OBJECTIVES FOR HYPOTHALAMUS I & II

Reading Assignment: Hypothalamus 1 & II "handouts"; Mason's Medical Neurobiology, Chapter 13, pages 263-275; Chapter 14 p. 334-335; Chapter 18, p. 431-432; Chapter 27, p. 607-624, 628; Review Chapters 1, 3, 9, and 16 (p. 388-389)

KEY CONCEPTS

1. The hypothalamus maintains a stable internal environment (homeostasis) and regulates reproduction.

2. The hypothalamus coordinates the endocrine system, autonomic nervous system and motivated behaviors (drives).

3. Although a relatively small part of the human brain (1%), the hypothalamus is
4. evolutionarily conserved.

5. Remember the 4 F's: feeding, fighting, fleeing and reproduction.

6. The hypothalamus is part of the forebrain and diencephalon.

7. For convenience the hypothalamus is divided into three parasagittal zones (periventricular, medial, lateral) and four rostrocaudal levels based on where they are relative to the optic chiasm, pituitary stalk (also called the tuber cinereum) and mammillary bodies (preoptic, supraoptic, tuberal, mammillary—also called posterior).

8. Hypothalamic nuclei are highly interconnected with each other and have reciprocal connections with the cortex, brainstem autonomic cell groups, amygdala, midbrain and reward pathways in the rostral forebrain. There are unidirectional neural inputs <u>from</u> the retina (retinohypothalamic tract) and <u>to</u> the pituitary (hypothalamohypophyseal tract).

9. Humoral and neural inputs; humoral and neural outputs.

10. The functions regulated or modulated by the hypothalamus are interrelated and
11. include: maintenance of energy homeostasis (feeding, macronutrient selection, growth, metabolism), water balance (drinking, water resorption, hemorrhagic responses), stress responses, thermoregulation, fever, immune responses, sickness behavior, circadian rhythms, sleep, arousal, reproduction (sexual behaviors, parental behaviors, control of gonadal function).

9. With few exceptions, a single function is carried out at multiple levels of the hypothalamus.

10. The hypothalamus and other brain regions are sexually differentiated in development and are sensitive to gonadal steroid hormones in adulthood.

ADDITIONAL OBJECTIVES FOR THE HYPOTHALAMUS I & II

1. Identify the classical hypophysiotropic (hypothalamic releasing) hormones, their general characteristics, and the main function of each in pituitary secretion. Recognize the large number of additional neuropeptides involved in hypothalamic function, and that new ones are identified frequently.

2. Understand that the hypothalamus regulates reproductive behavior and neuroendocrine function.

3. Understand the hypothesized role of the preoptic area in generation of fever.

4. Identify the part of the hypothalamus that is considered the body's "clock", and understand how the clock (the suprachiasmatic nucleus) is entrained.

4. Understand the multiple roles of the paraventricular nucleus, the “head ganglion” of the autonomic nervous system.

5. Identify the hypothalamic nuclei referred to as "feeding" and "satiety" centers, and the importance of these brain regions in regulation of energy balance, feeding behavior and macronutrient selection. Understand the concepts and neurotransmitters/peptides that are orexigenic vs anorexigenic.

6. Remember that the hypothalamus is important in many clinically relevant and serious, and sometimes just plain annoying, conditions: generation of fever, stress, jet lag, stress responses, cardiovascular regulation, stress, obesity, anorexia, cachexia, stress, growth, puberty, infertility, stress, thyroid regulation, diabetes, ‘roid rage, depression, stress.

7. Understand that the mammillary nuclei are involved in spatial learning and memory; they sense head position in space, and are highly interconnected with the hippocampal formation.

NOTE: Our current understanding of hypothalamic functions is rapidly evolving due to new methods in genetics. Many new therapies for obesity and anorexia/bulimia, diabetes, anxiety and depression, infertility, preocious/delayed puberty, growth hormone excess and deficiencies and so on are likely to result from these advances. In addition, the optimal timing for administration of specific therapies during the day will be better known, and information on which therapies are more likely to benefit men or women, specifically, is likely to become available. Stay tuned!

HYPOTHALAMUS 1 2011

The hypothalamus has two interrelated functions:
1) to maintain homeostasis, that is, a stable internal environment, by regulating energy and fluid balance, growth, temperature, daily rhythms, arousal, reproduction, and stress and immune responses

2) to regulate appetitive and defensive behaviors such as feeding, drinking, sex, parenting, sleep and sickness behaviors.

Note: Most of the first lecture on the hypothalamus will pertain to its general characteristics such as location, cellular compositiion, basic connectivity and global functions. The second lecture will provide a few examples, related to specific curricular objectives, of the more specific, and better known, functions. You will hear about the hypothalamus again in lectures on the limbic system, sleep, and autonomic function.

Remember its functions with 4 F's:
feeding, fighting, fleeing and reproduction.

It carries out these functions by coordinating the endocrine system, autonomic nervous system and motivated behaviors.

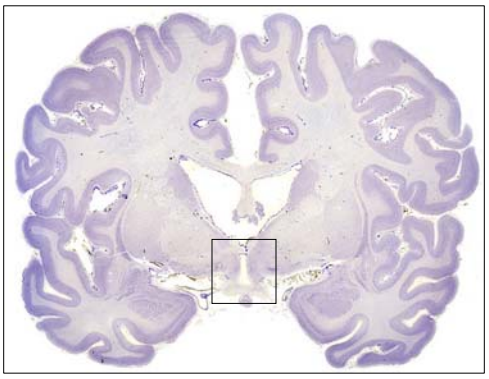
The hypothalamus is situated right in the middle of everything—it has an excellent blood supply, access to blood born substances via circumventricular organs that are "outside" the blood brain barrier, connections to and from virtually the entire nervous system and it receives massive hormonal inputs via its blood supply.

It is considered the "master" of the "master gland"—the pituitary.
It is considered the "head ganglion" of the autonomic nervous system.
It coordinates complex motivated behaviors with appropriate endocrine and autonomic output.

The functions that are regulated or modulated by the hypothalamus are highly interrelated to one another.
Regulation and maintenance of energy homeostasis (feeding, macronutrient selection, growth, metabolism), water balance (drinking, water resorption, hemorrhagic responses), stress responses, thermoregulation, fever, immune responses, sickness behavior, circadian rhythms, sleep, arousal, reproduction (sexual behaviors, parental behaviors, control of gonadal function) are all coordinately regulated.

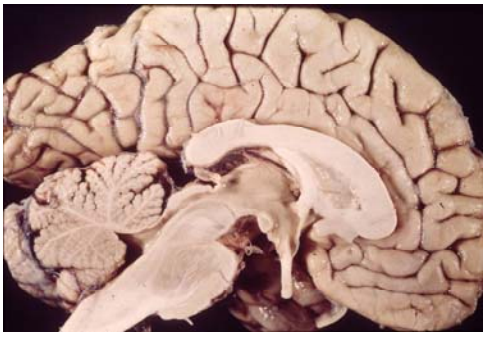
A corollary to this is that, with few exceptions, a single function is carried out by multiple intercommunicating cell groups within the hypothalamus.

The hypothalamus is small, only about 4 grams of tissue at the base of the brain, and therefore constitutes only **about 1% of the human brain.** Despite its small size, many of its functions are clearly critical for survival in most animals.



The hypothalamus is evolutionarily highly conserved. Its overall structure, functions, and neurochemistry are similar and recognizable, in fish, reptiles, amphibians, birds and mammals.

Where is the hypothalamus?



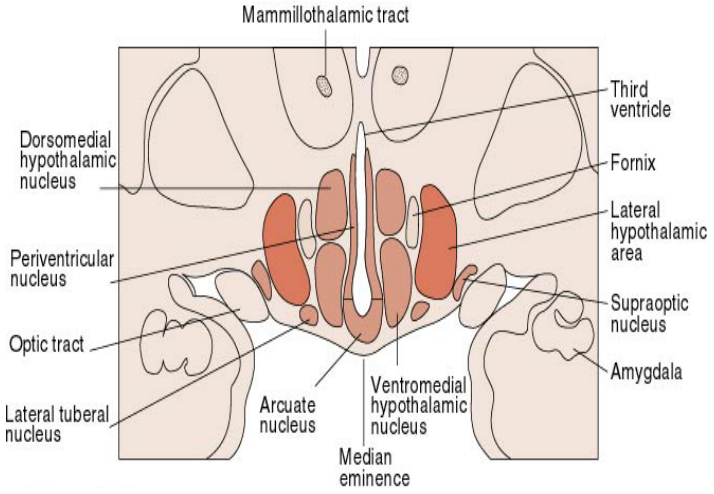
The hypothalamus is part of the forebrain and diencephalon. It is an anatomically symmetrical structure, situated on either side of the third ventricle, below the thalamus, just above the optic chiasm anteriorly and the pituitary posteriorly. The more rostral preoptic area is typically grouped with the hypothalamus because these regions are functionally intertwined and indistinguishable, except that the preoptic area develops as part of the telencephalon, whereas the hypothalamus proper develops as part of the diencephalon. For all practical purposes, you can lump the two together.

During development, the rostral end of the neural tube forms the lamina terminalis. As the rest of the cerebral hemispheres develop, they balloon around the lamina terminalis so that this structure is now covered anteriorly by the cerebral cortex and striatum. The preoptic area/hypothalamus begins at the lamina terminalis, as a structure called the organum vasculosum of the lamina terminalis, which, as the name implies, has many blood vessels running into it. The OVLT is one of several circumventricular organs that are notable because the blood brain barrier is more permeable at these locations. From the rostral OVLT, the third ventricle opens up and extends caudally through the middle of the diencephalon to the mammillary recess, finally communicating with the 4th ventricle via the cerebral aqueduct.

How are hypothalamic nuclei named?

The **hypothalamus is divided into four rostrocaudal levels**. The names for these levels are are based on their location relative to the optic chiasm and optic tracts, pituitary stalk or mammillary bodies. They are the **preoptic area** (anterior to and above the optic chiasm), the **supraoptic region** (above the optic chiasm and optic tracts), the **tuberal region** (above the tuber cinereum, or pituitary stalk), and the **mammillary region** (in proximity to the mammillary nuclei).

The hypothalamus is also divided into **three parasagittal zones**. The zones are the **periventricular zone**, adjacent to the third ventricle, the **medial zone**, and the **lateral zone**. These 3 zones are not only divided for convenience, but there are also some functional distinctions among them. For example, the periventricular cell groups are largely related to pituitary function. The medial cell groups are highly integrative. The lateral cell groups are largely concerned with sleep and arousal states.



Adapted from Kandel/Schwartz/Jessell Principles of Neural Science

Some of the cell groups within the hypothalamus are named based on whether they are dorsal or ventral within the hypothalamus.

Others are named based on the size or shape of the neurons in the region. Therefore, the names are highly descriptive of location, or, in the case of the mammillary bodies, appearance.

Commonly referred to Hypothalamic nuclei

Preoptic:
- Periventricular POA
- Medial POA
- Ventrolateral POA

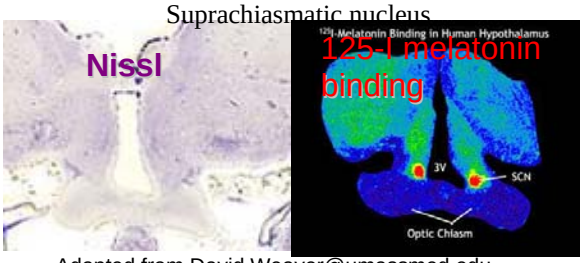
Supraoptic:
- Periventricular hypothalamic n.
- Suprachiasmatic n.
- Paraventricular n. and supraoptic n.

Tuberal:
- Medial tuberal n. (includes arcuate n. & ventromedial n.)
- Dorsomedial hypothalamus
- Lateral hypothalamus

Mammillary:
- Posterior hypothalamus
- Medial mammillary, lateral mammillary
- Tuberomammillary

Cellular characteristics:
Many of the hypothalamic cell groups are not easy to discern simply by looking at a Nissl stain. Only by using highly specific markers for specific neuropeptides, neurotransmitters, or specific activity can we easily detect most of these functionally related cell groups. There are no "layers", few obvious clusters of cells. The level of spontaneous activity is low, but the production of secretory peptides/neurotransmitters is high.

Suprachiasmatic nucleus



Adapted from David.Weaver@umassmed.edu

What are the connections of the hypothalamus?

Humoral inputs to the hypothalamus include all of the peripheral hormones produced by the various endocrine glands, such as gonadal steroids, adrenal steroids, and thyroid hormones, as well as:

Hormones that signal nutrient balance, examples:

Leptin: produced by adipose cells, conveys information regarding fat stores; satiety signal; one of a newly described class of hormones referred to as "adipokines".

Ghrelin: produced by the stomach upon gastric emptying; hunger signal.

Insulin: produced by pancreas upon ingestion of a meal; stimulates glucose uptake by cells (note—there is substantial new evidence that Type II diabetes, in some cases, is a primary disorder of the hypothalamus that in turn affects insulin sensitivity and pancreatic function).

Nutrients that directly signal and activate hypothalamic neurons:

Glucose
Fatty acids
Amino acids

Other stimuli that act directly on hypothalamic neurons

Temperature (either hot or cold)
CO2
Cytokines produced by immune system

Neural connections of the hypothalamus

Hypothalamic nuclei work together to coordinate all aspects of the endocrine system, autonomic nervous system, and behavioral systems, allowing maintenance of internal homeostasis. Therefore, hypothalamic nuclei **are highly interconnected with each other and have reciprocal connections with the cortex, brainstem and spinal cord autonomic cell groups, amygdala, midbrain and reward pathways of the rostral forebrain.** With a few exceptions, you will not learn a lot of point-to-point information about these connections.

Afferent inputs to the hypothalamus arrive from:

Cortex-- all sensory modalities (esp. olfactory & visual cortex; association regions); **sensory information**

Brainstem-- gustatory information (taste, visceral sensory, eg. gastric distention, hepatic sensation);
somatosensory information (esp. temperature, but also pain, light touch)

Brainstem monoaminergic cell groups— **general arousal states** (locus coeruleus, raphe nuclei)

Amygdala/ limbic areas—learning and memory, association areas, stress and fear related information; dopaminergic reward pathways

Retina—conveys light, thereby "setting" daily and annual rhythms

The major reciprocal neural pathways (tracts) into and out of the hypothalamus

***The pathways you will hear about most often and will be responsible for knowing are marked with an asterisk.

Medial Forebrain Bundle*: this is one of the most important pathways coursing through the hypothalamus. The MFB consists of loosely arranged; mostly thin, often unmyelinated fibers, extending from the septal area to the midbrain. The MFB is a complex bundle, with both short and long ascending and descending fibers. The MFB carries information that is critical to reward pathways; stimulation of this region activates "pleasure" centers. In this regard, it is important that the MFB carries not only hypothalamic interconnections, but also the ascending dopaminergic nigrostriatal fibers. Some of the projections of the hypothalamus to the brainstem and spinal cord autonomic cell groups also course through the MFB.

Stria Terminalis: this is a more cohesive, detectable bundle of fibers and it reciprocally connects the amygdala and the medial hypothalamus. When you think of amygdala, think of association of sensory information with context and behaviors—for example sounds or smells that spark fear, arousal, or pleasure, i.e.

emotions. The stria terminalis doesn't take the most direct route between the amygdala and hypothalamus; it arches behind and above the thalamus.

Stria Medullaris: this pathway primarily connects the lateral preoptic-hypothalamic region with the habenular complex (epithalamus, part of the diencephalon just above the thalamus and just below the pineal gland. The habenular complex is poorly understood but appears to be a relay between the diencephalon and midbrain and is involved in reward.

Dorsal Longitudinal Fasciculus: this is an extensive fiber system that travels close to the third and fourth ventricles, and connects the hypothalamus with the midbrain gray and other regions in the pons and medulla oblongata including preganglionic autonomic nuclei of the vagus nerve.

Fornix*: projection from hippocampus to mammillary nuclei and other regions
The fornix is one of the most recognizable fiber bundles in the hypothalamus, and a good landmark that separates the medial from the lateral hypothalamus. Like the stria terminalis, the fornix takes an indirect route, doing a back dive out of the hippocampal formation, through the septal region, anterior thalamus and hypothalamus to finally terminate in the mammillary nuclei.

Mammillothalamic Tract*: another tract that is recognizable, and in proximity to a portion of the fornix. It sends projections from the mammillary nuclei to the anterior thalamic nuclei. Collaterals of these axons descend, forming the mammillotegmental tract, a dense bundle terminating in tegmental nuclei and a reticular nucleus that appear to be involved in head movements (and therefore, assist the mammillary nuclei and hippocampal formation in spatial memory). See figure bottom of page 2.

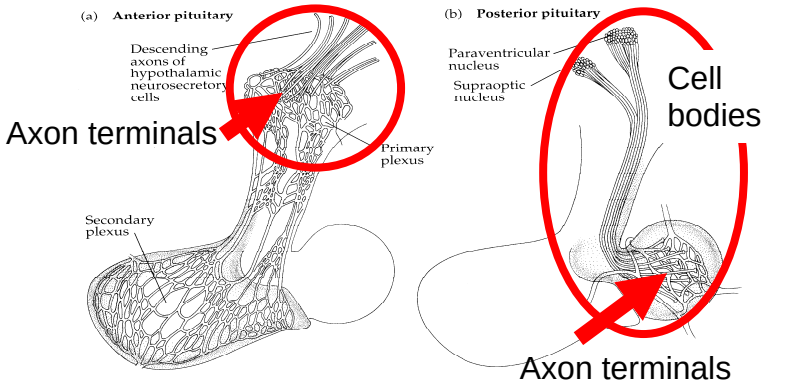
Unidirectional neural connections of the hypothalamus

Retinohypothalamic tract*: These axons exit the optic nerves at the optic chiasm and project directly into the suprachiasmatic nucleus, the "clock" in the brain. Light information "sets" the clock; this will be discussed further in the Hypothalamus II lecture.

Hypothalamohypophyseal tract*: Hypothalamic axons from two cell groups, the paraventricular nucleus and the supraoptic nucleus project directly into the posterior pituitary, secreting neurohormones into the posterior pituitary circulation (see later discussion of PVN and SON).

The hypothalamus regulates endocrine function.

Hypothalamic regulation of endocrine function:



adapted from Krieger and Hughes, 1980

1) **Posterior pituitary regulation:**

Large vasopressin and oxytocin producing cell bodies, called **magnocellular neurons**, are located in the paraventricular and supraoptic nuclei of the hypothalamus. These send axons directly into the posterior pituitary – the hypothalamohypophyseal tract-- to release the hormones directly into the blood stream. Oxytocin and vasopressin are derived from larger precursor molecules (neurophysins) that are packaged in dense core vesicles; the neuropeptides are cleaved from the precursor as they travel down the axons. Action potentials are generated in these neurons in response to specific stimuli, and, upon firing, the axon terminals release their hormones into the peripheral circulation. Unlike the anterior pituitary hormones, oxytocin and vasopressin of magnocellular origin act at a distance, and therefore have a somewhat longer half- life.

Magnocellular Vasopressin: primary function is to promote water retention and resorption (renin-angiotensin system); other name is antidiuretic hormone.

Magnocellular Oxytocin functions:

Milk let down reflex- upon stimulation of a neural pathway from the nipples, oxytocin is released and initiates a milk let-down reflex in the mammary glands.

Uterine contractions-- Oxytocin stimulates cervical and uterine contractions; the synthetic form “Pitocin” or “ptocin” is used to initiate or speed up labor. The word oxytocin is derived from the Greek for “fast labor”.

Love/social bonding/decreased anxiety—the “love” hormone. Release

during suckling and social encounters promotes maternal/social bonding, affection, trust and reduces anxiety; vasopressin has similar effects in males. An inhaled form of oxytocin is currently in clinical trials as a treatment for anxiety, as well as for autism; autistic individuals have lower levels of this hormone. Oxytocin has been shown to alter cooperation and altruism toward a group member and aggression toward non-group members (in human subjects).

2) **Anterior pituitary regulation:**

Hormones from hypothalamic neuroendocrine neurons that regulate anterior pituitary function reach the anterior pituitary via the portal system. **The pituitary portal system, also called the hypothalamohypophyseal portal system, consists of two capillary beds with communicating veins. Neuroendocrine neurons in the hypothalamus that affect the anterior pituitary project to the median eminence (also known as the infundibulum, pituitary stalk or hypophysis), terminating on specialized blood vessels in the primary capillary plexus.** The hormones are then carried via the portal veins to the secondary capillary plexus where they leave the bloodstream and act on pituitary cells to facilitate or inhibit release of pituitary hormones; these neurohormones are referred to as hypophysiotropic hormones. Not surprisingly, the hypothalamus and pituitary are extremely well vascularized, with blood arising directly from branches of the internal carotid artery.

Major hypothalamic releasing or inhibiting hormones	Anterior Pituitary Hormone	Target organs and major peripheral hormone	Major physiological actions
+Corticotropin releasing hormone (CRH)	Adrenocorti-cotropic hormone (ACTH)	Adrenal cortex: glucocorticoids	Stress responses; immune function
-Dopamine +Thyroid releasing hormone	Prolactin	Mammary gland (neural reflex feedback)	Promotes milk production; Alters libido, decreases gonadal steroid production*
+Gonadotropic hormone releasing hormone (GnRH) -Gonadotropic hormone inhibitory hormone (GnIH)	Luteinizing hormone (LH) Follicle stimulating hormone (FSH)	Ovaries: estradiol, progesterone Testes: androgens	Control of reproductive function
+Growth hormone releasing hormone (GHRH) -Somatostatin	Growth hormone (GH)	Cartilage Liver, adipose tissue: IGF-1	Promotes growth, calcium uptake. Major anabolic hormone; regulates metabolism of proteins, carbohydrates and lipids; glucose uptake and gluconeogenesis
+Thyrotropin releasing hormone (TRH)	Thyroid stimulating hormone (TSH)	Thyroid gland: thyroid hormone production	Metabolism, cardiac output, respiration, heat production

*drugs that affect dopamine synthesis or release may affect sexual function via alterations in prolactin secretion.

More blood flows through the median eminence and the pituitary portal system than through coronary arteries.

Important points to review regarding hypophysiotropic hormones:

1) These are small molecules (for example, TRH is 3-amino acids in length) with a short half-life; most are neuropeptides, but others are neurotransmitters. All have a short half-life. The hormones act via G-protein coupled receptors.

2) Co-regulatory molecules are often secreted in addition to the primary hypophysiotropic hormone, depending on specific contextual cues. Alone, these may have no effect on anterior pituitary secretion, but they may augment or inhibit the effect of the primary hypothalamic hormone. For example, in response to especially strong stressful stimuli, CRF containing cells upregulate synthesis and release of vasopressin; co-release of CRF and vasopressin enhances ACTH release.

3) At least 35 of these co-regulatory transmitters and peptides have been identified to date; these are important therapeutic targets.

4) Many of the hypophysiotropic hormones are players in other regions of the nervous system. For example, somatostatin is an important neuropeptide in the cerebral cortex.

Alert! Alert! The following is for those of you who are interested in the history of medicine and science, and how progress proceeds… if you are not, skip it! As for me, historical background helps me remember things…. Until 1969, most endocrinologists believed that the anterior pituitary controlled the gonads and brain independent of neural input, even though it had been discovered earlier in the century that the posterior pituitary secreted substances that were made in the brain but acted peripherally. It was in the late 1930's that Geoffrey Harris first proposed that the anterior pituitary was regulated by hypothalamic neurons. The proof required isolation of a substance produced by neurons that could elicit anterior pituitary hormone release-- this initiated a race to discovery that involved dozens of labs and over 30 years of effort, and similar research continues today, as new hypothalamic releasing factors and co-modulatory peptides continue to be isolated and characterized. Originally in the late 1930's the research teams set out to isolate CRF because an excellent bioassay for glucocorticoids was available; initial evidence of the existence of the releasing factor and its chemical nature as a peptide wasn't reported until 1955, and further attempts to characterize the factor proved difficult. Ultimately, TRH was the first to be identified, in 1969, because it was the smallest of the neuropeptides, being only 3 amino acids long. TRH (and later, several other neuropeptides) was discovered by Guillemin and Schally, who originally worked together but later became arch rivals and hated each other; their competition fueled the race and their two separate publications were eventually simultaneously published. To isolate 1 mg of TRH required endurance, persistence, and 300,000 sheep hypothalami (roughly a ton of tissue), a major freezer "incident" in which years worth of samples were lost—and a fight for funding at NIH because some endocrinologists decreed that anything requiring over 30 years to isolate probably didn't exist. CRF, now CRH, the original goal, turned out to be a more difficult-to-isolate 40 amino acid peptide, and after a mere 100,000 sheep hypothalami collected by a different group, and failed attempts by numerous other labs, the structure of CRH was finally reported in 1981 by Wylie Vale's group. A long lasting historical "accident' of the rivalry between Guillemin and Schally, and one that impacts you as a student, is that the terms "gonadotropin hormone- releasing hormone" or GnRH (the Guillemin term) and "luteinizing hormone releasing hormone" or LHRH (Schally's term) are both in use for the identical peptide—with both terms receiving about 30,000 PubMed "hits" since 1990. Half of the 1977 Nobel Prize in Physiology and Medicine was awarded to Rosalyn Yalow, developer of the radioimmunoassay, with the other half shared jointly by Guillemin and Schally, an ironic twist to their decades-long rivalry. Geoffrey Harris did not live to see the discovery of the molecules he had so clearly predicted decades earlier.

Hypothalamo-pituitary "axes"—examples related to anterior pituitary

Hypothalamo-pituitary-gonadal axis (HPG): Reproduction.

Gonadotropin releasing hormone (GnRH) from hypothalamus stimulates release of pituitary LH and FSH that act on ovaries and testes, increasing synthesis of androgens, estrogens, and progesterone that then provide both positive and negative feedback onto hypothalamus and pituitary (note that these "gonadal steroids" are also produced elsewhere in the body (e.g. adipose tissue, the adrenal glands, the brain) and contribute to homeostasis of various non-reproductive tissues; eg bone, cardiovascular system in addition to reproductive functions). Pulsatile release of GnRH is critical to normal function.

Hypothalamo-pituitary-adrenal axis (HPA): Stress.

Corticotrophin releasing hormone (CRH) from the hypothalamus stimulates release of adrenocorticotrophic hormone (ACTH) by the pituitary. This stimulates production and release of corticosteroids. Glucocorticoids, like cortisol, affect metabolism and inflammation (eg steroids are often given to combat inflammatory processes at work in asthma), whereas mineralcorticoids, like aldosterone, affect salt retention and fluid balance, and together with hormones from the adrenal medulla, mediate stress responses and then feedback onto the brain and pituitary.

Hypothalamo-pituitary-thyroid axis: Metabolism.

Thyrotropin releasing hormone (TRH) from the hypothalamus stimulates thyroid stimulating hormone production and release by pituitary which in turn stimulates production and secretion of thyroid hormones (thyroxine and triiodothyronine) from the thyroid gland. These affect basal metabolic rate and nutrient metabolism, heart rate, and respiration. These hormones then provide negative feedback onto the hypothalamus and pituitary.

Corollary: The receptors for the peripheral hormones are found in the hypothalamus.

The hypothalamus regulates autonomic function.

PVN: The paraventricular nucleus (parvocellular subdivision; pPVN) is the hypothalamic cell group that is most important in regulation of autonomic function. It is often called the "head ganglion" of the autonomic nervous system because it coordinates both the parasympathetic and sympathetic responses. In general, the autonomic nervous system operates without major need for input from the hypothalamus, but when "managerial" decisions are required, the PVN makes them.

> Clinical note, for future reference not exam: It is becoming increasingly clear that pathology of the PVN can contribute to hypertension, depression, and abnormal stress responses that can lead to chronic inflammation (eg Crohn's disease), among other common, and serious, disorders.

The PVN is a critical nodal point in autonomic integration of viscerosensory information and as such has massive inputs from a wide variety of regions, including viscerosensory nuclei in the brainstem (n. tractus solitarius; IX, X), sensory regions of the cerebral cortex, the amygdala (which integrates fear responses), and from all hypothalamic regions including the suprachiasmatic nucleus (the clock in the brain), and the arcuate nucleus (regulates energy balance, growth and reproduction).

Descending projections from the PVN coordinate cardiovascular responses (heart rate, peripheral vasodilation or vasoconstriction), respiration, sweat glands, hair follicles (piloerection), salivary glands secretion, GI motility, pupillary reflexes, bladder function and sexual functions. Very important in fear/defense reactions!

PVN neurons provide direct input to the preganglionic sympathetic neurons in the intermediolateral cell column in the thoracolumbar region.

PVN neurons also provide direct input to preganglionic parasympathetic neurons in the dorsal motor nucleus of the vagus (visceromotor).

The hypothalamus coordinates motivated behaviors.

Motivated behaviors satisfy drives, or motivational states.

Homeostatic drives include, for example, hunger or thirst or the need to sleep. Among the motivated behaviors that satisfy these drives are consummatory behaviors including, feeding, drinking, salt intake, voiding, sleep.

Survival drives include sexual behavior, parental behaviors, courtship (not necessarily in that order), affiliative behaviors (such as social grooming), territoriality, aggression, novelty seeking or curiosity, avoidance of aversive stimulation/stress, sickness behaviors.

The motivated behaviors are not simple reflexes, even in the case of eating to satisfy hunger. The behavioral outputs are often complex and multi-layered and the original stimulus and outcome may not be closely linked.

> For example, maternal behavior consists of a set of behaviors that include nursing, nest building, retrieval and aggression.

Inputs required to initiate and regulate motivated behaviors come from every region already discussed for autonomic and endocrine regulation and include neural, hormonal and other inputs (e.g., temperature, CO2, glucose).

Behavioral outputs involve forebrain reward circuitry, the cerebral cortex, hypothalamic and pontine regions involved in sleep, and midbrain "central pattern generators" that control locomotor output and orienting responses.

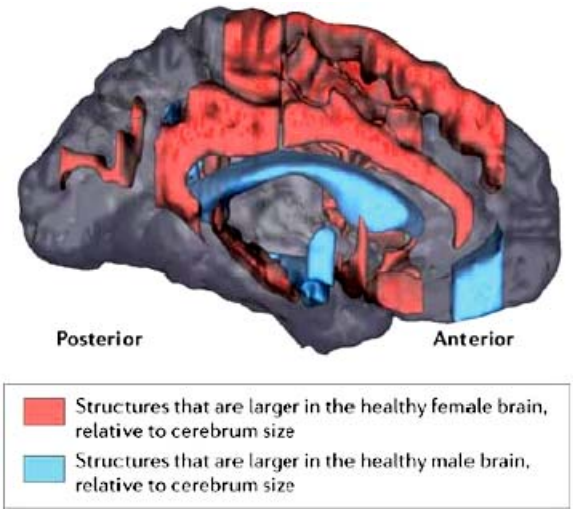
Motivated behaviors are rewarded—that is the forebrain reward circuitry is particularly important in the connections and functions of hypothalamic regions regulating motivated behaviors.

How do these hypothalamic functions work together?

Thermoregulation offers a good example, especially since the "set point" is roughly the same for all individuals. If the room becomes too cold, endocrine, autonomic and behavioral systems become activated to increase energy conservation and production. Over the short term, you will shiver, stop sweating, and your hair will stand on end to increase insulation. You will also increase sympathetic outflow through both neural and endocrine mechanisms. You may go get a sweater and put it on, drink some warm coffee or tea, rub your hands together and huddle. Over the long term, your endocrine system will also alter energy conservation systems so that additional heat is produced. Thus, the endocrine, autonomic and behavioral systems coordinate their activity to maintain body temperature appropriately.

Sex differences in the brain

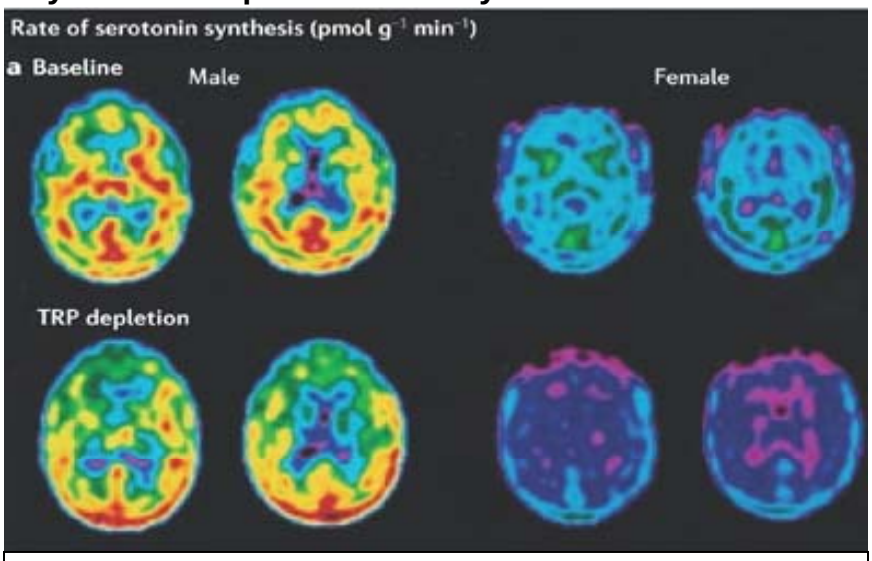
It may seem obvious that hypothalamic or spinal cord structures and chemistry would be different in men and women, boys and girls. After all, men have daily pulses of gonadotropin secretion that regulate testicular function, whereas women have monthly cycles regulating ovarian function, so those parts of the hypothalamus that regulate reproduction and gonadotropin secretion might be different. And men and women have some organs that they don't share, so innervation patterns might be different. And they are: gonadotropin releasing hormone producing neurons are not especially different, but their patterns of activity and regulation are quite different in men and women. In fact, sex differences in the brain are widespread.



Significant differences between the sexes exist in widespread brain regions. The size of the sex differences are related to the presence of sex steroid receptors in the brain regions during critical developmental periods suggesting that sex differences in the adult stem from sex hormone influences on brain development. The figure is best viewed in color. *Adapted from Cahill, Nature Reviews Neuroscience, 2006.*

Sex differences in the nervous system are important clinically.

Men and women differ in the incidence and symptomatology of neurological and mental disorders such as: Parkinson's disease, stroke, Tourette's syndrome, autism and autism spectrum disorders, schizophrenia, attention deficit hyperactivity disorder, drug abuse, Alzheimer's disease* **,** post-traumatic stress disorder, depression*, anorexia/bulimia* (*more common and/or worse symptoms in women). There are sex differences in neural responses to stressors and to treatments for endocrine abnormalities, autonomic dysfunction, cardiovascular disorders, inflammation, and pain.



PET scans were used to measure serotonin synthesis rates in healthy men and women before and after depletion of plasma tryptophan. The mean rate of synthesis was found to be 52% higher in males than in females. Note that unipolar depression involves serotonin dysfunction and does not equally affect men and women. *adapted from Nature Neuroscience, 2006*

Sex differences in the nervous system arise during critical periods in development and are maintained by circulating gonadal hormones.

