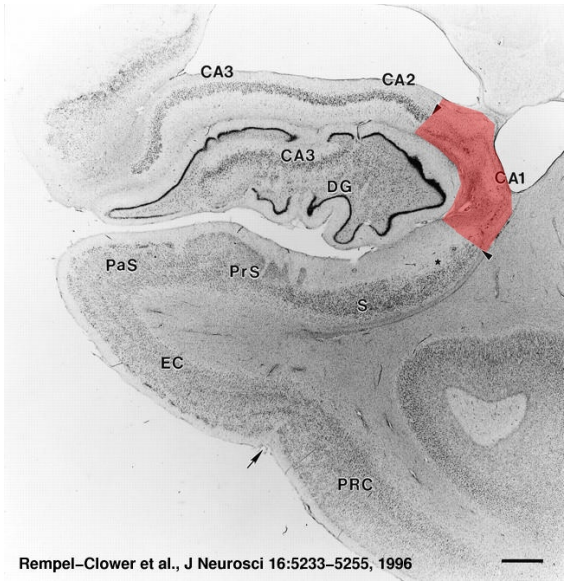
- Scoville WB and Milner B. Loss of recent memory after bilateral hippocampal lesions. *J Neurol Psychiat* 20:11-21, 1957.
- Corkin S. Lasting consequences of bilateral medial temporal lobectomy: clinical course and experimental findings in H.M. *Sem Neurol* 4: 249-259, 1984.
- LINK: Clive (*The Mind*)

Hippocampal Functions I: Patient GD Impaired Memory After Cardiac Arrest

Short term global brain ischemia, such as that occurring during cardiac arrest, can cause selective hippocampal CA1 damage in humans that correlates with severe anterograde and minor retrograde amnesia that are less severe than HM's but still significant. Many animal studies have documented CA1's high vulnerability to ischemia.



Normal hippocampus



GD's CA1 damage after ischemia

- Two figures above modified from ones in Rempel-Clower NL, Zola SM, Squire LR, and Amaral DG. Three cases of enduring memory impairment after bilateral damage limited to the hippocampal formation. *J Neurosci* 16:5233–5255, 1996.

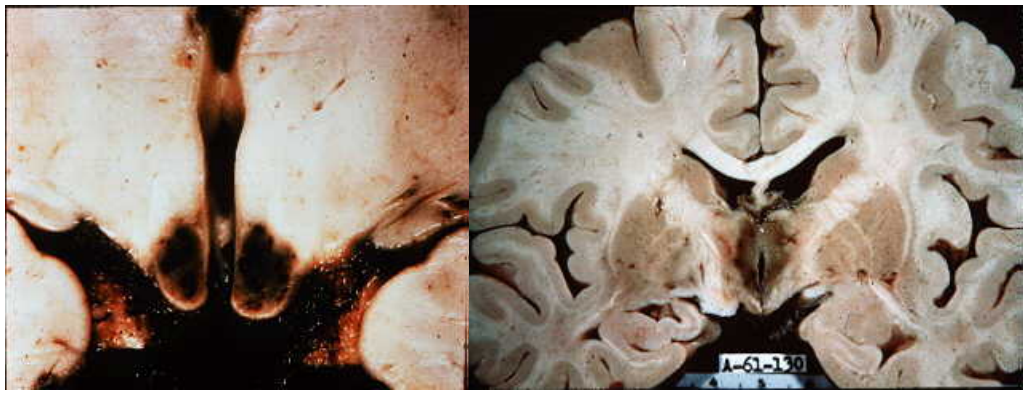
Hippocampal Functions I: Patient Clive
"Now I am awake for the very first time."

The Abyss: Music and Amnesia by Oliver Sacks (*The New Yorker* (9/25/2007)

Movie about Clive from TV series *The Mind*

Hippocampal Functions I: Wernicke-Korsakoff Syndrome

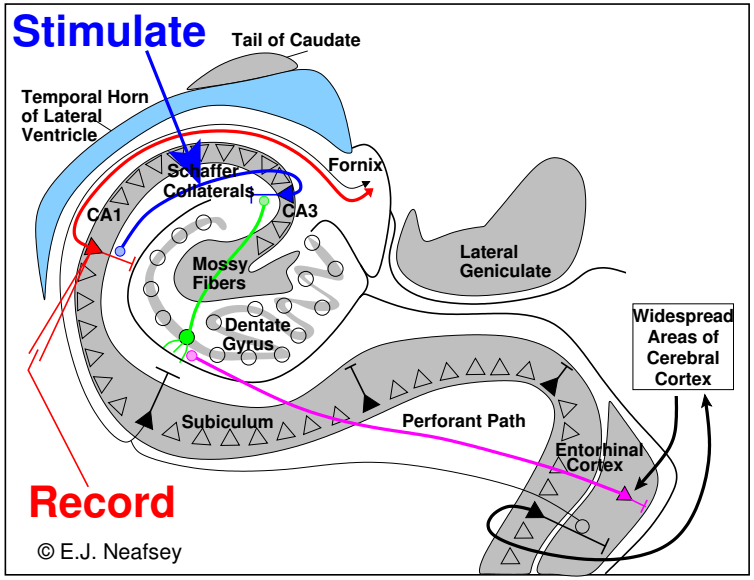
(http://www.ninds.nih.gov/health_and_medical_disorders/wernicke-korsakoff.htm)

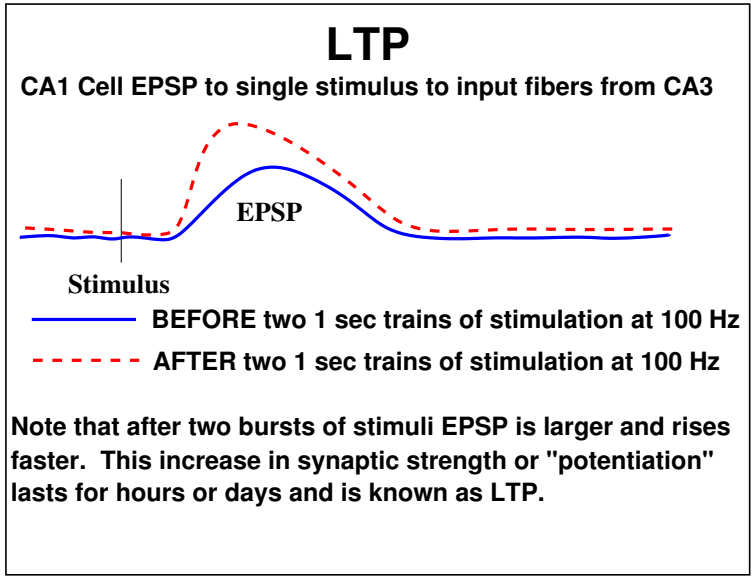


- *Wernicke's encephalopathy* is a degenerative brain disorder caused by the lack of thiamine (vitamin B1). It particularly affects brain regions near the third ventricle, including the mediodorsal nucleus of the thalamus and the mammillary bodies in the hypothalamus. It may result from alcohol abuse, dietary deficiencies, prolonged vomiting, eating disorders, or the effects of chemotherapy. Symptoms include mental confusion, vision impairment, stupor, coma, hypothermia, hypotension, and ataxia.
- *Korsakoff's amnesic syndrome*—a memory disorder—also results from a deficiency of thiamine, and is associated with alcoholism. The heart, vascular, and nervous system are involved. Symptoms include *amnesia*, *confabulation*, attention deficit, disorientation, and vision impairment. The main features of Korsakoff's amnesic syndrome are the impairments in acquiring new information or establishing new memories, and in retrieving previous memories.
- Wernicke's encephalopathy represents the "acute" phase of the disorder, and Korsakoff's amnesic syndrome represents the "chronic" phase.
- Treatment involves replacement of thiamine and providing proper nutrition and hydration. Most symptoms can be reversed if detected and treated promptly. However, improvement in memory function is slow and usually incomplete. Without treatment, these disorders can be disabling and life-threatening.

Hippocampal Functions I: Memory and LTP

Long-term potentiation (LTP) – a memory mechanism?





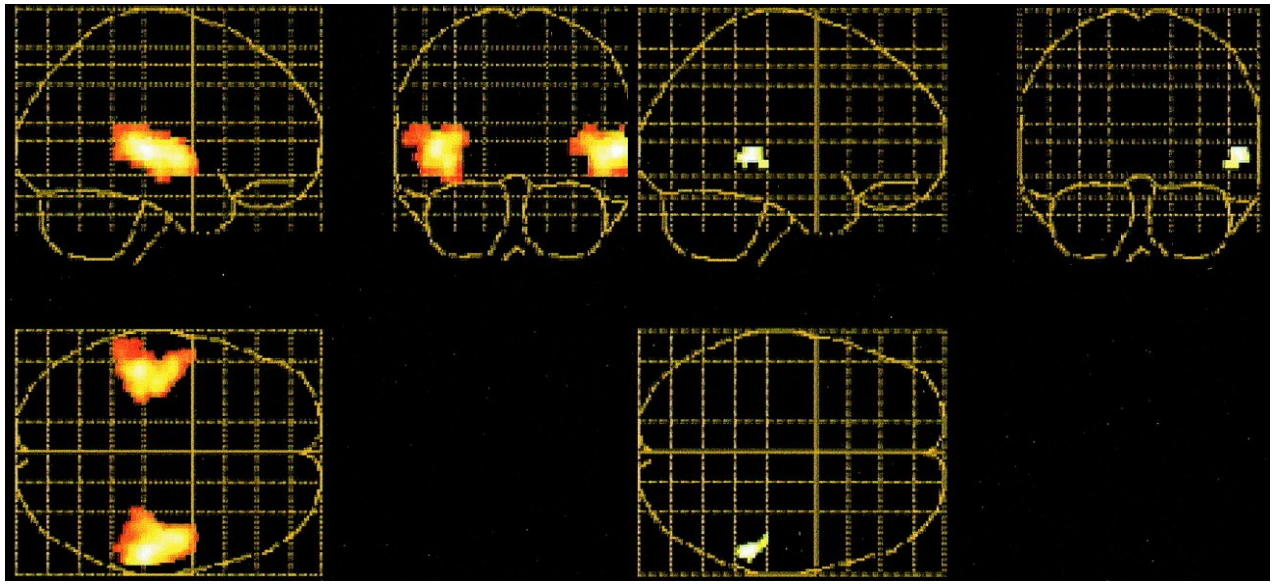
- *Blocking the N-methyl-d-aspartate (NMDA) type of glutamate receptor in hippocampus impairs both LTP and learning*
  - NMDA receptors activate intracellular signaling pathways that result in an increased number of AMPA type glutamate receptors in the post-synaptic cell synaptic region, thereby increasing the postsynaptic response to glutamate. This is the explanation of LTP.
  - New AMPA receptors synthesized in the cell body preferentially end up in the synapses activated by stimulation because such synapses have a molecular **tag** that flags the receptors down as they move down the dendrite.

Hippocampal Functions I: Where are long-term memories stored?

Not in the hippocampus or other parts of the medial temporal lobe!

Patients with damage limited mainly to the medial temporal lobe perform normally on tests of remote autobiographical memory, but patients with medial temporal lobe damage plus significant additional damage to neocortex were severely impaired in recollecting remote autobiographical events, which depends on the integrity of widely distributed neocortical areas, especially the frontal, lateral temporal, and occipital lobes.
(Bayley PJ, Gold JJ, Hopkins RO, Squire LR. The neuroanatomy of remote memory. *Neuron* 46:799-810, 2005)

Rather, long-term memories are stored in the neocortex, including the various sensory areas that initially "encoded" the experience



Encode. Retrieve.

- Overlapping activations in auditory responsive cortex during encoding (left) and retrieval (right) of auditory information

  (L. Nyberg, R. Habib, A. R. McIntosh, and E. Tulving. Reactivation of encoding-related brain activity during memory retrieval. *PNAS* 97:11120 - 11124, 2000)

Hippocampal Functions I: Kayla's Impaired Long-Term "Cortical" Memory After Concussion

Concussions can also cause significant retrograde amnesia that affects established, long-term memories, as seen in the story of Kayla (Sports Illustrated, Jan. 19, 2009.

Sports Illustrated

Helping Kayla Remember

Views
224
Comments
7

- 08:24 AM ET 01.13
- **Share**

At first, Kayla Hutcheson figured she'd just busted up her nose. No big deal, right? After all Kayla, a freshman power forward at Walla Walla (Wash.) Community College, had spent much of her life playing through sprained ankles and stitched-up chins. This is a girl who played *football* through the eighth grade. As a tight end. Against boys. A little blood didn't scare her.

So when she banged face-first into teammate Jeni Gabriel on a full-court press drill during practice in October, she tried to walk it off. Even persuaded her coach, Bobbi Hazeltine, to let her run sprints with the rest of the team at the end of practice. "Her fastest time of the year too," says Hazeltine, who clocks such things. (There's a reason Walla Walla was 9–2 at week's end.)

But that night, when Kayla got back to the apartment she shares with three teammates, she started feeling all kinds of wrong. Not only did her nose throb -- turns out she'd fractured it -- but her arms also started to go numb. Then she became disoriented, her mind fogging up like an '86 Civic on a cold, rainy day.

Kayla's roommates rushed her to the hospital, where she was given a CT scan and an MRI. Grade 3 concussion with a little short-term memory loss, a doctor said. Take her home and let her rest.

The thing about concussions is, doctors can't immediately predict their long-term effects. When football players get them there's a fun, familiar phrase -- "getting your bell rung" -- though there's nothing fun about the amnesia and dementia that may result.

In Kayla's case, she couldn't remember anything from before the accident. Her dad, Bart, drove in from Kimberly, Idaho. He showed her home movies. He knelt and stared in her eyes. Nothing. "I had to walk into that apartment and introduce myself to my own daughter," Bart says.

But instead of taking Kayla back with him, Bart decided to leave her in Walla Walla. At home she'd just sit in front of the TV while he and her stepmother were at work. (Kayla's mom and Bart divorced when she was five.) At school she had a family around her all the time. "At that point those girls and her coach were the only people she knew," he says. "I didn't want to take her away from them."

Teams are often referred to as families, and Kayla's roommates -- fellow freshmen Jaimie Berghammer, Jill Haney and Nancy Johnson -- did as much as any sisters could. They took turns watching over her, walking her to class and helping her with her schoolwork. "It was like taking care of a kid," says Haney. Indeed, for a few weeks Kayla spoke and acted like a toddler. She had no idea what a banana was; a toaster

flummoxed her. Cookies, though, she loved. "We had to hide them all because she wouldn't eat anything else," Johnson says.

As Kayla relearned life, she relearned basketball. You might not think that's a priority, but it's the one thing she quickly responded to. At practices she sat in a lawn chair, giving Hazeltine a thumbs-up whenever she understood something. She didn't recall the rules of the game, but when Hazeltine first handed a ball to her and told her to shoot, she raised it above her head -- Kayla always had a funky shooting motion -- and swished the shot. "It was like that was one part of her brain that still worked," says the coach.

As the weeks passed, Kayla's easygoing personality returned ("identical to before," says Haney) as well as her facility with language and physical skills. In early December she was cleared to return to noncontact practice, and she spent hours relearning the Warriors' six offenses and 28 set plays. Still, Kayla could only recall snippets of her life. A family trip to Six Flags. Listening to a dance song in the car. She went home for the holidays, but even "meeting" relatives didn't trigger her memory.

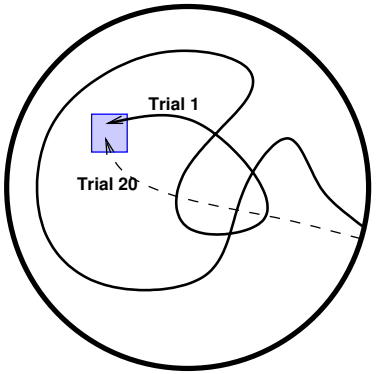
It hasn't gotten much better since. Kayla's frustrated and hasn't had a good night's sleep in months. Sometimes she cries. Other times she dreads going out, lest she meet another friend who is a stranger. "I feel like my life's like a puzzle," she says, "and I have to put it together."

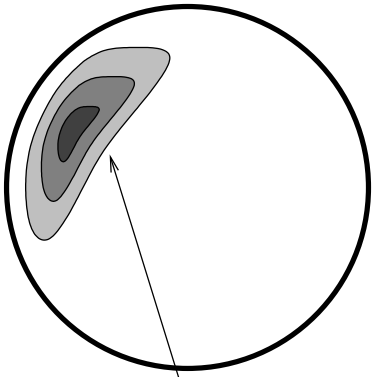
If that's so, she filled in one of the biggest pieces last week. Her doctor, Robert Carmody, cleared her to play, deeming it "therapeutic." Her dad gave the go-ahead too, figuring the benefits outweighed the potential risks. So on Jan. 7, Kayla suited up for her first college basketball game. Sure, she was nervous, and "a little scared." She blew an early layup, almost panicked when an elbow glanced her nose. But she ended up scoring 14 points in 13 minutes, even helping out once on the press.

After the buzzer, accepting her teammates' hugs, I saw on her face a true smile for the first time all day. The game had come back to her. As for the rest of her life, Kayla is still waiting.

-- Chris Ballard

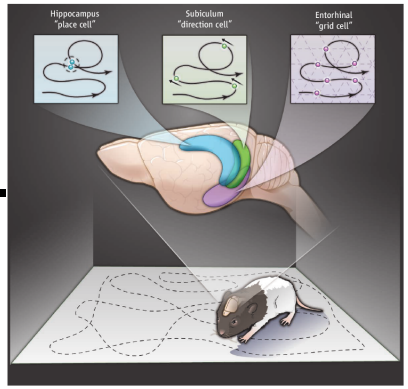
Hippocampal Functions II: Place and Direction (Where's my car?)



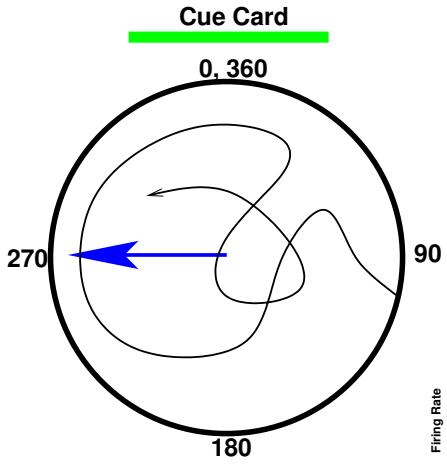


Morris Water Maze:
Rat learns to swim to small platform hidden under surface of water.
Rats with bilateral hippocampal lesions cannot learn the location of the platform.