Sex differences arise predominately because gonadal hormone levels are not the same in males and females. The testes develop more rapidly than the ovaries, and, by the 8th week of gestation, produce testosterone, with levels reaching adult male levels until about week 16, dropping off thereafter until just after birth. For the first 3 months or so after birth, testosterone is again secreted at high levels in boys, and although most of the androgen is bound to a binding globulin, free testosterone levels are still an order of magnitude higher in males than in females. Prenatal testosterone and its metabolite, estradiol, activate both androgen and estrogen receptors which in turn alter protein synthesis and permanently affect structure, chemistry and function of many regions of the central nervous system, including areas related to sensory, motor and cognitive function, not just homeostasis or reproduction per se. Abnormal exposure to steroid hormones during development can inappropriately sexually differentiate the brain, as in the case of congenital adrenal hyperplasia in girls, in which excess levels of adrenal androgens partially masculinize both peripheral tissues and the brain.

Once organized into the masculine or feminine phenotype during early development, gonadal steroids begin to act again at puberty and into adulthood, to sculpt the nervous system and activate particular regions as appropriate to hormone levels. The effects of hormones on neuronal and glial morphology and chemistry are not subtle or difficult to find.

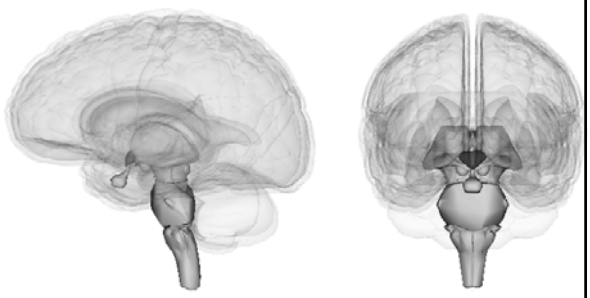
Note that the correct term is "sex differences" (as in male, female; referring to objective biological, genetic differences) not "gender differences" (as in masculine vs feminine, a societal construct that may be self-assigned). The term "gender" is frequently misused as a biological construct.

What you should remember is the concept that sex differences exist in brain structure and function in many brain regions, that these sex differences have a biological basis that depends in part on differential exposure to gonadal hormones during development, puberty and adulthood, and that these sex differences have clinical consequences.

Hypothalamus: Lecture 2

Lydia L. DonCarlos, Ph.D.
CaMP
ldoncar@lumc.edu
Ext 64975

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



http://appsychtextbk.wikispaces.com/Limbic+System

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, arterial blood

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.

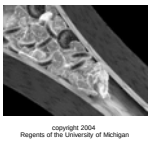
Endocrine mechanisms for heat conservation
Short term:
Increase in sympathetic outflow
Increased adrenal stress hormones
Increased heat conservation

Long term:
Increase thyroid hormone production
Increased metabolic rate
Increased sympathetic activation of brown fat (neonates only)

Autonomic mechanisms for coordinating thermoregulation

heat conservation

Stop sweating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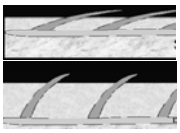
Peripheral vasoconstriction



Piloerection

Coordination of thermoregulation by the hypothalamus

Motivated behavioral mechanisms of heat conservation in response to cold

Add Clothing

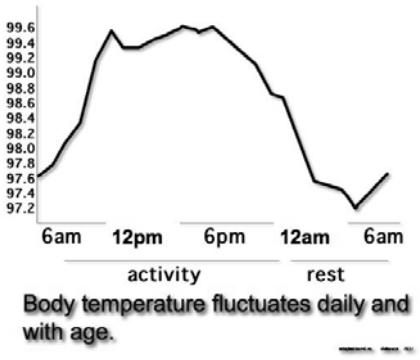
Huddle

Ingest warm Fluid or food.

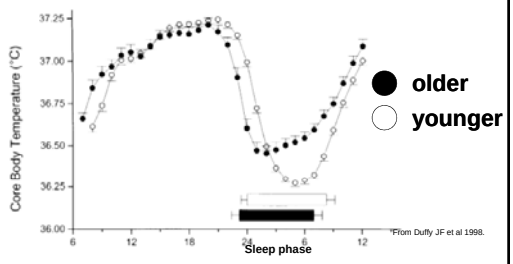
	Heat conservation	Heat dissipation
Endocrine	**Increase TRH** **Increase CRF/ACTH/cort**	**Decreased TRH** **Decrease adrenal activation**
Autonomic	**Peripheral vasoconstriction** **Piloerection** **Shivering** **Decreased sweating** **Epinephrine release from adrenal medulla**	**Peripheral vasodilation** **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**

What regulates thermal control?

Gonadal hormones –slight increase in core temperature at ovulation
hot flashes (core temperature increases 5-2-minutes before subjective response)
Emotional stimuli
CO2
Circadian rhythms/arousal state
Viral infection
Bacterial infection



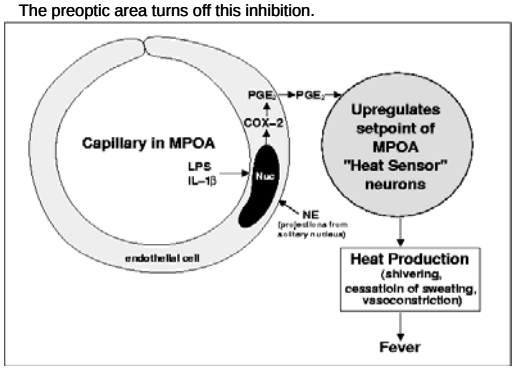
Body temperature fluctuates daily and with age.



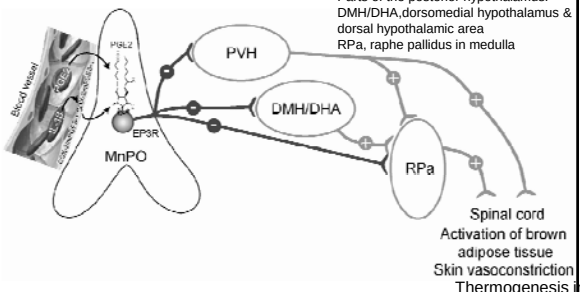
*From Duffy JF et al 1998.

The timing of the highs and lows in core body temperature and the magnitude of the fluctuation change with age.
The daily fluctuation in core temperature is 1.8º F/1º C.
The lowest temperature is 0.5º F lower in the younger group.

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



MnPO,median preoptic n.
PVH, paraventricular n of hypothalamus
Parts of the posterior hypothalamus:
DMH/DHA,dorsomedial hypothalamus & dorsal hypothalamic area
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.
Posterior hypothalamus and raphe activate shivering, thermogenesis by brown fat
(Aches and pains due to increased thermogenesis in muscle)

Adapted from Nature Neuroscience 2007

Control of shivering– probably posterior hypothalamus sends projections to reticular formation; tonically inhibited by preoptic area; other areas contribute as well

Sickness behavior: an adaptive, coordinated neuroimmune response.

Fever

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

Behavioral components:

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

Clinical notes:

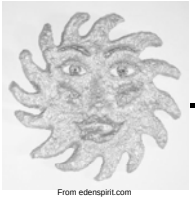
Hot flashes involve an increase in core body temperature that precedes subjective experience of the hot flash. Response to fluctuations in gonadal steroid levels in both women and men.

Spinal cord injury patients have limited abilities to thermoregulate, other than behaviorally.

Heat stroke is dangerous and not a form of fever.

Postoperative shivering after inhalation anesthetics is common and may contribute to pain.

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



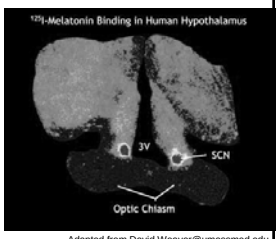
From edenspirit.com

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
Constant darkness or constant light–
have a rhythm slightly longer than 24 h, but still have a rhythm.
SCN sets the clock.

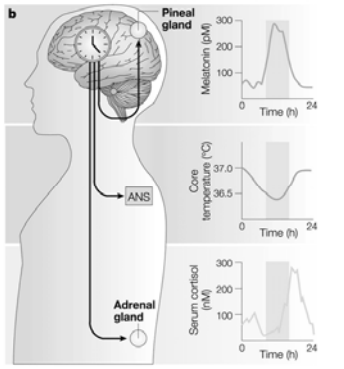


Adapted from David.Weaver@umassmed.edu

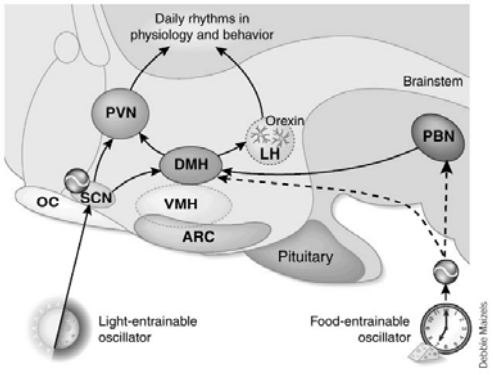
Dorsomedial n. = 2º clock

Entrained by feeding schedule
communicates reciprocally with the SCN

SCN regulation of circadian rhythms

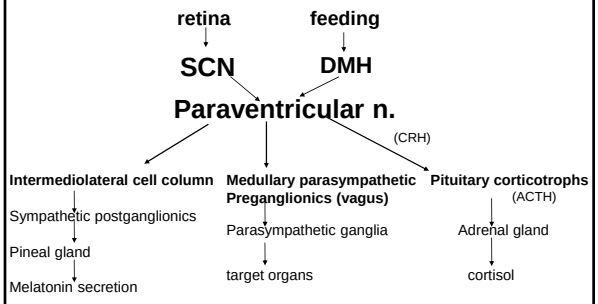


Hastings et al., 2003 Nature Reviews Neuroscience



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)

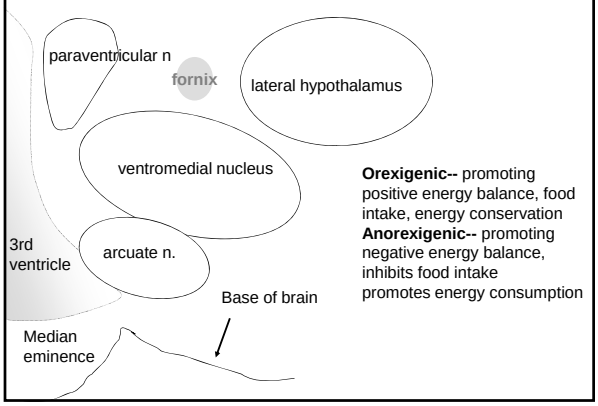
These can result in disturbances of GI tract, menstrual cycle, sleep, and altered stress responses.

Seasonal affective disorder

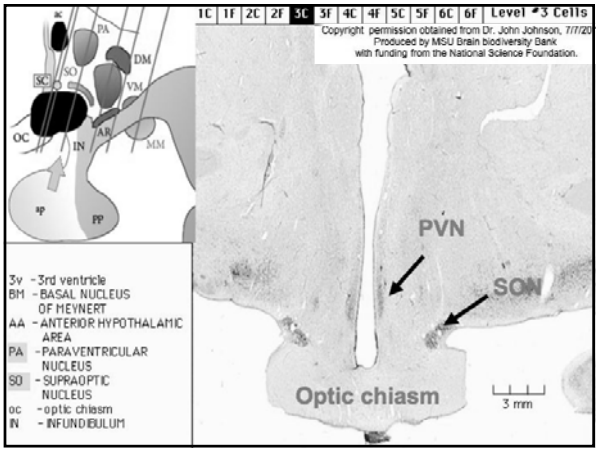
Hypothalamic regulation of energy balance

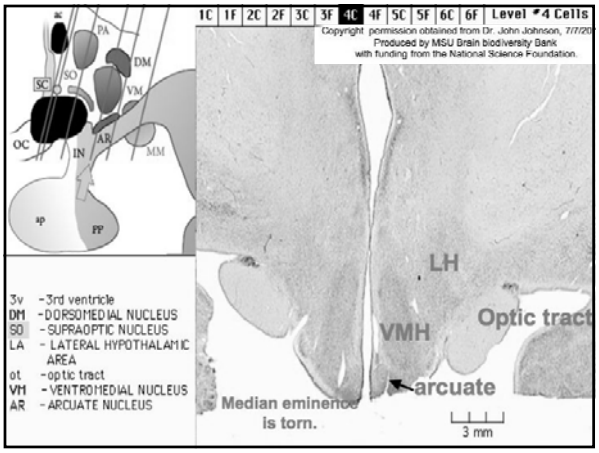
- Complex
- Set point is individual
- Set point may change over time (contrast with temperature)
- Small changes in nutrient intake and energy use can have marked effects on body weight
- Energy use is modified by behavior, endocrine and autonomic systems
- Obesity, anorexia, cachexia (wasting), eating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

Key hypothalamic regions involved in energy balance.



Orexigenic-- promoting positive energy balance, food intake, energy conservation
Anorexigenic-- promoting negative energy balance, inhibits food intake promotes energy consumption

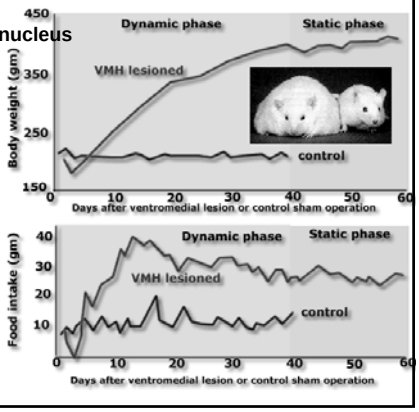




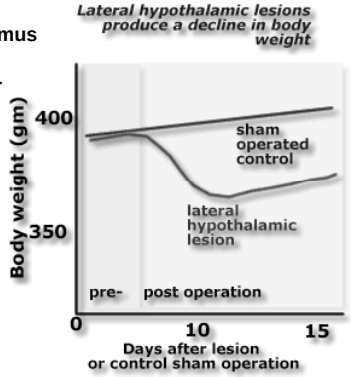
The ventromedial nucleus is often called the satiety center.

(Satiety= state of being full.)

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



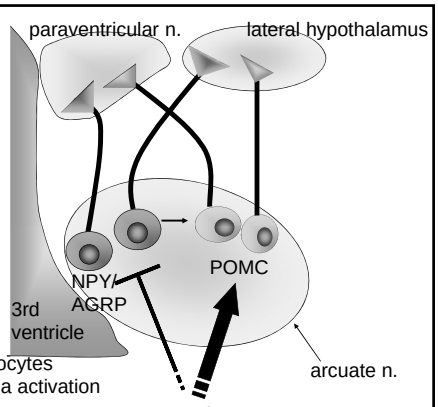
The lateral hypothalamus Is often called the "feeding center"-- again, not exactly accurate.



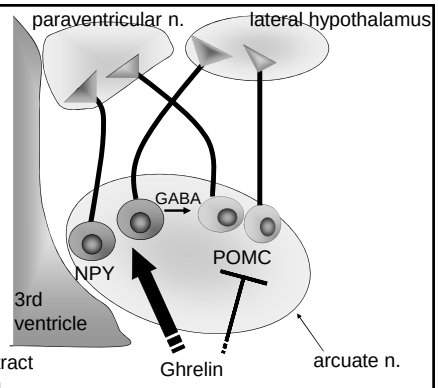
Genetic obesity due to recessive, spontaneous single locus point mutations.

ob/ob mouse:
Leptin deficient

fa/fa rat:
Leptin receptor deficient



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.

Peripheral signals to hypothalamus re: energy balance--

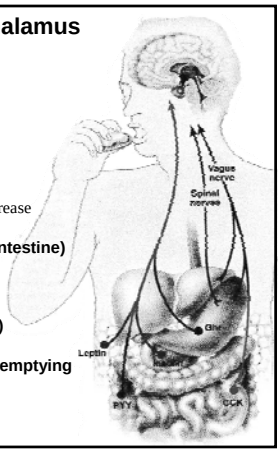
Adipokines:
Hormones from white adipose tissue
Leptin (satiety signal)

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



Clinical notes on energy homeostasis

Obesity-- genetic, environmental (the thrifty gene)

Cachexia-- associated with specific illnesses

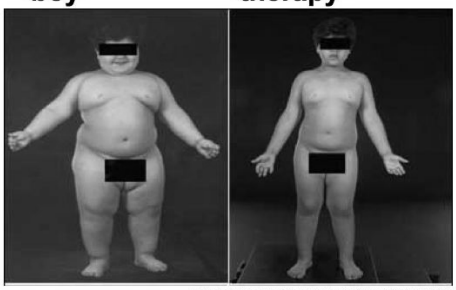
Anorexia/bulimia

Fertility in women

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

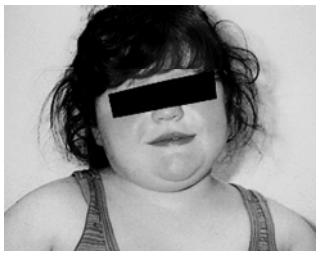
Leptin deficient boy

Same boy Post Leptin therapy

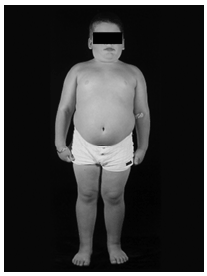


Adapted from THE GENETICS OF OBESITY IN HUMANS 2005
Prof.Stephen O'Rahilly, MD and I. Sadaf Farooqi, MD

3 year old girl with human POMC deficiency



6-year old male patient with melanocortin 4 receptor gene deficiency



The precursor, POMC, is cleaved into numerous peptides, including alpha-melanocyte stimulating hormone. Alpha-MSH binds to the melanocortin 4 receptor, which activates satiety and decreases food intake.

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

The MC4R mutation accounts for about 6% of severe childhood obesity and is the most common monogenic obesity disorder yet identified.

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

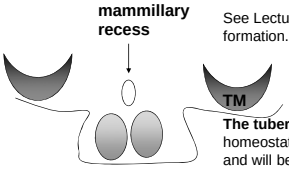
Show that body weight and appetite are controlled at multiple different levels. Also provide possible pharmacologic tools.

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

Epigenetic effects of nutrition on hypothalamic function can cross generations.

Why are't we discussing the mammillary nuclei 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.

Cartoon of hypothalamus, at mammillary level base of the diencephalon

HYPOTHALAMUS 2 2011

3 Examples of hypothalamic functions

A Reminder:
The hypothalamus has two interrelated functions:
1) to maintain maintain homeostasis, that is, a stable internal environment, by regulating energy and fluid balance, growth, temperature, daily rhythms, arousal, reproduction, and stress and immune responses

2) to regulate appetitive and defensive behaviors such as feeding, drinking, sex, parenting, sleep and sickness behaviors.

Example 1:
Thermoregulation—a classic example of hypothalamic homeostatic mechanisms

Normal oral temperature has traditionally been reported to be maintained at 98.6^{o}, although it is probably closer to 98.2^{o}, with some individuals averaging either a degree under or over, but not much more variation than that. Temperature regulation is essentially a steady-state system in which heat produced equals heat out.

Warm-blooded animals are able to generate and preserve heat, as well as dissipate heat physiologically, through rapid autonomic activation as well as slower hormonal mechanisms and also are capable of responding to changes in temperature behaviorally, by altering the external environment.

Heat production occurs through the metabolic activity of the body, mostly in the larger internal organs, as well as through physical exercise and activation of brown fat.

Heat transfer occurs through convection, evaporation and radiation, and is prevented by insulation. The hypothalamus directs the autonomic nervous system to alter heat production as well as heat transfer (predominately by affecting convection, evaporation and insulation), whereas behavioral mechanisms include the above as well as radiant heat exchange.

The primary control system and rheostat (thermal set point) for thermoregulation is found within the medial preoptic area (MPOA).

The region is often called the preoptic area of the anterior hypothalamus; this is somewhat inaccurate because, although the preoptic area and hypothalamus function as a unit, they are developmentally somewhat distinct, in that the POA is telencephalic whereas the hypothalamus is diencephalic).

Temperature information reaches the MPOA, the main integrative region for temperature control, in several ways.

---**Temperature sensitive neurons exist in the MPOA** that are directly sensitive temperature. Some respond to heat, others to cold. Thus, alterations in body temperature that affect the body core are sensed directly by MPOA neurons.

----**Peripheral temperature receptors** sense skin temperature, as affected by air currents, humidity, insulation, and light absorption, as well as actual temperature; this information is transmitted from peripheral sensory neurons to the MPOA via relays in the brainstem.

The MPOA then coordinates various autonomic, behavioral and endocrine outputs to regulate heat conservation of dissipation. A variety of output pathways are involved.

The Posterior Hypothalamus (PH) is a secondary thermoregulatory center and activates sympathetic activity as well as shivering, therefore, heat conservation. Temperature information from spinal cord relays and from the MPOA is transmitted to the posterior hypothalamus. The posterior hypothalamus then sends direct projections to the lateral horn of the spinal cord, activating sympathetic pathways as well as motoneurons, increasing muscle tone and initiating shivering.

Limited sudomotor (sweat gland) and vasomotor responses may occur via local regulation at the level of the spinal cord, but these responses play a minor role in thermoregulation.

Heat conservation occurs via:

Autonomic/neural mechanisms:	Peripheral vasoconstriction
	Piloerection (goose bumps; erector pilli muscles)
	Shivering thermogenesis
	Decreased sweating
	Epinephrine release from adrenal medulla (increases metabolic activity; ATP production by muscles)
Endocrine mechanisms:	Increasing metabolic activity via:
	Increased TRH, TSH and thyroid hormone production
	Increased adrenal corticosterone release
	Increased production of appetite-stimulating hormones and neurotransmitters

Heat dissipation occurs via:

Autonomic/neural mechanisms: Peripheral vasodilation
Sweating*
Panting
Reduced sympathetic activity overall
*Not all animals sweat

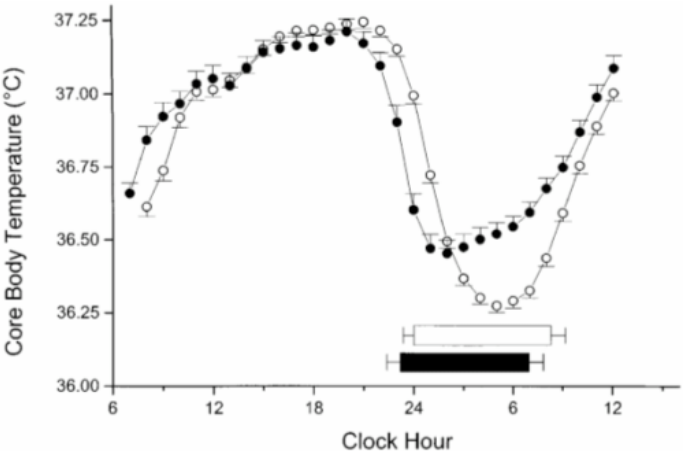
Endocrine mechanisms: Decreased adrenal corticosterone release
Decreased TRH release
Decreased production of appetite-stimulating hormones and neurotransmitters

Plus, motivated behavioral mechanisms affect body temperature:

Shelter	Clothing	Ingestion of food or liquid
Fanning	Swimming	Altered exertion (ie siestas in summer)

Given the considerable changes in ambient temperature that can occur rapidly or seasonally in non-temperate climates, adjustments must be made continually. Age can affect body temperature; it is lower in babies, increasing at puberty and into middle age. These changes are due to alterations in hypothalamic mechanisms governing body temperature. Ingestion of food or beverages, physical exertion, strong emotions, and, in women, the phase of the menstrual cycle (slightly elevated at ovulation) all impact regulation of body temperature. Changes in skin and body temperature also occur as a result of time of day, as there is a normal circadian rhythm in temperature, with core body temperature being lower at night during inactivity. Furthermore, during REM sleep and during deep anesthesia, body temperature varies with the ambient temperature.

Another point of clinical relevance is that spinal cord injury affects the ability to thermoregulate if descending hypothalamic input to the thoracolumbar sympathetic neurons is disrupted, limiting vasomotor and sudomotor mechanisms, as well as shivering, for thermoregulation.



Core body temperatures for young and older subjects.
Solid circles = Older subjects
Open circles = young subjects
Solid bars = sleep in older subjects
Open bars = sleep in younger subjects.

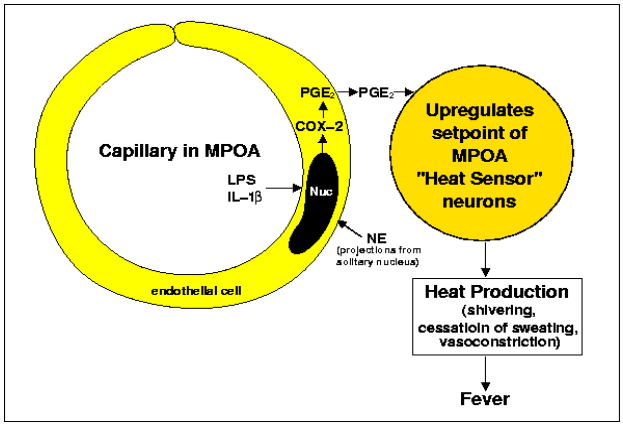
The daily fluctuation in core temperature is 1.8° F/1° C.
The lowest temperature is 0.5° F lower in the younger group.

The timing of the highs and lows is different in young vs old subjects.

From Duffy JF et al 1998.

Fever is regulated by the medial preoptic area.

Thermogenesis is normally inhibited, but specific activation of the medial preoptic area can turn off this inhibition via descending pathways.



Cytokines are produced in response to peripheral inflammation and bacterial infection. These upregulate cyclooxygenase 2 production, and therefore prostaglandin E2 (PGE2), in macrophages of the lung and liver as well as and endothelial cells in the preoptic area. The PGE2 diffuses into the preoptic area where it turns off tonic inhibition of thermogenesis, essentially altering the set point of heat sensitive neurons. The projections of the preoptic area modify sympathetic activity, upregulating peripheral vasoconstriction and muscle activity, as well as activating metabolism of brown fat. Ultimately, if successful, the increased temperature both activates the immune system and kills bacteria.

During fever, some of the normal thermogenesis pathways are upregulated to a higher than normal degree, and others are not activated. For example, although actual physical exertion is generally reduced, nevertheless, activation of ATP production causes aches and pains normally associated with being sick. Instead of increasing appetite, those neurotransmitters and hormones that would normally upregulate food intake are shut down, in part because systems that promote normal arousal states are shut down.

Fever and Sickness behaviors:

Given that cytokines (peripheral as well as those produced by the brain) act by provoking autonomic and endocrine responses in the hypothalamus, it is perhaps not surprising that they provoke a well-coordinated set of motivated behaviors referred to as "Sickness Behaviors".

These behaviors include:

Sleep (Note: coordination of sleep occurs within the preoptic area as well)
Food aversion
Social isolation
Fatigue/malaise
Hypersensitivity to light, sound
Hyperalgesia (aches and pains due to thermogenic response of muscles)

This coordinated response is an important adaptive mechanism to fight bacterial infections and promote healing, allowing immune responses to clear infection, and preventing transmission of infections from individual to individual.

On the other hand, long term, chronic exposure to cytokines, due to long term inflammatory processes or dysregulation of brain cytokine production, can have profound behavioral consequences, leading to major depression in some individuals.

Heat stroke is caused by an inability to dissipate sufficient heat. Heat stroke is not the same as fever, although high heat in later phases causes the tonic inhibition of thermogenesis by the preoptic area to go haywire, thus shutting down important cooling mechanisms such as vasodilation and sweating. It is usually caused during by physical exertion when ambient temperatures and humidity are high. Behavioral mechanisms—taking breaks, getting sufficient hydration, and jumping in a pool or getting out of the heat can prevent most cases of heat stroke.

Example 2:

Circadian rhythms

Circadian rhythms are daily rhythms that serve to entrain the body so that functions are coordinately regulated. Hormone secretion, activity (sleep or wakefulness), and body temperature all show daily rhythms. The timing of the clock is approximately 24 hours, although under constant dark conditions, it will become longer.

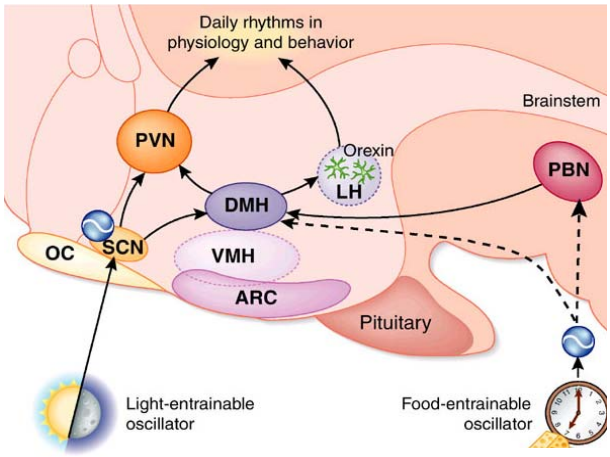
Circannual rhythms are annual rhythms that correspond to season, and can trigger changes in food intake, reproduction, sleep patterns, and trigger hibernation and hibernation-like behaviors and physiological functions.

The Suprachiasmatic nuclei of the hypothalamus (SCN) are the primary "biological clocks" in the brain. These small, bilateral collectiosn of neurons sit just above the optic chiasm, receiving axons via the retinohypothalamic tract that begins in light sensitive neurons of the retina and exits from the optic chiasm to innervate the SCN.

Light signals carried by the retinohypothalamic tract "set" the SCN clock.

The Dorsomedial nucleus of the hypothalamus (DMH) is a secondary "clock" in the brain. Feeding signals from the gut are relayed to the DMH by the parabrachial nucleus of the brainstem. The DMH also plays a role in energy homeostasis per se.

So both light and food intake entrain daily rhythms.



Hypothalamic nuclei
SCN- suprachiasmatic n.
PVN- paraventricular n.
DMH- dorsomedial n.
VMH- ventromedial n.
ARC- arcuate n.
LH- lateral hypothalamus

oc- optic chiasm

orexin—LH peptide;
promotes wakefulness

Adapted from Nature Neuroscience 9, 300 - 302 (2006)

The SCN and DMH projections converge on the PVN which then communicates timing information to the hypothalamo-pituitary-adrenal axis (to regulate cortisol), the sympathetic preganglionic neurons (regulating, e.g., melatonin secretion), and the dorsal motor nucleus of the vagus (parasympathetic; e.g. altering GI motility), as well as regulating some aspects of feeding behavior and other motivated behavioral systems.

Importantly, the SCN also communicates with the DMH directly. The DMH then sends projections to neurons in the lateral hypothalamus that produce orexin. Orexin neurons are involved in arousal and wakefulness as well as food intake and reward (so important in drug abuse). These neurons have widespread projections that largely parallel those of the brainstem monoaminergic pathways that are also involved in arousal.

Orexin refers to “orexic” or “orexigenic” (see discussion below on energy homeostasis and lecture on sleep) as in, stimulating eating and energy conservation, (compare with “anorexic” or “anorexigenic” which you are probably familiar with.

Clinical significance of disrupted circadian rhythms

Jet lag—disturbances of sleep, GI motility, menstrual cycle while adjusting to new time zone

Seasonal affective disorder—depression due to insufficient natural

Shift workers—confusion, disorientation, clumsiness, poor reflexes due to activity during normal nighttime hours

Example 3:

Energy Homeostasis

The hypothalamus regulates all aspects of energy balance through complex, integrated mechanisms. This region maintains a set point, around which daily energy intake and utilization is maintained. Unlike the set point for body temperature, which is similar from person to person, the set point for body weight varies from person to person, and even varies for the individual, changing with the season, during puberty, during pregnancy, with age and with specific types of illness. Relatively small differences in the balance of energy intake vs use can have large effects on body weight; the equivalent of 100 extra calories a day more than used, over the course of a year, can add up to a ten pound weight gain.

In women, energy homeostasis and reproduction are intimately associated, and the hypothalamic regions controlling these two functions largely overlap. Pubertal onset is linked in part to sufficient fat stores. Maintaining normal menstrual cycles also depends on sufficient fat stores; women who are elite athletes with low body fat and women who are anorexic frequently stop menstrual cycling.

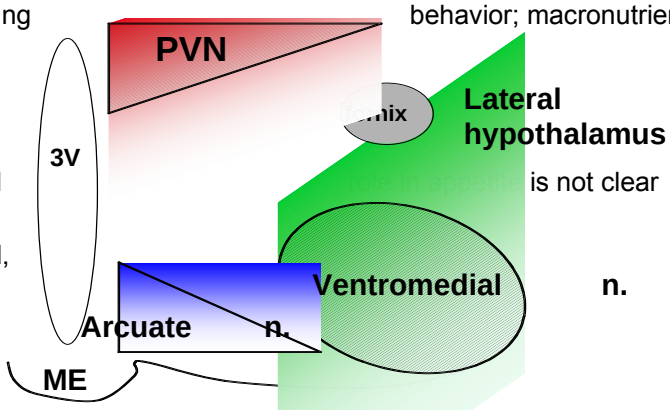
The major cell groups known to be involved in regulation of energy balance are:

Arcuate nucleus: receives peripheral signals; transmits this information to other cell groups

Paraventricular nucleus: feeding behavior; macronutrient selection (specific appetites)

Ventromedial nucleus: Considered the satiety center (the state of being sated; "full"), but actual

Lateral hypothalamus: Arousal, wakefulness (hunger promotes wakefulness and activity)



Cell groups in the tuberal hypothalamus that play a role in energy balance. Cartoon is of a coronal section of ½ of hypothalamus; ME is median eminence and base of brain.

Before 1994, most of our understanding of energy regulation by the hypothalamus was based on lesion studies and some naturally occurring genetic models in which obesity was inherited; progress was slow. Molecular genetics analyses paved the way to an enormous acceleration in the pace of new knowledge on appetite regulation and energy expenditure/conservation.

The concept of the ventromedial nucleus as a "satiety center" persists, but is considered somewhat out-of-date. Over 70 years ago, it was demonstrated that lesions of the ventromedial hypothalamus cause animals to increase food intake and rapidly gain weight; in rats, the lesion led to a doubling of body weight within a month. The ventromedial nucleus was therefore dubbed "the satiety center", because without it, animals gained weight. This idea has lost favor, in part because appetite regulation involves more than one cell group, not a single center. In addition, it was later shown that animals with ventromedial hypothalamic lesions will not work as hard as control animals for a food reward, so the motivation to eat (which we would associate with hunger) is actually lower. Furthermore, stimulation of the ventromedial nucleus has effects on lipid storage; the hormones produced by adipose tissues can affect appetite. Finally, the ventromedial nucleus clearly does play a role in social and sexual behaviors as well as energy balance.

Similarly, the **lateral hypothalamus** was considered to be a "feeding center" based on the results of lesion studies, and this too is considered an out-of-date concept. Lesions of the lateral hypothalamus (LH) caused animals to lose weight, and the lateral hypothalamus was thus referred to as the feeding center. Further examination showed that LH lesioned animals not only ate less, but also drank less, were unresponsive to many stimuli, and were lethargic. Eventually, genetic studies of narcoleptic (sleep-walking) humans and dogs identified a mutation in a gene encoding a peptide now referred to as "orexin". Orexin is produced by LH neurons and these neurons project to many parts of the central nervous system, promoting arousal and activity, as well as food intake and these neurons participate in reward circuitry as well. So, although the LH does respond to peripheral signals and have some effects on feeding directly, in addition, being awake is typically important to food seeking and eating….

Hypothalamic regulation of feeding and energy use responds to peripheral signals.

Leptin is a satiety signal produced by adipose tissue. Higher levels of leptin indicate higher fat stores. It was the first of many "adipokines" (hormones produced by adipose tissue) to be discovered and shown to affect hypothalamic function. Leptin (Greek for "thin") was discovered in 1994 when the identity of the protein encoded by the "obese" gene was discovered in a strain of mouse; in these ob/ob mice, a recessive, single locus mutation causes profound obesity. Giving leptin to the ob/ob mice normalized weight. However, leptin administration did not alter weight in another model of obesity, also caused by a recessive, single locus mutation, the fa/fa rat. Instead, mutation in the fa/fa rat involves the leptin receptor. Identification of leptin led to an acceleration of research and greater understanding of the hypothalamic basis of appetite regulation and energy balance.

Ghrelin is a hunger signal produced mostly by the GI tract. Ghrelin (growth hormone secretogogue) was also recently discovered. Ghrelin levels increase linearly with time since a last meal. Ghrelin promotes hunger and food intake by acting on the hypothalamus. Multiple other gut signals convey a message of satiety (rather than hunger) to the hypothalamus. Sources of ghrelin are the stomach, liver, and brain, among others.

What happens in the hypothalamus?

Within the arcuate nucleus, there are two sets of neurons that are key to appetite regulation and energy balance; these neurons have receptors for leptin, ghrelin and other hormones and peripheral signals related to energy balance.

POMC neurons in the arcuate nucleus are anorexigenic.

POMC (proopiomelanocortin) neurons inhibit eating and promote energy utilization.

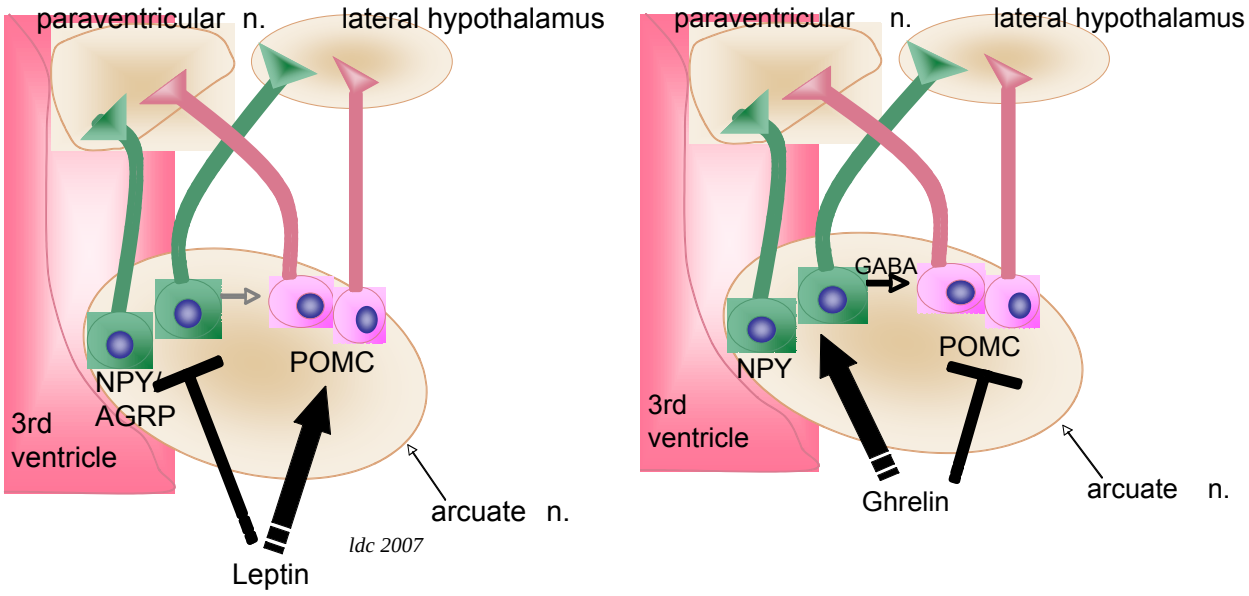
POMC is can be cleaved into many separate, bioactive peptides. In the arcuate nucleus, POMC is the precursor for alpha melanocyte-stimulating hormone; its receptor is melanocortin 4 receptor, MC4R.

Neuropeptide Y/agouti related peptide producing neurons in the arcuate nucleus are "orexigenic".

NPY neurons stimulate eating and promote energy conservation.

POMC and NPY neurons project to the paraventricular nucleus and lateral hypothalamus to appropriately inhibit or stimulate food intake and energy use.

Each of these sets of neurons produces numerous additional neuropeptides that also modify energy homeostasis.



Some players in the "see-saw" model of energy homeostasis

Hormone	Source	POMC neurons	NPY neurons	Appetite	Energy use
Leptin	Fat	Stimulates	Inhibits	Decreased	Increased
Ghrelin	GI tract; brain	Inhibits	Stimulates	Increased	Decreased

Other peripheral and central signals also regulate, directly or indirectly, the activity of POMC and NPY neurons in the arcuate nucleus, including: additional gut peptides (cholecystokinin, pancreatic polypeptide Y, among others); additional adipokines from fat; insulin; glucose; adrenal and gonadal steroid hormones; heat and cold; light; and gastric fullness (conveyed via vagus nerve).

Clinical problems associated with hypothalamic regulation of energy homeostasis.

Obesity: The incidence of obesity is increasing and has serious health consequences.

Mutations of genes encoding leptin, POMC, and MCR4 are known to cause obesity. In each of these, the pattern of increased food intake is different, as is the severity of the obesity. The involvement of so many different neuropeptides and receptors in energy homeostasis, many more than mentioned here, makes it likely that additional mutations will be identified that induce specific types of obesity.

For example, Prader-Willi syndrome is a genetic disorder associated with obesity, as well as dystonia and some forms of mental retardation. Prader-Willi syndrome is caused by a disorder of chromosome 15 and found in about 1:15,000 children. It causes insatiable eating that is difficult to manage, probably due to hypothalamic dysfunction.

Obesity can be linked to the modern environment (i.e., excess palatable food and insufficient exercise.) The "thrifty gene" idea of evolution of appetite posits that maintaining fat stores and a strong appetite is evolutionarily advantageous and highly adaptive, given that food was not readily available eons ago.

Cachexia— "wasting", common in cancer patients, AIDS, some other illnesses. Cause: abnormally high anorexigenic signals or low orexigenic signaling?

Anorexia/bulimia—these are complicated psychological disorders that may have some endocrine/hypothalamic components, but certainly have endocrine consequences.

Note that permanent alterations in set-point for energy homeostasis and weight may occur in response to illness that destroys or modifies the responses of hypothalamic neurons.

Other key functions of the hypothalamus/preoptic area include:

Control of reproductive function (Gonadotropin releasing hormone production; sexual behaviors; parental behaviors)

Stress responses

Sleep (separate lecture)

Memory formation (mammillary nuclei communicate with hippocampus and play an important role in memory formation; associated with head movements that are critical for understanding spatial orientation in spatial learning; see lecture on Limbic system).

LIMBIC SYSTEM

Date: September 06, 2011- 10:30 AM
Reading Assignment: Mason, Chapter 13

Be able to answer the following questions.

1. Give several examples of self-preservation or species-preservation activities and behaviors regulated by the limbic system.
2. How many different types of olfactory receptor molecules are expressed in humans? How many are expressed by an individual olfactory receptor cell?
3. What is the cortical target of olfactory sensory inputs? Where is it located in the brain?
4. Recognition of which facial expression (fear, anger, surprise, happiness, sadness, or disgust) is most affected by amygdala lesions in humans?
5. Which limbic system structures directly affect autonomic outflow?
6. What part of the hippocampal formation gives rise to the fornix? Where does the fornix terminate?
7. What is the "trisynaptic pathway" circuitry of the hippocampus? What is long term potentiation (LTP)?
8. What hormone is regulated by the hippocampus?
9. What aspect of memory is impaired by bilateral hippocampal lesions?
10. What is the Papez circuit?
11. What are the symptoms of the Kluver-Bucy syndrome?

Limbic System

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

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Outline

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

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History of Limbic System Concept

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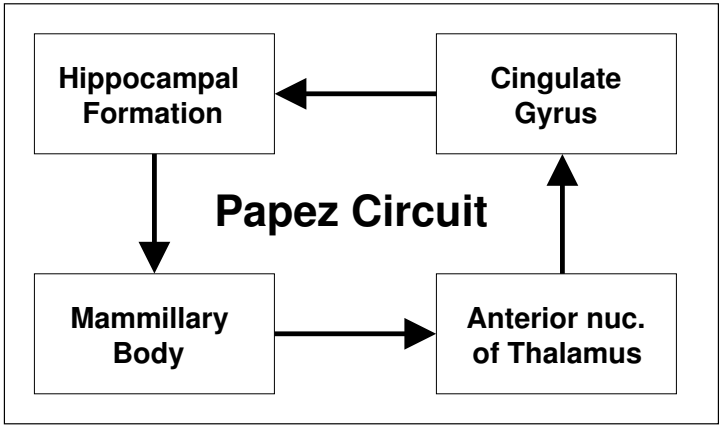
Papez Circuit ➜ Limbic System

- 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

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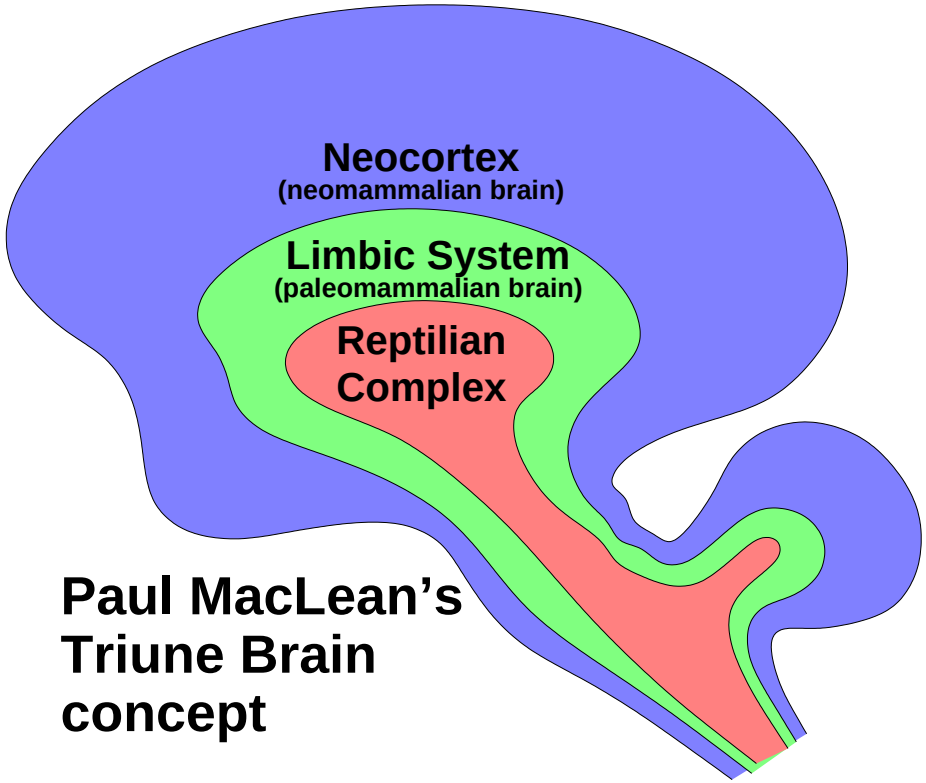
MacLean's Triune Brain and the Limbic System

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



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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

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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.

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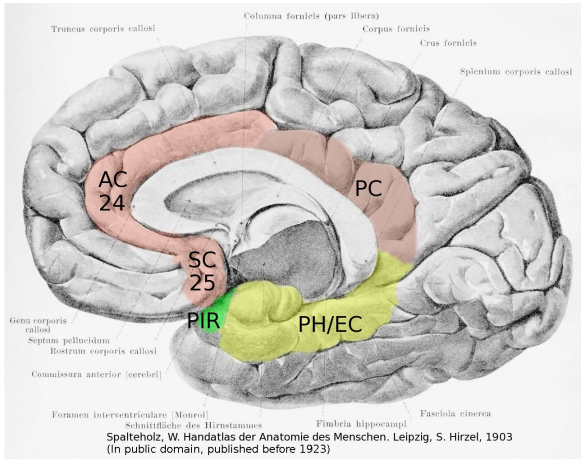
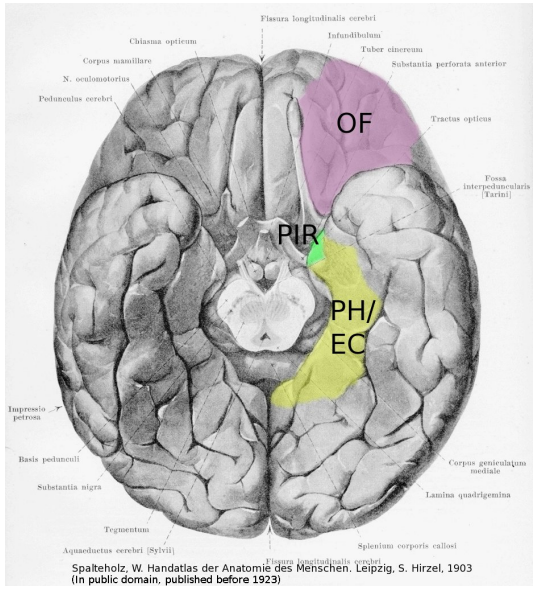
Limbic Ring of Cortex



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



Spalteholz, W. Handatlas der Anatomie des Menschen. Leipzig, S. Hirzel, 1903
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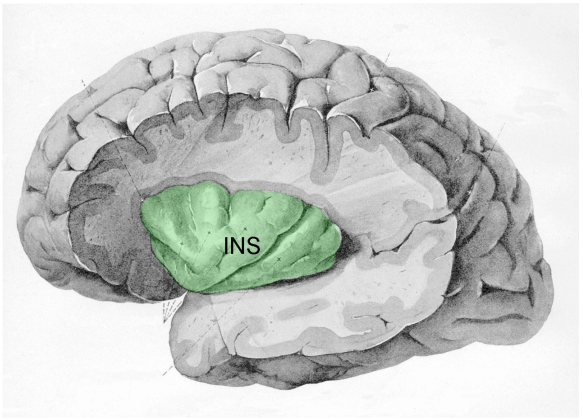

- "Limbic" means "pertaining to a border or margin" and refers to cortex and structures at medial edge or limit of the cerebral hemisphere.

- 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.

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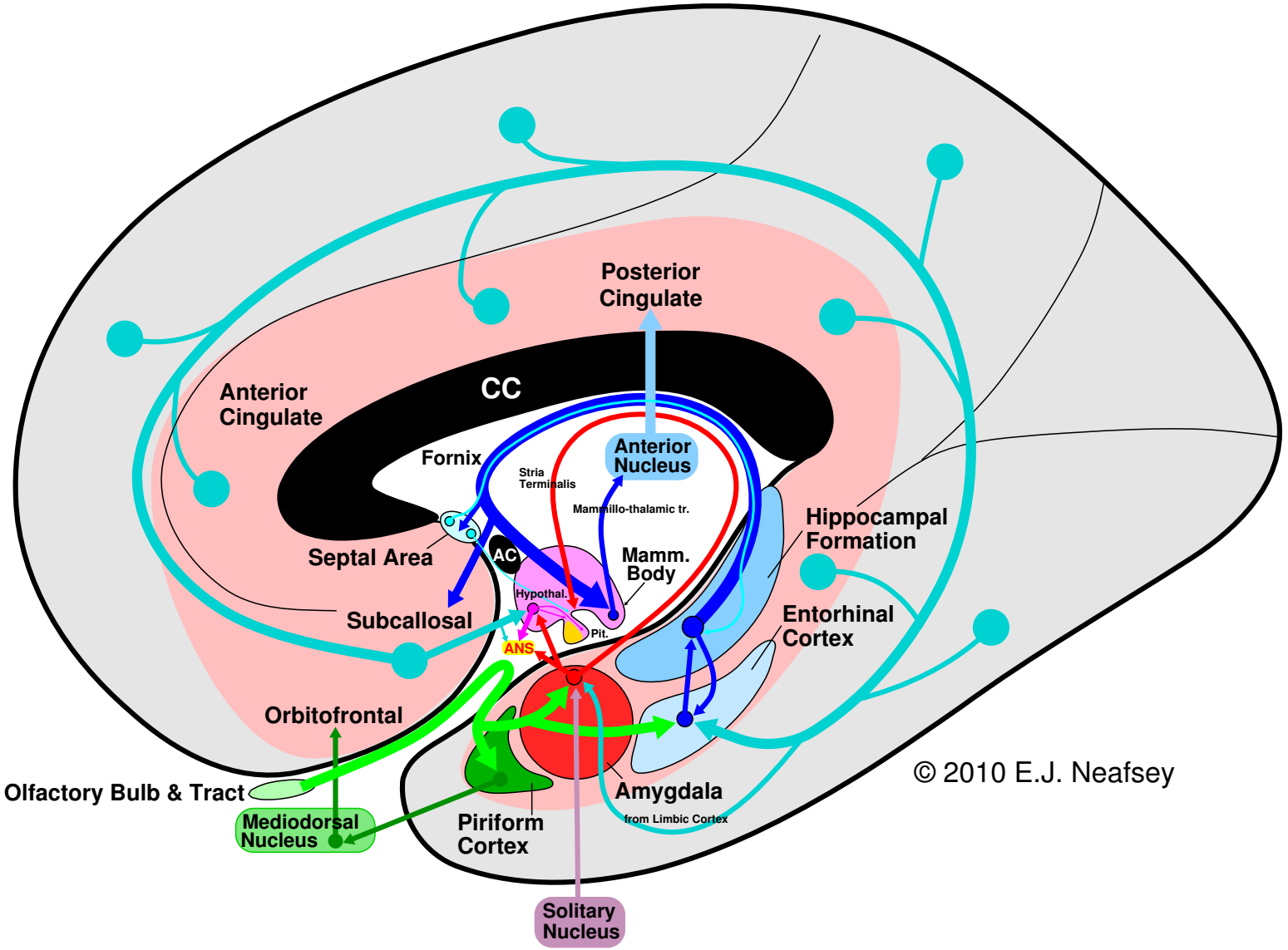
Limbic System Diagram

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?)*

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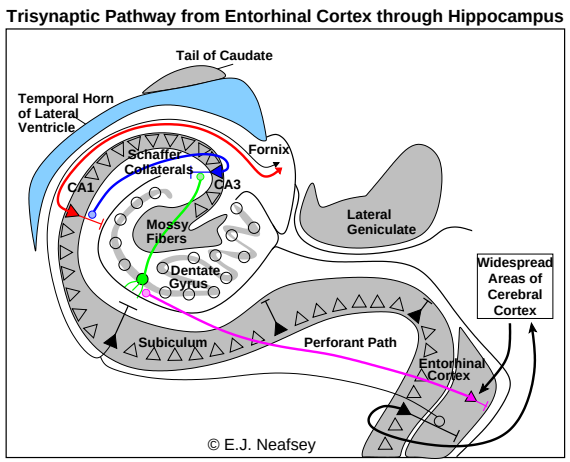
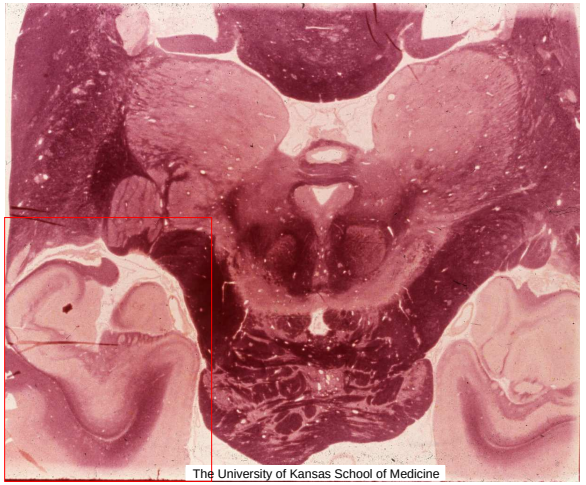
Hippocampal Formation





- 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

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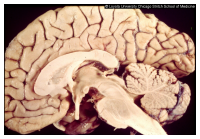
Hippocampal Connections



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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.

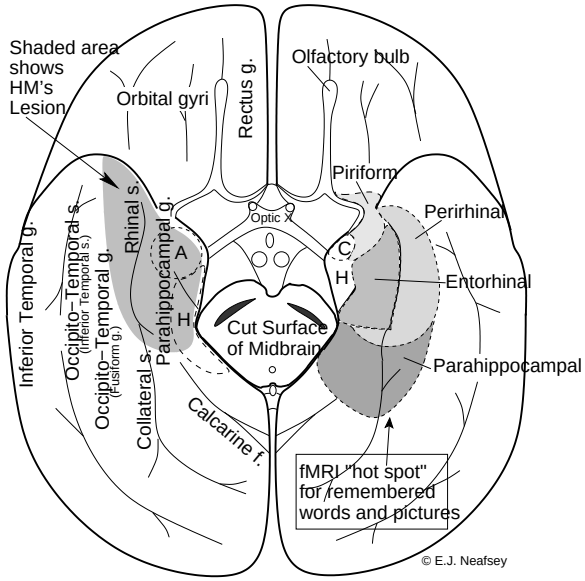
Fornix carries output of hippocampus to *mammillary body*, *septal area nuclei*, and *subcallosal cortex*.

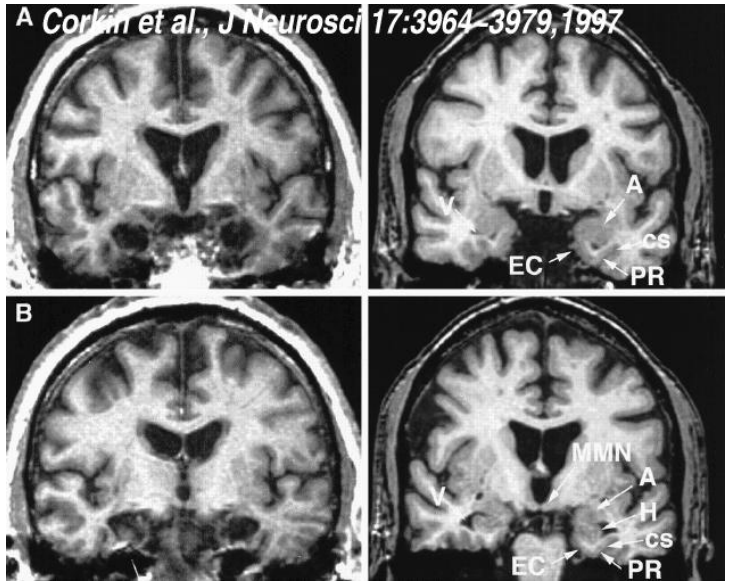
Hippocampal Functions I: Patient HM
Permanent Anterograde Amnesia

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*)

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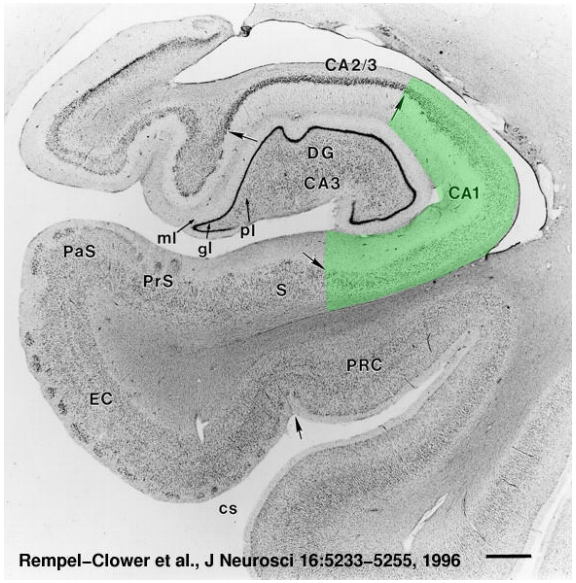
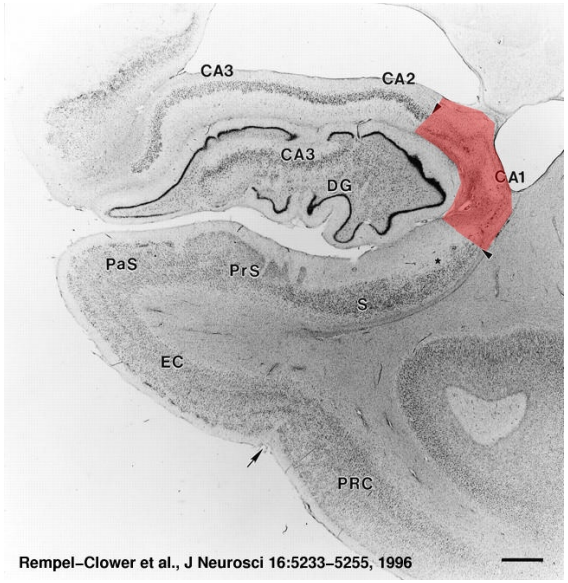
Hippocampal Functions I: Patient GD Impaired Memory After Cardiac Arrest

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.

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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*

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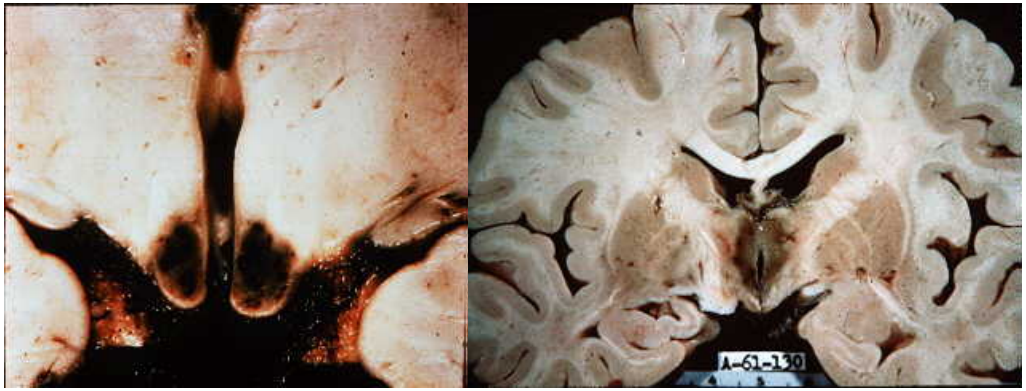
Hippocampal Functions I: Wernicke-Korsakoff Syndrome

(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.

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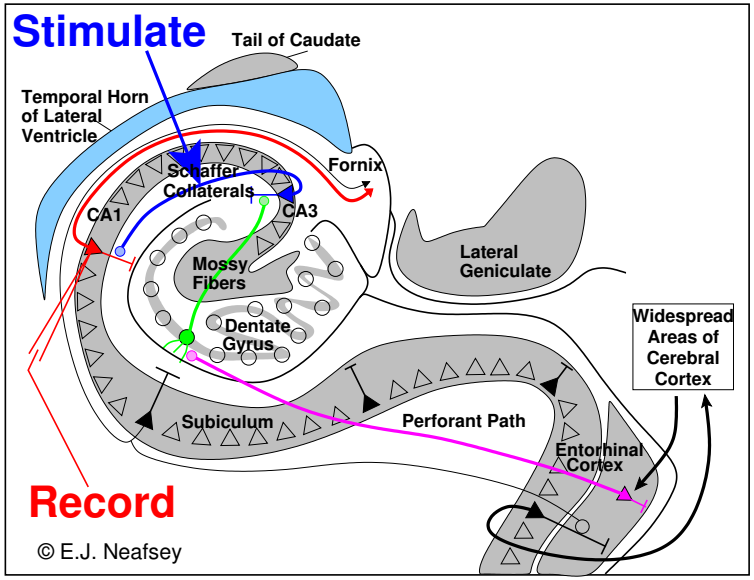
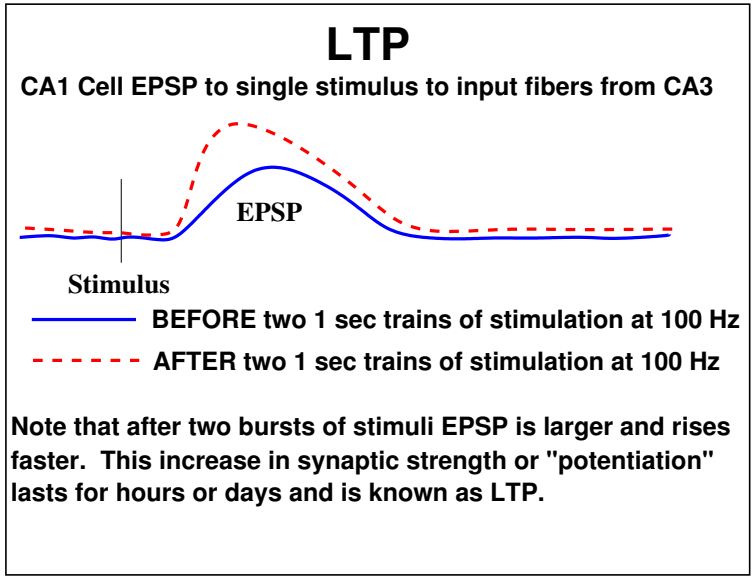
Hippocampal Functions I: Memory and LTP

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.

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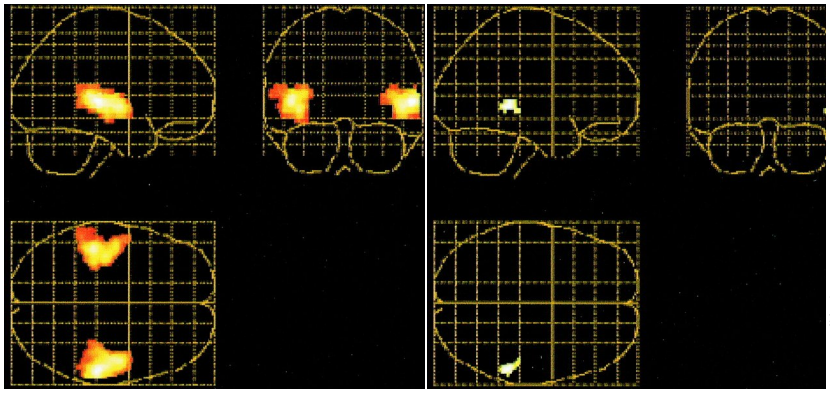
Hippocampal Functions I:
Where are long-term memories stored?

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

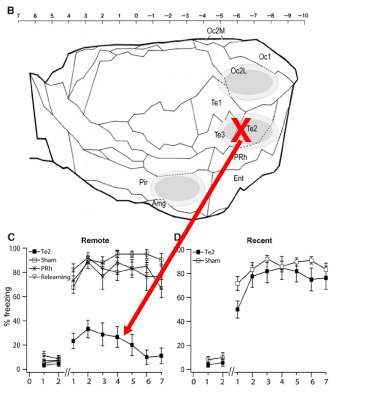
Patients with damage limited mainly to the medial temporal lobe perform normally on tests of remote autobiographical memory, but patients with medial temporal lobe damage PLUS significant additional damage to neocortex were severely impaired in recollecting remote autobiographical events, which depends 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, particularly the secondary sensory areas for each modality.



Encode

Retrieve



Secondary Auditory Cortex (Te2) lesion impairs remote memory.

- Overlapping activations in auditory responsive cortex during encoding (Left) and retrieval (Center) of auditory information

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

- Right: Sacco T and Sacchetti B. 2010. Role of secondary sensory cortices in emotional memory storage and retrieval in rats. *Science* 329:649-656.

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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

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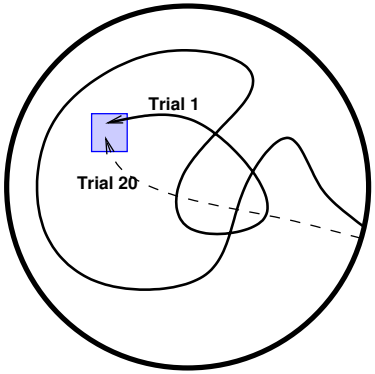
Hippocampal Functions II: Place and Direction (Where's my car?)



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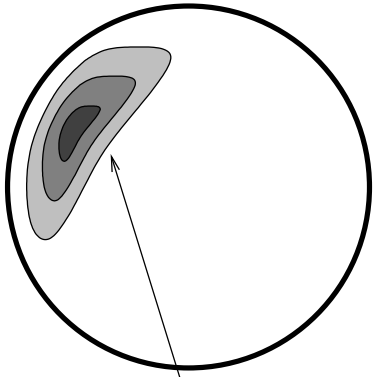
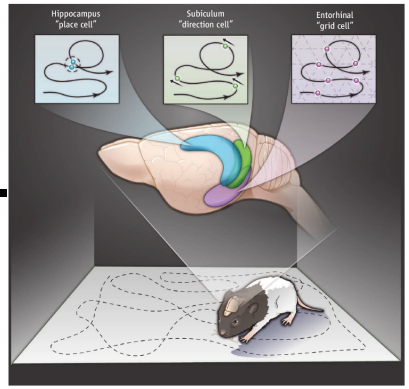
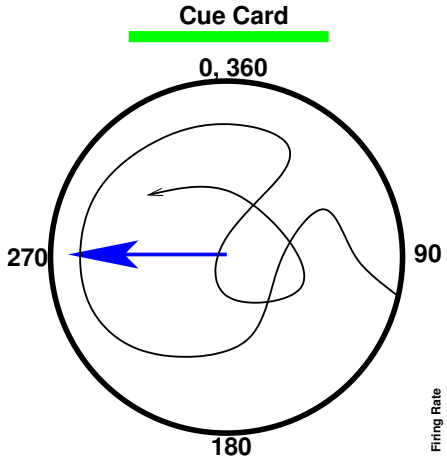


Morris Water Maze:
Rat learns to swim to small platform hidden under surface of water.
Rats with bilateral hippocampal lesions cannot learn the location of the platform.

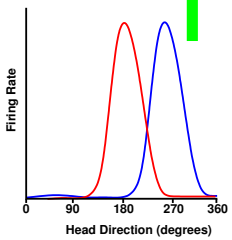
Hippocampal and entorhinal cortex cells have "place fields," defined as the region in the chamber where the cell fires action potentials.