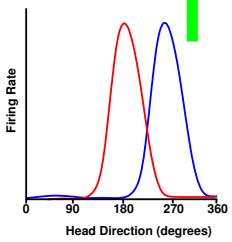
Hippocampal and entorhinal cortex cells have "place fields," defined as the region in the chamber where the cell fires action potentials.

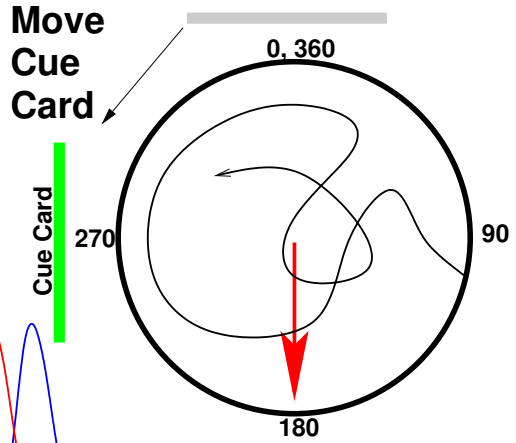


Science 328:1487, 2010



(Based on Sharp et al., Trends Neurosci. 24:289–294, 2001)

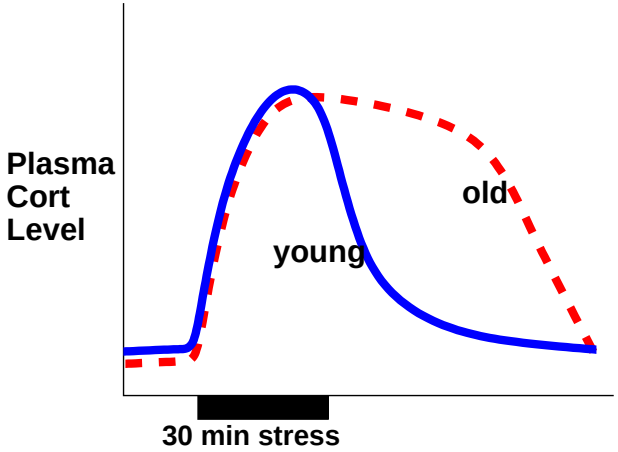




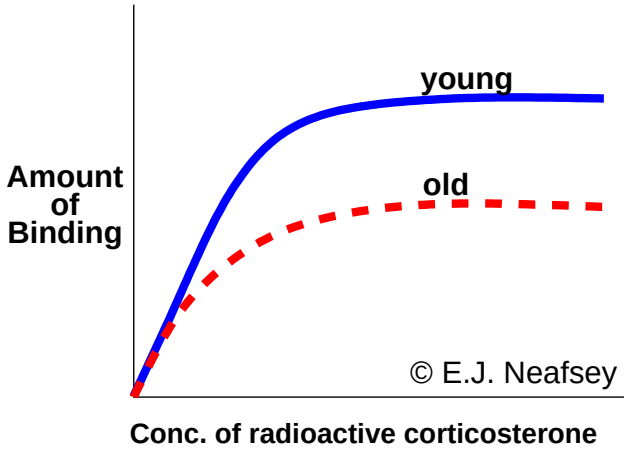
Head direction cells in mammillary bodies, anterior thalamic nucleus, and entorhinal cortex rely on landmarks such as the cue card to define their preferred head direction. If landmark shifts, cells change their preferred direction. This is basis of "sense of direction."

Hippocampal Functions III: Endocrine Regulation

- **Glucocorticoid hormone (cortisol) control**
  - *Hippocampus contains* ***highest concentration of glucocorticoid receptors in brain*** *and exerts an inhibitory control over plasma corticosteroid levels*
  - ***Aging*** *leads to* ***loss of hippocampal neurons and their glucocorticoid receptors****, explaining why aged animals cannot promptly terminate stress-related secretion of corticosteroids once stress has ended*



Old rats or those with hippocampal lesions have a prolonged corticosteroid response to restraint stress.



Binding of radioactive steroid hormone is reduced in the hippocampus of old rats due to loss of corticosterone receptors.

Hippocampal Functions IV: Neurogenesis

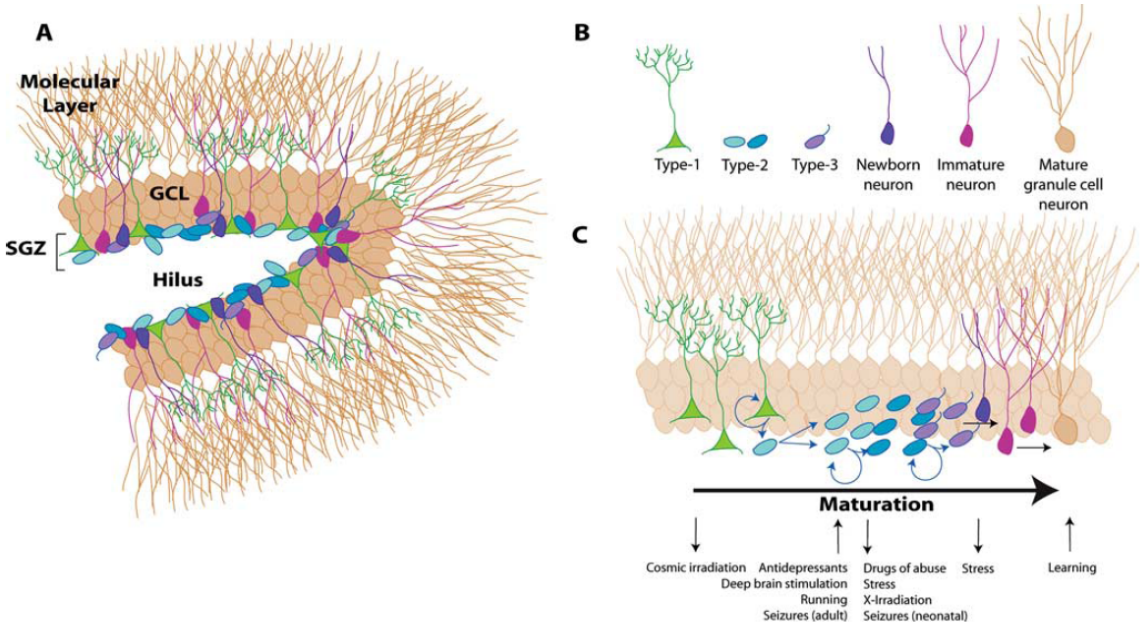
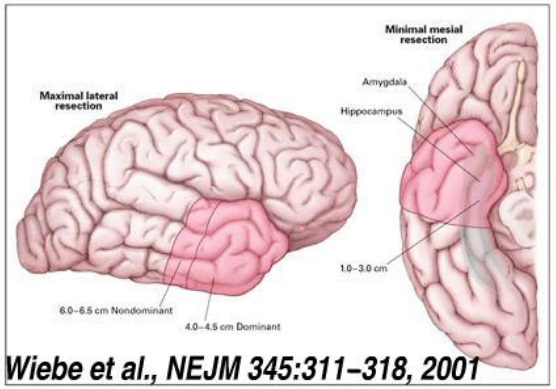
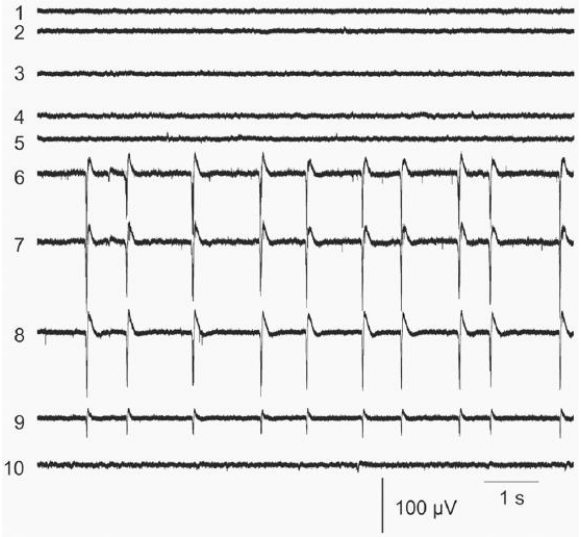


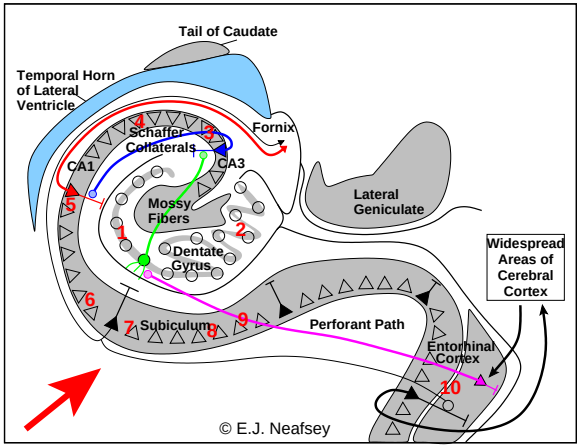
Figure 1. Stages of adult hippocampal neurogenesis. ***A***, The SGZ straddles the border of the hippocampal dentate gyrus granule cell layer (GCL) and hilus. The neurogenic SGZ contains cells at various stages of neurogenesis, which are individually shown in ***B***. ***C***, Cells in discrete stages of maturation are differentially influenced by pharmacological and physiological stimuli. This list is not meant to be comprehensive but rather highlight stimuli discussed in this review. Figure by Jessica L. Ables.

- **Neurogenesis**
  - *Hippocampus is one of only a few sites in the brain where* ***new neurons are continuously produced throughout life.***
  - *New granule cell neurons in the dentate gyrus are generated from hippocampal stem cells (HSCs) in the subgranular zone (SGZ) immediately beneath the dentate gyrus.*
  - *The function(s) of hippocampal neurogenesis is/are currently unknown, but it may contribute to a variety of neurological and psychiatric disorders, including learning, depression, and schizophrenia.*

Complex Partial Seizures Often Arise in Hippocampal Formation



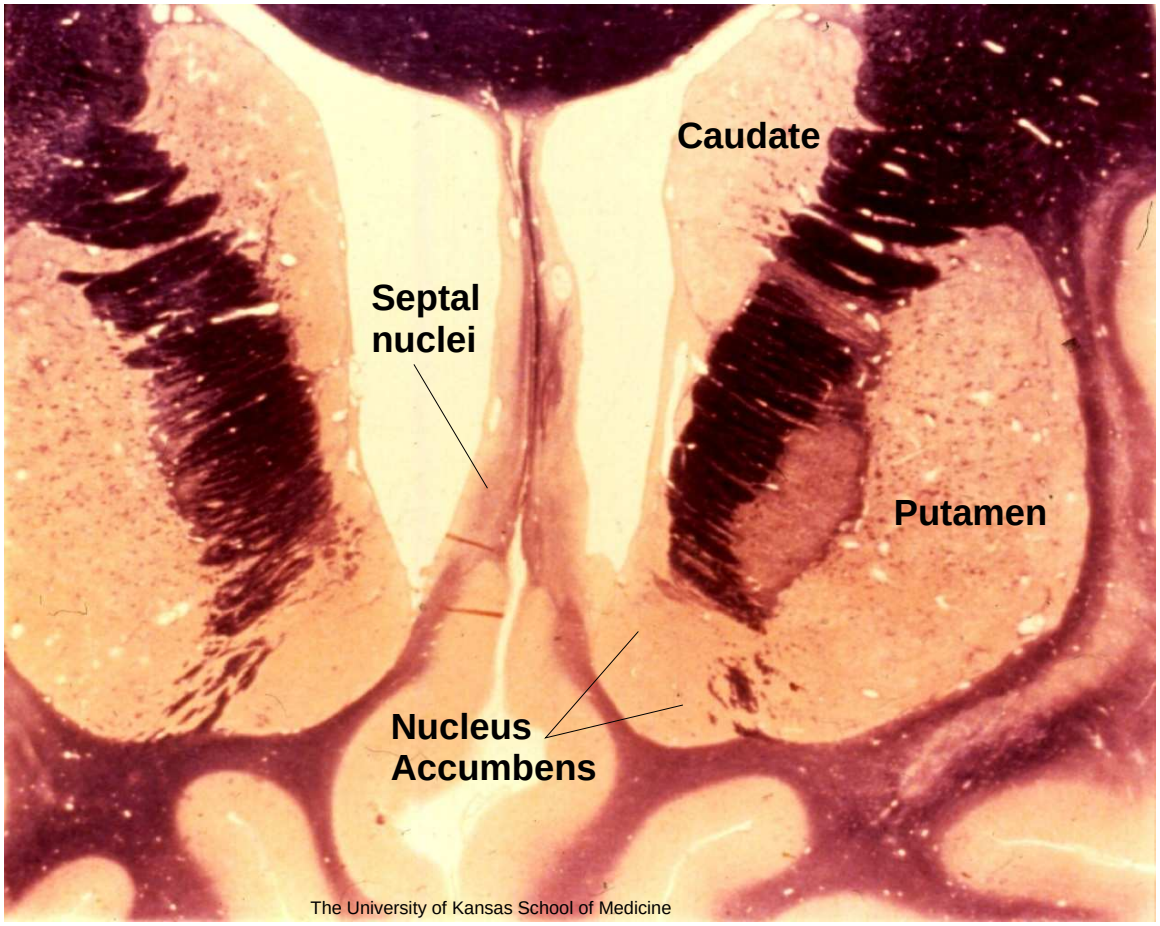




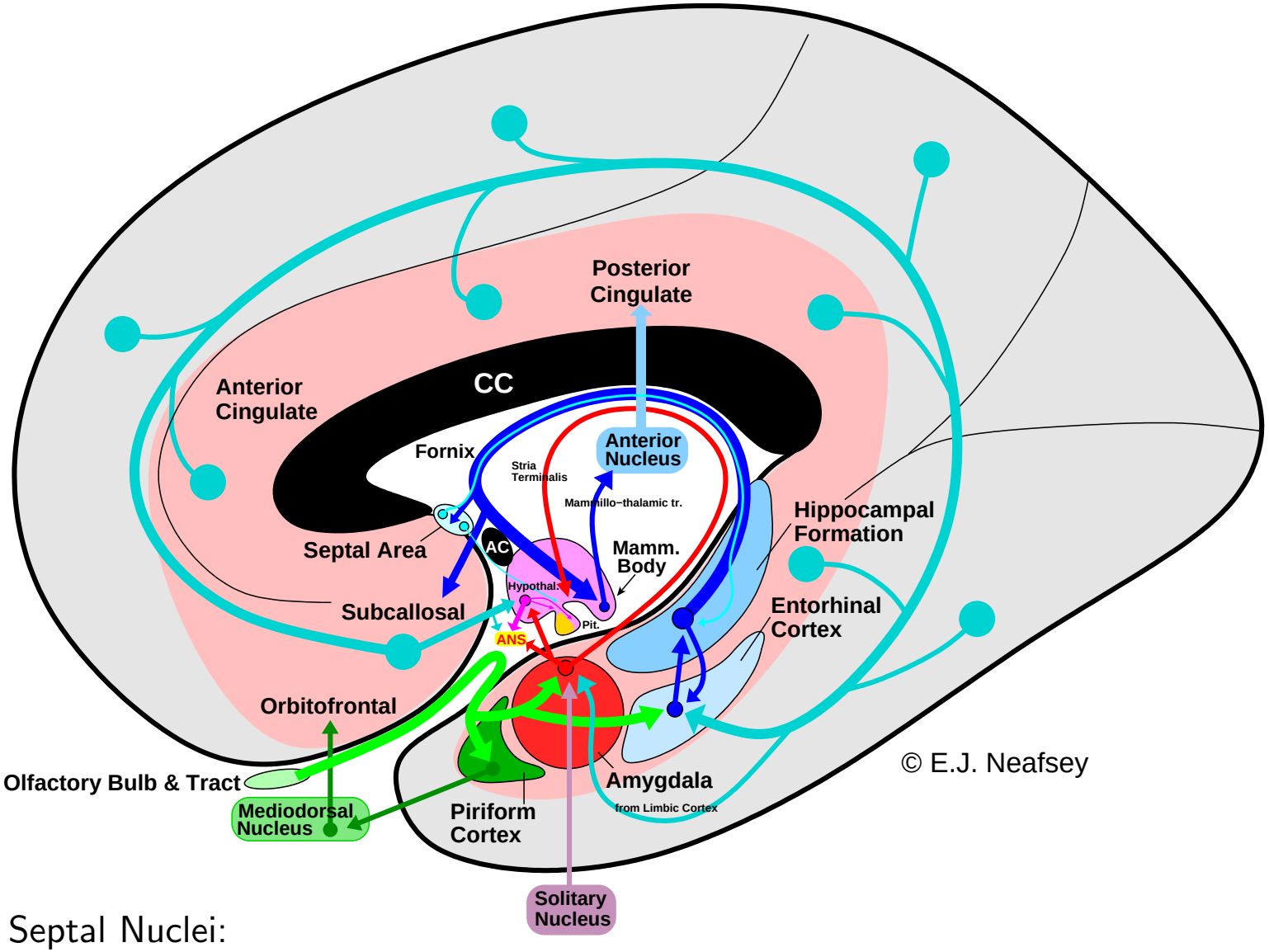
Source of epileptiform interictal spikes in EEG is subiculum region of the hippocampal formation. No spiking is seen in dentate gyrus, CA fields, or entorhinal cortex.

Adapted from Cohen I, Navarro V, Clemenceau S, Baulac M, and Miles R. On the origin of interictal activity in human temporal lobe epilepsy in vitro. *Science* 298:1418–1421, 2002.