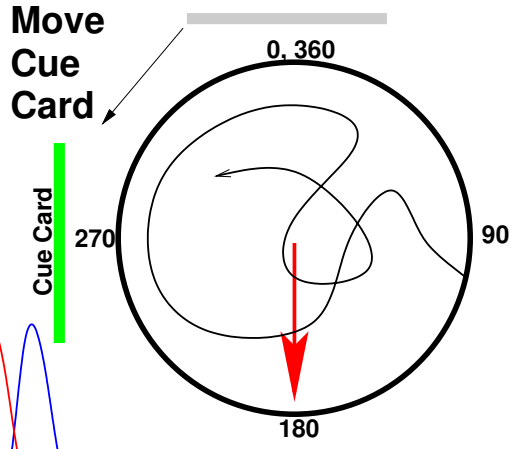


Science 328:1487, 2010



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





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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."

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Superior Autobiographical Memory (Sixty Minutes)

- http://www.cbsnews.com/video/watch/?id=7166313n&tag=contentBody;housing

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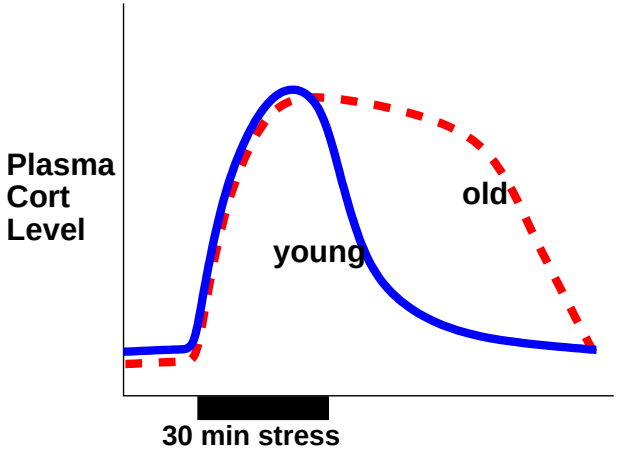
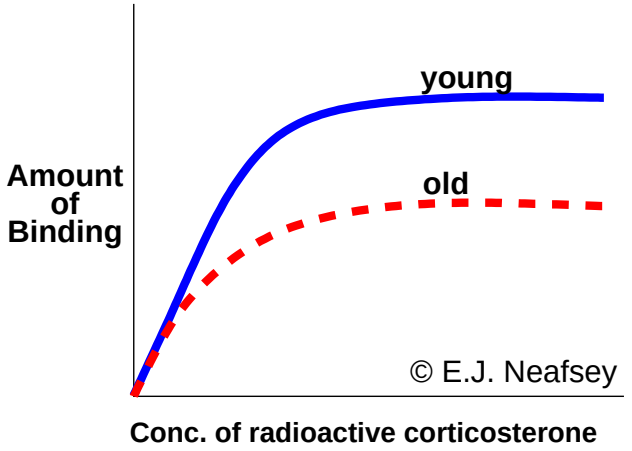
Hippocampal Functions III: Endocrine Regulation

- **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.

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Hippocampal Functions IV: Neurogenesis

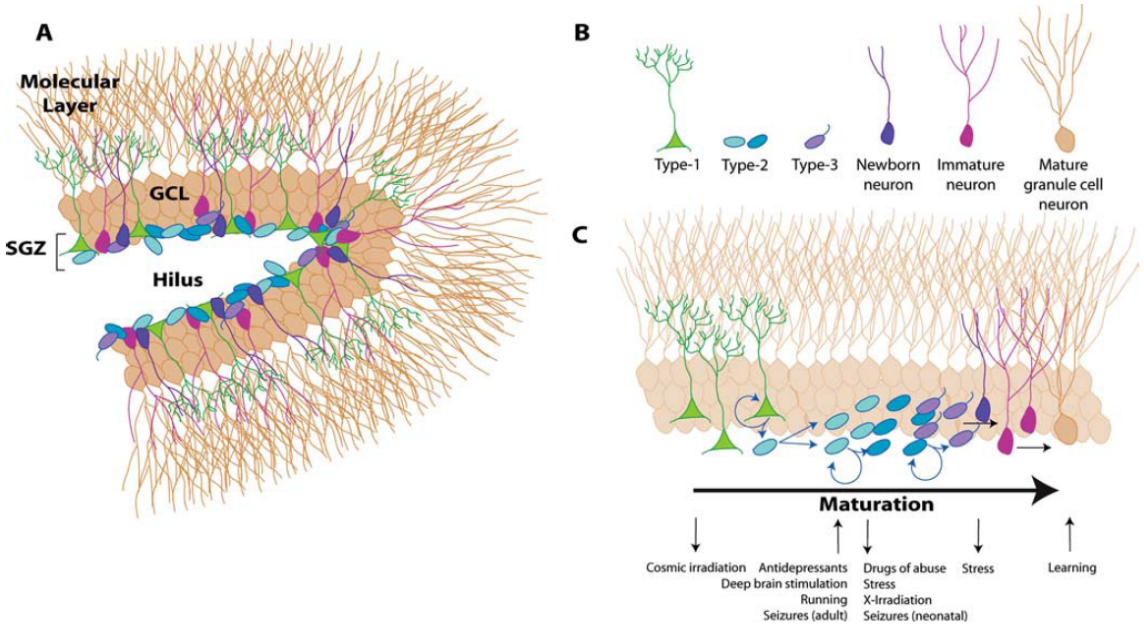

Figure 1. Stages of adult hippocampal neurogenesis. ***A***, The SGZ straddles the border of the hippocampal dentate gyrus granule cell layer (GCL) and hilus. The neurogenic SGZ contains cells at various stages of neurogenesis, which are individually shown in ***B***. ***C***, Cells in discrete stages 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.*

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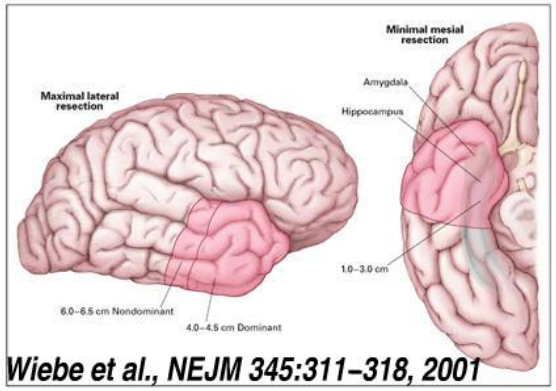
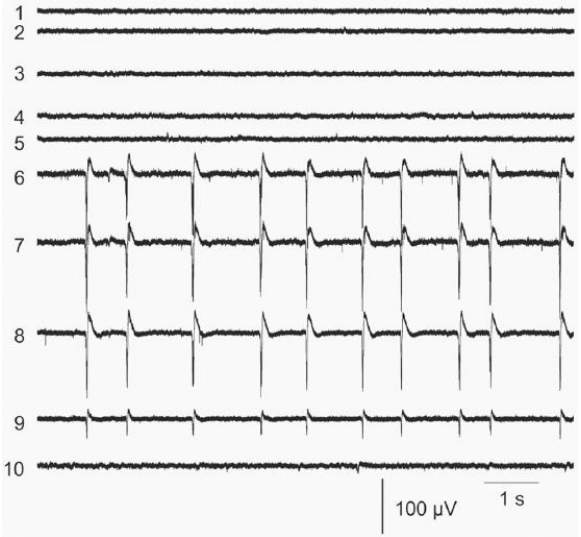
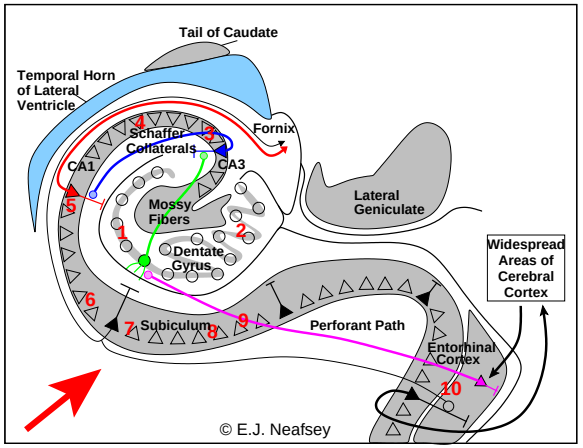
Complex Partial Seizures
Often Arise in Hippocampal Formation







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.

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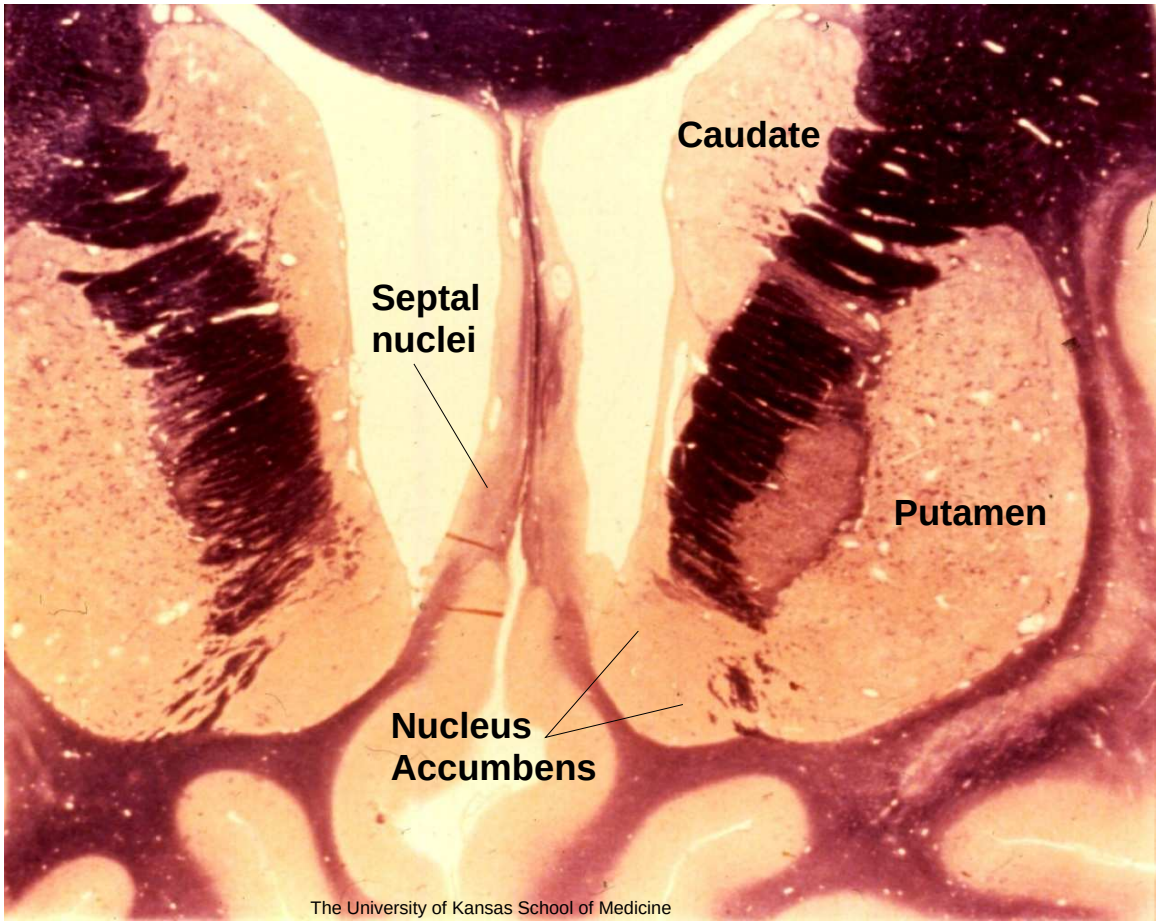
Septal Nuclei



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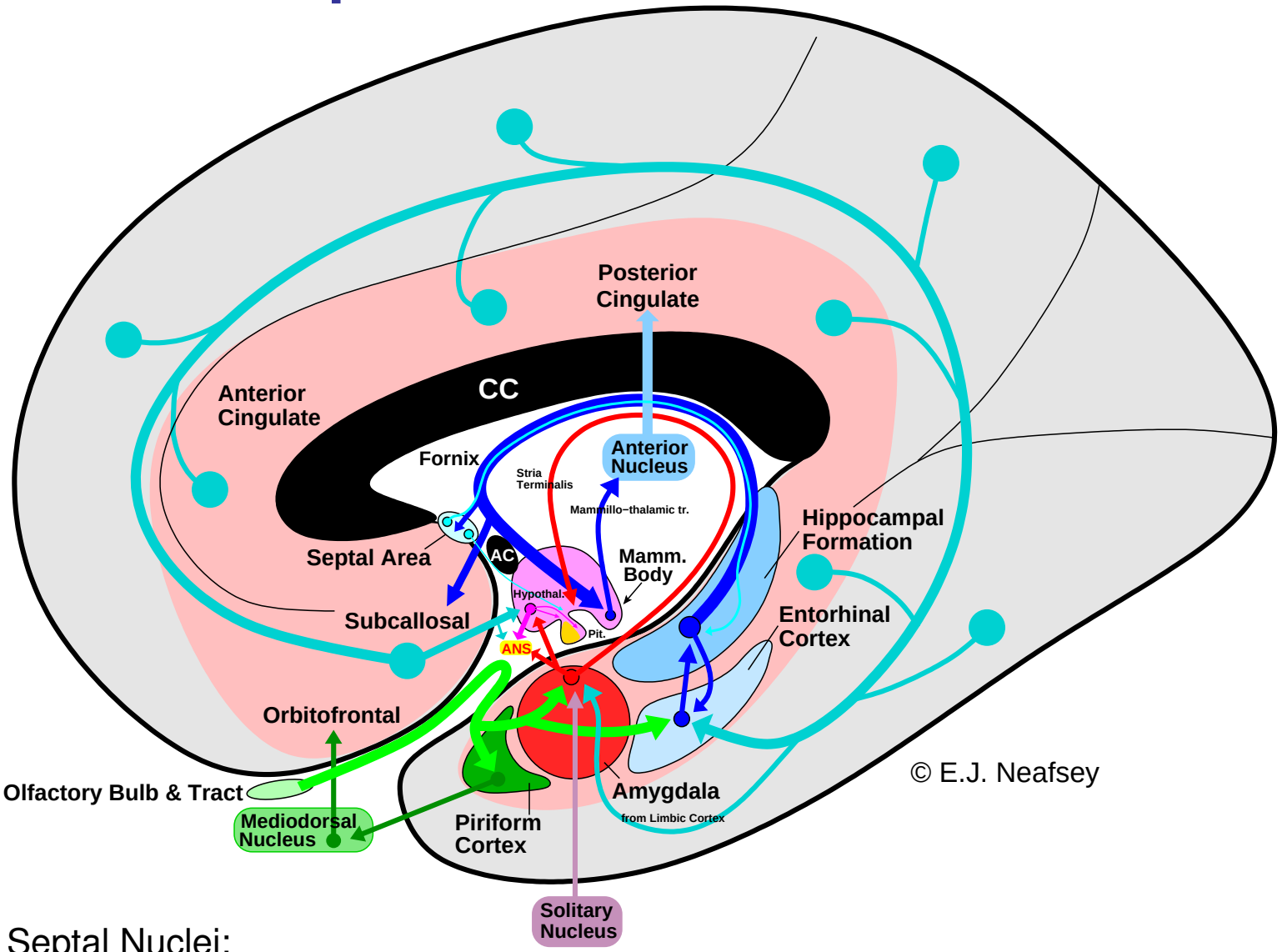
Septal Nuclei Connections



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.

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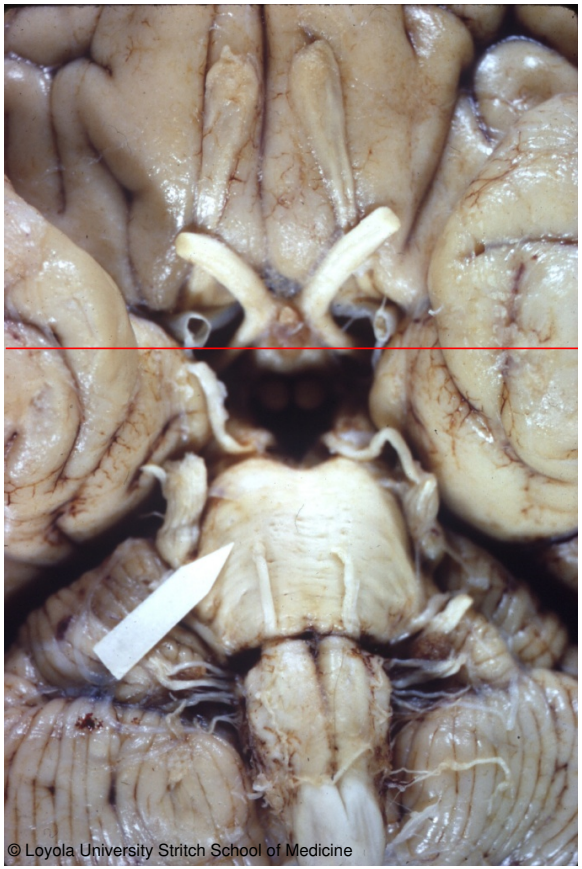
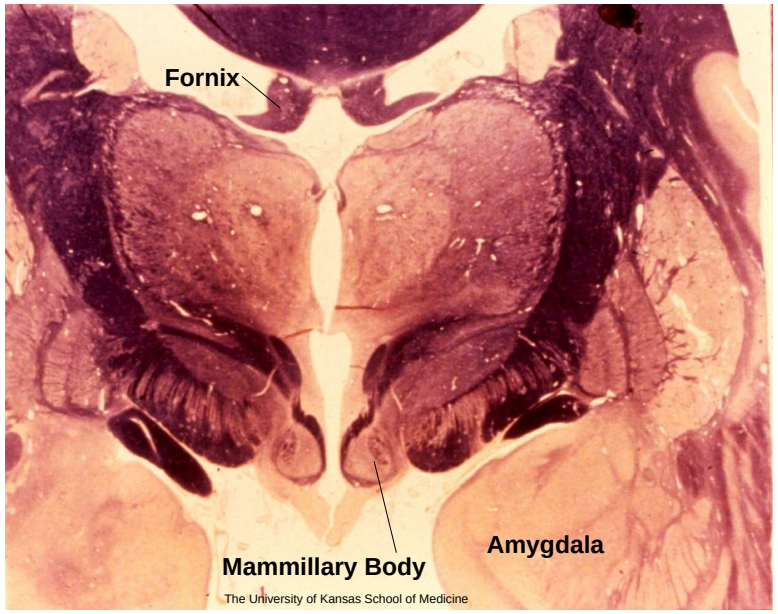
Amygdala

- 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.

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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.

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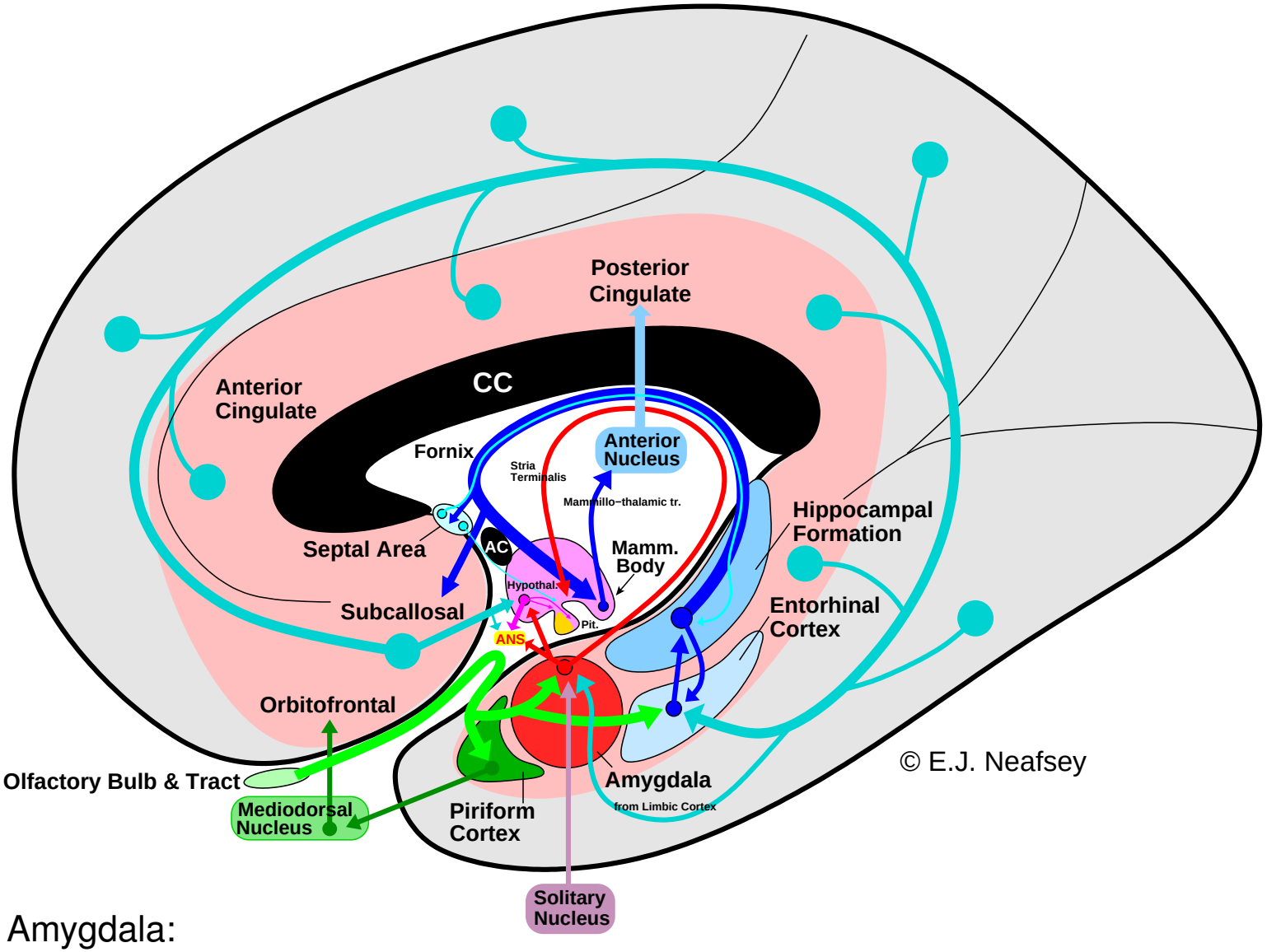
Amygdala Connections



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*.

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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.

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Cats with Bilateral Temporal Lobe Lesions

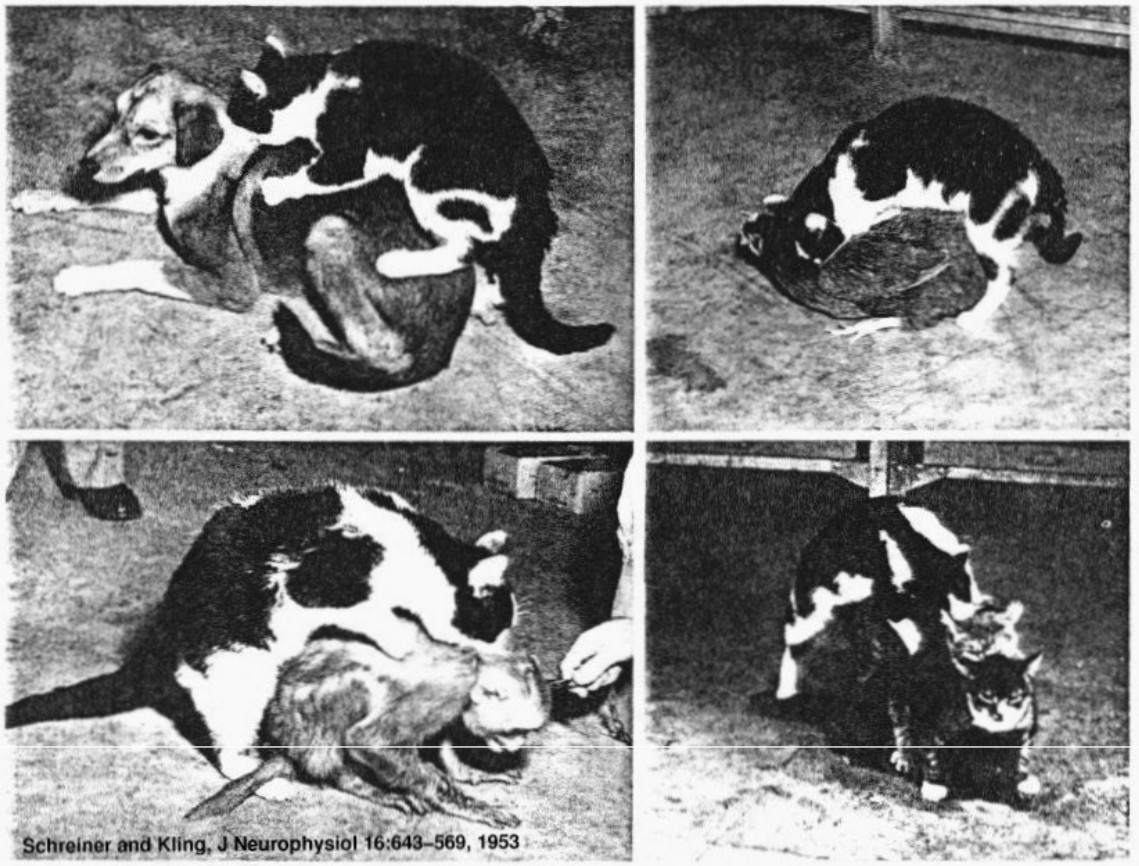

FIG. 5. Illustrations of various phases of sexual activity displayed by male preparations. Photos on right side were prepared from 16 mm. color film. Lower right photo illustrates attempts at "tandem copulation" among four male preparations. See text for additional descriptions.

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.

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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. Thus, olfactory information is already "sorted" into molecular receptor categories at the level of the olfactory bulb.

- Smells are important elements in self and species preservation behaviors such as mating and reproduction (perfume and deoderant), among others.

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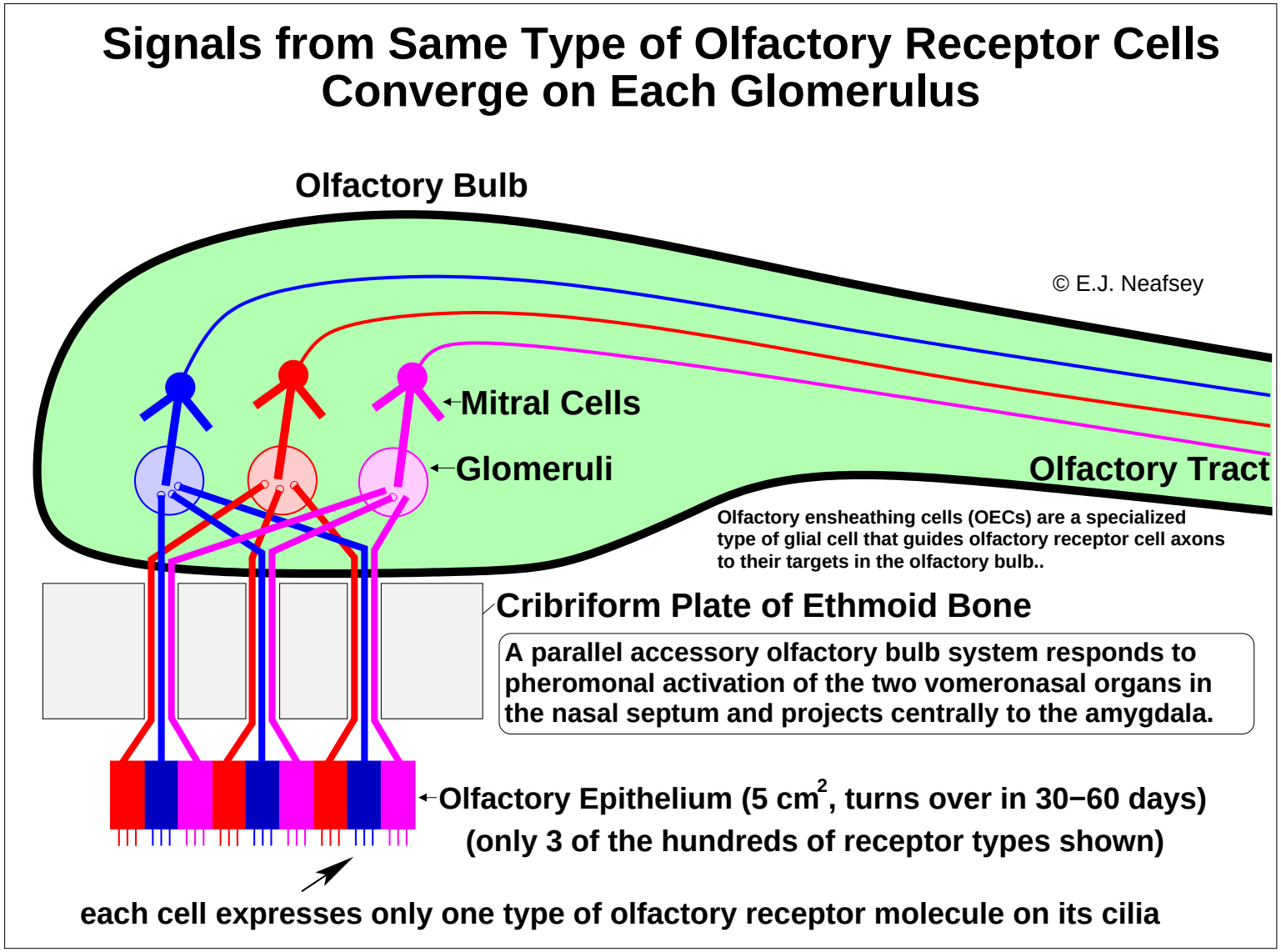
Olfactory Epithelium and Bulb



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Olfactory Bulb: Cajal

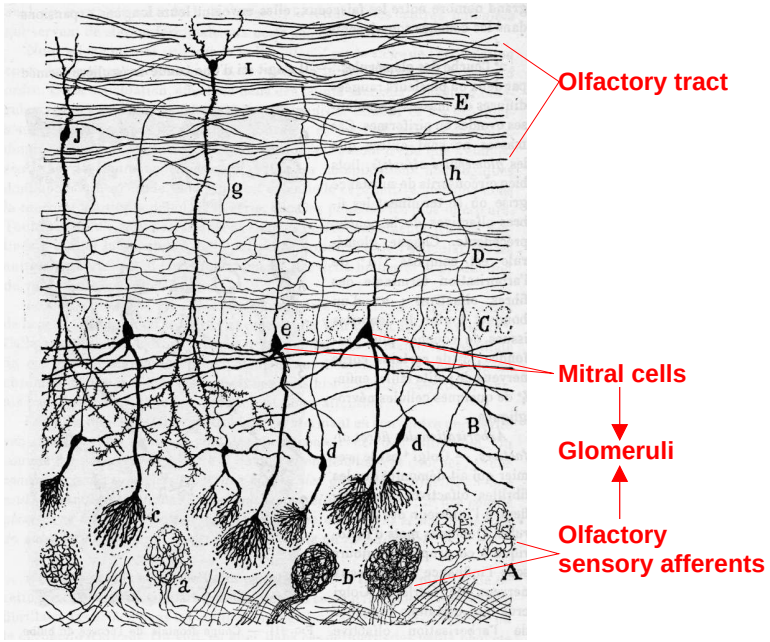

Figure 412 of Volume II: Cajal, S.R., 1909, 1910, Histologie du système nerveux de l'homme et des vertébrés. (Translated by L. Azoulay). Paris: Maloine. In public domain.

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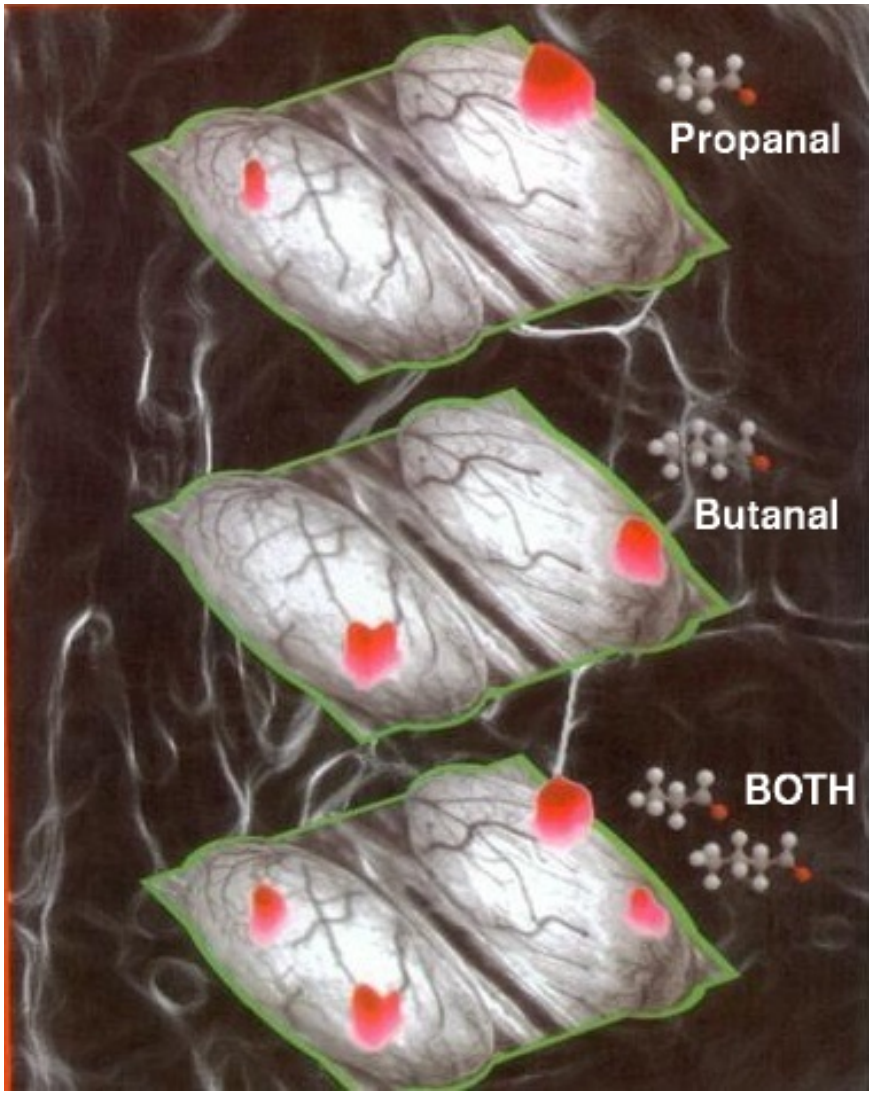
Different Olfactory Bulb Glomeruli Respond to Different Molecules



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

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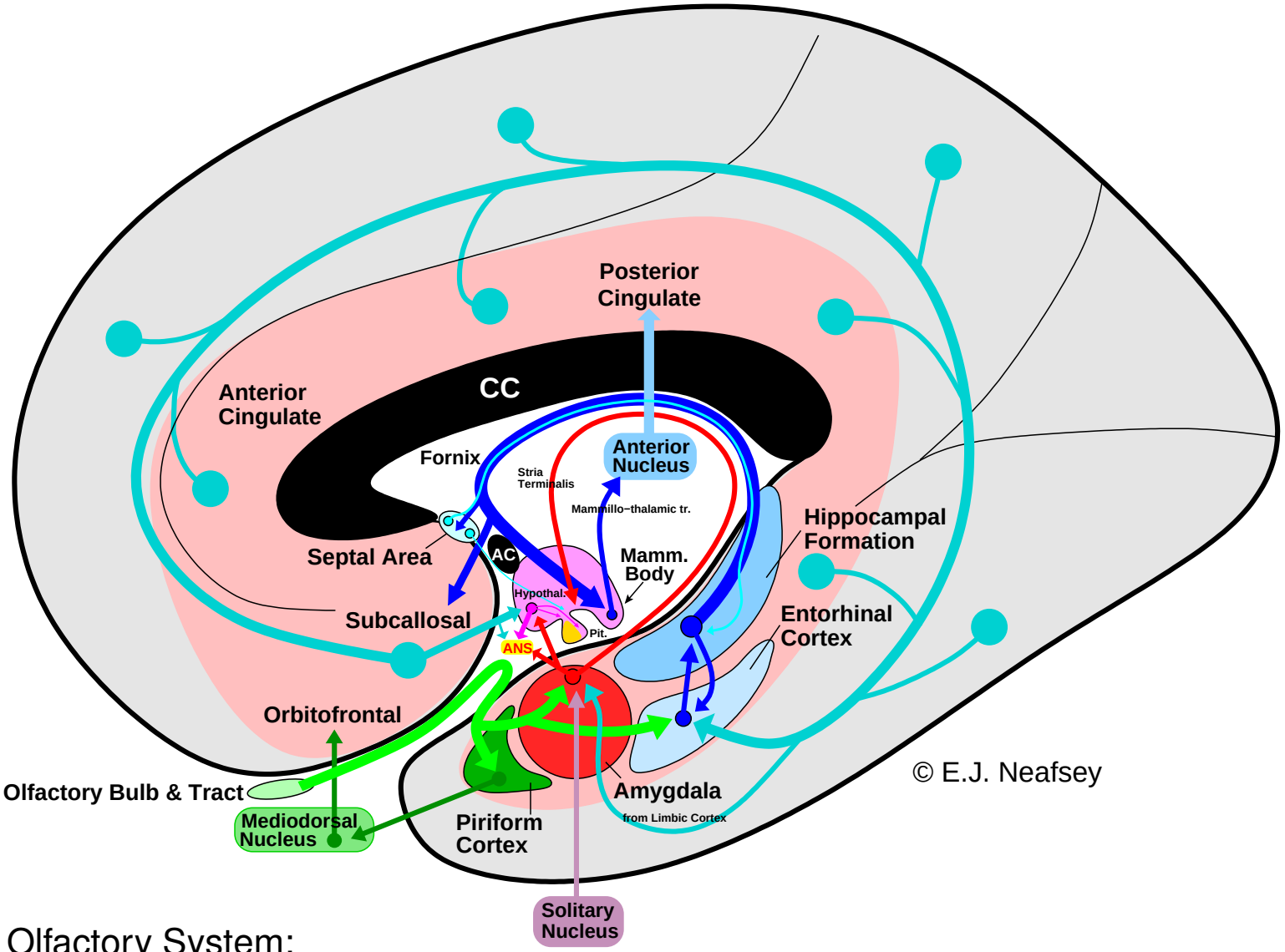
Olfactory Connections Define the "Rhinencephalon"



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.

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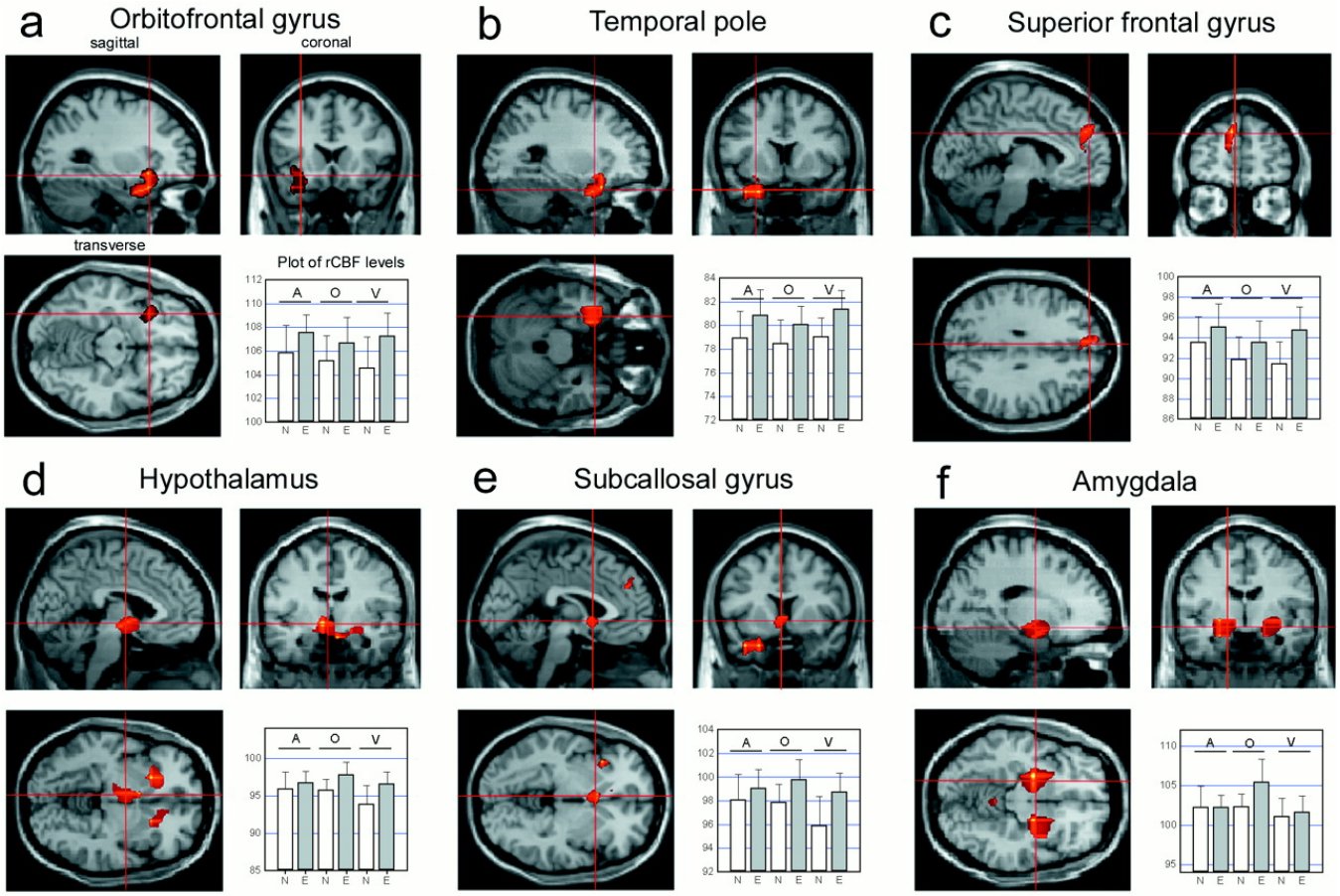
PET Studies Confirm Role of Limbic Cortex, Amygdala, and Hypothalamus in Emotion



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.

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Limbic System

E.J. Neafsey, Ph.D.

1 Limbic System

1. An interconnected set of nuclei in telencephalon and diencephalon
2. Function in various types of **self-preservation and species-preservation activities and behaviors**
   (a) Neuroendocrine and autonomic regulation
   (b) Olfactory sensory processing
   (c) Emotion and motivation
   (d) memory
3. Principal Components
   (a) Olfactory bulb
   (b) Hypothalamus
   (c) Amygdala
   (d) Septal nuclei
   (e) Anterior nucleus of thalamus
   (f) Piriform olfactory cortex
   (g) Hippocampal formation
   (h) Limbic ring of neocortex (includes the insular, orbitofrontal, subcallosal, cingulate, and parahippocampal-entorhinal cortex) (Fig. 26.1)

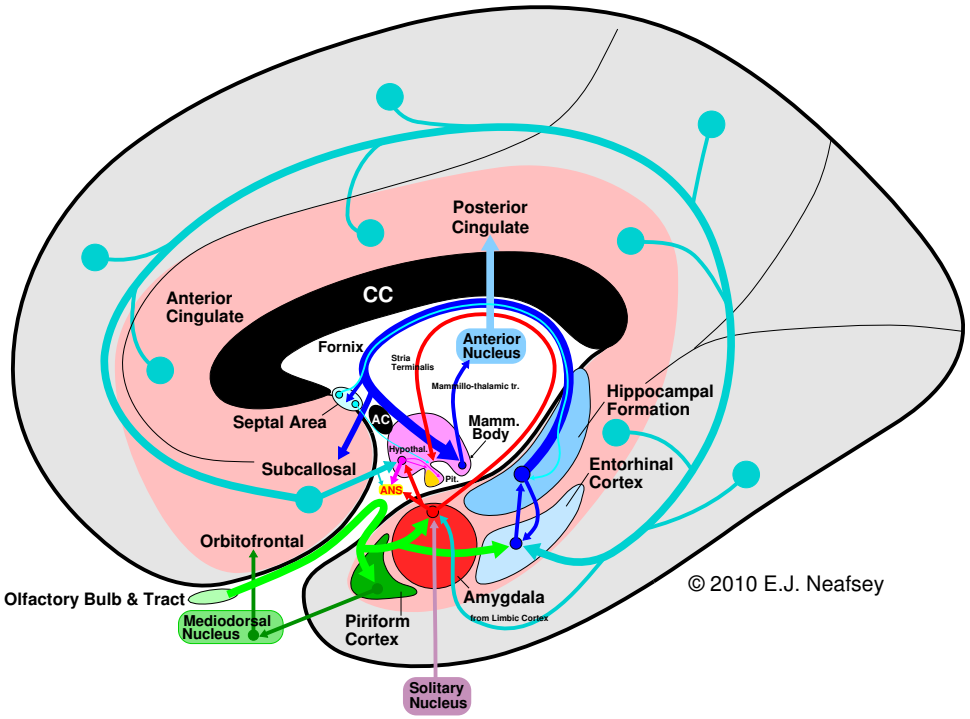


Figure 1: Medial view of cerebral hemisphere with major limbic structures indicated. AC, anterior commissure; MTT, mammillothalamic tract; ST, stria terminalis; VMN, ventromedial nucleus of hypothalamus.

2 Papez Circuit

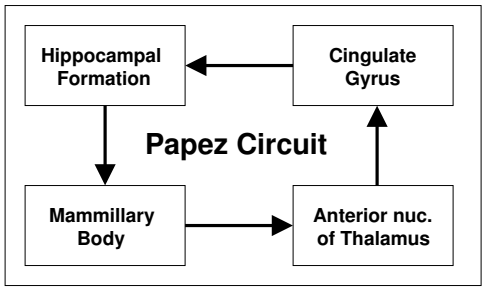


Figure 2: Diagram of Papez circuit.

In 1937 James Papez proposed that a complex functional circuit existed in the brain that was the CNS pathway underlying emotional experience. The circuit included hippocampal projections via the fornix to the mammillary bodies, mammillary projections to the anterior nucleus of the thalamus via the mammillothalamic tract, anterior nucleus projections to the cingulate cortex, and finally cingulate cortex projections back to the hippocampal formation. Current research does not support such a lofty role for this circuitry.

However, Papez's idea laid the groundwork for the concept of a "limbic system"

3 Hippocampus

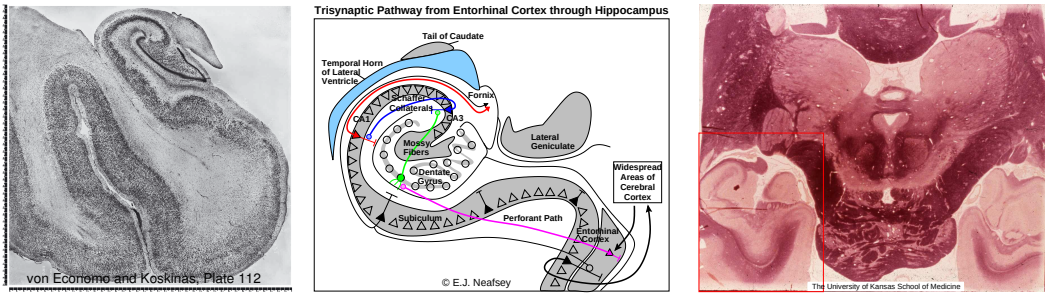


Figure 3: Left and right panels show location of hippocampus on coronal cross-sections of brain. Middle panel shows trisynaptic pathway from entorhinal cortex through the hippocampal formation and out via the fornix. Filled triangles denote pyramidal cells, filled circle denotes a dentate gyrus granule cell, open circles denote synapses. (Adapted from Nauta WJH, Feirtag M: Fundamental neuroanatomy, WH Freeman, 1986, New York.)

1. Allocortical (three layers) region folded under medial aspect of temporal lobe where it forms medial wall of lateral ventricle
2. Components
   (a) Subiculum (adjacent to the entorhinal cortex)
   (b) CA1-CA4 pyramidal cell regions (CA = cornu ammonis)
   (c) Dentate gyrus (granule cells)
3. Afferents
   (a) Septum
   (b) Entorhinal cortex
      i. Located in adjacent parahippocampal gyrus

ii. Major source of input to the hippocampus
iii. Receives projections from most of the neocortex, especially limbic areas
iv. Receives olfactory input from the piriform cortex
v. Funnels all these input to dentate gyrus of hippocampus to begin trisynaptic circuit (see Fig. 25-3)

4. Efferents
   (a) Fornix projects to:
      i. Mammillary bodies
      ii. Anterior nucleus of thalamus
      iii. Subcallosal cortex
   (b) CA fields and subiculum also send a reciprocal projection back to entorhinal cortex

5. Functions
   (a) **Declarative memory** (memories expressed by statements such as "I had corn flakes for breakfast this morning")

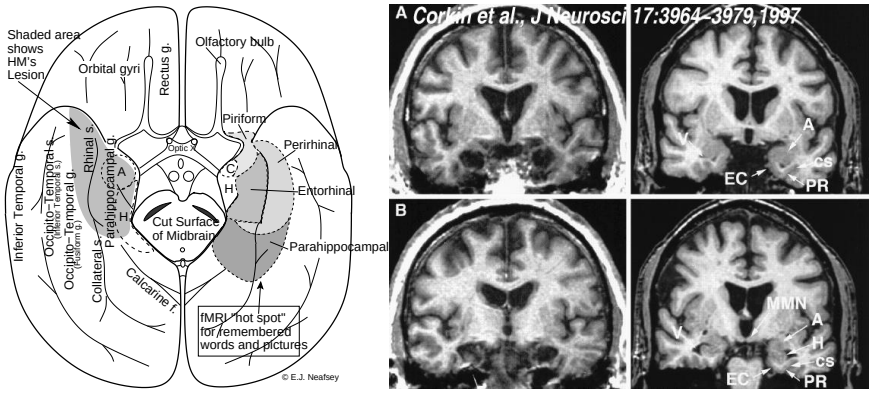


Figure 4: HM's lesion and MRIs

i. 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.
(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.)

ii. Long-term memories are NOT stored in the hippocampal formation!!! 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, including the various sensory areas that initially "encoded" the experience, particularly the secondary sensory areas for each modality.
(Bayley PJ, Gold JJ, Hopkins RO, Squire LR. The neuroanatomy of remote memory. *Neuron* 46:799-810, 2005.)

(b) **"Mapping" the environment**

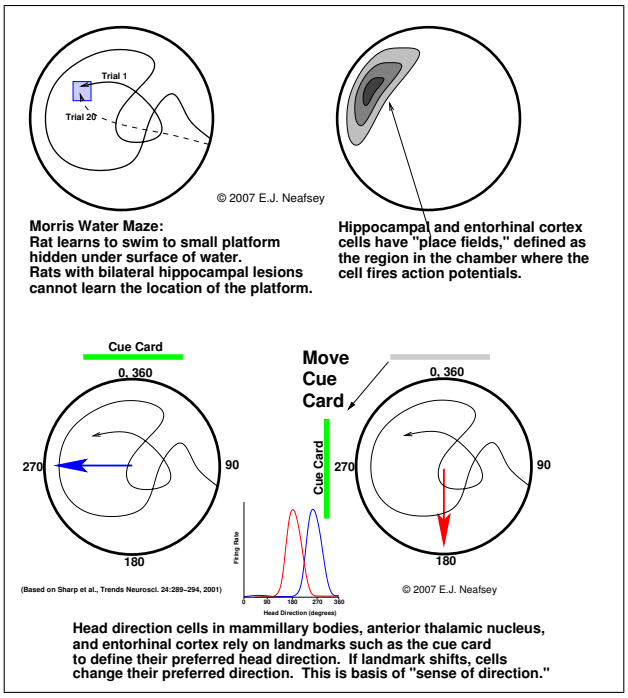


Figure 5: Place and Direction.

In rats many hippocampal cells are considered "place cells" that fire only when animal is in a particular spot
Lesions of hippocampus prevent rats from learning a water maze task, in which they swim to remembered location of a small platform they cannot see just beneath surface of water in a small pool ("Where did I park my car at the mall?")

(c) **Long-term potentiation (LTP)** a proposed memory mechanism

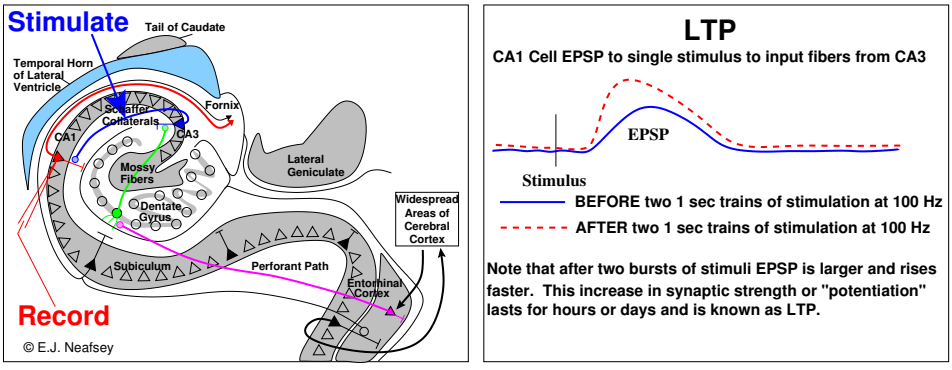


Figure 6: LTP.

i. High frequency, repetitive excitatory synaptic input to a cell may cause a long duration (hours

to days) enhancement of effects of a single activation of the same or other excitatory synaptic inputs to cell

ii. Long-term potentiation demonstrated in hippocampal CA1 neurons receiving synaptic inputs from CA3 neurons via Schaffer collaterals

iii. In rats blocking the N-methyl-d-aspartate (NMDA) type of glutamate receptor in hippocampus impaired both long-term potentiation and learning and memory

A. Glutamate NMDA receptors cause activation of various postsynaptic second messenger systems and kinases, leading to increased transcription factors, oncogene activation, selective DNA activation, and selective protein production, altering postsynaptic sensitivity

B. In addition, presynaptic side of synapse may be “retrogradely altered” by release of diffusible factors (nitric oxide, carbon monoxide, or arachidonic acid) from postsynaptic neuron

(d) **Wernicke-Korsakoff Syndrome**

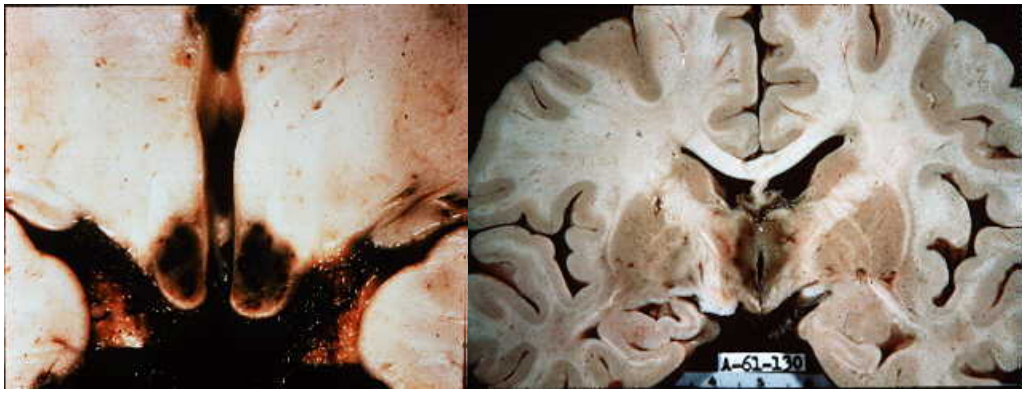


Figure 7: Wernicke-Korsakoff neuropathology.

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.

(e) **Neuroendocrine Regulation of Cortisol**

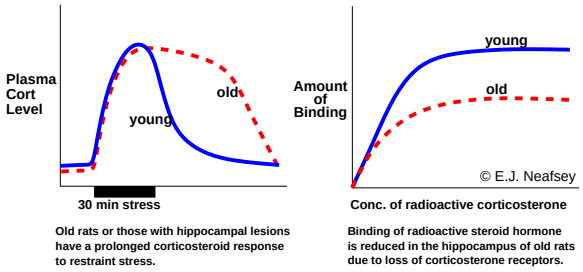


Figure 8: Cortisol regulation in young and old rats and its relation to hippocampal cortisol receptors.

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

(f) **Movement**

i. Hippocampal rhythmic, slow-wave electroencephalograph activity (6 to 12 Hz, theta activity) changes during locomotion and other motor acts

(g) **Neurogenesis**

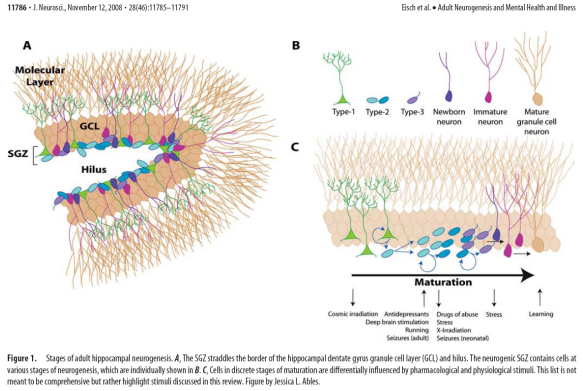


Figure 9: Neurogenesis in the hippocampus.

Hippocampus is one of the most important 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.

(h) **Complex Partial Seizures**

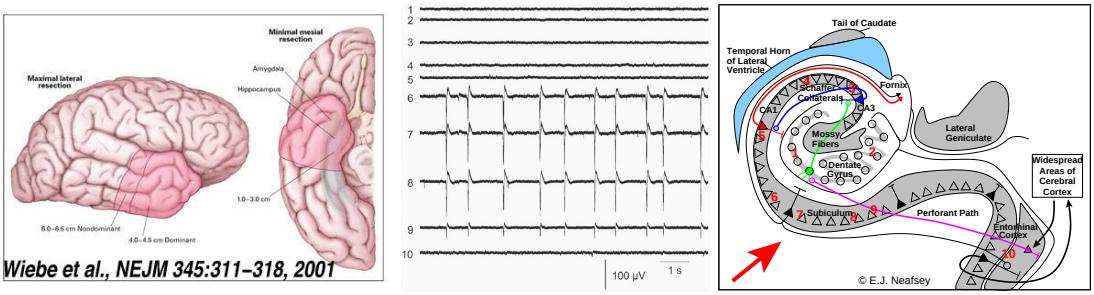


Figure 10: Epilepsy and the hippocampus.

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.)

4 Central Olfactory Pathways

Many olfactory-related brain regions are not only olfactory sensory but also are important for sexual behavior, with “sexual” defined broadly to include not only mating behavior but also maternal behavior and male agonistic (fighting) or territorial behaviors

(a) Olfactory receptors (Fig. 26-2)

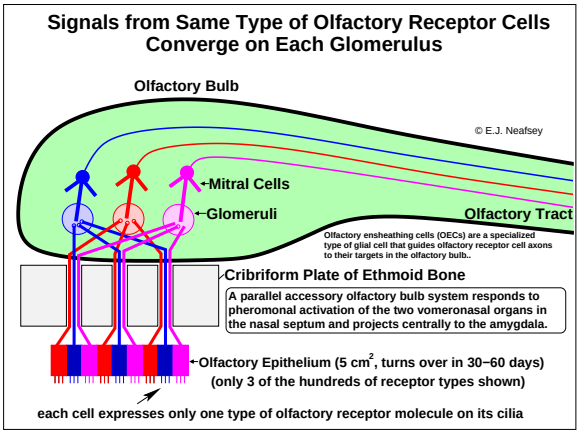


Figure 11: Diagram of connections from olfactory receptor cells in olfactory mucosa in roof of nasal cavity to mitral cells of olfactory bulb that give rise to olfactory tract. OECs, olfactory ensheathing cells, a specialized neuroglial cell.

i. Approximately 25 million olfactory receptor cells are located in olfactory epithelium in roof of nasal cavity
ii. Each receptor cell responds preferentially to odor molecules of only one type via highly specific receptor molecules on its surface cilia
iii. Each receptor cell expresses only one of the thousand or more different olfactory receptor molecules encoded by the large olfactory receptor gene family

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

(b) Olfactory bulb mitral cells
  i. Send their axons centrally as the olfactory tract (Fig. 26-2), which terminates in four primary targets
    A. Olfactory tubercle in the anterior perforated substance (recall the olfactory tubercle is part of ventral striatum)
    B. Piriform olfactory cortex on rostral surface of the uncus
    C. Medial amygdala located in medial uncus
    D. Entorhinal cortex

(c) Other diencephalic and telencephalic olfactory structures
  i. Mediodorsal nucleus of thalamus
    A. Receives olfactory signals from ventral pallidum, which receives part of its input from olfactory tubercle (part of ventral striatum)
    B. Receives olfactory signals directly from piriform cortex
    C. Projects to orbitofrontal cortex
  ii. Ventromedial nucleus of the hypothalamus
    A. Receives olfactory inputs from medial amygdala via stria terminalis

5 Amygdala

(a) Large, nuclear group located in rostral medial portion of temporal lobe beneath uncus

(b) Afferents
  i. Olfactory tract
  ii. Solitary nucleus and parabrachial nucleus, carrying taste and general visceral afferent signals
  iii. Limbic neocortex

(c) Efferents
  i. Hypothalamus
  ii. Limbic neocortex
  iii. Various central autonomic centers such as central gray, parabrachial nuclei, solitary nucleus, parasympathetic dorsal motor nucleus of vagus, and sympathetic preganglionic neurons in thoracic intermediolateral cell column

(d) Functions
  i. Relates environmental stimuli to coordinated behavioral, autonomic, and endocrine responses seen in self-preservation or species-preservation behaviors
    A. Feeding and drinking
    B. Agonistic (fighting) behavior
    C. Mating
    D. Maternal care
    E. Responses to physical or emotional stressors
  ii. Lesions of amygdala reduce endocrine, autonomic, and behavioral responses during emotional stress
  iii. In humans bilateral amygdala lesions selectively eliminate recognition of fearful emotional facial expressions

6 Septal Nuclei

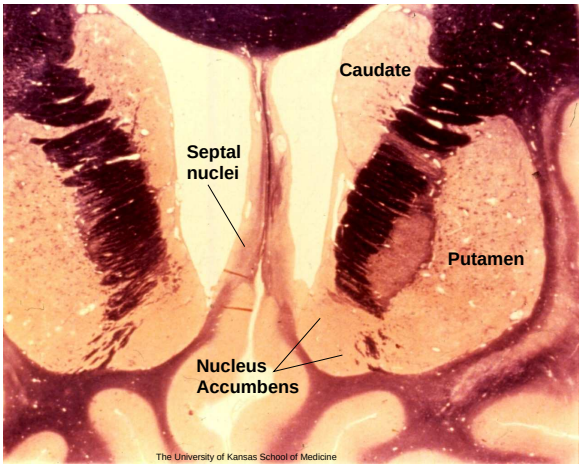


Figure 12: Septal nuclei

(a) Located between frontal horns of lateral ventricles, ventral to corpus callosum and dorsal to anterior commissure
(b) Afferents
    i. Hippocampal formation (CA1 and subiculum)
    ii. Amygdala
    iii. Hypothalamus-preoptic area
(c) Efferents
    i. Hippocampal formation (a cholinergic pathway)
    ii. Amygdala
    iii. Hypothalamus-preoptic area
    iv. Mammillary body
    v. Median eminence
(d) Functions
    i. Regulates gonadal hormone secretion and various reproductive and sexual behaviors by way of its gonadotropin-releasing hormone projections to median eminence
    ii. 2. Facilitates memory formation via its massive cholinergic projection back to hippocampus
    iii. 3. Lesions produce septal syndrome consisting of general behavior overreaction, particularly evident as “septal rage” after trivial stimulation

7 Kluver-Bucy Syndrome

(a) Behavioral changes first described in monkeys with bilateral lesions of the temporal lobe, including the temporal neocortex, olfactory cortex, amygdala, and hippocampus
    i. **Visual agnosia** (“psychic blindness”); all objects, living or not, familiar or unfamiliar, food or feces, are approached and compulsively examined, often orally
    ii. **Oral tendencies**; everything is compulsively put into the mouth, licked, chewed, and smelled
    iii. **Loss of emotions of fear and anger**; animals are “docile”
    iv. **Hypersexuality**; male monkeys display frequent erections and copulate with other monkeys (male or female) whenever possible

PAIN

Date September 07, 2011 - 9:30
Reading Assignment: Mason, Chapter 18

KEY CONCEPTS

1. Pain can be classified according to pathophysiology (e.g. nociceptive or neuropathic pain), etiology (eg, postoperative or cancer pain), or the affected area (eg, headache or low back pain).

2. Nociceptive pain is caused by activation or sensitization of peripheral nociceptors, specialized receptors that transduce noxious stimuli. Neuropathic pain is the result of injury or acquired abnormalities of peripheral or central structures.

3. Acute pain can be defined as pain that is caused by noxious stimulation due to injury, a disease process, or the abnormal function of muscle or viscera. It is nearly always classified as nociceptive.

4. Chronic pain is defined as pain that persists beyond the usual course of an acute disease or after a reasonable time for healing to occur; this period can vary from 1 to 6 months. Chronic pain may be nociceptive, neuropathic, or mixed.

5. The primary afferent nociceptors comprise free, unmyelinated nerve endinings that are responsive to mechanical, thermal, and chemical stimuli. Following tissue trauma the release of chemical mediators initiates nociception while activating an inflammatory response.

6. Stimulation of these nociceptive afferents leads to propagation of impulses along the peripheral nerve fibers to the spinal cord by two parallel pathways. The first is via myelinated rapidly conducting A-δ fibers. This type of pain is fast, localized and sharp, and provokes reflex withdrawal responses. The second route to the spinal cord is via small diameter non-myelinated C-fibers which conduct impulses more slowly. C-fibers medated pain sensations that are diffuse and dull.

7. The primary afferents terminate in the dorsal horn of the spinal cord. The cell bodies lie in the dorsal root ganglia. A-δ fibers synapse in the lamina of Rexed I and V, while the C-fibers synapse in substantia gelatinosa (lamina II and III). They relay with various classes of second order neurons in the cord, some of which are nociceptive specific, which respond selectively to noxious stimuli and are located in the superficial lamina., others of which are ‘wide dynamic range’, are non-specific and are located in the deeper lamina.

8. Most of the secondary afferents decussate to ascend in the lateral spinothalamic tract, although some do pass up the posterolateral part of the cord. These fibers pass through

the medulla, mid-brain and pons giving off projection axons as they do so before terminating in the ventral posterior and medial nuclei of the thalamus.

9. From the thalamus there is a specific sensory relay to sensory discriminative of the contralateral cortex: to somatic sensory area I (SSI), the somatic sensory area II (SSII). There is also a projection to the cingulate gyrus, which is thought to mediate the affective component of pain.

10. One of the major complexities of pain pathways is the modulation of afferent impulses which occurs at numerous levels, including the dorsal horn where there is a complex interaction between afferent input fibers, local intrinsic spinal neurons and descending central efferents. Afferent impulses arriving at the dorsal horn themselves initiate inhibitory mechanisms which limit the effects of subsequent impulses. As pain fibers travel rostrally they also send collateral projections to higher centers such as periaqueductal grey (PAG) matter and the locus ceruleus of the mid-brain. Descending fibers from the PAG project to the nucleus raphe magnus in the medulla, and to the reticular formation to activate descending inhibitory neurons. This modulation can either inhibit (suppress) or facilitate (aggravate) pain.

11. Neural blockade with local anesthetics can be useful in delineating pain mechanisms, but more importantly, it plays a major role in the management of patients with acute or chronic pain. The role of the sympathetic system and its pathways can be evaluated.

Pain Types, Mechanisms and Pathways

Joseph R. Holtman, Jr. MD, Ph.D.
Professor Anesthesiology and Molecular Pharmacology and Therapeutics
Director Pain Program and Fellowship Training
Loyola University Medical Center

Overview - Basic

- **Pain – basic aspects**
  - Definitions/Terminology
  - Types of Pain
  - Pain Transmission System
    - Nociceptors
    - Ascending Pathways
    - CNS nuclei
    - Descending Pathways
  - Pain Classification
    - Visceral vs Somatic Pain
    - Referred Pain

Overview - Clinical

- **Pain – clinical aspects**
  - Measurement/Assessment of Pain
  - Characterization of Types of Pain
  - Pain Syndromes
  - Treatment of Pain
    - Acute Pain
    - Chronic Pain

Pain Definition

Pain – unpleasant sensory (nociception) and emotional (suffering) experience associated with potential or actual tissue damage.

Pain Terminology

- **Acute Pain**
  - Resolves once normal healing occurs
  - No lasting plastic changes in CNS
  - Sports injuries, post-operative pain, childbirth, medical/dental procedures
- **Chronic Pain**
  - Pain persists beyond expected healing time (3-6mo)
  - Plastic changes in CNS
  - Complex often involving psychological issues, disability, drug misuse/abuse

Chronic Pain

- **Cancer Pain** – pain at multiple sites including nerve, plexus, bone, muscle or organ due to invasion by tumor.
- **Non-malignant Pain –** pain at any of multiple sites not associated with malignant origin
  - **Low back pain**
  - **Postherpetic neuralgia**

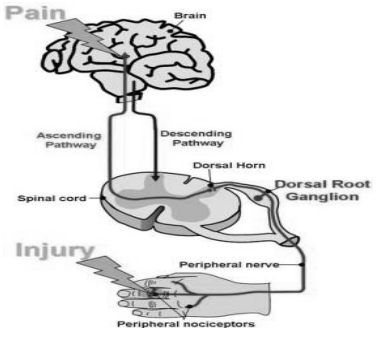
Pain Types

- **Nociceptive Pain** – normal acute pain elicited by noxious stimulation of intact tissue.
- **Inflammatory Pain** – elicited with tissue pathology due to injury and/or disease.
- **Neuropathic Pain** – elicited when any element of the peripheral or central nervous system is injured.