Septal Nuclei



Septal Nuclei Connections



Septal Nuclei:

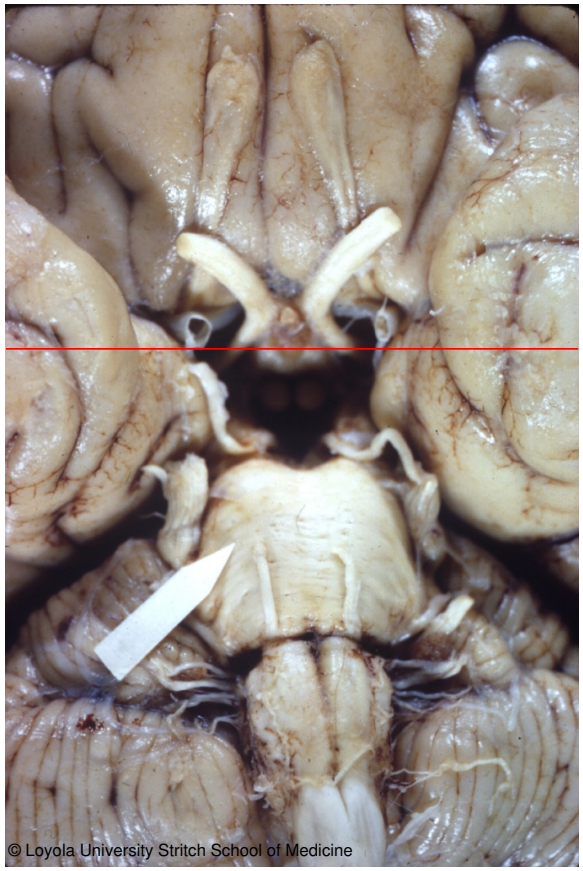
Fornix brings output of hippocampal formation to *septal nuclei*.

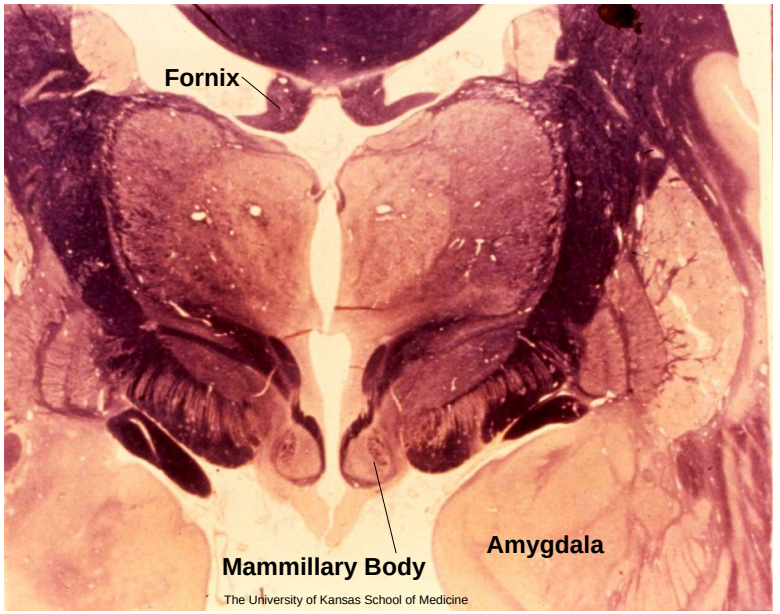
Septal nuclei project back to hippocampus via fornix; this *cholinergic pathway* is thought to enhance memory formation and shows degeneration very early in Alzheimer's disease. Aricept (donepezil hydrochloride) and other reversible inhibitors of acetylecholinesterase are used to treat AD.

In addition, *GnRH neurons in septal nuclei* project to *median eminence of hypothalamus* and regulate secretion of gonadal hormones and related behaviors.

Amygdala

- Large nuclear group located in rostral medial portion of temporal lobe *beneath uncus*





Section through amygdala at level of red line in picture at left.

Amygdala Functions

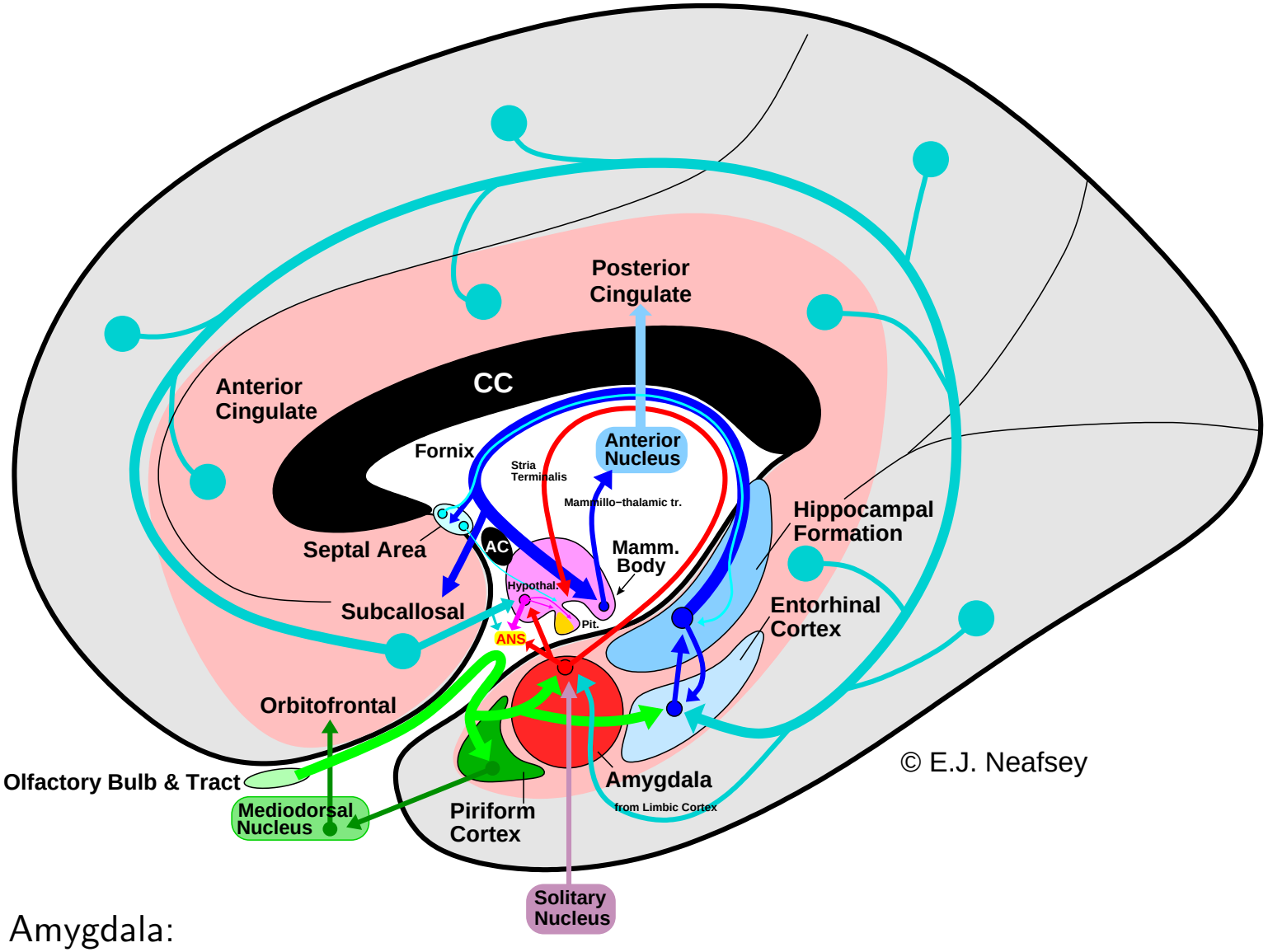
- Amygdala sends **stria terminalis** pathway to **ventromedial nucleus of hypothalamus** and also sends its own direct connections to ANS.

- Relates environmental stimuli to coordinated behavioral, autonomic, and endocrine responses seen in self-preservation or species-preservation behaviors:
  - *Feeding and drinking*
  - *Agonistic (fighting) behavior*
  - *Mating*
  - *Maternal care*
  - *Responses to physical or emotional stressors*

- Lesions of amygdala reduce endocrine, autonomic, and behavioral responses during **emotional stress**.

- In humans bilateral amygdala lesions selectively eliminate **fear** emotional responses and, if they occur in childhood, impair the ability to recognize facial expressions of fear.

Amygdala Connections



Amygdala:

Note *olfactory inputs* as well as *GVA and SVA (taste) inputs* from solitary nucleus.
Note also inputs from the *limbic cortex*.
Amygdala sends this information to the *hypothalamus*, which controls the ANS and pituitary;
in addition, amygdala also has its own *direct connections to ANS*.

Kluver-Bucy Syndrome

Behavioral changes first described in *monkeys with bilateral lesions of the temporal lobe*, including the amygdala, temporal neocortex, olfactory cortex, and hippocampus*

- **Visual agnosia** ("psychic blindness"): all objects, living or not, familiar or unfamiliar, food or feces, are approached and compulsively examined, often orally
- **Oral tendencies**: everything is compulsively put into the mouth, licked, chewed, and smelled
- **Loss of emotions of fear and anger**: animals are "docile"
- **Hypersexuality**: male monkeys display frequent erections and copulate with other monkeys (male or female) whenever possible

*Kluver H, Bucy PC. Preliminary analysis of functions of the temporal lobes in monkeys. *Arch Neurol Psychiatry* 42:979-1000, 1939.

Cats with Bilateral Temporal Lobe Lesions

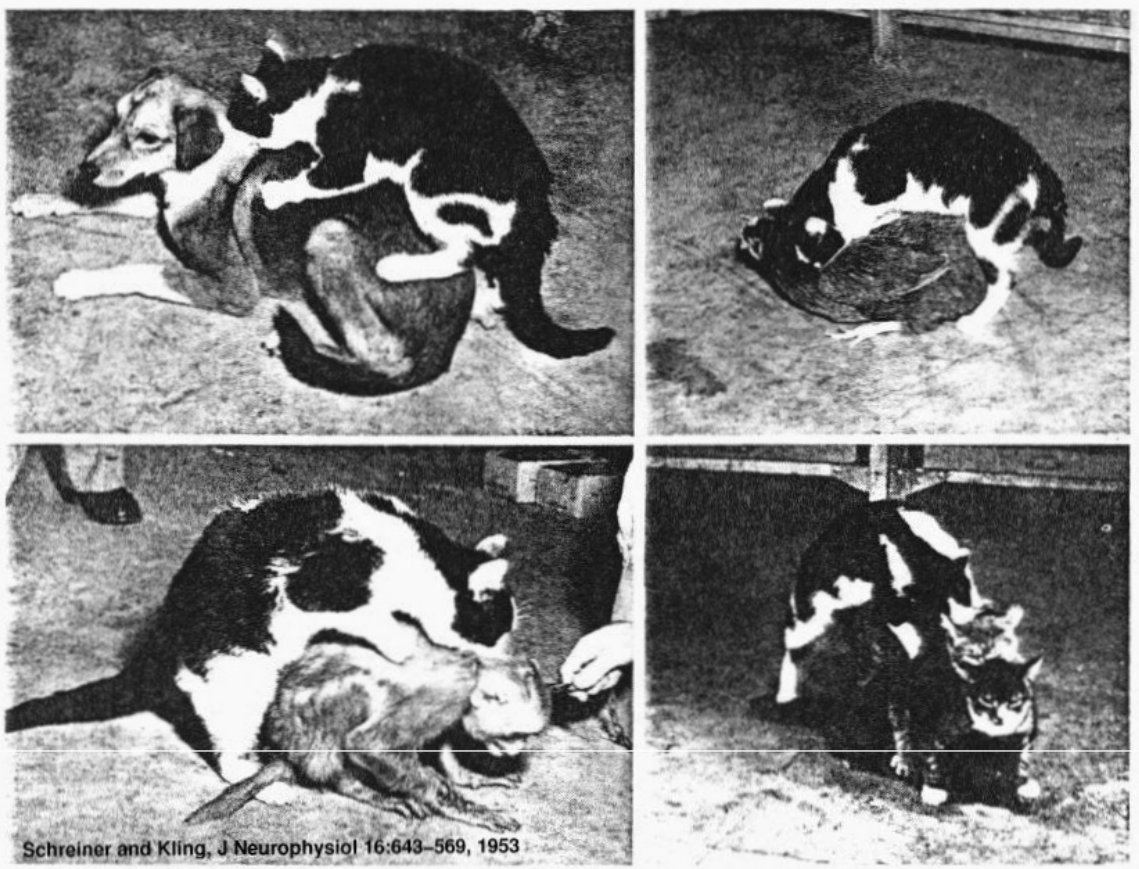


FIG. 5. Illustrations of various phases of sexual activity displayed by male preparations. Photos on right side were prepared from 16 mm. color film. Lower right photo illustrates attempts at "tandem copulation" among four male preparations. See text for additional descriptions.

An additional surgery not involving the brain abolished this behavior.
What was that treatment? What does that mean?
Schreiner, L and Kling, A. 1953. Behavioral changes following rhinencephalic injury in cat. *J Neurophysiol* 16:643-569.

See civil commitment of sex offenders and Europeans Debate Castration of Sex Offenders for discussions related to this topic.

Olfactory Receptors

- Approximately 25 million olfactory receptor cells are located in olfactory epithelium in roof of nasal cavity

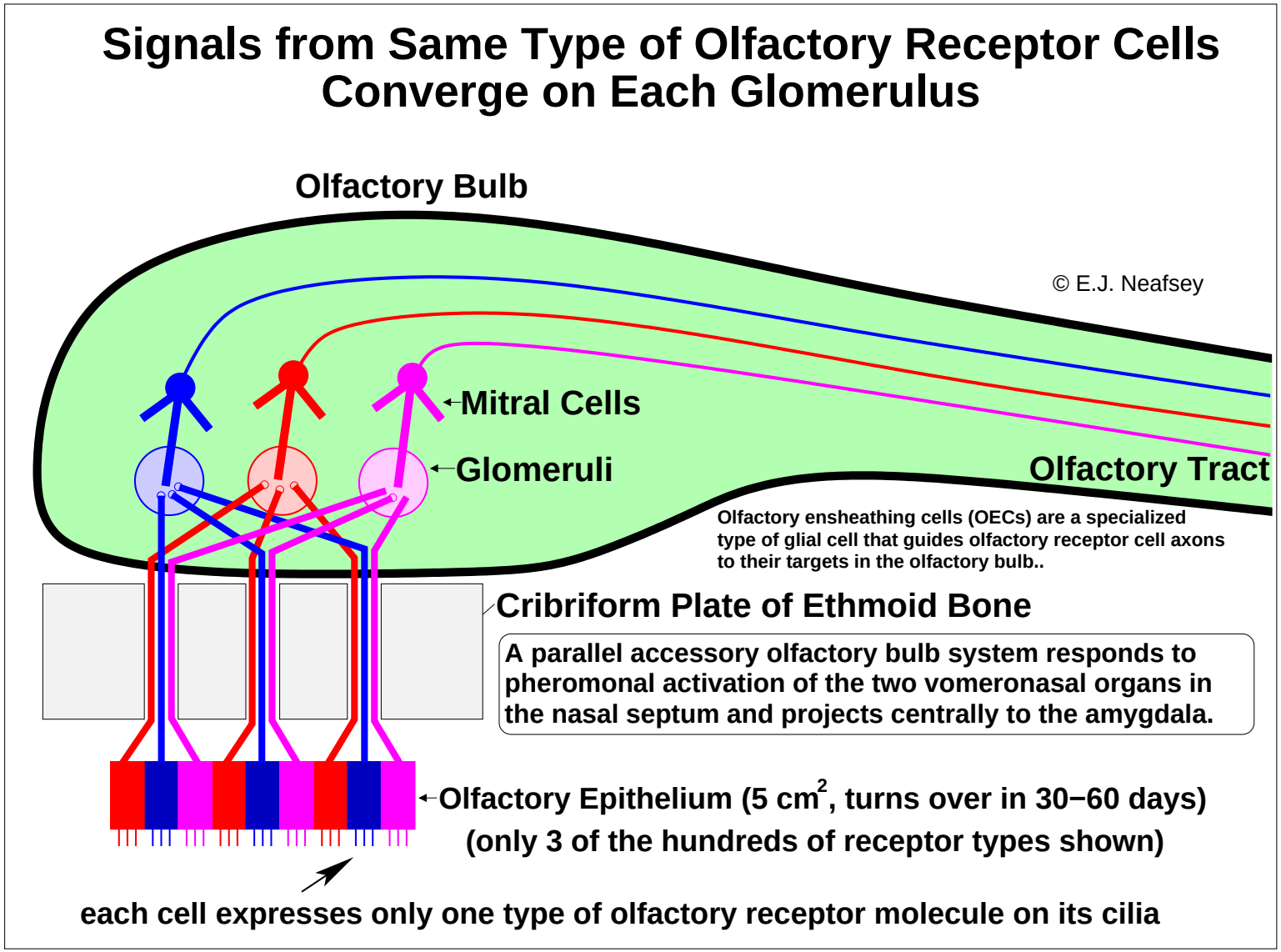
- Each receptor cell responds preferentially to odor molecules of only one type via highly specific receptor molecules on its surface cilia

- **Each receptor cell expresses only one of the hundreds of different olfactory receptor molecules encoded by the large olfactory receptor gene family (300 genes, about 1.5% of the 20,000 genes in the human genome!)**

- All receptor cells send their axons through cribriform plate of ethmoid bone into olfactory bulb located on orbital surface of frontal lobe

- Within olfactory bulb each glomerulus (a specialized region of synaptic contacts between receptor axon terminals and dendrites of mitral cells of olfactory bulb) receives axons from olfactory receptor cells expressing just one olfactory receptor type