"Pain Pathways"

René Descartes, 1664.

Pain Pathways



Pain Transmission System Anatomy

- **Peripheral Nociceptors** – peripheral "pain receptors" projecting to dorsal horn of spinal cord.
- **Spinal Cord and Ascending Pain Pathways** – nociceptive information from dorsal horn spinal cord to CNS.
- **CNS Nuclei** – involved in pain processing including the discriminative (location), affective (emotional) and motor control aspects.
- **Descending Pain Pathways** – allow CNS nuclei to modulate (inhibit) nociceptive information arriving in dorsal horn of spinal cord.

Nociceptor Characteristics

- **What are they?** Free nerve endings of primary afferents activated by noxious stimuli
  - A delta fibers - transmit rapid, sharp, intense pain ("First Pain")
  - C fibers - transmit delayed, prolonged, burning pain ("Second Pain")
- **Where are they found?**
  - Somatic – skin, muscle, joints
  - Visceral – CV, GI, GU systems
  - Cell bodies in dorsal root ganglion

Nociceptor Fiber Classification

Table 1. Classification of fibers in peripheral nerves

Fiber group	Innervation	Mean diameter (μm)	Mean conduction velocity (m/sec)
A-alpha	Primary muscle spindle motor to skeletal muscle	15	100
A-beta	Cutaneous touch and pressure afferent fibers	8	50
A-gamma	Motor to muscle spindle	6	20
A-delta	Mechanoreceptors, **nociceptors,** thermoreceptors	<3	15
B	Sympathetic preganglionic	3	7
C	Mechanoreceptors, **nociceptors,** thermoreceptors, sympathetic postganglionic	1	1

Nociceptor Stimuli

- Nociceptor Stimuli – 3 types
  - Thermal
  - Mechanical
  - Chemical
- A delta fibers – thermal, mechanical
- C fibers – all three
  - "Polymodal" nociceptors
  - Firing threshold decreased by inflammatory mediators
  - Respond to capsaicin (found in chili peppers)

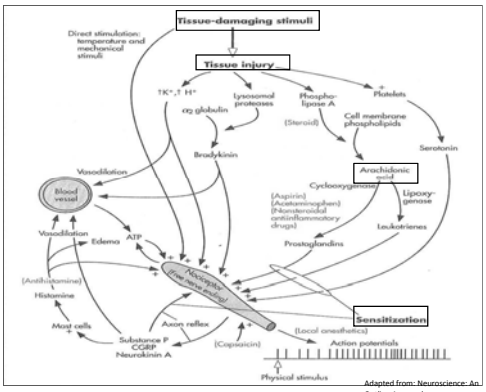
Capsaicin

- Found in chili peppers ("hot" or "burn" aspect of peppers)
- Activates receptor (TRPV1) on peripheral end of C fiber
- Topical application depletes substance P
- Used for treatment of postherpetic neuralgia ("shingles")

Peripheral Sensitization

- **Peripheral Sensitization**: reduction in threshold and an increase in responsiveness and firing rate of nociceptors
  - Contributes to pain hypersensitivity found at site of tissue damage and inflammation
  - Arises due to release and activation of inflammatory mediators at site of tissue injury
  - Explains hyperalgesia and allodynia at site of injury (e.g. surgical incision)
- **Hyperalgesia** – increased response to a stimulus that is normally painful **("primary hyperalgesia")**
- **Allodynia** – pain from a stimulus that does not normally produce pain

Peripheral Sensitization



Adapted from: Neuroscience: An Outline Approach

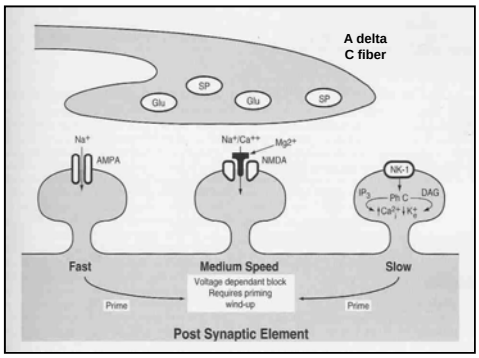
Spinal Cord Dorsal Horn

- **A delta fibers**
  - Terminate on second order neurons in lamina I and V
  - Transmitter: Glutamate (excitatory) - fast ("first pain")
  - Receptors: AMPA, NMDA (central sensitization)
- **C fibers**
  - Terminate on interneurons in lamina II (substantia gelatinosa)
  - Transmitter: substance P, CGRP (excitatory) - slow ("second pain")
  - Receptors: neurokinin (NK-1)
- **Interneurons**
  - Synapse on presynaptic terminals of A delta and C fibers
  - Postsynaptic on second order neurons projecting to CNS nuclei
  - Transmitter: GABA, enkephalin (inhibitory)
  - Receptors: GABA-A, mu, delta, kappa

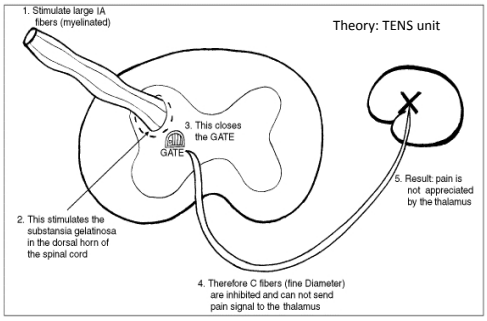
Central Sensitization

- **Central Sensitization** – increase in excitability of neurons within the dorsal horn of the spinal cord so that normal nociceptive throughput is enhanced ("increase in gain of system")
  - Occurs as result of increased activity of nociceptors
  - Hyperalgesia ("secondary")
  - Allodynia
- NMDA receptor mechanism
- Other mechanisms

Central Sensitization



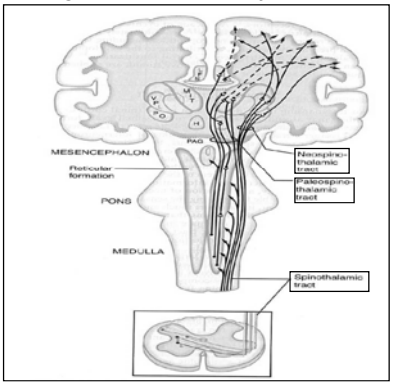
Gate Theory of Pain



Ascending Pain Pathways

- **Spinothalamic Tract** – sometimes divided into paleospinothalamic and neospinothalamic tracts
- **Paleospinothalamic** – "motivational/affective" component, i.e., pain as an unpleasant sensation
  - Spinal cord to medial and intralaminar nuclei of thalamus, reticular formation, periaqueductal gray, hypothalamus,
  - Thalamus to anterior cingulate cortex, insular cortex
- **Neospinothalamic** – "sensory/discriminative" ability to perceive where pain is and appropriately respond
  - Spinal cord to lateral nuclei of thalamus (VPL)
  - Thalamus to primary sensory cortex, motor cortex

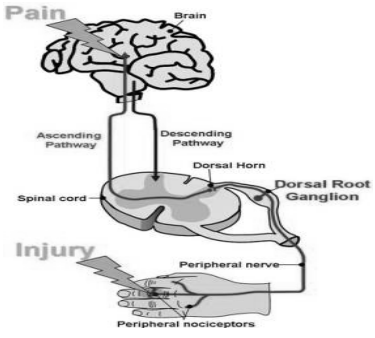
Ascending Pain Pathways and Nuclei



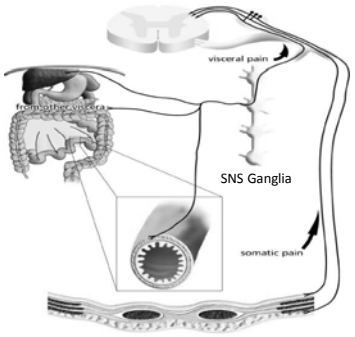
Descending Inhibitory Pain Pathways

- Projections from brainstem to dorsal horn of spinal cord
- Allow for higher CNS nuclei to modulate (inhibit) nociceptive information at spinal level
- Two primary pathways
  - PAG to NRM (enkephalin) to SC (serotonin)
  - LC to SC (norepinephrine)
- Inhibits incoming nociceptive input from A delta and C fibers
- May explain analgesic actions of drugs such as tramadol and antidepressants (e.g. amytriptyline)

Pain Pathways



Visceral Pain vs Somatic Pain

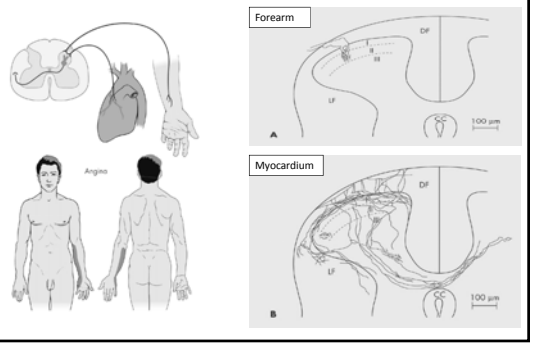


- Mediated primarily via the sympathetic nerves
- Diffuse and poorly localized
- Often felt as vague discomfort
- Elicited by distension, contraction, ischemia, and inflammation e.g. appendicitis

Referred Pain

- Pain in internal organs sensed on surface of body (heart – left arm; gall bladder – right shoulder; appendix – umbilicus)
- **Theory**: nociceptors from skin and organ converge on single ascending second order neuron.

Referred Pain



Overview - Clinical

- **Pain – clinical aspects**
  - Measurement/Assessment of Pain
  - Characterization of Types of Pain
  - Pain Syndromes
  - Treatment of Pain (Acute, Chronic)
    - Pharmacological (drugs)
    - Interventional (blocks, implantable systems)
    - Behavioral Therapy
    - Physical Therapy

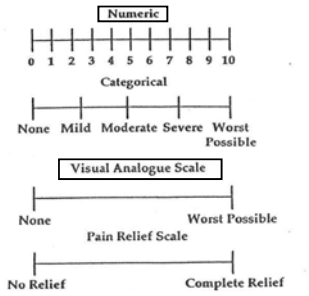
Measurement of Pain

- Why do we try to measure pain?
  - Determine severity of pain
  - Determine type of treatment – what drug is most appropriate?
  - Quantify effects of treatment
- No objective way to measure pain
  - "Pain is what the patient reports it is."
- Acute versus chronic pain – different scales apply

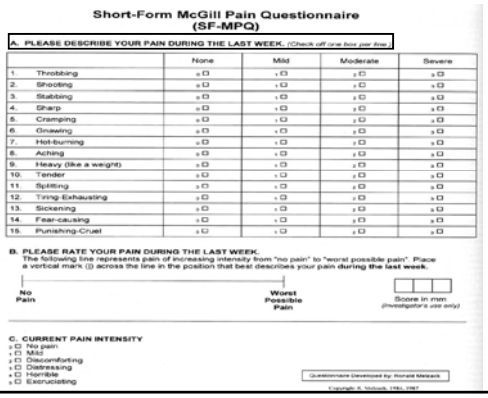
Pain Scales

- Single Dimension Pain Scales - acute pain
  - Verbal Descriptor
  - Numerical
  - Visual Analog Scale
- Multi-Dimensional Pain Scales - chronic pain
  - McGill Pain Questionnaire
  - Brief Pain Inventory
- Special Populations Pain Scales – pediatric and geriatric pain
  - "Faces Scales"

Adult Pain Measurement (Single Dimension Scales)



Multidimensional Adult Pain Scale



Short-Form McGill Pain Questionnaire (SF-MPQ)

A. PLEASE DESCRIBE YOUR PAIN DURING THE LAST WEEK. (Check off one box per line.)

	None	Mild	Moderate	Severe
1. Throbbing	0 ☐	1 ☐	2 ☐	3 ☐
2. Shooting	0 ☐	1 ☐	2 ☐	3 ☐
3. Stabbing	0 ☐	1 ☐	2 ☐	3 ☐
4. Sharp	0 ☐	1 ☐	2 ☐	3 ☐
5. Cramping	0 ☐	1 ☐	2 ☐	3 ☐
6. Gnawing	0 ☐	1 ☐	2 ☐	3 ☐
7. Hot-burning	0 ☐	1 ☐	2 ☐	3 ☐
8. Aching	0 ☐	1 ☐	2 ☐	3 ☐
9. Heavy (like a weight)	0 ☐	1 ☐	2 ☐	3 ☐
10. Tender	0 ☐	1 ☐	2 ☐	3 ☐
11. Splitting	0 ☐	1 ☐	2 ☐	3 ☐
12. Tiring-Exhausting	0 ☐	1 ☐	2 ☐	3 ☐
13. Sickening	0 ☐	1 ☐	2 ☐	3 ☐
14. Fear-causing	0 ☐	1 ☐	2 ☐	3 ☐
15. Punishing-Cruel	0 ☐	1 ☐	2 ☐	3 ☐

B. PLEASE RATE YOUR PAIN DURING THE LAST WEEK.
The following line represents pain of increasing intensity from "no pain" to "worst possible pain". Place a vertical mark (|) across the line in the position that best describes your pain during the last week.

No Pain — Worst Possible Pain

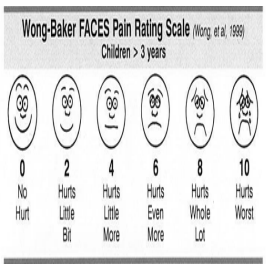
Score in mm (investigator's use only)

C. CURRENT PAIN INTENSITY
0 ☐ No pain
1 ☐ Mild
2 ☐ Discomforting
3 ☐ Distressing
4 ☐ Horrible
5 ☐ Excruciating

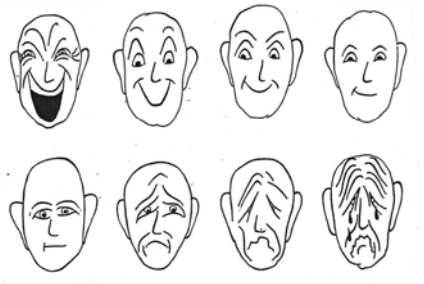
Questionnaire Developed by: Ronald Melzack

Copyright R. Melzack, 1984, 1987

Pediatric Pain Measurement



Geriatric Pain Measurement



Characterization Types of Pain (Mechanism)

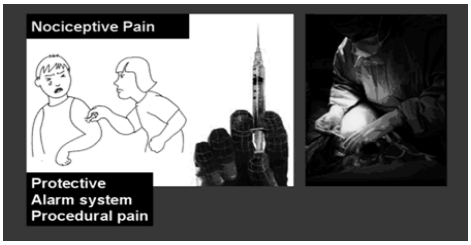
- **Nociceptive Pain** - pain caused by typical activation of nociceptive afferent fibers (A delta, C fibers) followed by transmission to spinal cord, thalamus and cortex.
- **Inflammatory Pain** - often considered as a type of nociceptive pain with involvement of chemical mediators and resultant pathology.
- **Neuropathic Pain** - caused by a primary lesion (pathology) or dysfunction in peripheral or central nervous systems.

Types of Pain

- Why as a clinician do I care about these details about the classification of types of pain?

*** Understanding what type of pain a patient has, either nociceptive, inflammatory, neuropathic or mixed, will determine the appropriate choice of pharmacological (drugs) and interventional (blocks, implantable devices) treatments.**

Nociceptive Pain



- Acute pain
- Sharp, aching nature

Adapted from "Unraveling Mechanisms and Clinical Consequences of Pain", medscape.com., 2004.

Inflammatory Pain

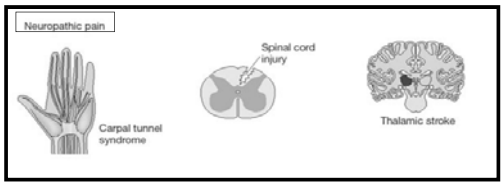
- Tissue injury and/or pathology
- Release of chemical mediators
- Peripheral sensitization may lead to central sensitization and contribute to maintenance of chronic pain states
- Constant, aching, quality
- Spontaneous and evoked pain

Adapted from "Unraveling the Mechanisms and Clinical Consequences of Pain, medscape.com., 2004

Inflammatory Pain Syndromes

- Rheumatoid arthritis
- Degenerative joint disease
- Irritable bowel syndrome
- Degenerative disc disease
- Post-operative pain

Neuropathic Pain



- Direct injury to PNS or CNS
- Spontaneous and evoked pain
- Cardinal feature is abnormalities of sensation
- Burning, tingling in nature

Adapted from Scholz and Woolf, 2002

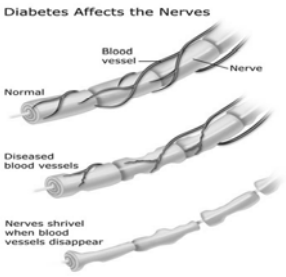
Abnormal Sensations of Neuropathic Pain

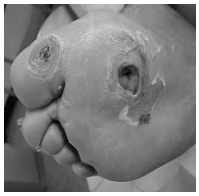
- **Spontaneous pain**: burning, shooting, lancinating
- **Dysethesias**: abnormal sensation that may be spontaneous or evoked (unpleasant tingling)
- **Hyperalgesia**: an exaggerated painful response to a normally noxious stimulus
- **Allodynia**: a painful response to a normally non-noxious stimulus (e.g. light touch perceived as burning pain.)

Neuropathic Pain Syndromes

- Diabetic peripheral neuropathy
- Post-herpetic neuralgia
- Complex regional pain syndrome (I,II)
- Phantom limb pain
- AID's related peripheral neuropathy
- Multiple sclerosis
- Spinal cord injury
- Stroke

Diabetic Peripheral Neuropathy





- Burning, tingling
- Hyperalgesia, allodynia
- Numbness
- Antalgic gait
- Falls

Complex Regional Pain Syndrome (Type I, RSD – mixed etiology)

- Hyperalgesia
- Allodynia
- Dysethesia
- SNS mediated pain

Treatment Modalities For Pain I

- **Pharmacological** – drugs (PO, IV, transdermal)
  - Opioids
  - NSAID's
  - Adjuvant agents (antidepressants, anticonvulsants)
- **Interventional**
  - Nerve or joint blocks, Nerve destruction (neurolytics, radiofrequency)
  - Neuroaxial (epidural, intrathecal)
  - Implantable devices (intrathecal pump, spinal cord, peripheral nerve or deep brain stimulators)

Treatment Modalities For Pain II

- **Psychological/Behavioral** – CBT, biofeedback
- **Physical Therapy**
- **Others** - Acupuncture, TENS

Drugs for Pain

- **Nociceptive and Inflammatory Pain**
  - Opioids – fentanyl, morphine, hydrocodone, oxycodone
  - NSAIDs – ibuprofen, naproxen
  - Steroids – methylprednisolone
- **Neuropathic Pain – "Adjuvant Agents"**
  - Antidepressants – amytriptyline, duloxetine
  - Anticonvulsants – gabapentin, pregabalin
  - Local anesthetics – lidocaine, mexilitene
  - Others - clonidine ("sympathetic maintained pain"- CRPS I)

Treatment Modalities for Acute Pain

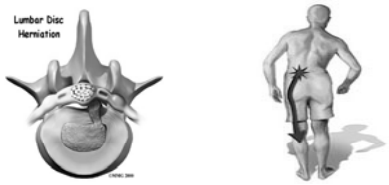
- **Procedural, Post-operative, Obstetric pain** - most often nociceptive, inflammatory in nature.
- **Pharmacological**
  - NSAID
  - Opioid
- **Interventional**
  - Regional Nerve Block – brachial plexus block
  - Neuroaxial Analgesia – local anesthetic, opioid
    - Epidural
    - Spinal

Treatment Modalities for Chronic Pain

- **"Multi-modal approach" is required**
- Pain is often mixed in nature
- Pharmacological
  - NSAID's
  - Opioids
  - Adjuvants
- Interventional
  - Neuroaxial – epidural, intrathecal (steroids, local anesthetics, opioids)
  - Nerve, Plexus, Joint Blocks – intercostal nerve, celiac plexus, lumbar facet joint (local anesthetic, steroids)
  - Neurolytic – cancer pain (alcohol, phenol)
  - Implantable systems – intrathecal pump, stimulators (CNS, PNS)
- Behavioral Medicine
- Physical Therapy

Lumbar Disc Herniation

(multimodal treatment)



- Disc herniates and impinges on descending nerve root
- Mixed pain etiology (inflammatory, neuropathic)
- Low back pain from disc degeneration
- Radiating pain into lower extremity

- Pharmacological: opioid, NSAID, adjuvant drug
- Interventional: lumbar epidural steroid
- Physical therapy

Summary

- **Pain – basic aspects**
  - **Pain Transmission System**
  - **Pain Mechanisms – peripheral, central sensitization**
  - **Somatic, Visceral and Referred Pain**
- **Pain – clinical aspects**
  - **Measurement/Assessment of Pain**
  - **Pain types**
  - **Pain syndromes**
  - **Treatment of pain**

The Management of Pain, Ed. J. Bonica, 2nd ed., 1990

"Laocoonte"

CLINICAL CORRELATION: HEADACHE

Date: September 8, 2011 - 9:30 am
Reading Assignment: Refer to posted handout

KEY CONCEPTS AND LEARNING OBJECTIVES

1. Describe the clinical features of migraine, including the aura, photophobia and phonophobia. Recognize that female gender and positive family history are risk factors for migraine, which begins early in adult life.

2. Describe the clinical features of cluster headache. Recognize that male gender is a risk factor for cluster headache.

3. List the abortive and prophylactic treatments for migraine. Recognize that several chemically unrelated drugs here have therapeutic effects on serotonin receptors.

4. Describe the clinical features of tension headache and treatments for it.

5. Explain why headaches occur after lumbar puncture (traction headaches), from pseudotumor cerebri, or in temporal arteritis.

Headache (Dr. Merchut)

The common symptom of headache can be produced by several mechanisms. When a brain tumor or hemorrhage causes a headache, it does so by stretching, compressing, and distorting intracranial blood vessels or cranial nerves. The mere presence of an intracranial lesion does not directly create pain, since pain is not produced by the brain parenchyma itself, but by effects on blood vessels, sensory nerve afferents, and other adjacent structures. Inflammation or infection of mucosal structures, nasal sinuses, meninges, or perivascular areas may also cause headache. Once a headache begins, sustained contraction or tenseness of skeletal muscles of the neck and scalp may exacerbate the pain.

Migraine and Vascular Headaches

1. Types of vascular headache

Vascular headaches typically have a throbbing, pounding, pulsatile quality of pain that seemed to arise from cranial blood vessels. Although there is an abnormal tendency for arterial vasodilation in migraine, current research suggests that it does not cause, but rather is an effect, of spontaneous neuronal dysfunction specific to this type of headache. **Women are more apt to have migraine and often have a family history of it.** Migraines often arise in the teen years when menstruation begins, or by early adulthood. The hormonal changes during the menstrual cycle are a predisposing factor for many women with migraine headaches.

Migraine may occur with aura, formerly called "classical migraine," or without aura, formerly called "common migraine." The **aura of migraine** is a distinctive, often rather diagnostic, symptom attributed to a wave of depolarization over focal areas of cerebral cortex, lasting a few minutes in duration. Auras usually precede, sometimes accompany, and rarely follow the migraine headache. **Often the aura is visual, with flashing, flickering, scintillating lines or dots** arising in one part of the visual field and slowly spreading out like ripples in a pond. A scotoma or patch of blindness may exist in the midst of the lights, a "scintillating scotoma." The flashing lights may have a zig-zag orientation, resembling an aerial view of a walled, fortified medieval town, hence the description "fortification phenomenon." Both the flashing lights and scotoma are due to depolarization of occipital visual cortex. Less common auras include the spreading of tingling or abnormal sensation over one half of the body, dysarthria, and aphasia.
The migraine headache itself often is severe and incapacitating, preventing the patient from continuing a task. A throbbing, pounding pain arises unilaterally and may generalize, accompanied by intolerance to light (**photophobia**) and sound (**phonophobia**). Autonomic symptoms of sweating, nausea, vomiting, and dizziness may also occur. The headache may last hours to 1-2 days, while a sense of malaise or illness may continue for a longer period afterwards. Migraine without aura involves the same kind of headache syndrome. Although an aura is absent, patients often vaguely "feel sick" before the migraine begins.

Other types of vascular headache include complicated migraine and cluster headache. **Complicated migraine** consists of dramatic, frightening symptoms that

precede, accompany, or follow the headache and mimic an acute stroke syndrome. Indeed, in rare instances ischemic infarction does occur with some of these migraine variants. The symptoms may be hemiplegia or ophthalmoplegia, such as an oculomotor (third cranial nerve) palsy. Basilar migraine consists of a variety brainstem symptoms or blindness from occipital lobe involvement, areas all in the vascular territory of the basilar artery. **Cluster headache** is a vascular headache **more common in men**. These are severe headaches of shorter duration (2 to 3 hours) occurring in clusters of days or weeks, followed by long periods of remission. There is a unilateral, **periorbital pain** of boring or stabbing nature. The painful eye appears red, watery, and tearing, occasionally with a transient **Horner's syndrome.** When nasal discharge and congestion accompanies these symptoms, the headaches may be incorrectly attributed to seasonal allergies.

2. Mechanisms of migraine

A **spreading wave of cortical depolarization** appears to be an early component of migraine. This activity arises spontaneously or in response to various triggers in migraine-prone patients, such as dietary factors, changing hormonal levels, and different types of stress. How it is exactly initiated is unknown. If the depolarization affects the occipital cortex, a visual aura (scintillating scotoma) occurs. When the depolarization reaches trigeminal afferent nerves, the **trigeminovascular system** is activated. Perivascular trigeminal afferent nerves transmit impulses to parts of the brain stem and hypothalamus, causing nausea, vomiting, and photophobia. Subsequent activation of thalamic or cortical areas leads to the perception of pain and other neurological symptoms. These stimulated trigeminal ganglia may then depolarize their afferent nerves antidromically (in reverse direction) to release vasoactive neuropeptides such as substance P, an important component of peripheral pain pathways, at their terminal perivascular location. This process is called **neurogenic inflammation** and enhances or prolongs the pain of migraine by causing vasodilatation and increased permeability of blood vessels, including those in the meninges.

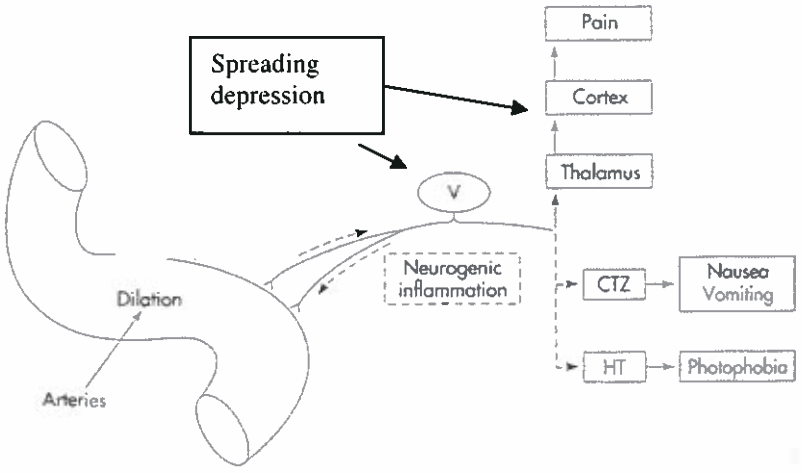


Fig. 1 Theoretical mechanism of migraine. **(adapted from Saxena PR, Ferrari MD. *Trends Pharmacol Sci* 10:200-204, 1989)**

3. Diagnosis and treatment of migraine

The visual aura of migraine is distinctive and diagnostically helpful. However, the patient having a severe, first migraine without aura raises concerns about an underlying brain tumor or hemorrhage, and a brain scan, preferably an MRI, is usually performed. Brain scans are also required whenever focal neurological findings are found on examination, even in a patient with a lifelong history of migraine, or when severe headaches arise later in life, since migraine usually begins in the teens or twenties. Other "red flags" meriting brain scans are headaches getting progressively worse, or accompanied by seizures, cognitive or behavioral changes.

The treatment of migraine is tailored to the severity of the headache symptoms and consists of **abortive treatment**, to lessen or stop an ongoing headache, or prophylactic treatment, to prevent future headaches. Milder migraines may stop by taking over-the-counter **nonsteroidal anti-inflammatory drugs** (NSAIDs) such as ibuprofen or naproxen, or **analgesics** like acetaminophen or aspirin. If nausea and vomiting are a significant symptom, an **antiemetic** drug may be very helpful. Prescription narcotics or sedatives are sometimes used, but carry the risk of tolerance and addiction if used frequently. **Triptan medications** are more specific for aborting a migraine headache, are quite effective, and come in oral, injectable, and nasal spray formulations. Non-oral routes are preferred if nausea and vomiting is a significant problem. Sumatriptan was the first triptan drug, followed by several newer preparations. Dihydroergotamine is another drug helpful in aborting a severe migraine, delivered by injection or nasal spray.

Abortive treatment is appropriate if migraines are as infrequent as once or twice monthly. Basic non-pharmacological methods of preventing migraine include avoiding dietary precipitants, stress management, and relaxation techniques like biofeedback, meditation or yoga. Some find benefit from various herbal (feverfew), vitamin (riboflavin), or mineral (magnesium) supplements. If these methods are ineffective in preventing migraines which are more frequent, more severe, or more frightening due to their associated neurological symptoms, **prophylactic treatment** with daily medication is used. For many women, migraine is worse, or occurs exclusively, during their menstrual period. Oral contraceptives may help prevent menstrual migraine, although there may be some increased risk of stroke in women having migraine with aura, especially if they are smokers over 35 years of age. Several other types of drugs can be used prophylactically for migraine, including **beta-adrenergic blockers** like propranolol, **calcium channel blockers** like verapamil, **tricyclic antidepressants** like amitriptyline, and **anticonvulsants** like valproate, gabapentin, and topiramate. All of these drugs, like the triptans and dihydroxyergotamine, **have effects at serotonin receptors**. Serotonin is a neurotransmitter in some of the pathways which produce migraine headache, and is also present in blood vessels, gastrointestinal tract, and platelets, all of which react abnormally in migraine.

Headaches other than migraine

1. Tension headaches

These are the most common type of headache, experienced by virtually everyone at some time. Tension headaches were formerly called "muscle contraction headaches" in the belief that various stressors led to prolonged muscle contraction in the neck, shoulders, and scalp, which may be present on physical examination. The pathogenesis of tension headache may actually be more complicated, however, and may involve overly sensitive pain pathway afferents and central connections which create pain in response to innocuous stimuli. Tension headaches are described as a **steady pressure or band-like feeling around the head, not as severe or incapacitating as migraine, and without significant nausea and vomiting, photophobia, or phonophobia. These headaches often last hours to all day,** but may not be noticeable when one is distracted or preoccupied with other tasks. Patients with frequent tension headaches often have several **chronic psychosocial stresses** and may report continuous tension headaches lasting days, weeks, or even years. Helpful medications include **non-steroidal anti-inflammatory drugs, analgesics, and tricyclic antidepressants like amitriptyline**. Treatment is complex in those patients with both migraine and tension headache. Chronic daily use of combination headache medications which include butalbital, a barbiturate, leads to rebound headaches when they are discontinued. Dose withdrawal programs, drug substitutions, and hospitalization may be required to "break" the cycle and relieve headache.

2. Other headaches

Traction headaches typically occur after a lumbar puncture because of a persistent leak of cerebrospinal fluid (CSF). It is characteristically a **positional headache**, relieved when lying flat, and recurring when sitting or standing upright. If these headaches do not resolve spontaneously, injection of the patient's own blood into the epidural space produces an "epidural blood patch" which seals off the dural leak of CSF.

Pseudotumor cerebri involves headaches which are throbbing, and sometimes accompanied by nausea and vomiting, similar to migraine. These patients are often obese and have **papilledema** (bilaterally swollen optic discs) on examination. The papilledema is due to increased intracranial pressure from impaired CSF reabsorption and **can lead to permanent blindness** if not diagnosed and treated in timely fashion. In these patients, brain scans fail to find any causative brain tumor, hence the term "pseudotumor." A subsequent lumbar puncture reveals normal CSF at very high pressure, and the headache may be temporarily relieved by removing large volumes of CSF. Long term normalization of intracranial pressure can be achieved by weight loss, acetazolamide medication to inhibit CSF production, or a surgical shunt procedure (optic nerve fenestration or lumboperitoneal shunting of CSF).

Temporal arteritis can cause nonspecific headaches in elderly patients. It is an immune-mediated inflammation of arteries perfusing the head, known also as "cranial arteritis." The temporal arteries may be tender to palpation, and while chewing the jaw

muscles may get sore and painful. There may be achiness and stiffness of the shoulder and hip muscles (polymyalgia), a low grade fever in the absence of infection, or a **very elevated sedimentation rate** blood test. Arteritis is confirmed by biopsy of a temporal artery, and prompt **corticosteroid treatment is needed to prevent blindness** from involvement of the ophthalmic arteries.

Trigeminal neuralgia consists of sudden, brief, repeated, lightning jabs of pain in the territory of a branch of the trigeminal nerve on one side. It is often provoked by talking, chewing, or touching the face, and is discussed further in "Cranial Nerves."

Headaches or facial pain associated with fever may be due to meningitis or infections of the ears, nasal sinuses, or teeth. Allergy related inflammation may also cause pain or discomfort of the eyes or nasal sinuses.

EPILEPSY

Date: September 08, 2011
Reading Assignment:

KEY CONCEPTS & LEARNING OBJECTIVES

1. How are epilepsies classified? What are two types of "partial" seizures? What are two types of "generalized" seizures?
2. What is an interictal spike in the EEG?
3. What are neurons in an epileptic focus doing during an interictal spike?
4. What mechanisms normally prevent neurons from firing too much?
5. What part of brain is malfunctioning in complex partial seizures?
6. What is a temporal lobectomy?

Visual System I, II, & III

Reading Assignment: Mason, Ch. 16

Learning Objectives:

1. Be familiar with the embryonic development of the eye (see chapter 2 for additional reference).

2. Know the anatomy of the eye, including its concentric tissue layers and the function of its various chambers.

3. Be able to describe what aqueous humor is and how it is produced within the eye. Be able to define the anatomical structures involved with its removal. What happens when there is pathology associated with these structures?

4. Understand what structures of the eye are responsible for determining optical power. How do these structures change for distant or near vision?

5. Be able to describe the major optical deficits, identify their anatomical distinctions, and explain how to correct these deficits.