Olfactory Epithelium and Bulb



Olfactory Bulb: Cajal

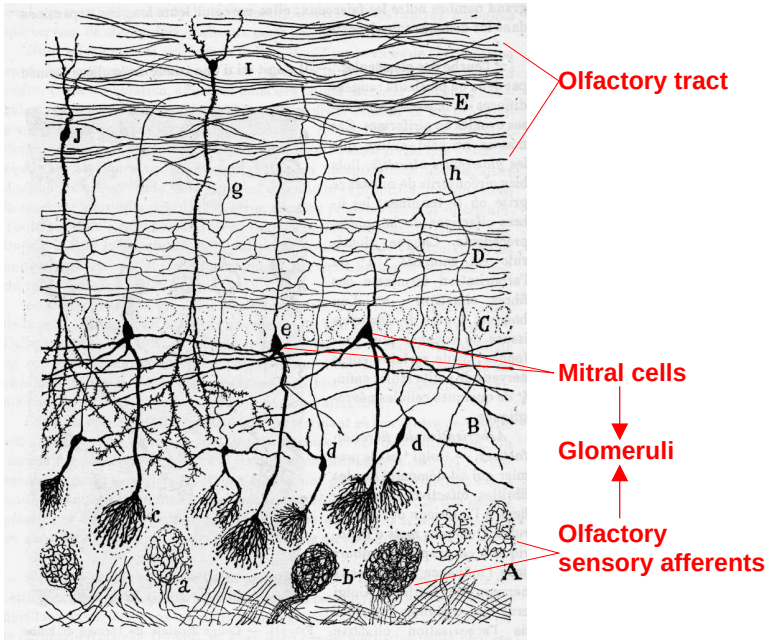
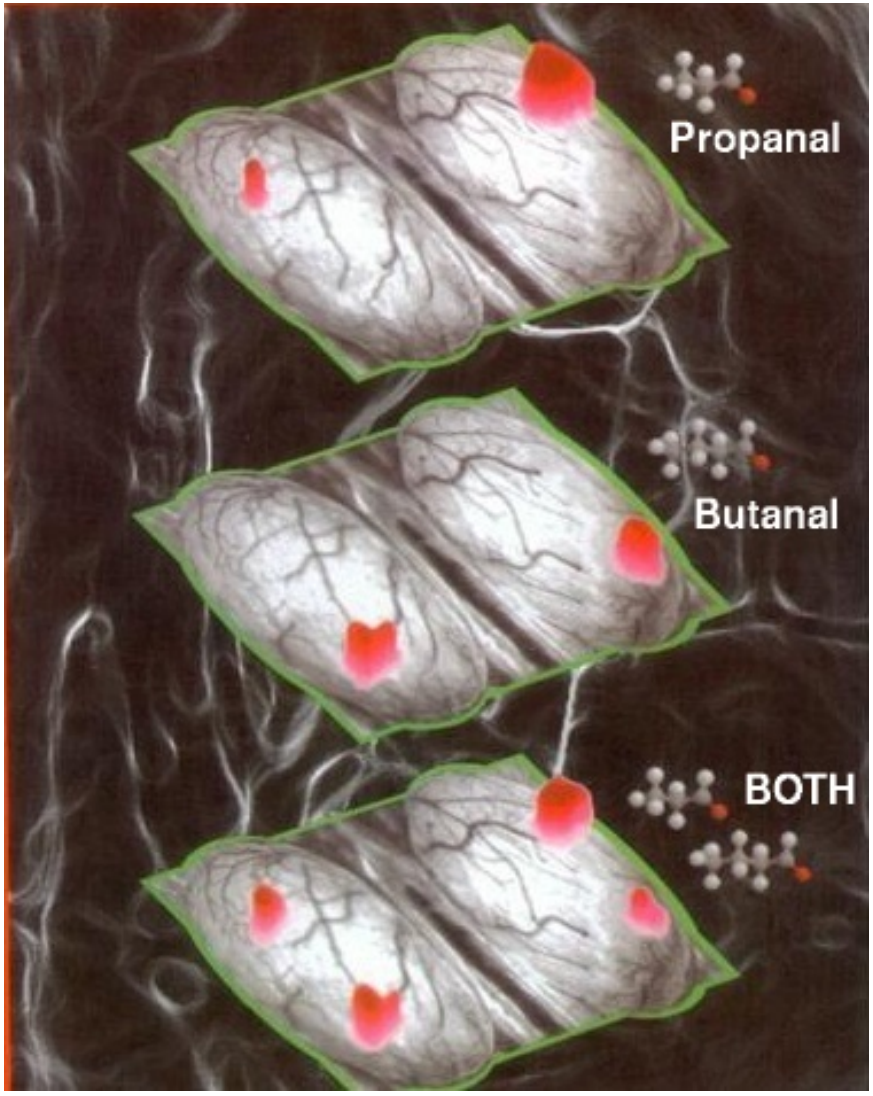


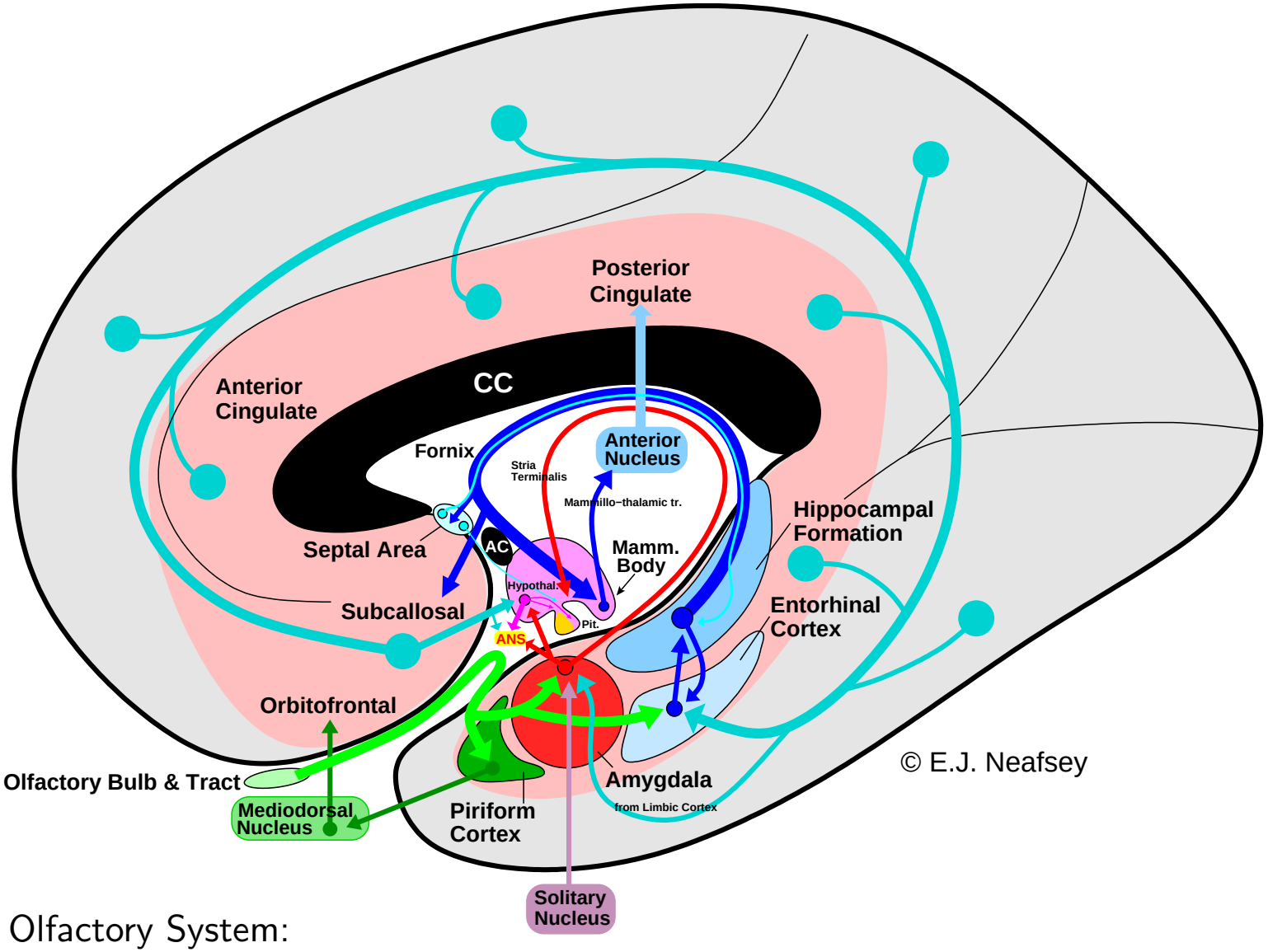
Figure 412 of Volume II: Cajal, S.R., 1909, 1910, Histologie du système nerveux de l'homme et des vertébrés. (Translated by L. Azoulay). Paris: Maloine. In public domain.

Different Olfactory Bulb Glomeruli Respond to Different Molecules



Belluscio L and Katz LC. Symmetry, stereotypy, and topography of odorant representations in mouse olfactory bulbs. *J Neurosci* 21:2113-2122 (2001).

Olfactory Connections



Olfactory System:

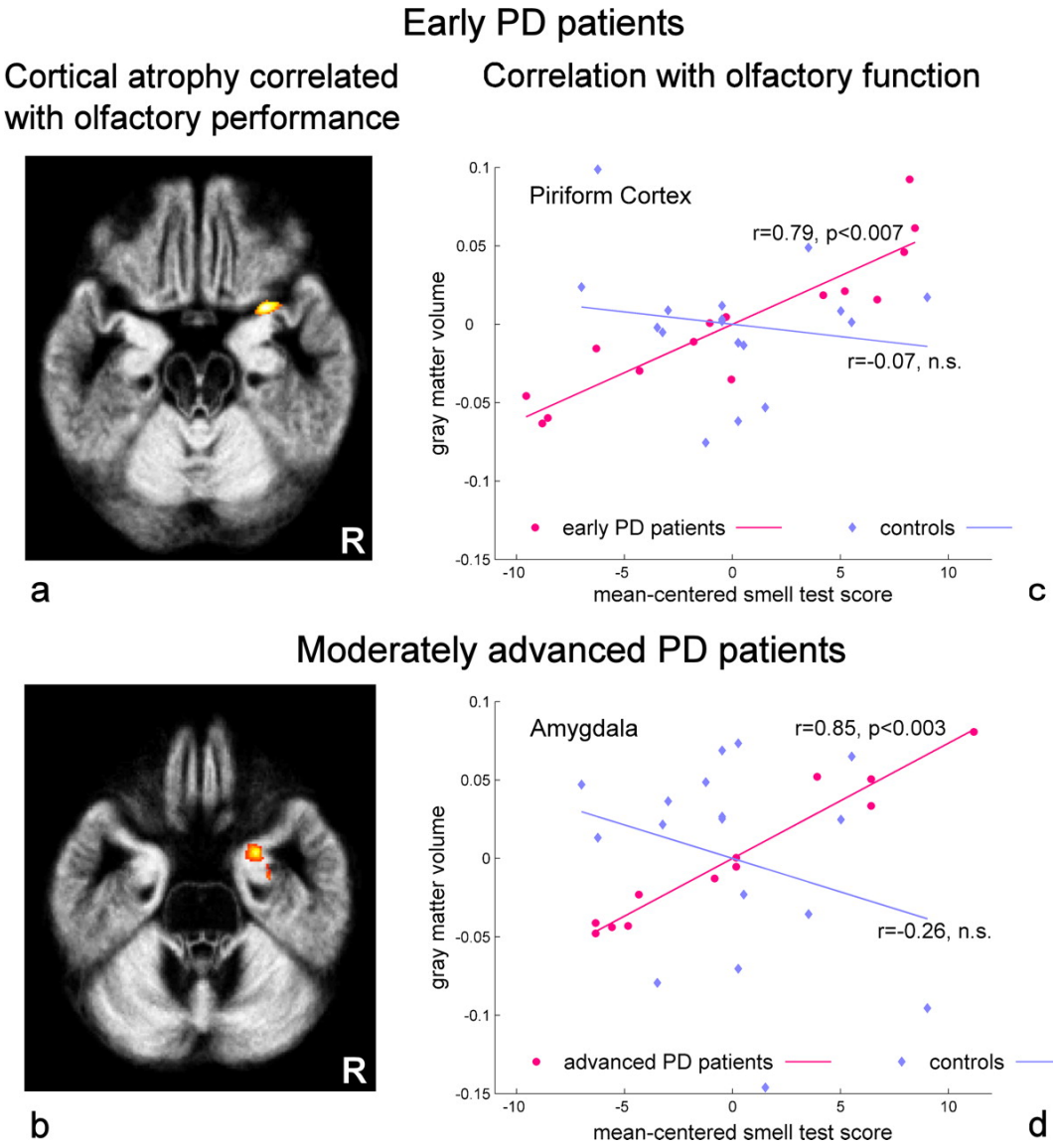
Olfactory tract projects piriform cortex, medial amygdala, and entorhinal cortex.

Piriform cortex projects to thalamic *mediodorsal nucleus*, which projects to the *orbitofrontal cortex*.

Amygdala projects to the hypothalamus.

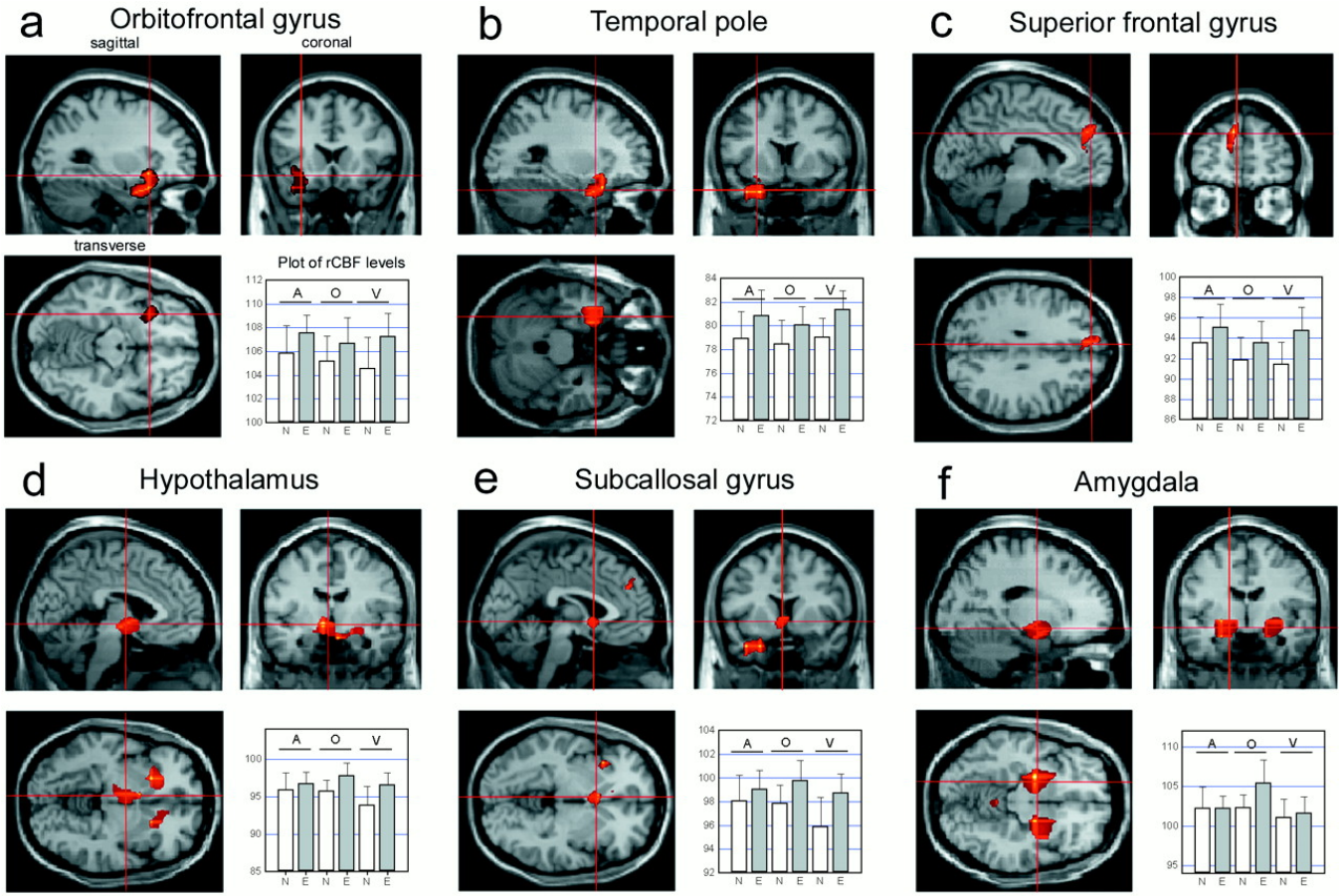
Entorhinal cortex projects to the hippocampal formation.

Olfactory Degeneration in Early Parkinson's Disease



- Wattendorf *et al.* 2009. Olfactory Impairment Predicts Brain Atrophy in Parkinsons Disease. J Neuroscience 29:15410-15413.

PET Studies Confirm Role of Limbic Cortex, Amygdala, and Hypothalamus in Emotion



Emotional Responses to Pleasant and Unpleasant Olfactory, Visual, and Auditory Stimuli: a Positron Emission Tomography Study. Royet et al., *The Journal of Neuroscience* 20:7752-7759, 2000,

- Orbitofrontal and subcallosal limbic cortex are very important elements of brain's system for emotion, as seen in patient EVR.

Epilepsy

E.J. Neafsey, Ph.D.
Loyola University Stritch School of Medicine
June 30, 2010

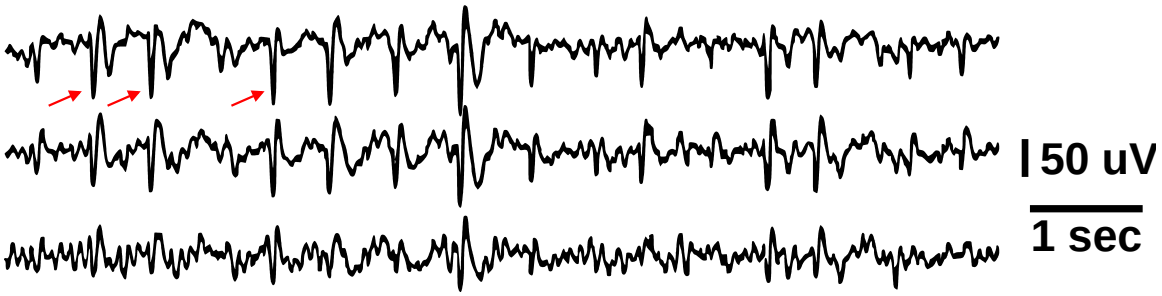
Outline

- Classification
- EEG
- Mechanisms
  - Impaired Membrane Potential Stabilization Systems
  - Calcium action potentials?
  - Channelopathies
- Temporal Lobectomy

Seizure Classification (simple version)

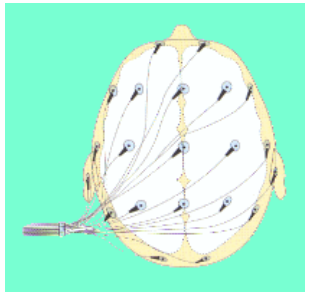
- Partial seizures (focal) (Partial seizures may secondarily generalize.)
  - **Simple** (have motor, sensory, autonomic, or psychological symptoms but leave consciousness intact)
  - **Complex** (impair consciousness, also known as psychomotor or temporal lobe seizures)
- Generalized seizures
  - **Non-convulsive** (formerly known as *absence* or *petit mal*)
  - **Convulsive** (tonic-clonic, formerly known as *grand mal*)

Interictal Spikes or Sharp Waves in EEG



Adapted from Cohen I, Navarro V, Clemenceau S, Baulac M, and Miles R. On the origin of interictal activity in human temporal lobe epilepsy in vitro. *Science* 298:1418–1421, 2002.

- Interical EEG "spikes" recorded from mesial temporal lobe intracranial electrodes in a patient with epilepsy. These brief (50-100 msec), large amplitude changes are ABNORMAL and are not seen in the EEG from normal subjects. Finding them confirms a diagnosis of epilepsy.



- EEG is normally recorded from the scalp by an array of electrodes.

Neuron Firing

Play Movie from local file

or directly from internet:

`http://info.med.yale.edu/neurobio/mccormick/movies/cortex1.mpg`

Relation Between EEG and Neuronal Activity

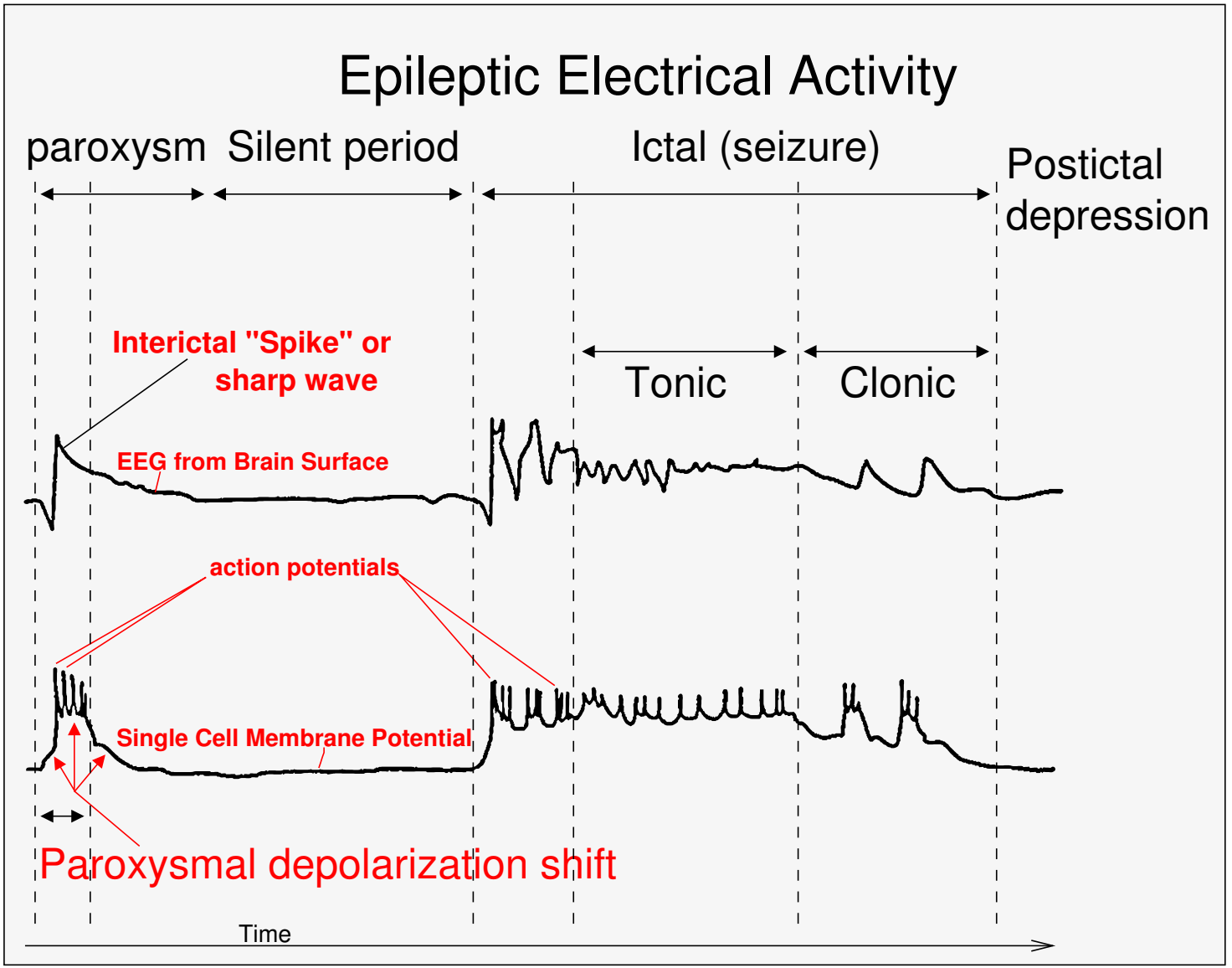
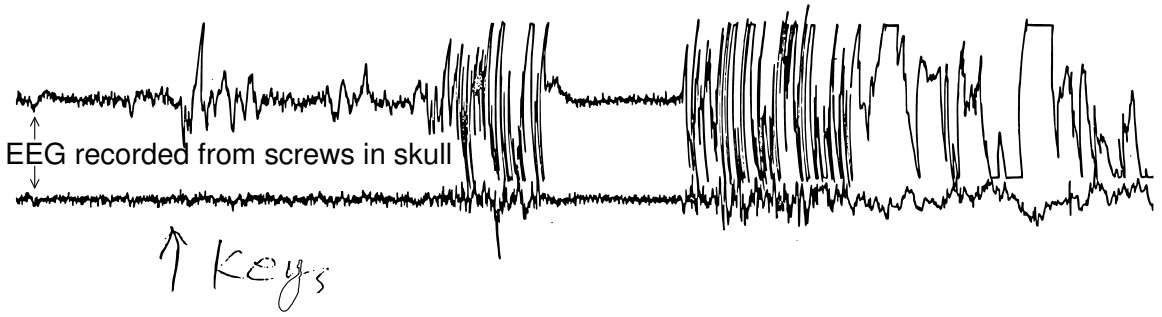
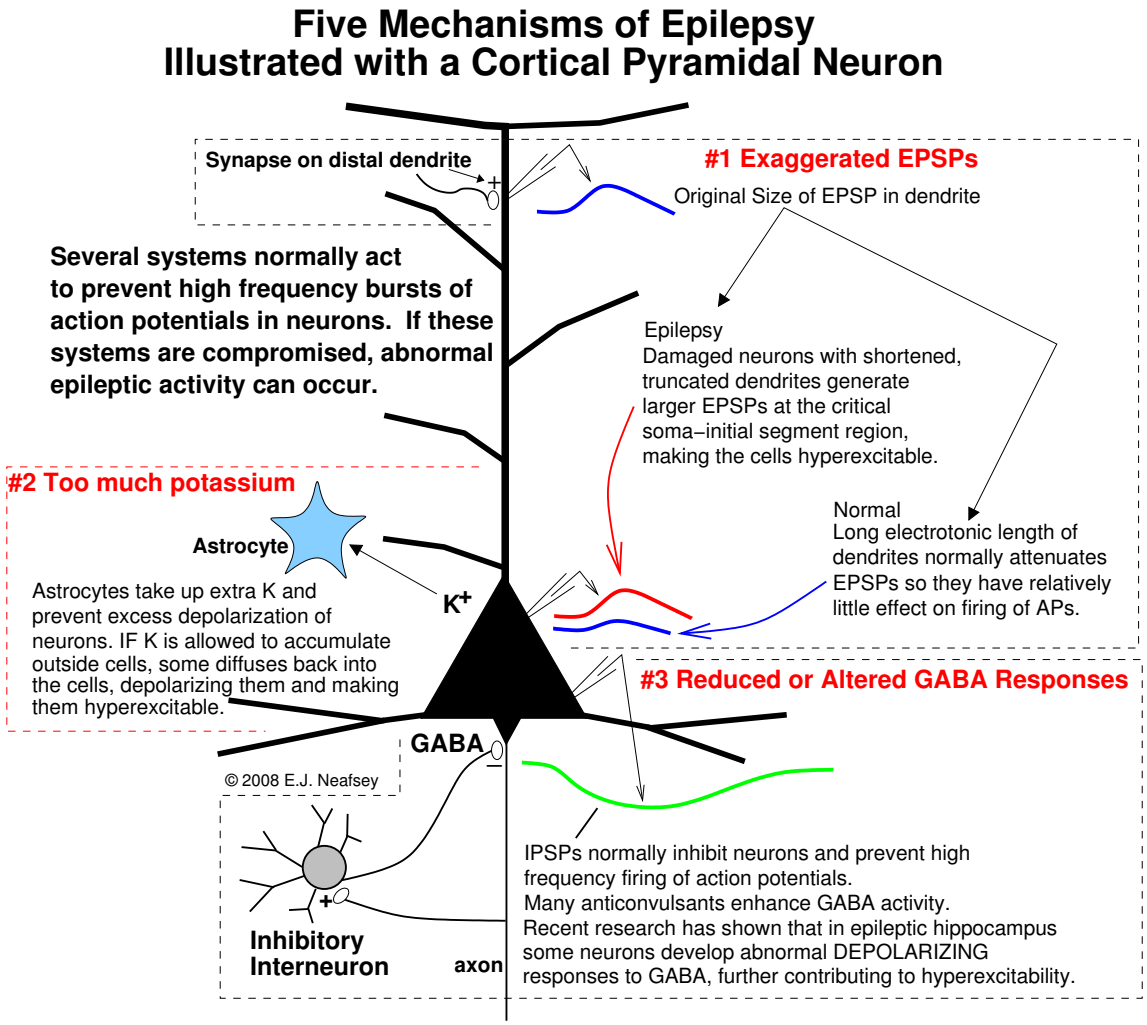


Figure modified from Figure 27-1 of *Neuroscience: An Outline Approach.*

Rat Alcohol Withdrawal Seizure Induced by Jangling Keys



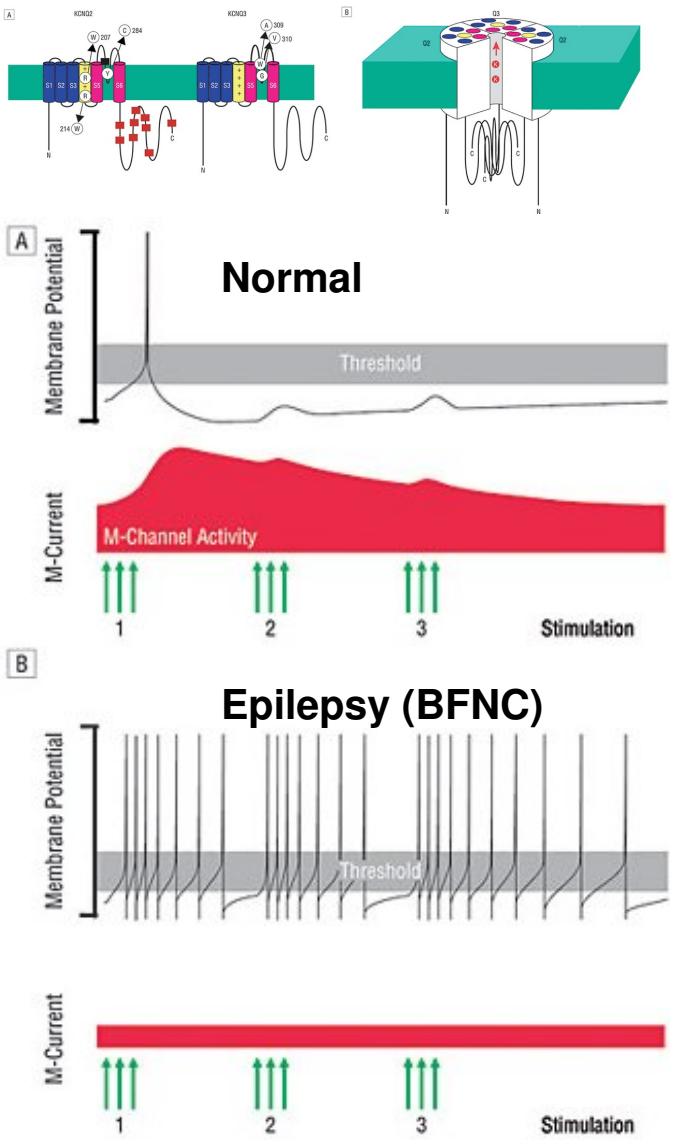
Mechanisms



#4 The "natural tendency" of pyramidal neurons to fire in high frequency bursts of action potentials because of their ability to produce long duration calcium action potnetials.

#5 Inherited "channelopathies" due to mutations in genes for K, Ca, and Na channels also contribute to various types of inherited epilepsies such as Benigh Famillial Neonatal Convulsions.

CHANNELOPATHY: Potassium M-Channels and Benign Familial Neonatal Convulsions (BFNC)



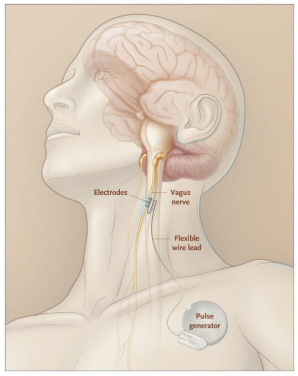
- The structure of Potassium M-channels. Membrane folding pattern of KCNQ2 and KCNQ3 subunits and locations of benign familial neonatal **convulsions** (BFNC) gene mutations resulting in amino acid substitutions (circles) or truncation of the polypeptide (red boxes).

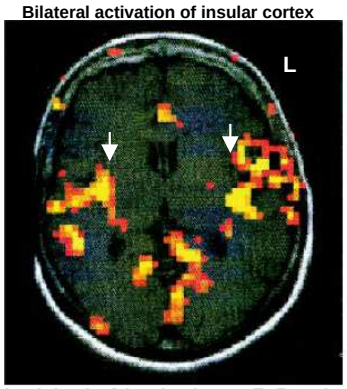
- **Normally** excitatory inputs (green arrows) cause membrane depolarization and **a single action potential**. Afterward, increased activation of M-channels **hyperpolarizes** the membrane potential, preventing spiking in response to recurrent excitation.

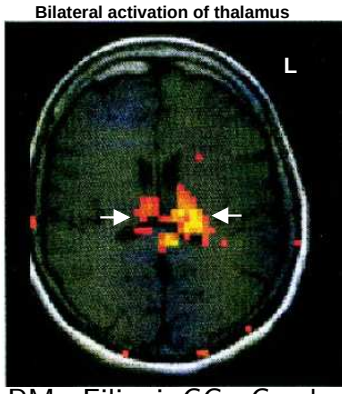
- When M-channel activity is reduced due mutations in the gene that causes BNFC or to neurotransmitters such as acetylcholine), excitatory inputs lead to **multiple action potentials**.

- Note that M-Channel is NOT the "delayed rectifier" potassium channel.
(Cooper and Jan: Arch Neurol 60:496, 2003)

Left Vagal Nerve Stimulation (VNS) for Epilepsy Activates Insular Cortex and Thalamus



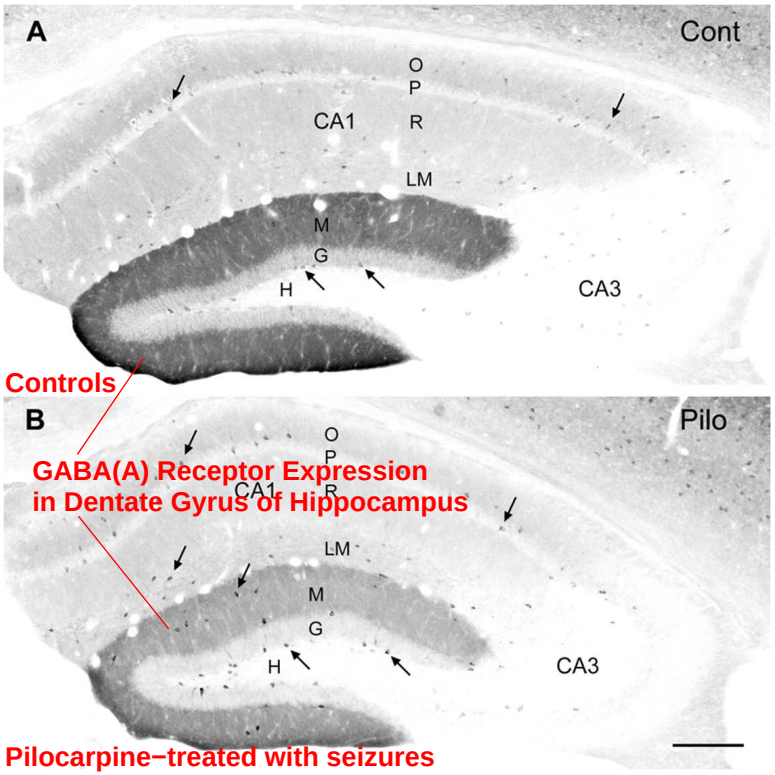




Narayanan JT, Watts R, Haddad N, Labar DR, Li PM, Filippi CG. Cerebral activation during vagus nerve stimulation: a functional MR study. *Epilepsia* 2002 Dec;43(12):1509-14.

- This cortical activation is thought to underlie the anti-epileptic effect of VNS.
- It reaches the cortex by vagal activation of the solitary nucleus in the medulla, which projects to the intralaminar nuclei in the thalamus, which also relay spinothalamic tract pain signals to cortex.
- The vagal stimulation may produce some interference with the STT pathway.
- VNS is also used as a treatment for depression, but this remains controversial (*NEJM* 356:1604-1607,2007).