6. Be able to describe the clinical significance of the fundal exam.

7. Where on the fundus can the macula/fovea be found? Describe the unique cellular composition of the fovea and explain why macular degeneration is so devastating.

8. Know the various layers of the mammalian retina and the cells associated with these layers. Describe their various cellular contributions to phototransduction. What are Müller cells? What is the function of the pigment epithelium?

9. Know the structural and functional differences between rod and cone photoreceptors. How do they differ in morphology, light sensitivity, adaptation, wavelength of light absorbed, number of biopolar cell synaptic contacts made?

10. Know how light is absorbed by the photoreceptor and what chemical changes occur following light absorption.

11. Be able to explain how photons cause photoreceptor membranes to hyperpolarize. What ion channels are affected by photons? How are they affected?

12. What is meant by amplification and how does it apply to phototransduction?

13. If photoreceptors hyperpolarize in response to light, than explain how we can see in the daylight?

14. Define visual receptive fields.

15. What is the significance of center-surround receptive fields?

16. Define visual fields and be able to correctly project objects in our visual fields onto the retina.

17. Know how objects within our visual fields are represented in the visual pathway.

18. Where do the optic tract neurons terminate? How are they distributed?

19. Know the subdivisions of the lateral geniculate nucleus and the significance of these subdivisions.

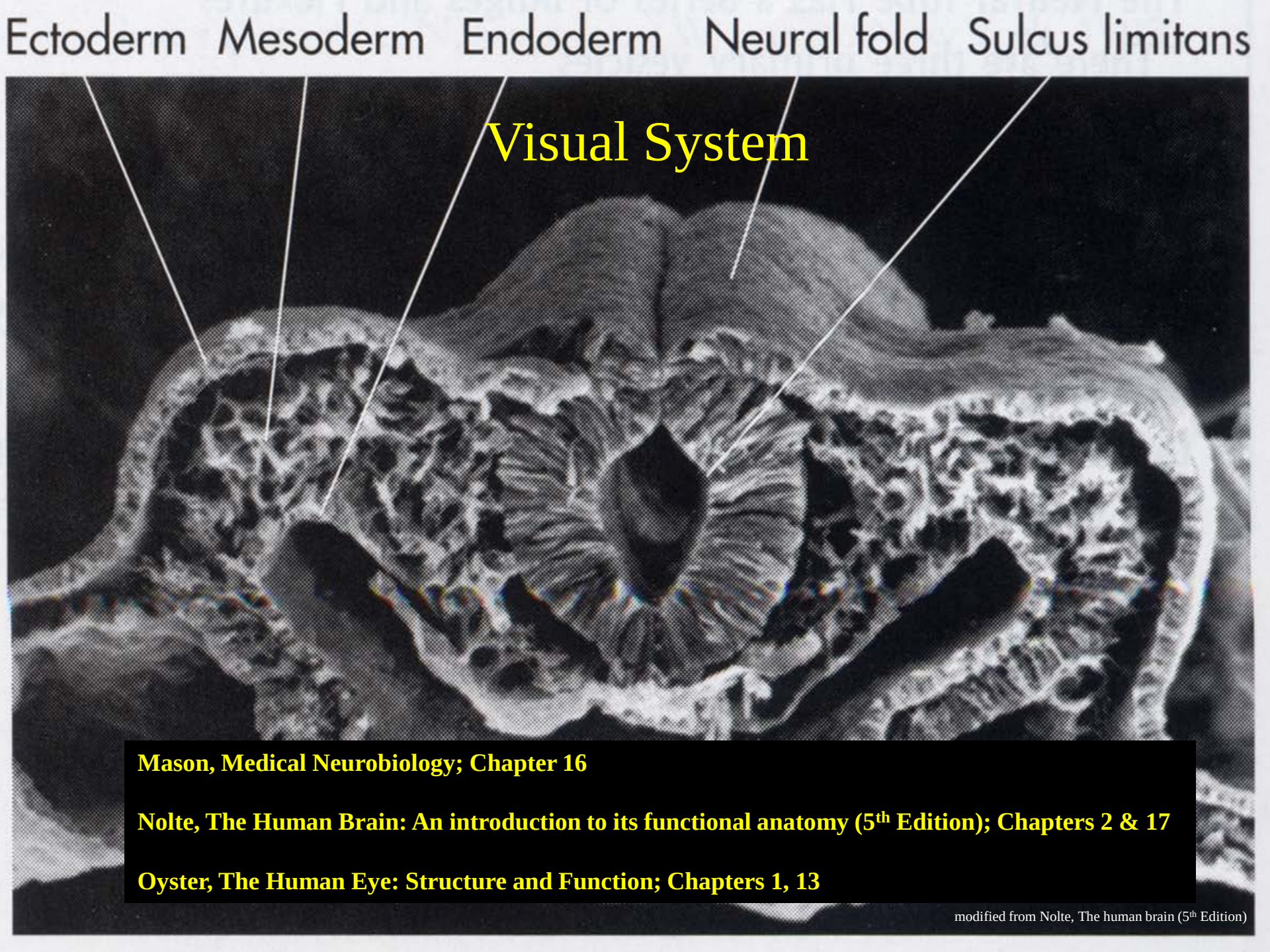
20. What are the basic types of ganglion cells?

21. Know how retinotopic tomography is maintained. Neurons carrying information about objects in our inferior visual fields project to what part of our visual cortex? What structures do they circumvent on their way to the visual cortex?

22. Be able to draw visual field deficits resulting from lesions affecting selected parts of the visual pathway. Bitemporal heteronymous hemianopsia is suggestive of what structural defect? What might cause this structural defect?

23. What is the significance of macular sparing within a visual field deficit?

24. Describe the receptive fields of the LGN and how they relate to cortical processing of visual information.



Visual System

Mason, Medical Neurobiology; Chapter 16

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

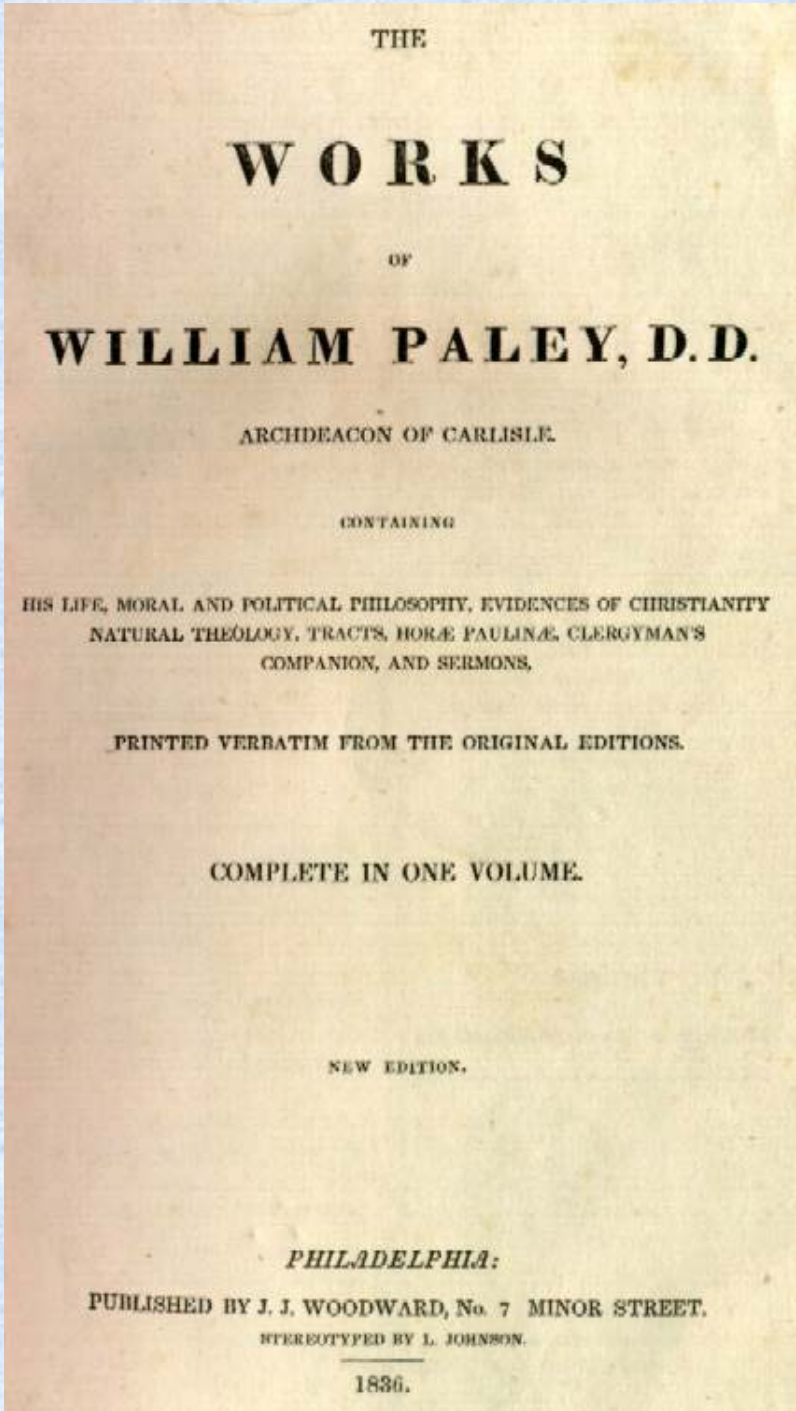
modified from Nolte, The human brain (5th Edition)

"Were there no examples in the world of contrivance except that of the eye, it would be alone sufficient to support the conclusion which we draw from it, as to the necessity of an intelligent creator"

William Paley, *Natural Theology*

Reason tells me, that if numerous gradations from a simple and imperfect eye to one complex and perfect can be shown to exist, each grade being useful to its possessor, as is certainly the case; if further, the eye ever varies and the variations be inherited, as is likewise certainly the case; and if such variations should be useful to any animal under changing conditions of life, then the difficulty of believing that a perfect and complex eye could be formed by natural selection, though insuperable by our imagination, should not be considered as subversive of the theory.

Charles Darwin, *On the Origin of Species* (1859)



THE

WORKS

OF

WILLIAM PALEY, D.D.

ARCHDEACON OF CARLISLE.

CONTAINING

HIS LIFE, MORAL AND POLITICAL PHILOSOPHY, EVIDENCES OF CHRISTIANITY NATURAL THEOLOGY, TRACTS, HORÆ PAULINÆ, CLERGYMAN'S COMPANION, AND SERMONS.

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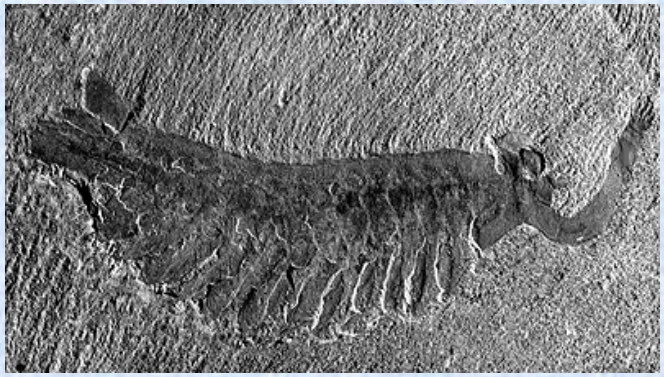
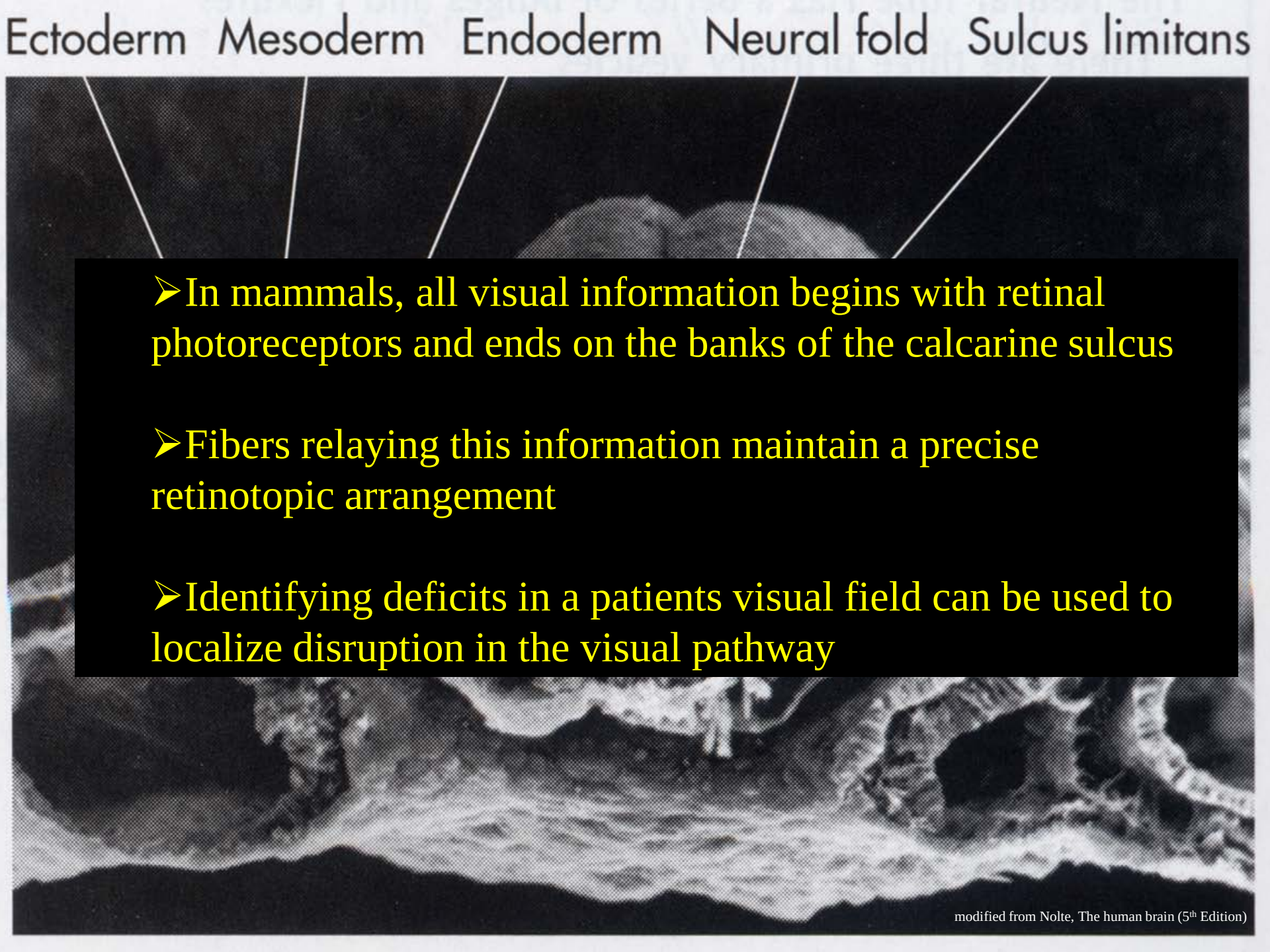
STEREOTYPED BY L. JOHNSON.

1836.

Species	Simple (refraction)	Compound
Vertebrate	+++	--
Avian, reptilian, primate	+++	--
Invertebrate	+	+++
(insects)		+++
(Arthropods)		
Jumping spiders/Scorpions	++	+++
(Mollusca)		
Snails	++	
Shellfish (abalone)	++	
Bivalves (scallop)	++	
(cephalopods)		
Octopus, squid, cuttlefish	+++	
Jellyfish	+	
Worms	+	

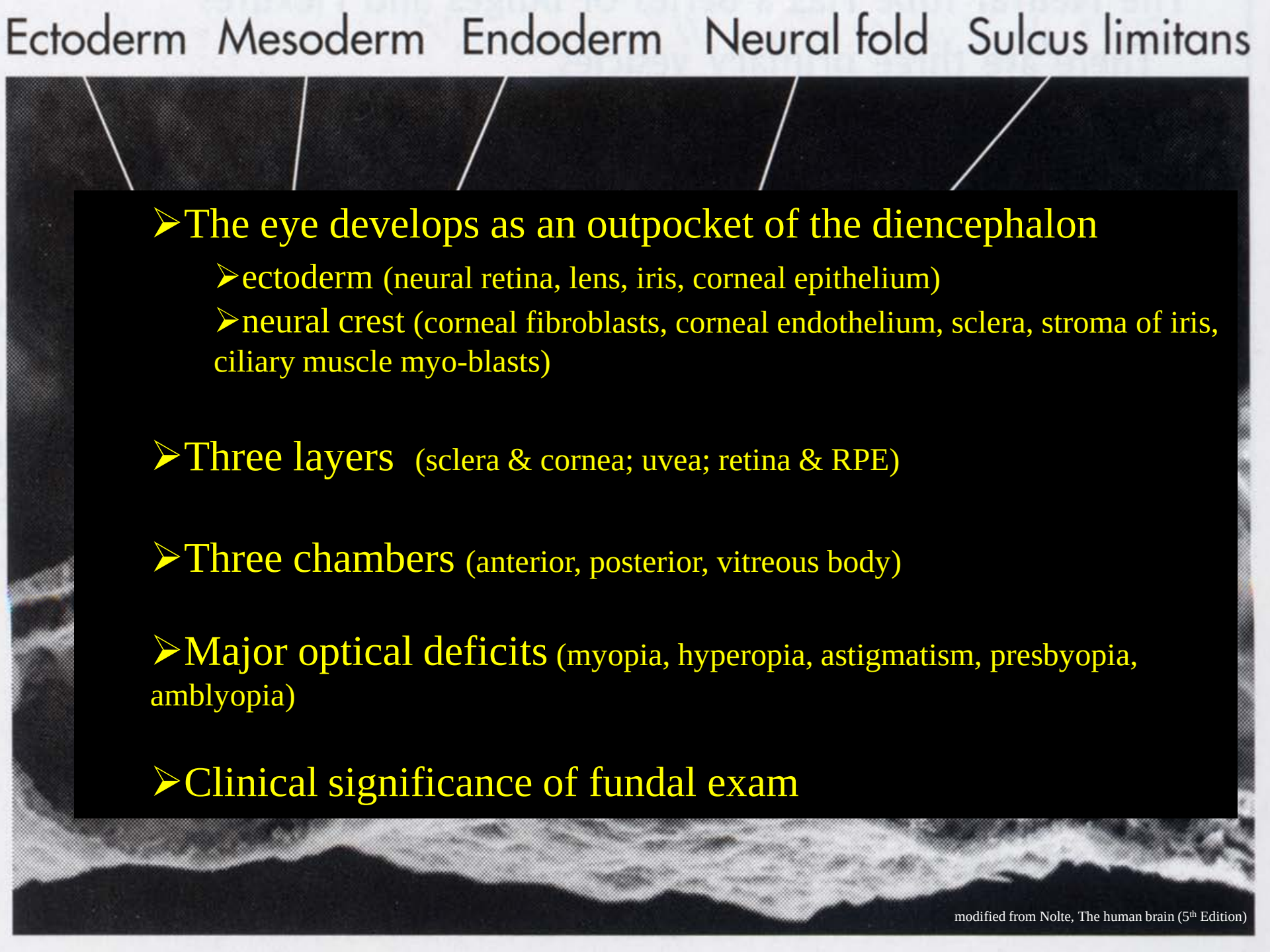


Opabina (530 million years old; Burgess Shale, British Columbia)



- In mammals, all visual information begins with retinal photoreceptors and ends on the banks of the calcarine sulcus
- Fibers relaying this information maintain a precise retinotopic arrangement
- Identifying deficits in a patients visual field can be used to localize disruption in the visual pathway

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

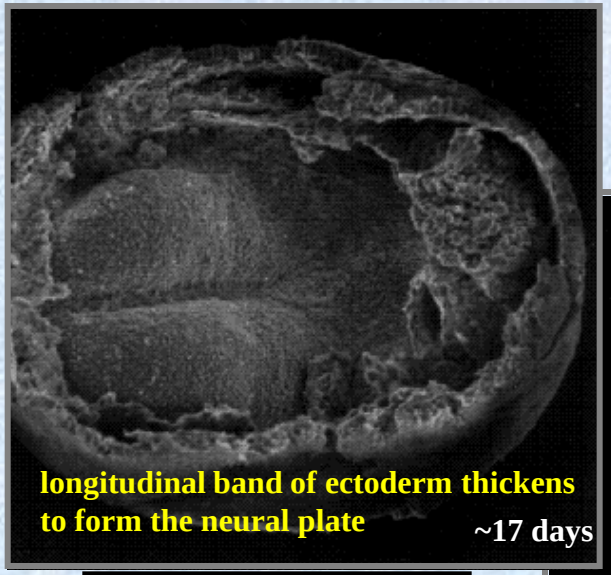


- The eye develops as an outpocket of the diencephalon
  - ectoderm (neural retina, lens, iris, corneal epithelium)
  - neural crest (corneal fibroblasts, corneal endothelium, sclera, stroma of iris, ciliary muscle myo-blasts)
- Three layers (sclera & cornea; uvea; retina & RPE)
- Three chambers (anterior, posterior, vitreous body)
- Major optical deficits (myopia, hyperopia, astigmatism, presbyopia, amblyopia)
- Clinical significance of fundal exam

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

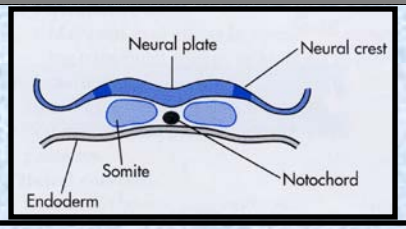
modified from www.med.unc.edu

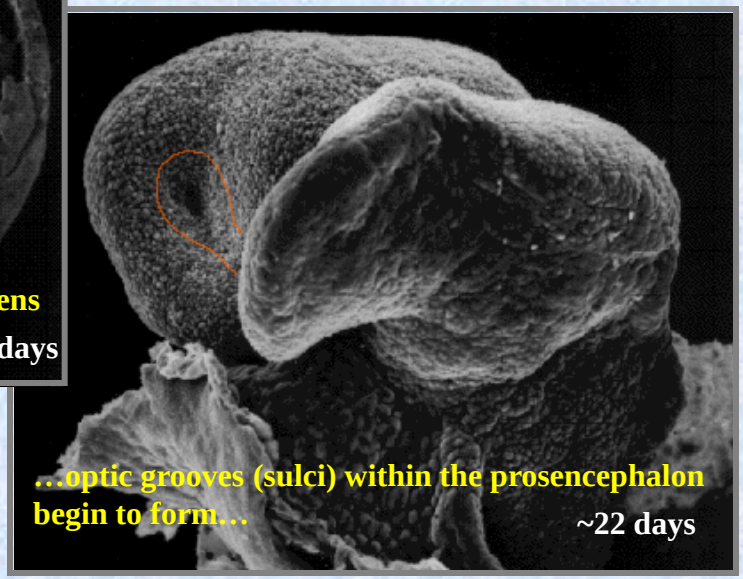
Eye Development



longitudinal band of ectoderm thickens to form the neural plate

~17 days

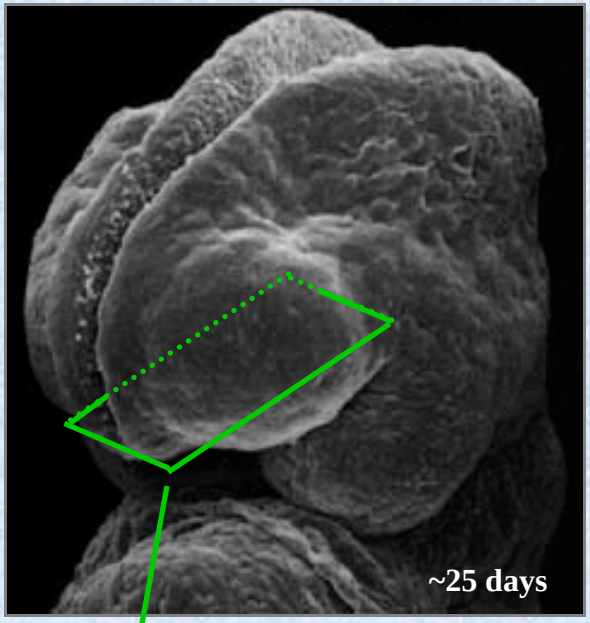




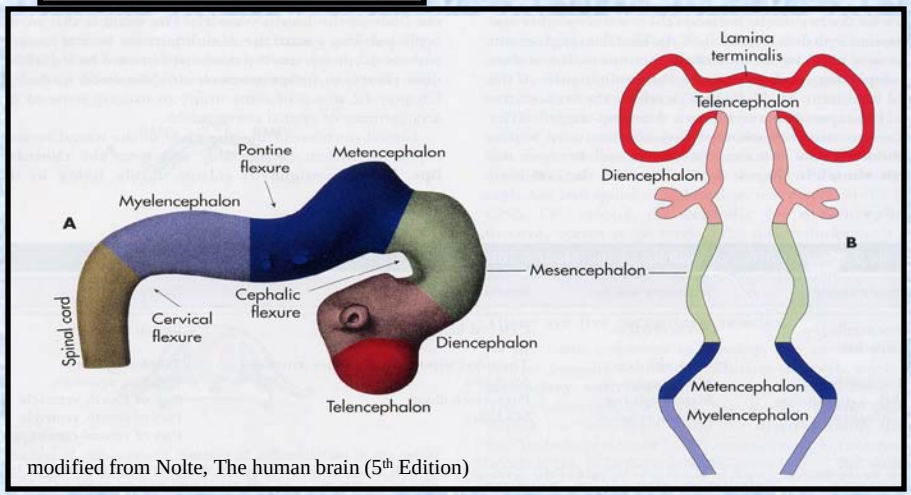
…optic grooves (sulci) within the prosencephalon begin to form…

~22 days

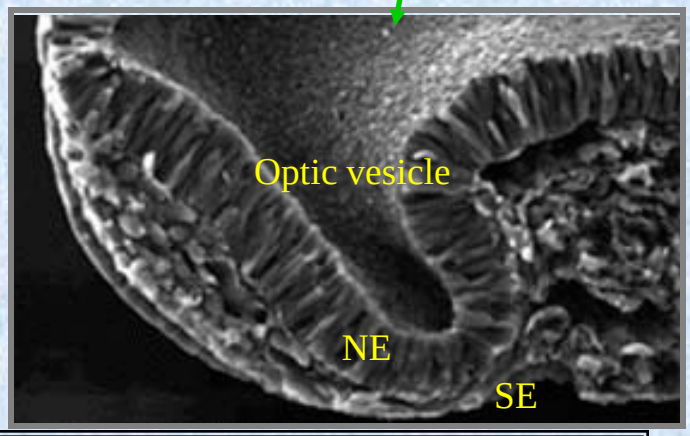
…as the edges of the neural fold come together, the neural ectoderm comes into close contact with the surface ectoderm…



~25 days

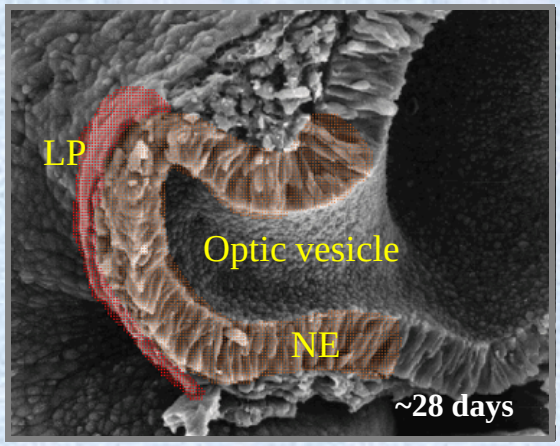


modified from Nolte, The human brain (5th Edition)



Retina and optic nerve develop as an outpocket of the diencephalon

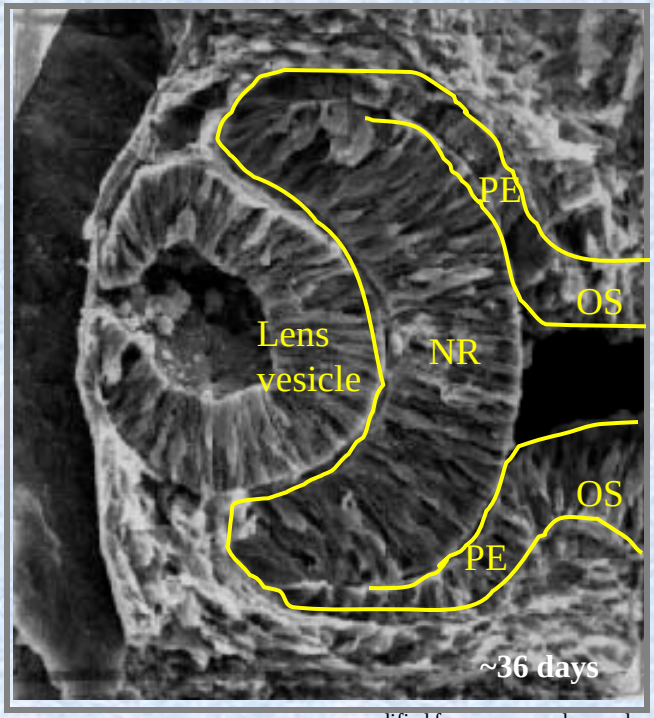
Eye Development



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…



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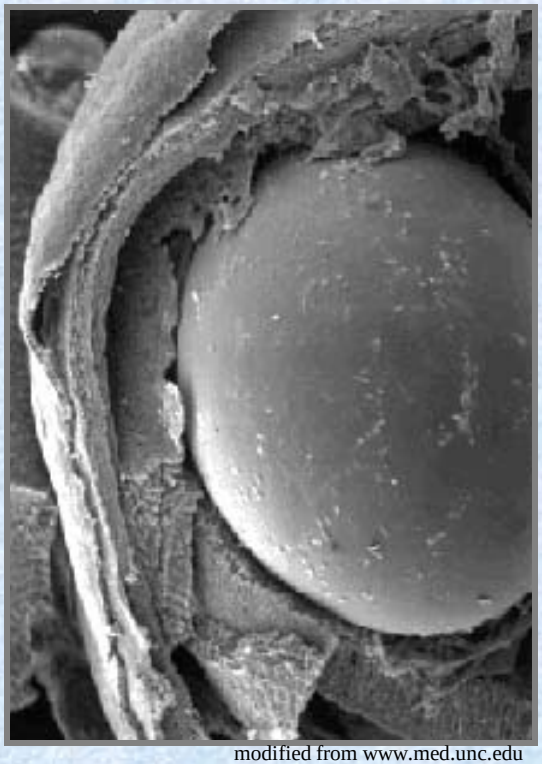
…invagination of the optic vesicle gives rise to the two-layered optic cup



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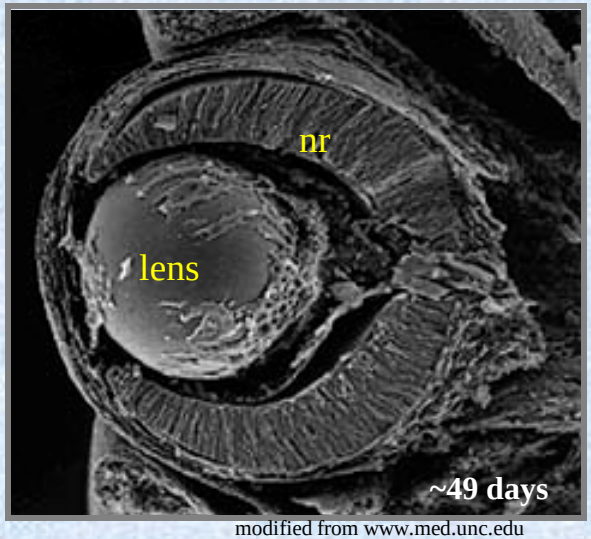
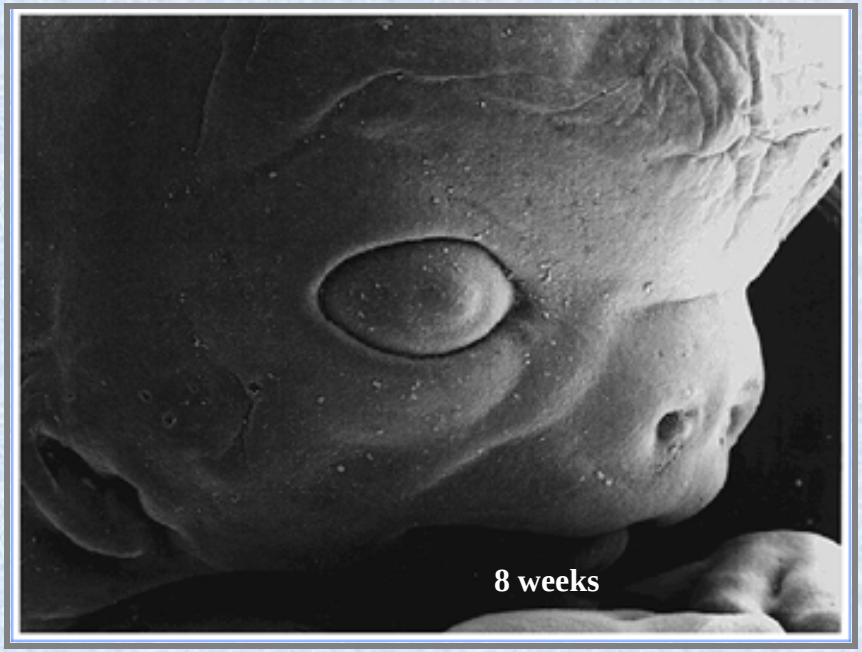


modified from www.med.unc.edu

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

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



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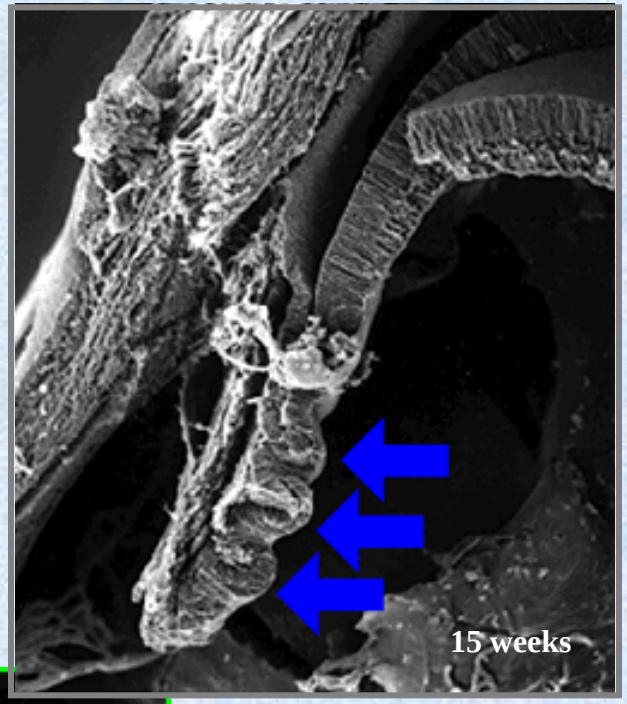
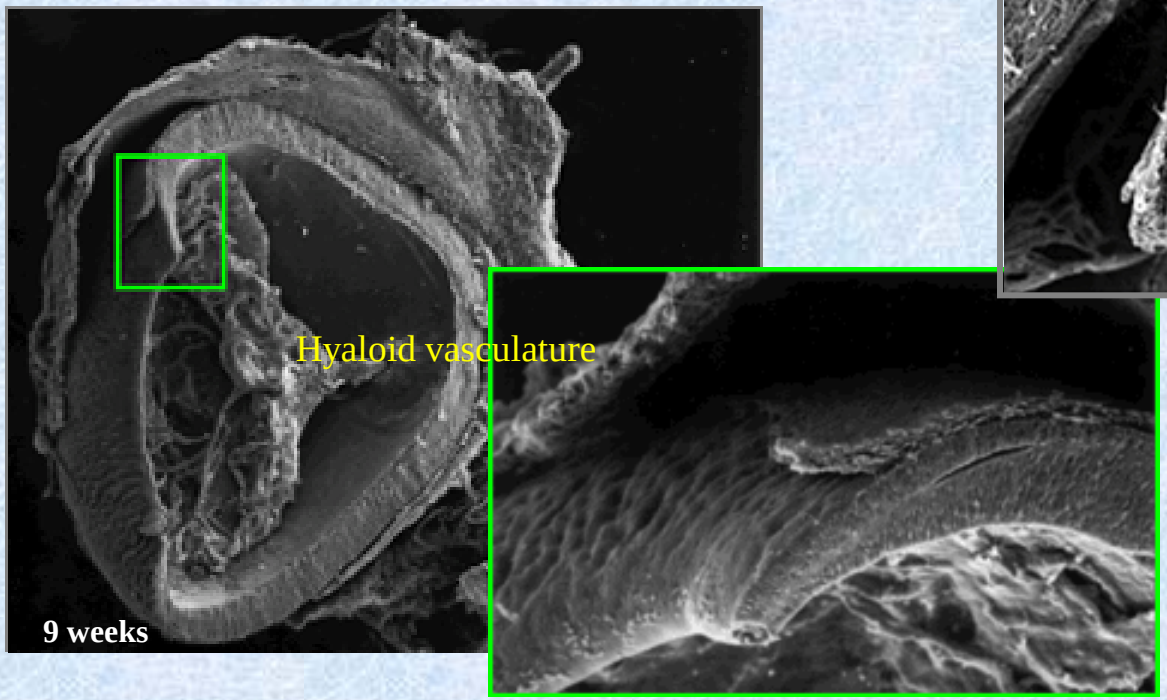
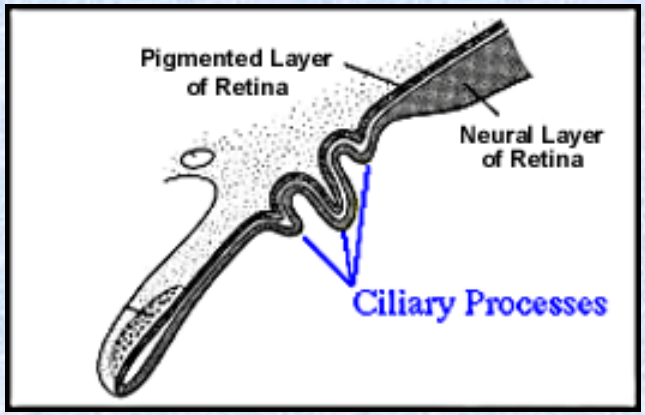