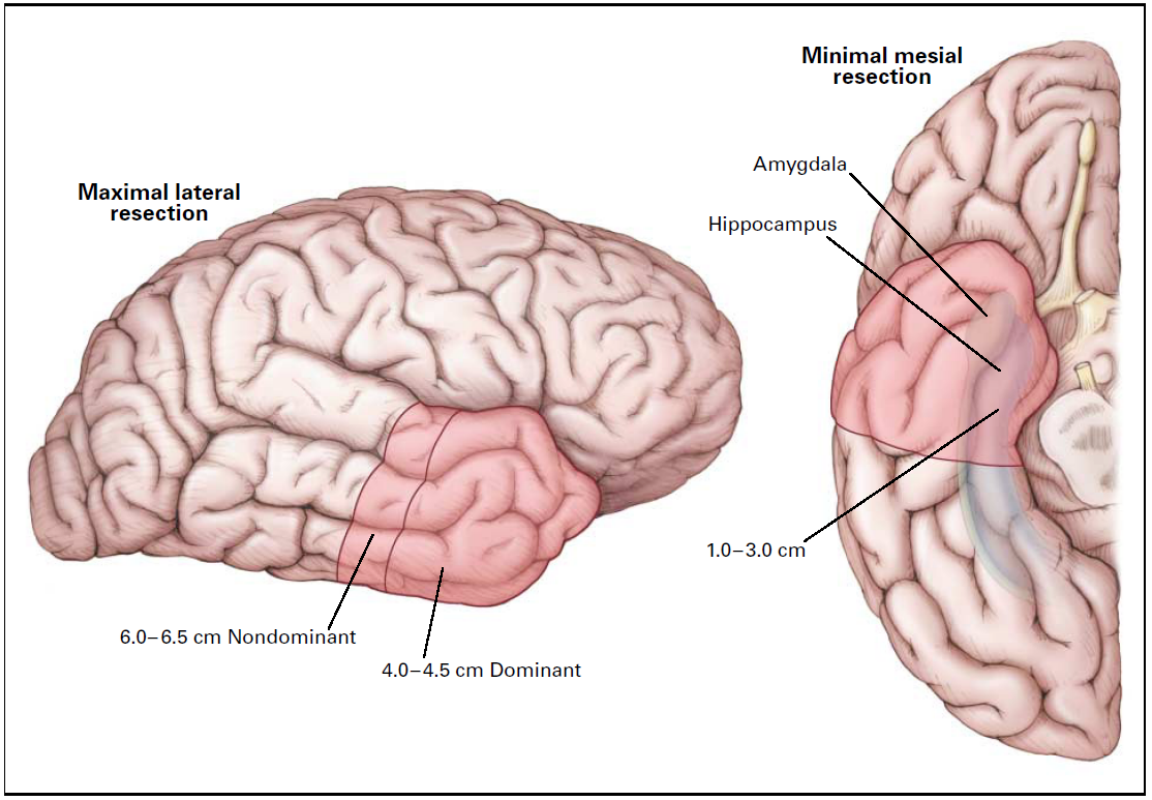
Reduced GABA Receptors Lessen Inhibition and Can Lead to Epilepsy



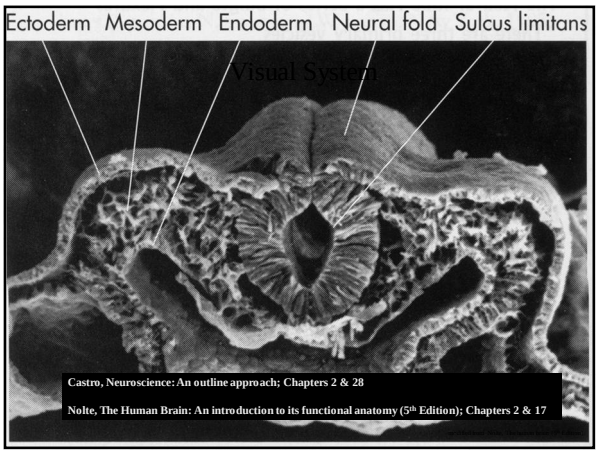
- Following one episode of status epilepticus induced by pilocarpine treatment, mice develop spontaneous "temporal lobe" seizures in the following weeks. Note the lighter staining denoting decreased GABA(A) receptors in the dentate gyrus in the lower panel.

- Figure adapted from Peng Z, Huang CS, Stell BM, Mody I, Houser CR. Altered expression of the delta subunit of the GABA(A) receptor in a mouse model of temporal lobe epilepsy. *J Neurosci* 24:8629-39, 2004.

Temporal Lobectomy for Complex Partial Seizures ("Temporal Lobe Epilepsy")

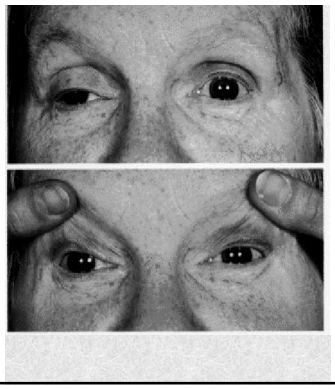


- Note that less tissue is removed from the language dominant hemisphere
- Wiebe S, Blume WT, Girvin JP, Eliasziw M. Effectiveness and Efficiency of Surgery for Temporal Lobe Epilepsy Study Group. A randomized, controlled trial of surgery for temporal-lobe epilepsy. *N Engl J Med* 345:311-8, 2001.
- Wada test is used to definitively determine language hemisphere.

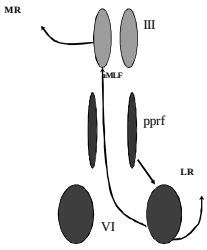


Peripheral Optomotor System

- Ømuscles/nerves responsible for opening/closing of the eyelids
- Øaccommodation and pupillary reflexes
- Ømuscles/nerves responsible for eye movements
- Øtypes and control of eye movements in the orbit



Central Optomotor System

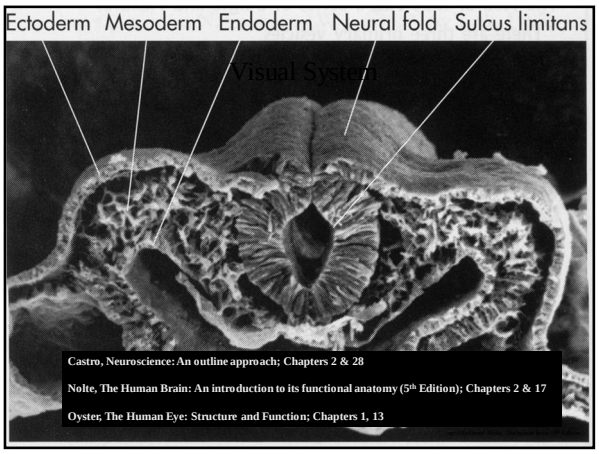


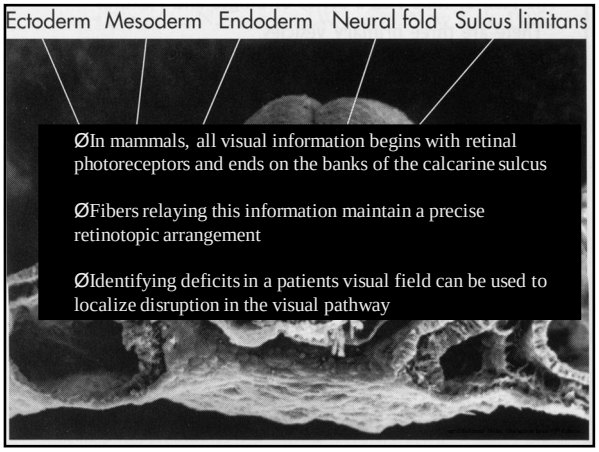
Five Major Eye Movements

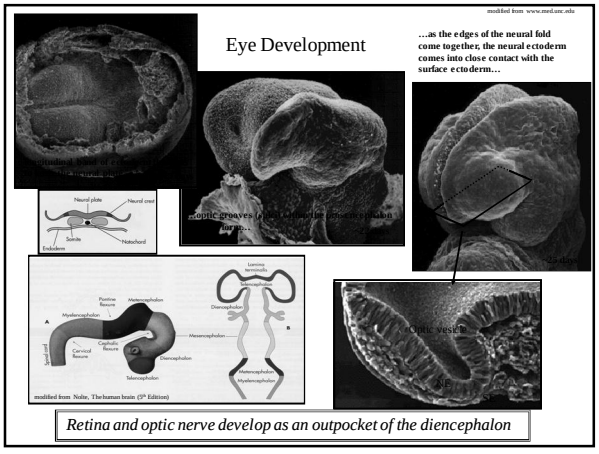
- Saccades (PPRF, riMLF; frontal lobe)
- Fixation (occipital lobe)
- Smooth Pursuit (occipital lobe)
- Vergence (occipital lobe)
- VOR

A Pt has a focal epileptic seizure that begins upon turning their head and eyes to the right. Immediately after the seizure, the Pts head and eyes turn to the left.

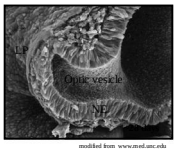
Nystagmus (form, type & classification)


Ectoderm Mesoderm Endoderm Neural fold Sulcus limitans
Visual System
Castro, Neuroscience: An outline approach; Chapters 2 & 28
Nolte, The Human Brain: An introduction to its functional anatomy (5th Edition); Chapters 2 & 17
Oyster, The Human Eye: Structure and Function; Chapters 1, 13


Ectoderm Mesoderm Endoderm Neural fold Sulcus limitans
ØIn mammals, all visual information begins with retinal photoreceptors and ends on the banks of the calcarine sulcus
ØFibers relaying this information maintain a precise retinotopic arrangement
ØIdentifying deficits in a patients visual field can be used to localize disruption in the visual pathway


modified from www.med.unc.edu
Eye Development
…as the edges of the neural fold come together, the neural ectoderm comes into close contact with the surface ectoderm…
Optic vesicle
modified from Nolte, The human brain (5th Edition)
Retina and optic nerve develop as an outpocket of the diencephalon

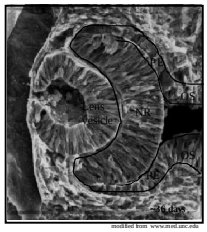
Eye Development



modified from www.med.unc.edu

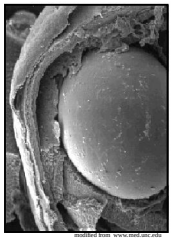
…contact with optic vesicle causes differentiation of the overlying surface ectoderm to form the lens placode…

…continued development of the lens placode gives rise to the lens vesicle which separates from the surface ectoderm forming the primitive lens…



modified from www.med.unc.edu

…invagination of the optic vesicle gives rise to the two-layered optic cup



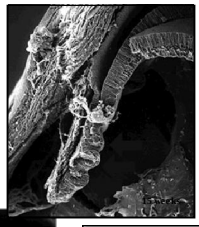
modified from www.med.unc.edu

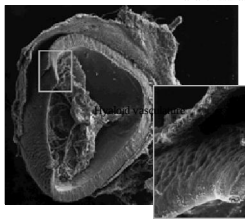
modified from www.med.unc.edu

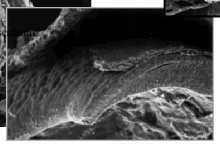
Cornea consists of an outer epithelial layer derived from the surface ectoderm…and inner layers derived from neural crest cells

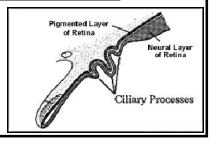
modified from www.med.unc.edu

The iris and the ciliary processes form from the outer rim of the optic cup





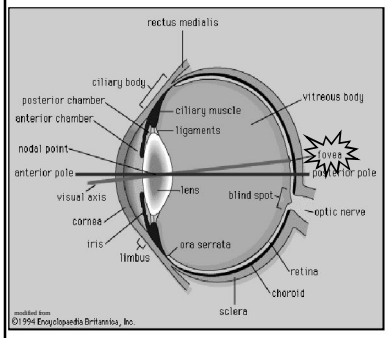




…take home message

- The retina, lens, iris, and epithelial layer of the cornea are of ectodermal origin
- At ~ 3 weeks, optic vesicles evaginate from the walls of the diencephalon
- The optic vesicle approaches the overlying ectoderm and induces the formation of the lens vesicle
- The lens vesicle separates from the surface and induces the formation of the cornea from the overlying ectoderm
- The optic vesicle folds back on itself to form a two-layered optic cup with the inner layer developing into the retinal pigment epithelium and the outer layers forming the neural retina
- The iris and the ciliary body develop and differentiate from the optic cup margins

the eye is formed from three concentric tissue layers…



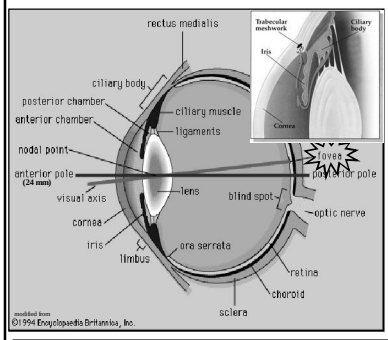
External Layer (*dura mater*)
- Øsclera
- Øcornea
  - •avascular
  - •densely innervated (V_1)

Middle Layer (uvea, *pia mater*)
- Øchoroid capillaries (permeable, contain melanin)
- Øciliary body & muscles
- Østroma of the iris

Inner Layer (CNS)
- Øretinal pigment epithelium
  - **Øphototransduction and BRBarrier**
- Øneural retina
  - Øretinal detachment, separation of the optocel

PR are metabolically dependent on the RPE cells and the adjacent choroidal vasculature

the eye is a three chambered organ



Anterior Chamber
cornea & iris
- Øaqueous humor reabsorbed at the trabecular meshwork
- Øspaces of Fontana
  - •canal of Schlemm
  - •anterior ciliary vein

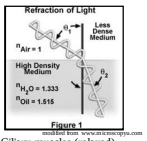
Posterior Chamber
iris & lens
- Øaqueous humor produced by ciliary processes
  - •Na^+-K^+ ATPase, HCO_3-Cl^- exchange, carbonic anhydrase
- ØCSF, ~3 µl/min, ~15 mm Hg
- Øsupplies nutrients to cornea and lens

Vitreous body
lens & retina
- Øgelatinous vitreous humor
  - ØWater (99%), collagen (II) and hyaluronic acid
- Ø80% of interior volume
- Øslow turnover
- Ø fibroblast and hyalocytes (macrophages, remove debris)

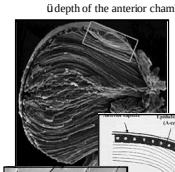
An imbalance in aqueous humor clearance leads to elevated intraocular pressure (>25 mm Hg) with subsequent loss of vision (glaucoma)

refractive power of the eye

- üfocusing requires refraction of light across interfaces (Δη)
- üη aqueous and vitreous humor ~ η lens
- ümost refraction occurs at air-water interface (cornea)

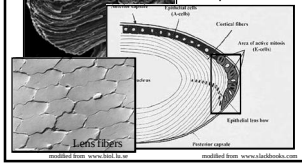


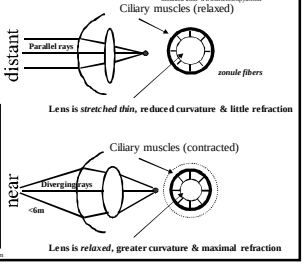
optical power of the eye (~ +60 D)
- ücurvature of the cornea (+41.1 D)
- ücurvature of the lens (+20 D to +30D)
  - üincreased by the opposing elasticity of the lens and the ciliary zonule fibers on the lens capsule
- üdepth of the anterior chamber



Accommodation is mediated by the capsule surrounding the lens.

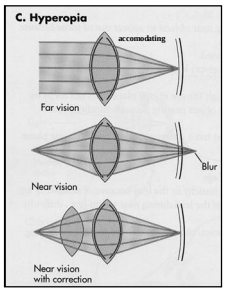
E-cells are responsible for the production of new lens cortical fibers.



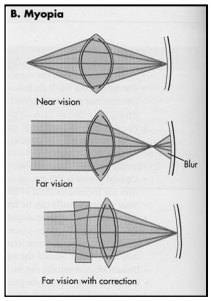


myopia

- optical power of the cornea/lens is abnormally strong relative to the axial length
- focusing on near objects requires little contraction of the ciliary muscle
- distant objects are focused in *front* of the retina
- correctable with diverging (concave) lenses (negative diopter)



modified from Castro, Neuroscience: An outline approach, 2002



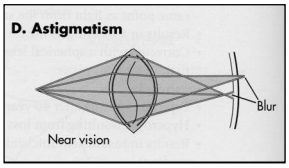
modified from Castro, Neuroscience: An outline approach, 2002

hyperopia

- optical power of the cornea/lens is abnormally weak relative to the axial length
- accommodation is insufficient, near objects are focused *behind* the retina
- distant objects are focused on the retina
- correctable with converging (convex) lenses (positive diopter)

astigmatism

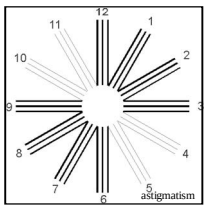
- optical power of the eye is heterogenous
- different planes of light are focused differently resulting in light from a point source focusing in front of and behind the retina
- correctable with spherical lenses (different optical powers in different planes)



modified from Castro, Neuroscience: An outline approach, 2002

presbyopia

- optical power of the lens weakens *with age*
- accommodation *becomes* insufficient, near objects remain focused *behind* the retina
  - a myopic person will develop difficulty with both far *and* near vision
  - correctable with bifocal lenses (negative and positive diopters)



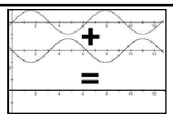
amblyopia

- visual deficit in one eye with no gross pathology
- not correctable with glasses

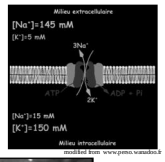
- poorly developed visual pathway
- results from disuse of one eye at an early age (<7y): cataract, ptosis, strabismus, refractive errors
- irreversible if not corrected promptly

Transparency of the cornea and lens

- the healthy cornea/lens is normally *dehydrated*
- scattering of light as it passes through the dehydrated cornea/lens results in phase cancellation due to optical interference



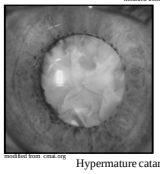
- relative dehydration
  - anterior surface of the cornea and lens
  - energy-demanding process using the Na^+-K^+ ATPase pump to move Na^+ ions (and water) out of the cells
  - cornea uses aerobic metabolism to provide energy to the Na^+-K^+ ATPase pump
  - Lens uses anaerobic metabolism



modified from www.pmeo.wanadoo.fr

- contacts lenses blocked corneal diffusion of oxygen, restricting aerobic metabolism. Now, contact lenses are perforated to allow for oxygen diffusion

- cataracts: opacity of the lens
  - failure of the Na^+-K^+ ATPase pump
  - free radical formation
  - UV light alteration of proteins
  - Diabetes Mellitus
  - trauma
  - aging



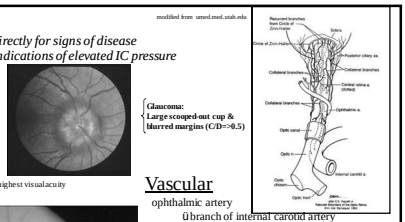
modified from cmai.org

Hypermature cataract

Fundus

Blood vessels can be examined directly for signs of disease
Optic disc can be examined for indications of elevated IC pressure

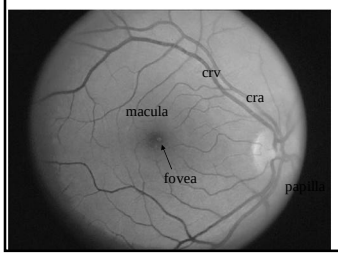
modified from umed.med.utah.edu



macula lutea
- ü lateral to the optic disc (*papilla*)
- ü contains the fovea at center

fovea
- ü 1.5 mm depression
- ü contains only cones
- ü center directly in line with the visual axis
- ü elongated cones responsible for highest visual acuity

Glaucoma:
Large scooped-out cup & blurred margins (C/D=>0.5)



Vascular

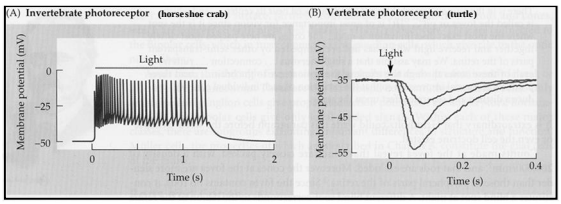
ophthalmic artery
- ü branch of internal carotid artery
- ü extend through the optic canal
- ü supplies the entire eye

central retinal artery (BRBarrier)
- ü branch of the ophthalmic artery
- ü supplies the inner retina

ciliary arteries
- ü branch of the ophthalmic artery
- ü supply choroidal capillaries
- ü outer retina (PR)

venous return via central retinal veins
- ü Ciliary veins
- ü Ophthalmic veins
- ü Cavernous sinus

Photoreceptor response to light

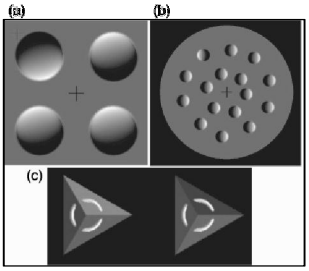


- Ø Hyperpolarized in dark
- Ø Depolarizes to light
- Ø Action potentials elicited

vs.

- Ø Depolarized in dark
- Ø Hyperpolarizes to light
- Ø Graded response

Light *hyperpolarizes* vertebrate photoreceptors



Wendy J. Adams .A common light-prior for visual search, shape, and reflectance judgments. *Journal of Vision* 2007;7(11):11, 1–7.

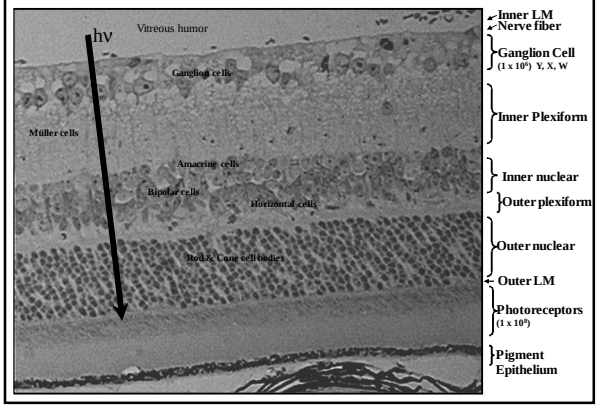
Visual Perception

- Ø Light defines surfaces
- Ø Changes in light intensity across a 2D surface can provide clues to 3D shape
- Ø Our visual system infers surface contours using a perceptual assumption that "light comes from above"
- Ø Primary task of the human retina is detecting, selecting, and signaling

- Ø Various layers of the mammalian retina and the cells associated with these layers
- Ø How light is absorbed by the photoreceptor and what chemical changes occur following light absorption (phototransduction)
- Ø What is meant by center-surround concentric receptive fields

Phototransduction

10 identifiable retinal layers

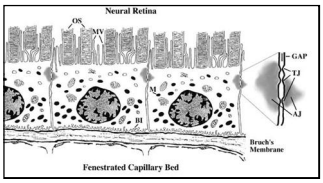


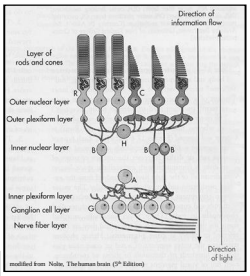
Retina is anatomically simplistic

- 100s million neurons
- 5 basic cell classes directly involved in the processing of visual information
- patterns of interconnections remain constant throughout the retina

- somata of these cells are neatly arranged in three distinct layers (ONL, INL, GCL)

- terminals synapse in two additional layers (OPL, IPL)
  - information is delivered by a cell type
  - information is received by a separate cell type
  - information is shared *laterally* using a third cell type





Retinal Pigment Epithelium

- outer layer of the optic cup
- separates the neural retina from the fenestrated choroid capillaries
- metabolically supports photoreceptors
- forms the outer blood-retinal barrier

Bipolar cells

- receive input from PR/Hz cells and synapse with amacrine and ganglion cells
- respond to PR stimulation in a graded manner
- exhibit *concentric receptive fields*

Horizontal Cells

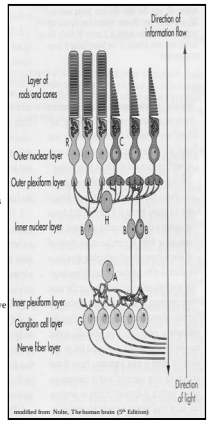
- receive input from *neighboring* PR and synapse with bipolar cells and PR cells
- respond to PR stimulation in a graded manner
- establish *concentric receptive field responsiveness* of bipolar and ganglion cells (contrast/edge enhancing function)

Amacrine cells

- extensive processes that receive input from BP cells and synapse with ganglion cells and *neighboring* BP cells
- exhibit action potentials in response to stimulation
- contribute to the *temporal* aspect of *concentric receptive field responsiveness* of ganglion cells

Ganglion cells

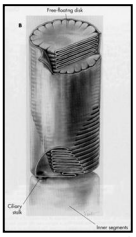
- receive input from BP cells and amacrine cells
- exhibit action potentials in response to stimulation, unmyelinated axons are the nerve fiber layer. Acquire myelin sheath distal to the lamina cribrosa
- two functionally distinct classes
  - large Y class (large receptive fields, responsive to onset and movement of light, little color discrimination, project to the magnocellular division of LGN)
  - small X class (small receptive fields (fovea); responsive to cones, project to the color discriminating cells in the parvocellular division of the LGN)



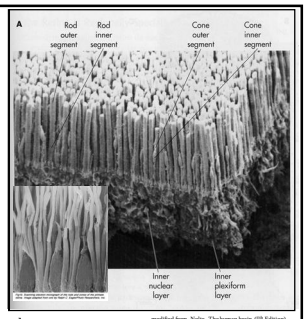
W

vertebrate photoreceptors are derived from ciliary cells

- convert light energy into chemical energy
- *rods* mediate low-acuity vision
- *cones* mediate high-acuity color vision
- respond to light in a *graded* manner
- glutamate



modified from Nolte, The human brain (5th Edition)



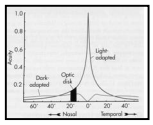
modified from Nolte, The human brain (5th Edition)

outer segment
- site of phototransduction
- rods: contains 100s of *individual* membranous discs impregnated with rhodopsin (400-575 nm)
- discs are continuously synthesized
- "old" discs are phagocytosed by adjacent PE

rods
- high sensitivity, responding to as little as one photon
- saturated in daylight, only respond to moonlight levels of intensity
- convergent: ~130 rods synapse with a single bipolar cell, resulting in decreased visual acuity

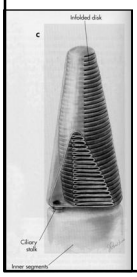
Multiple populations of cone photoreceptors….

outer segment
- three varieties of cones, each containing a different photopigment (RGB, 350-650 nm)
- dichromatic (dogs, rabbits, deer); tetrachromatic (amphibians, fish, birds)
- less sensitive to light, responsible for color sensitivity
- membranous discs are less extensive and are infoldings of the plasma membrane
- localized to the macula; cones to midget bipolar cells (2:1) producing high-acuity vision



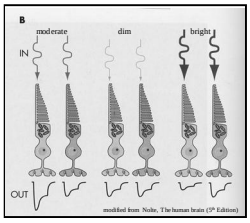
- genes for the red and green opsins are located next to each other on the X chromosome
- gene for the blue opsin is located on chromosome 7

……are the starting point for color vision



modified from Nolte, The human brain (5th Edition)

Perception of color
- Ø individual PR respond to the photons absorbed
- Ø different λ can be discriminated by the CNS by comparing the *output* of different classes of cones
  - Ø Red cones respond similarly to green, yellow or red light
  - Ø Green cones, however, produce decreasing output potentials



modified from Nolte, The human brain (5th Edition)

Visual Pigment (opsin + chromophore)

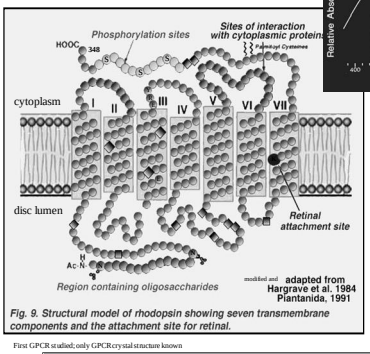
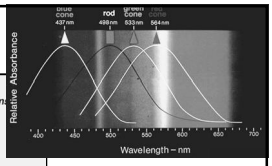


Fig. 9. Structural model of rhodopsin showing seven transmembrane components and the attachment site for retinal.

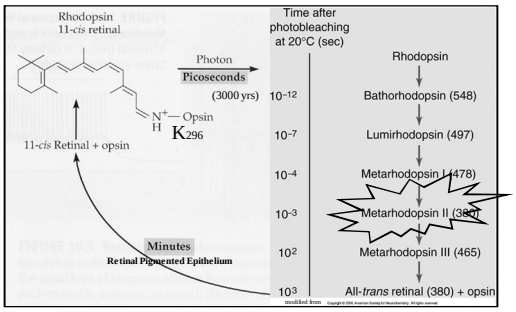


- Ø Each rod contains ~1 x 10^8 pigment molecules (80% of total disc protein)
- Ø Pigment molecules are aggregated at high density on hundreds/thousands of discrete membrane discs within a single rod photoreceptor
- Ø Rods express a single pigment (opsin, chromosome 3) that absorb light max. ~ 500nm
- Ø Cones express three distinct opsins that absorb light max. ~437nm, ~533 nm, or ~564 nm
- Ø Rods and cones contain the same chromophore: 11-cis-retinal

First GPCR studied; only GPCR crystal structure known

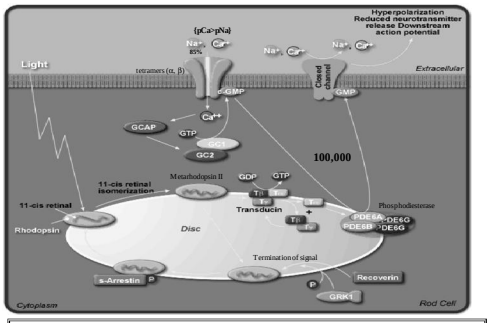
How does photoisomerization give rise to phototransduction?

The absorption of a single photon initiates the rapid isomerization of rhodopsin in the rod outer segment



Metarhodopsin II is the "trigger" that activates second messenger signaling

Light causes a *decrease* in cGMP levels…

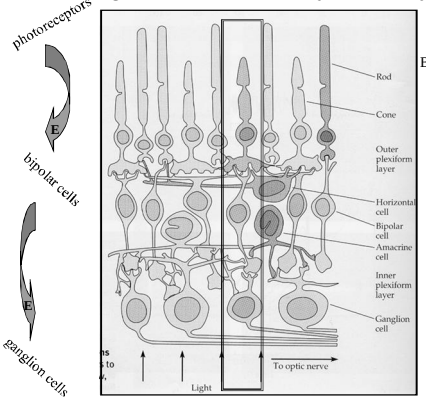


…resulting in the closure of cGMP-gated ion channels… thereby *hyperpolarizing* the photoreceptor… and *reducing* tonic release of glutamate

So…..if light *decreases* photoreceptor excitability….

……..than how do we perceive vision?

In the retina…glutamate can be excitatory or inhibitory…

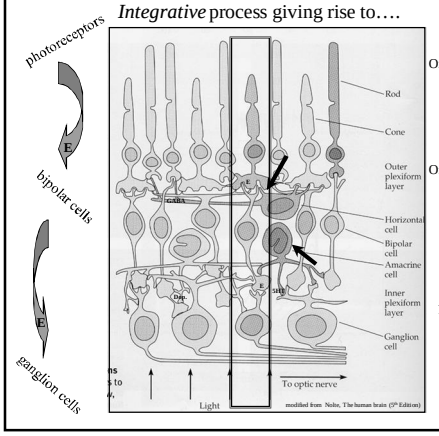


Bipolar Cells

- Direct input from rods or cones
- Rod BC
  - 1:15-45
- Cone BC
  - 1:5-20
  - Midget BC
    - 1:1
    - Fovea
- BC respond to light
  - Depolarization
  - Hyperpolarization

…depending on the receptor

Integrative process giving rise to….



On-center BC (depolarizing)

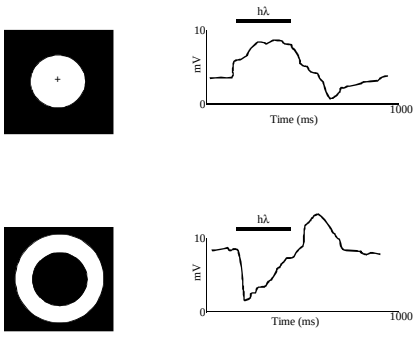
- Glutamate is an *inhibitory* NT
- Metabotropic
  - *inhibits* excitatory ligand-gated ion channels

Off-center BC (hyperpolarizing)

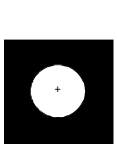
- Glutamate is an *excitatory* NT
- AMPA
  - depolarization

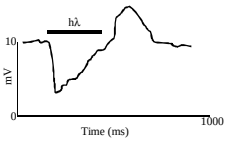
… receptive fields

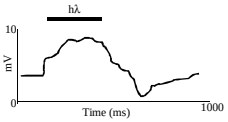
On-center (depolarizing) Bipolar Cells



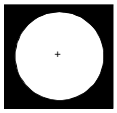
Off-center (hyperpolarizing) Bipolar Cells

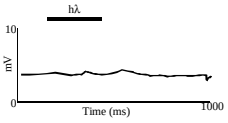






Bipolar Cells





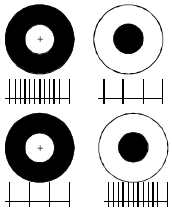
… receptive fields of retinal bipolar and ganglion cell neurons

> the area of the retina from which the activity of a neuron can be enhanced or suppressed by light

…exhibit concentric center-surround characteristics

ON-center (D) bipolar neurons ***depolarize*** in response to light in the center of their receptive field and ***hyperpolarize*** in response to light in their surround

OFF-center (H) bipolar neurons hyperpolarize in response to light in the center of their receptive fields and ***depolarize*** in response to light in their surround

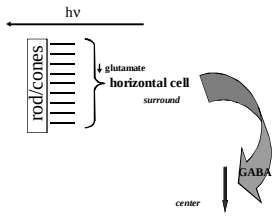


Stephen Kuffler, 1953

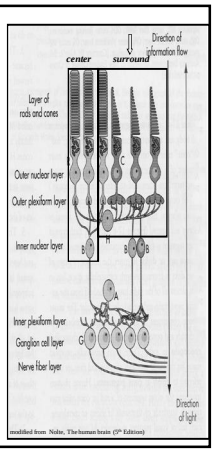
The smaller the field size, the finer the resolution of sensation

Smallest within the fovea (2.5 μm, 0.5 minutes of an arc; 1 mm = 4 degrees)

Center-surround receptive fields are formed in the outer plexiform layer mediated in part by the horizontal cell



"*dis*-inhibits" *center* PR & BP cells



All retinal neurons, including PR, have receptive fields that…

> the area of the retina from which the activity of a neuron can be enhanced or suppressed by light

…exhibit concentric center-surround characteristics

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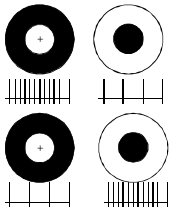

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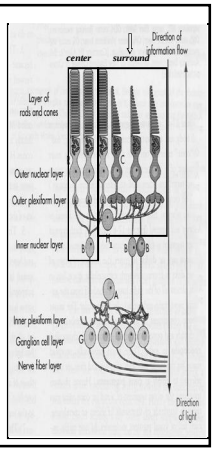
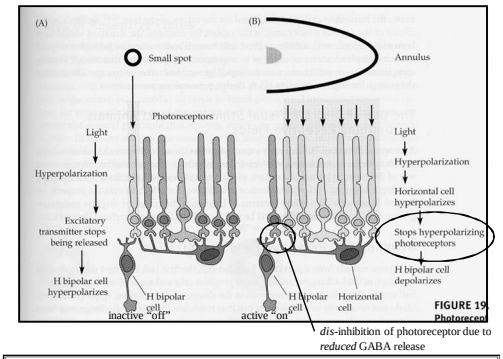
Smallest within the fovea (2.5 µm, 0.5 minutes of an arc; 1 mm = 4 degrees)

Retinal Information Processing

- Rod and cone photoreceptors respond to light intensity (the number of photons captured)
- Hz cells provide lateral communication, establishing a contrast-enhancement (receptive field)
- Amacrine cells provide lateral communication, establishing a temporal-aspect to contrast-enhancement
- Receptive fields
  - Allow for detection of contrast, rather than light intensity
  - Ganglion cells report *how* the light is distributed through space and time



"Off"-center surround responses in the retina



dis-inhibition of photoreceptor due to *reduced* GABA release

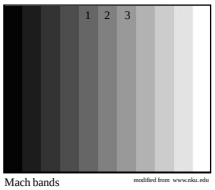
Every point in the visual field is represented by both ON-center and OFF center ganglion cells

Concentric center-surround receptive fields

Øa cell at any given level of the visual system can be characterized by its receptive field (retinal area)

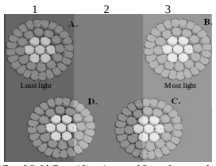
Øintensity of illumination is relatively unimportant in determining a cell's level of activity

Ø*contrast* between different areas within the receptive field that determines the retinal cell activity



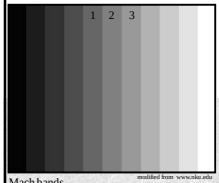
Mach bands

modified from www.nku.edu



PRs of field D residing in panel 2 are hyperpolarized by the lighter shade. These hyperpolarized PRs lead to dis-inhibition of the fields center, making field D appear "darker" than field "A"

Concentric on-center receptive field



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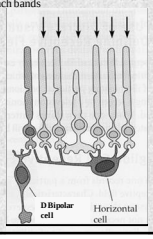


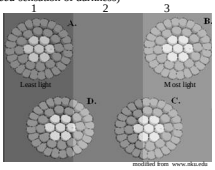
Ølight causes hyperpolarization of photoreceptors

Øhyperpolarized PR release *less* glutamate
- glutamate *inhibits* on-center bipolar cells

ØOn-center bipolar cells *depolarize* in response to light
- giving rise to the sensation of light

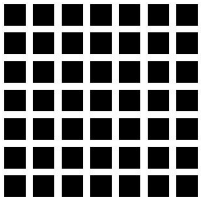
Øillumination of the surround
- hyperpolarizes surround PR
- hyperpolarized surround PR release *less* glutamate
- less excitation of the horizontal cell
- reduced release of GABA to center PR
- reduced tonic *inhibition* of center PR

Øresults in the center PR releasing *more* glutamate (giving rise to the *enhanced* sensation of darkness)



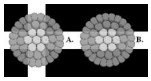
modified from www.nku.edu

The Hermann Grid



Gray spots appear and disappear at the intersections between the black squares as a result of ….

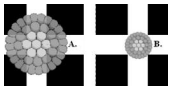
Øreceptive field reporting



more surround PRs are hyperpolarized in field A (compared to field B), *dis-inhibiting* the center PR of field A and making the area look gray

Øreceptive field size

receptor fields vary in size according to their location on the retina, gradually becoming smaller toward the fovea



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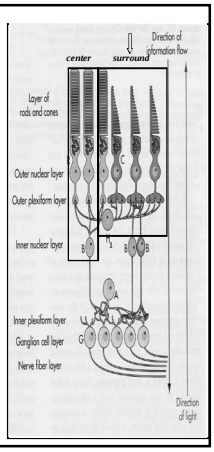
•Rod and cone photoreceptors respond to light intensity (the number of photons captured)

•Hz cells provide lateral communication, establishing a contrast-enhancement (receptive field)

•Amacrine cells provide lateral communication, establishing a temporal-aspect to contrast-enhancement

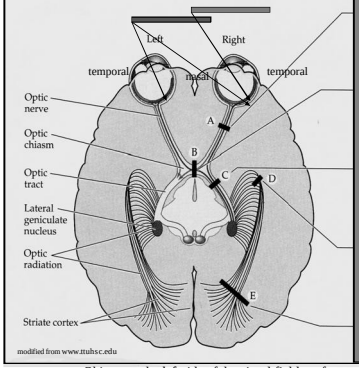
•Ganglion cells report how the light is distributed through space and time

- •Two distinct types of horizontal cells (H_1 and H_2)
- •30 types of Amacrine cells
- •Multiple types of bipolar cells
  - •Rods (ON; metabotropic glutamate receptor)
  - •Midget BP cells
    - •Green cones (ON and OFF)
    - •Red cones (ON and OFF)
  - •Diffuse BP cells
    - •Green and Red cones (ON and OFF)
      - •Terminate in three different levels
  - •Blue cone BP cells (ON; OFF)

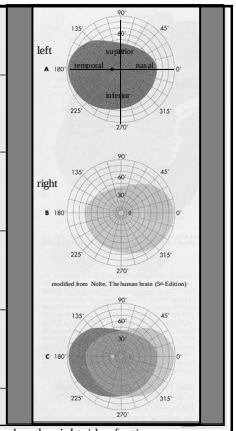


Visual fields and the visual pathways

(Visual defects are always named according to the visual field loss)

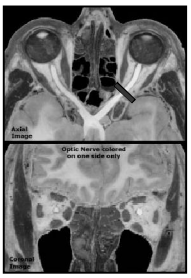


modified from www.ttuhsc.edu

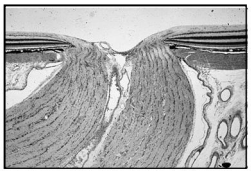


Objects on the *left* side of the visual field are focused on the *right* side of retina

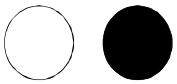
Optic nerve



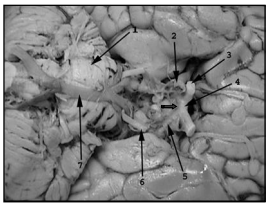
- extends from the eye to the optic chiasm
- carries information received and processed by the ipsilateral retina
- contains myelinated axons of all three classes of retinal ganglion cells
- axons are myelinated by oligodendrocytes
- nerve fibers maintain retinotopic tomography within the optic nerve
- Surrounded by pia, arachnoid, and dura sheath



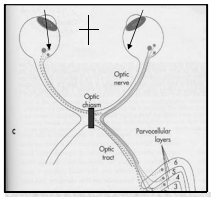
Lesions of the optic nerve result in loss of vision on the affected eye



Optic chiasm



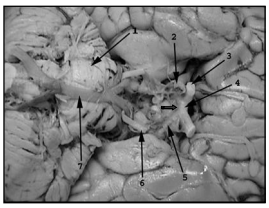
- located on the ventral surface of the brain, rostral to the infundibulum
- nerve fibers arising from the *nasal* retina (temporal visual fields) decussate to the contralateral optic tract
- nerve fibers arising from the temporal retina (nasal visual fields) remain *uncrossed*
- Some fibers exit dorsally and project to the suprachiasmatic nucleus (circadian rhythms)



Pituitary tumor enlargement can compress the midline of the optic chiasm affecting decussating fibers.

Draw the visual field deficit of a patient with a pituitary tumor compressing the midline optic chiasm

Optic chiasm



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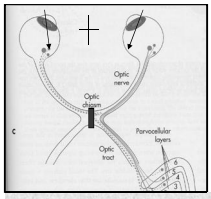
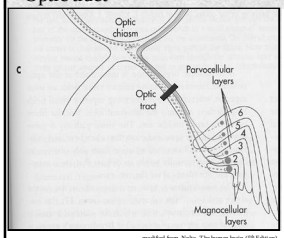
modified from Noback, The human brain (5th Edition)



bitemporal heteronymous hemianopia

hemianopia is visual loss in half of the visual field of each eye

Optic tract

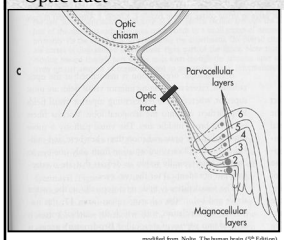


modified from Nolte, The human brain (5th Edition)

- extends posterior from the optic chiasm around the cerebral peduncle to the lateral geniculate nucleus
- nerve fibers with similar receptive fields align next to one another
- most (90%) axons of the retinal ganglion cells terminate in the LGN
- some (10%) course through the superior brachium and project to the pretectal region and the superior colliculus (motion sensitive and light intensity sensitive)

Draw the visual deficit of a lesion affecting the right optic tract.

Optic tract



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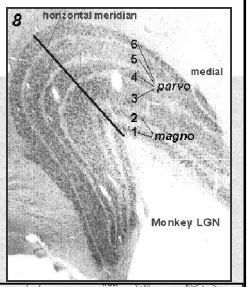
Lesions of the optic tract result in homonymous hemianopia

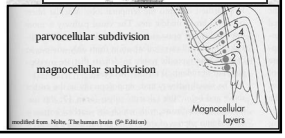
left homonymous hemianopia

lateral geniculate nucleus of the thalamus

- retinal ganglion fibers from each eye terminate on one of six laminae in a precise retinotopic pattern such that a given point in the visual field is represented in a column extending through all six layers
- each layer receives input from only one eye
- laminae 2, 3, & 5 of each LGN receive input from the ipsilateral eye
- laminae 1, 4, & 6 of each LGN receive input from the contralateral eye
- axons from small (parvocellular, X) retinal ganglion cells terminate on one of four outer laminae (color vision and high visual acuity)
- axons from large (magnocellular, Y) retinal ganglion cells terminate on one of two inner laminae (perception of movement, depth, contrast)
- receives visual cortical input that can suppress activity from one eye if the images are not aligned or in focus



left homonymous hemianopia

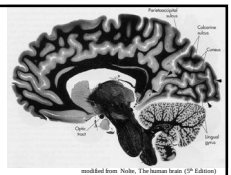


modified from Nolte, The human brain (5th Edition)

Geniculocalcarine tract

- project from the LGN through the retrolenticular and sublenticular parts of the internal capsule to the medial portion of the occipital cortex surrounding the calcarine sulcus
- retinotopic tomography is maintained (the *left* visual field of each eye is represented by the *right* visual cortex)
- projections corresponding to the *inferior* visual field (light blue) of each eye course *over* the lateral ventricles to terminate *above* the calcarine sulcus
- projections corresponding to the *superior* visual field (light green) of each eye course *around* the inferior horn of the lateral ventricles (Meyer's loop) to terminate *below* the calcarine sulcus
- fibers corresponding to the *inferior* central (dark blue) portion of each visual field terminate *above* the calcarine sulcus in the *posterior* occipital pole.
  - fibers corresponding to the *peripheral* retina are represented in the *anterior* occipital lobe
  - the macula portion of the retina has a *disproportionately large* cortical representation

Draw the visual deficit of a lesion affecting the right Meyer's loop.



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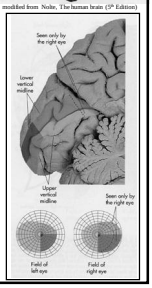
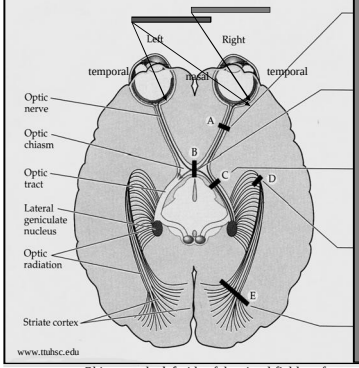
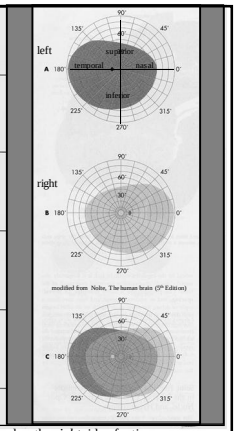


Visual fields and the visual pathways





modified from Nolte, The human brain (5th Edition)

Objects on the *left* side of the visual field are focused on the *right* side of retina

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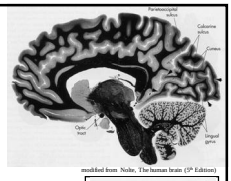
  - the macula portion of the retina has a *disproportionately large* cortical representation

left superior homonymous quadrantanopia



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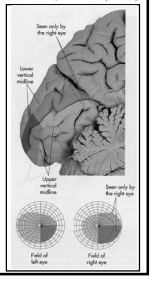
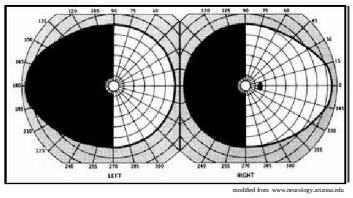
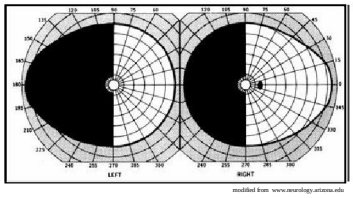


Identify and Localize the lesion



modified from www.neurology.arizona.edu

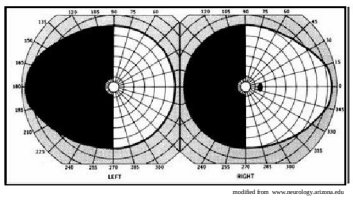
Identify and Localize the lesion



modified from www.neurology.arizona.edu

- Visual field
  - hemianopia or quadarantanopia?
  - homonymous or heteronymous?

Identify and Localize the lesion

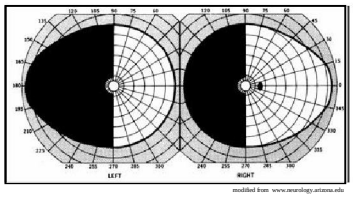


modified from www.neurology.arizona.edu

- Visual field
  - left homonymous hemianopia (with macular sparing)

- Visual pathway
  - right or left?
  - optic nerve, optic chiasm, optic tract, optic radiations (Meyer's loop), occipital lobe?

Identify and Localize the lesion



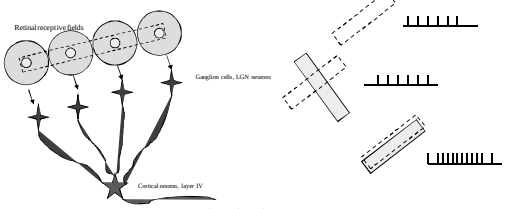
modified from www.neurology.arizona.edu

left homonymous hemianopia (with macular sparing) arising from a lesion affecting the right occipital lobe

sparing of central vision in an affected visual field suggests an occipital lobe lesion

cortical processing of visual information

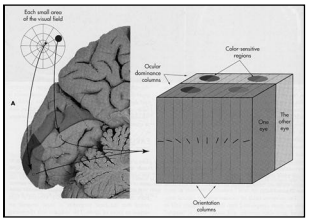
- neurons of the LGN exhibit concentric center-surround receptive fields similar to bipolar cells and retinal ganglion neurons
- incoming information is broken down in the striate cortex into component elements (color, motion, depth, orientation)
- adjacent LGN neurons converge upon "simple" cells in cortical layer IV, creating a *bar-shaped* receptive field



- simple cells with similar bar-shaped receptive fields form functional *orientation columns* aligned perpendicular to the cortical surface
- orientation columns of simple cells can excite other cortical cells, resulting in complex receptive fields (cells that respond to unidirectional movement)

striate cortex (area 17)

- array of cortical modules repeated every square mm
- each module receives information from one area of the contralateral visual field
- each module is an assembly of smaller wedge-shaped pinwheel-like slabs (*orientation columns*) that respond to stimuli with specific orientation
- color, motion, and depth are also mapped in each module



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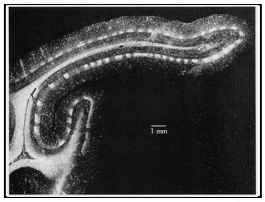


modified from Noback, The human brain (5th Edition)

- collectively, these small slabs cover all possible orientations
- the half of the slabs in one module that prefer input from one eye constitute an ocular dominance column

Monkey visual cortex radiolabeled with an amino acid injected into the ipsilateral eye. Ocular dominance columns show up as light areas in layer IV. The interspersed dark areas are the ocular dominance columns of the contra-lateral eye.

cortical processing of visual information

- incoming visual information is dissected into its component elements (orientation, color, depth, and motion)

- magnocellular (non-color discriminative) and parvocellular (color and high visual acuity discriminative) portions of the LGN the represent the same portion of the visual field are processed in *parallel* in area 17, contributing to the speed of visual processing

- identified elements are distributed to a multitude of specialized *extrastriate* cortical areas
  - posterior parietal lobe
    - non-color discriminative information on *where* an object is within the visual field
  - inferior temporal cortex
    - non-color discriminative information on the form and shape of an object (*what* the object is; *visual agnosia*)
    - color discriminative information on the color of an object in the visual field (*achromatopsia*, central color-blindness from bilateral lesions of the inferior temporal gyrus near the occipital lobe border)
  - medial superior temporal gyrus
    - non-color discriminative information on motion and depth perception

Motion Blindness

43 y/o female suffered bilateral infarcts of lateral parts of the parietal, occipital, and posterior temporal lobes due to thrombotic occlusion of the superior sagittal sinus.

Visual fields, color vision, depth perception, and reading where unaffected. She could perceive moving sound sources and somatosensory stimuli moving across her skin.

Chief complaint was of a persisting deficit in perceiving visual motion:

She had difficulty pouring tea or coffee into a cup because the fluid appeared to be frozen like a glacier. She could not stop pouring at the right time as she was unable to perceive the movement in the cup/pot. She had difficulty following dialogue because she could not see the movement of the faces of the people talking. In a crowded room, people suddenly appeared since she could not see them moving. She could not cross the streets because she could not judge the speed of a car. She had no difficulty identifying the car itself.

Color Blindness and Prosopagnosia

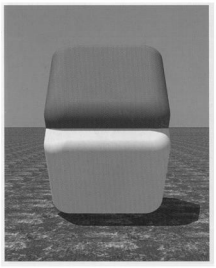
51 y/o male with abrupt onset of headache and confusion without loss of consciousness. He was amnestic over the next 12h. Upon awaking the next morning he noticed several visual deficits.

Bilateral loss of parts of his foveal fields, an incomplete left superior homonymous quadrantanopia. He was unable to recognize colors (achromatopsia) or faces (prosopagnosia). He could identify common objects and form, motion and depth perception were preserved.

Chief complaint was everything appears in shades of grey.

To him, his shirts all look dirty and he couldn't distinguish between different shirts. He had difficulty recognizing certain kinds of food on his plate unless he tasted or smelled them. An omelete looked like a piece of meat. Faces appeared chalk-like and neutral. He could not recognize people in photographs or even himself in the mirror.

Angiogram indicated a partial occlusion of the right posterior cerebral artery. Damage to his visual cortex below the right calcarine sulcus would account for his left visual field deficits. Smaller deficits in his right visual field suggest damage to parts of the left occipital lobe. It is likely the patient had bilateral damage in the occipitotemporal gyri including extrastiate areas.



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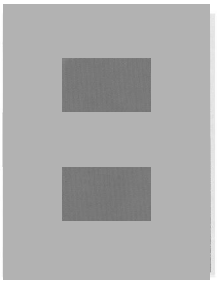

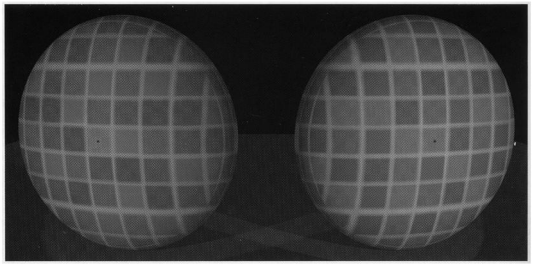

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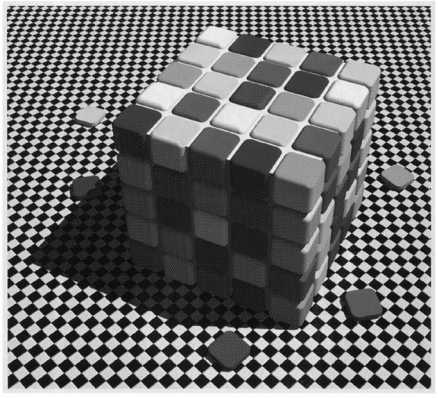

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