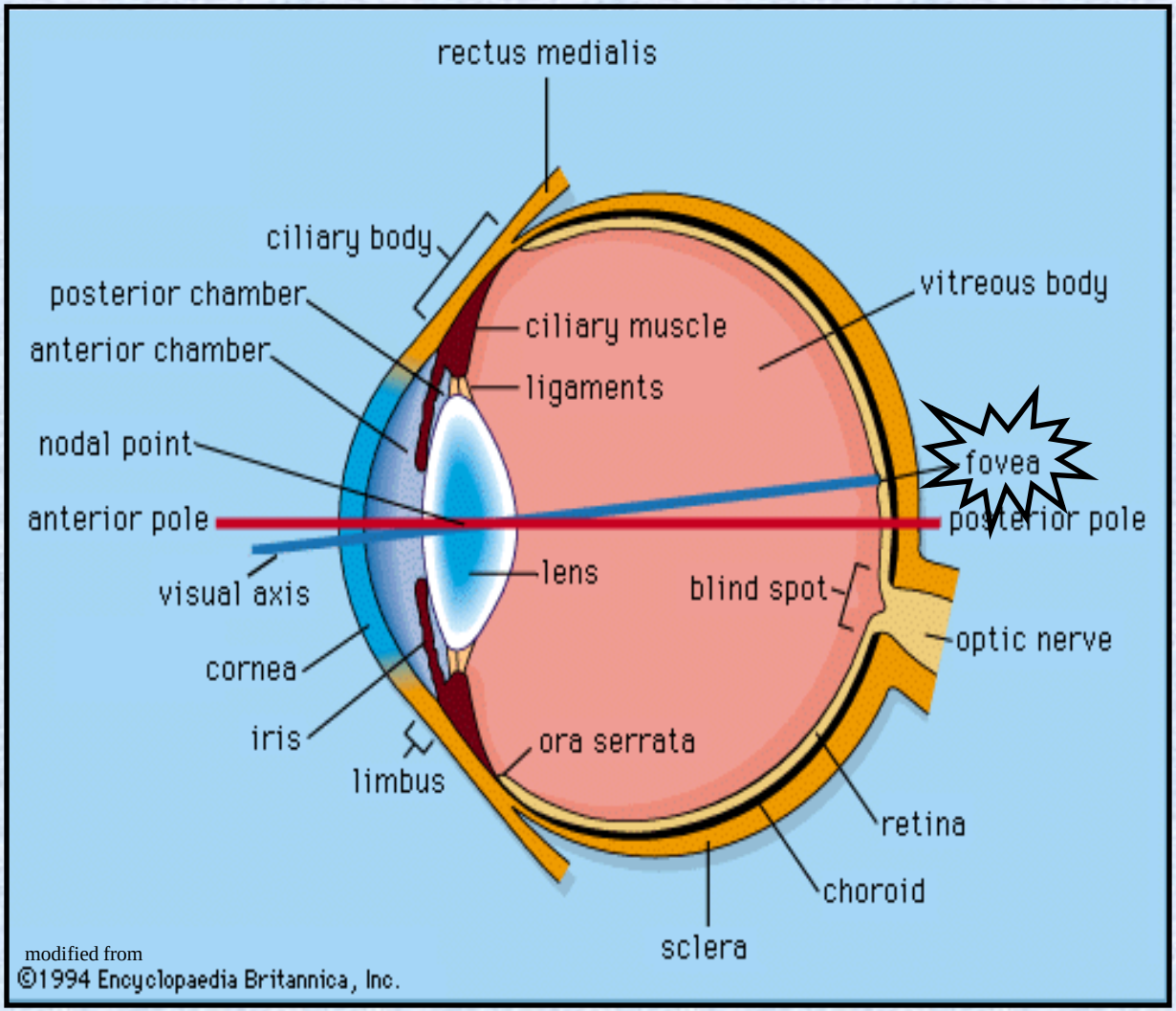




…take home message

- 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*)

- sclera
- cornea
  - •avascular
  - •densely innervated (V_1)

Middle Layer (uvea, *pia mater*)

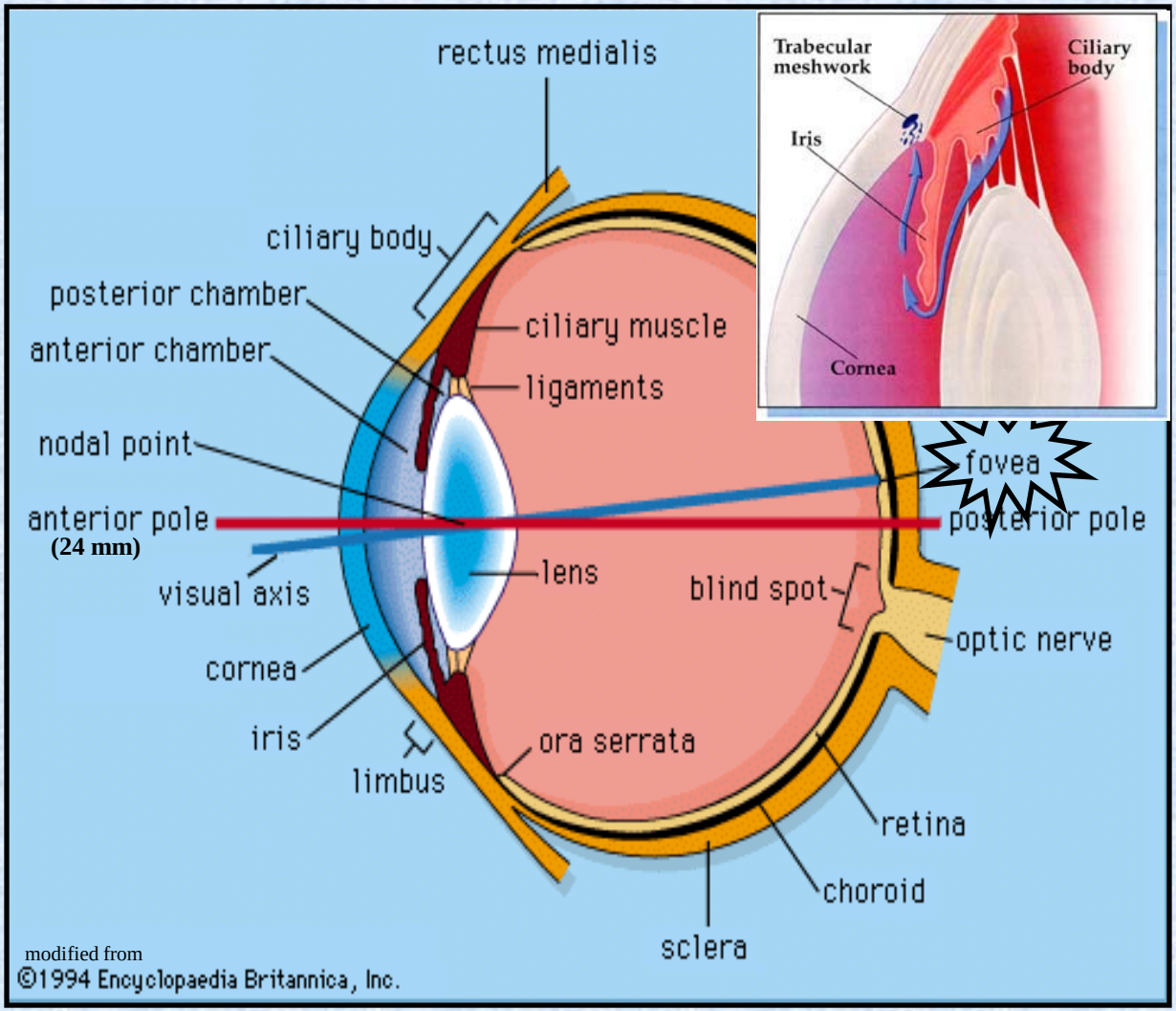
- choroid capillaries (permeable, contain melanin)
- ciliary body & muscles
- stroma of the iris

Inner Layer (CNS)

- retinal pigment epithelium
  - **phototransduction and BRBarrier**
- neural retina
  - retinal 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

- aqueous humor reabsorbed at the trabecular meshwork
- spaces of Fontana
  - canal of Schlemm
  - anterior ciliary vein

Posterior Chamber

iris & lens

- aqueous humor produced by ciliary processes
  - Na^+-K^+ ATPase, HCO_3-Cl^- exchange, carbonic anhydrase
- CSF, ~3 µl/min, ~15 mm Hg
- supplies nutrients to cornea and lens

Vitreous body

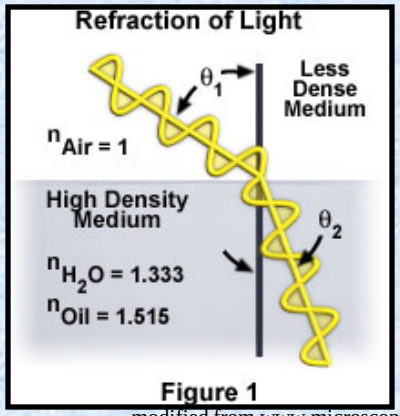
lens & retina

- gelatinous vitreous humor
  - Water (99%), collagen (II) and hyaluronic acid
- 80% of interior volume
- slow turnover
- 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

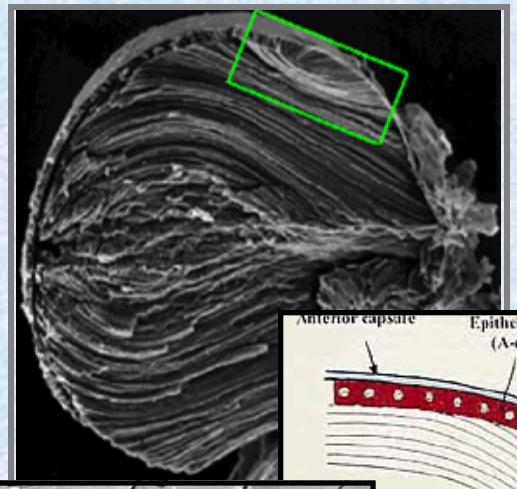
- ✓focusing requires refraction of light across interfaces (Δη)
- ✓η aqueous and vitreous humor ~ η lens
- ✓most refraction occurs at air-water interface (cornea)



modified from www.microscopyu.com

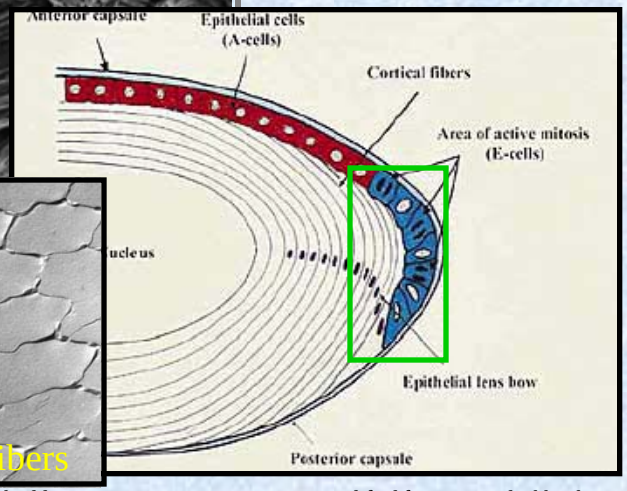
optical power of the eye (~ +60 D)

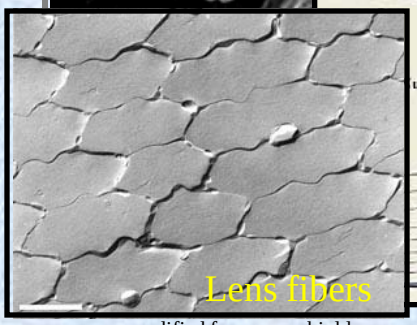
- ✓curvature of the cornea (+41.1 D)
- ✓curvature of the lens (+20 D to +30D)
  - ✓increased by the opposing elasticity of the lens and the ciliary zonule fibers on the lens capsule
- ✓depth of the anterior chamber



Accommodation is mediated by the capsule surrounding the lens.

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





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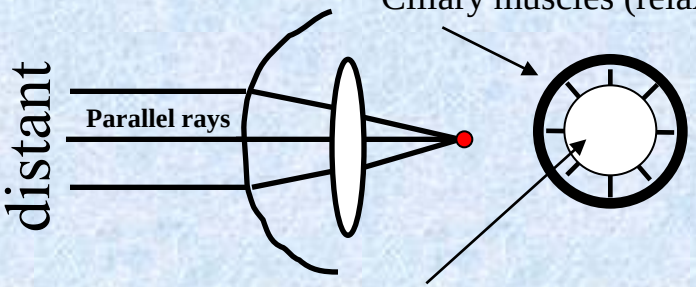
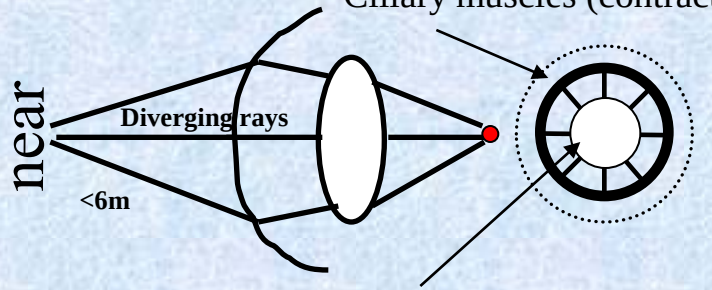
modified from www.slackbooks.com

Ciliary muscles (relaxed)



Lens is *stretched thin*, reduced curvature & little refraction

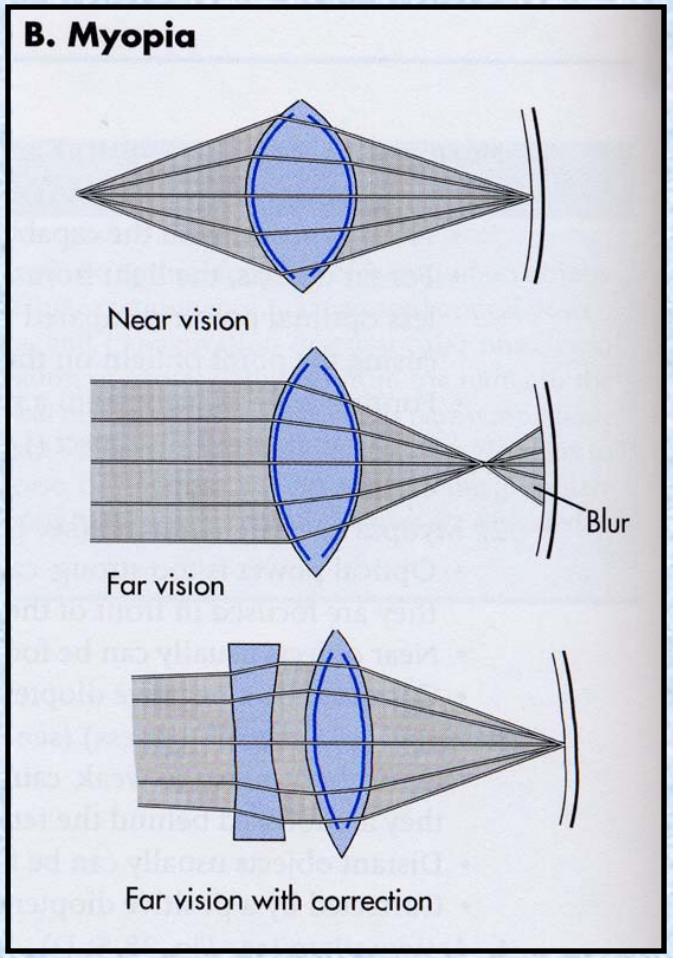
Ciliary muscles (contracted)



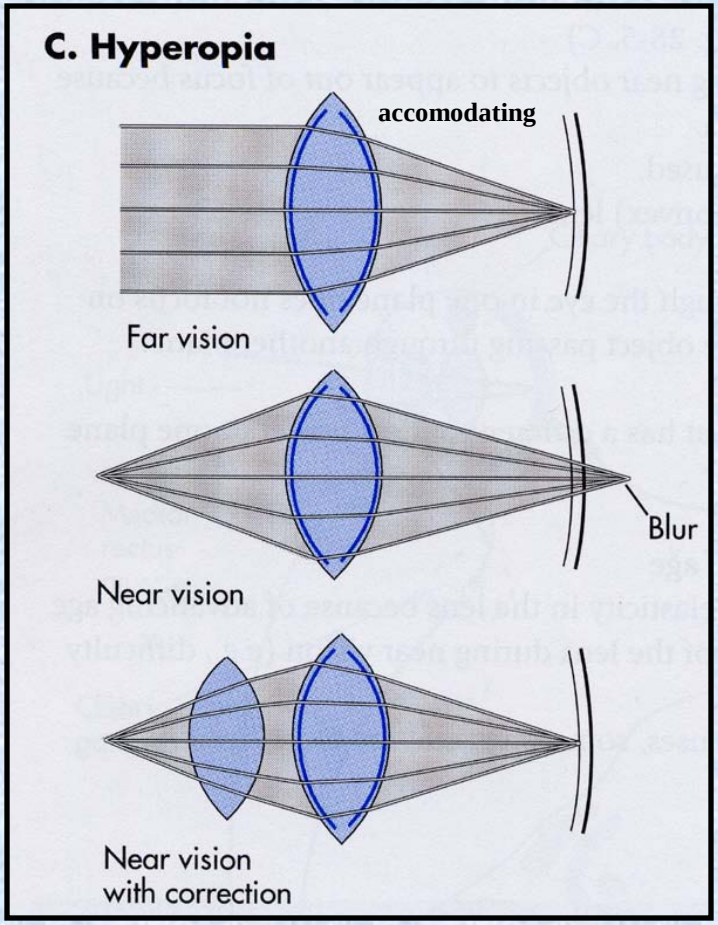
Lens is *relaxed*, greater curvature & maximal refraction

myopia

✓optical power of the cornea/lens is <u>abnormally strong</u> 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



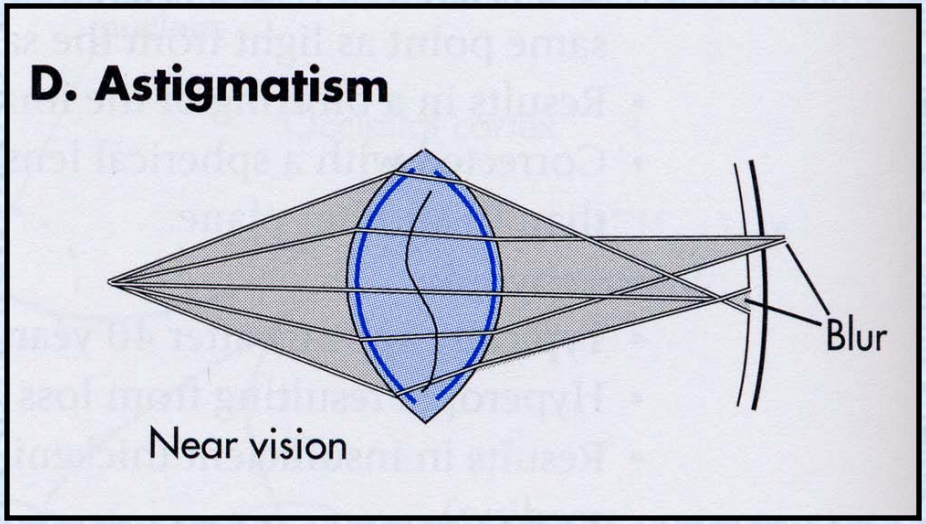
modified from Castro, Neuroscience: An outline approach, 2002

hyperopia

✓optical power of the cornea/lens is abnormally <u>weak</u> 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

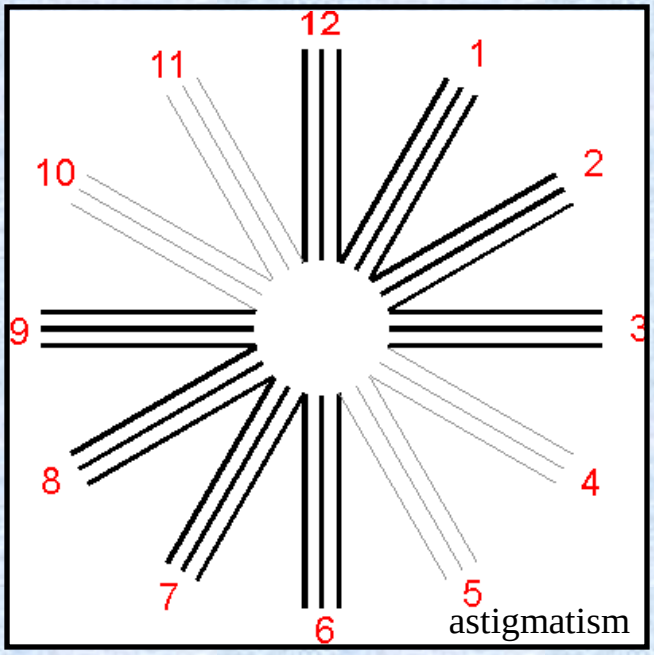
presbyopia

✓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)

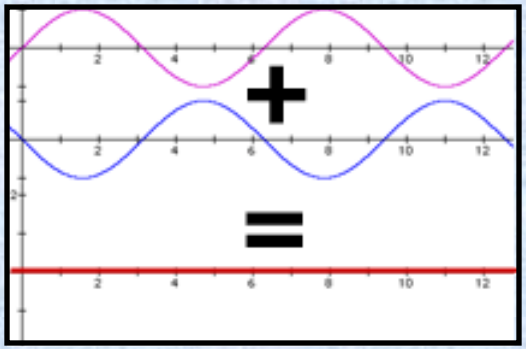
amblyopia

✓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

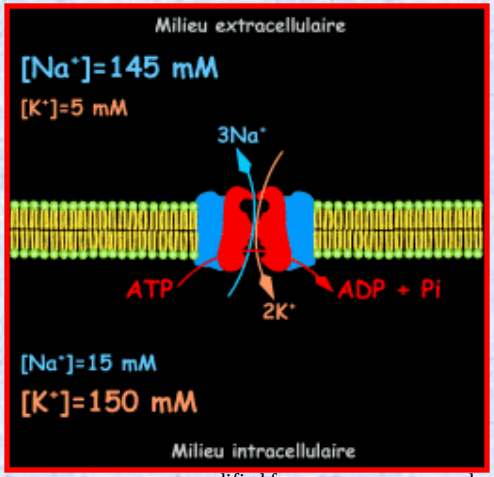


Transparency of the cornea and lens



✓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.perso.wanadoo.fr

✓Contact lenses are perforated to allow for oxygen diffusion

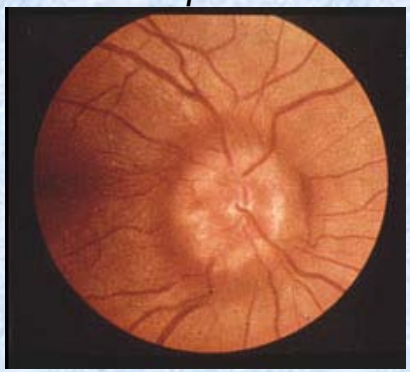
✓cataracts: opacity of the lens
- ✓failure of the Na^+-K^+ ATPase pump
- ✓free radical formation
- ✓UV light alteration of proteins
- ✓Diabetes Mellitus
- ✓trauma
- ✓aging

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



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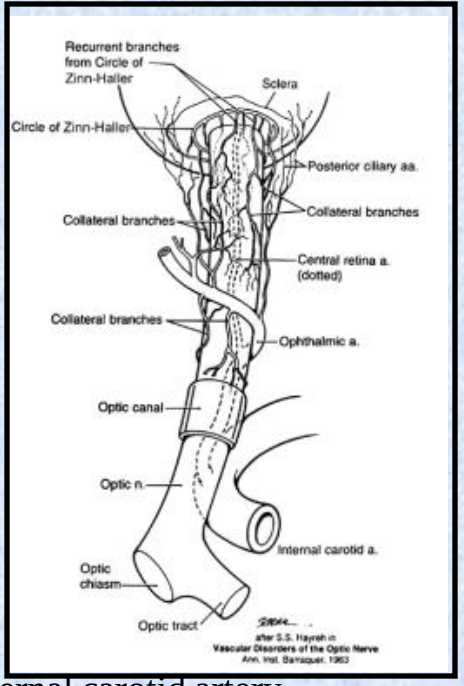
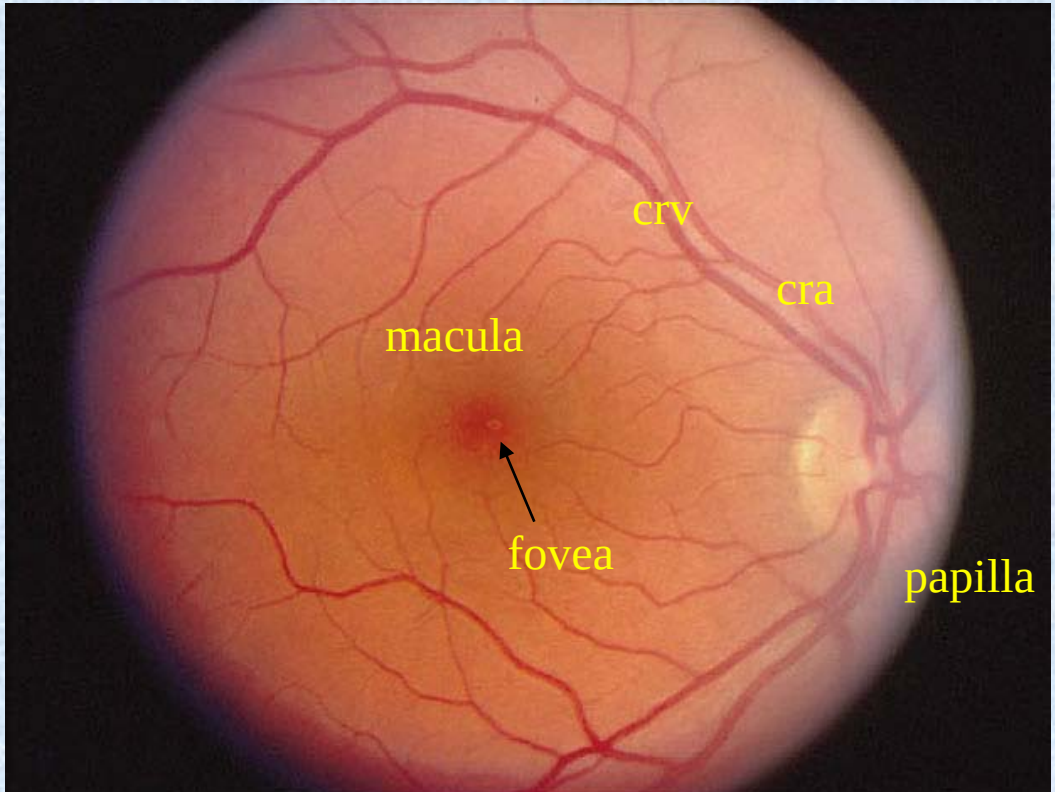


macula lutea
- ✓lateral to the optic disc (*papilla*)
- ✓contains the fovea at center

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

Cup/Disc Ratio
Large scooped-out cup & blurred margins (C/D=>0.5)



Vascular

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

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

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

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

Session VI: A Mixture of Clinical Cases

Reading Material: refer to posted handouts

- Gait, Cerebellar Function, and Movement Disorders (Dr. Merchut)
- Epilepsy, Types of Clinical Seizures (Dr. Merchut)

Key Concepts and Learning Objectives

1. Explain the clinical features of simple partial seizures, complex partial seizures, generalized nonconvulsive seizures (absence), and generalized tonic-clonic seizures.

2. Contrast how consciousness, recall of event, and postictal state are affected in simple partial seizures, complex partial seizures, generalized nonconvulsive seizures (absence), and generalized tonic-clonic seizures.

3. Define "aura," "automatisms," and "pseudoseizures."

4. Explain what causes primarily generalized seizures and secondarily generalized seizures and which diagnostic tests are done for each.

5. Define "generalized tonic-clonic status epilepticus" and the general treatment approach for it.

CLINICAL CORRELATION: GAIT, CEREBELLAR & MOVEMENT DISORDERS

1. List the various systems or components of the nervous system which are required to adequately stand up and walk.

2. Explain the Romberg sign and its significance.

3. Explain the lesion(s) associated with these abnormal gait patterns and describe how they appear clinically: broad-based ataxic, hemiplegic, tabetic, steppage, waddling, scissors, and Parkinsonian gaits.

4. Describe the clinical features of cerebellar dysfunction (gait ataxia, dysmetria, kinetic tremor, dysdiadochokinesia, rebound phenomenon, dysarthria, and nystagmus) and which bedside tests demonstrate them.

5. Contrast the clinical deficits in the cerebellar hemispheral versus vermian syndromes.

6. Recognize that the spinocerebellar degenerations or ataxias are a group of hereditary disorders where there is progressive loss of nuclei and tracts in the cerebellum and dorsal (posterior) spinal cord.

7. List the neurological disorders associated with resting tremor, postural tremor, and kinetic tremor.

8. Describe the following movement disorders and the related lesion or disorder, if known: choreoathetosis, hemiballismus, dystonia, tic, myoclonus, and asterixis.

9. List the currently available treatments for these movement disorders.

Case 1

A 62-year-old woman has not been feeling well and lost 45 pounds in weight over the past five months. She is gradually having more trouble walking, feels off balance,

and may stagger and fall. She has smoked a pack of cigarettes daily for the past 40 years. She has had no previous neurological problems.

On examination you note that she sways and staggers when standing up, and spreads her feet widely to keep her balance. This continues as she walks with difficulty. She cannot walk "in a straight line," since she nearly falls in the attempt. Motor movements of both legs are uncoordinated, "broken-up" and "off target" in the heel-shin-knee maneuver, with accompanying tremor. Her left arm exhibits a tremor when reaching out for your hand and the finger-nose-finger maneuver on the left is uncoordinated. No resting tremor is seen. Strength appears intact, with symmetrical 2+ reflexes and normal sensation to pinprick (pain), cotton (touch) and proprioception. The cranial nerves and visual examination are normal.

1. What lesion could account for her trouble walking and the motor difficulties in her lower limbs?

2. What lesion could account for her uncoordinated left upper limb?

3. What diagnostic testing would you recommend here?

4. What is the likeliest pathology causing these lesions?

Case 2

Two years ago, a 72 year-old Polish man got up after a nap, promptly lost consciousness and fell to the floor, lacerating his forehead. He was given a pacemaker for presumed heart block, but more episodes ensued. He would feel

"faint" even when seated, during which he could not talk or remember family members. At other times, he was seen lying in bed, aimlessly staring into space and unable to speak, later speaking "nonsense" for the next two hours. He would slowly return to normal thereafter. His previous health was normal.

On examination, he spoke "broken English" with a heavy accent, but had normal comprehension and mental status. Vision, cranial nerves, motor and sensory function and coordination and gait were all normal.

1. What could these episodes represent?

2. What diagnostic testing should be done?

3. What treatment should be given, and would the decision for treatment depend on the results of the tests ordered in (2)?

4. Six to seven months after his initial visit with you, the patient begins forgetting names of family members, and is often confused and repeats things. You note that he speaks slowly, is disoriented for the time and place, and cannot repeat phrases given to him. He makes errors in arithmetic and cannot remember three items given to him five minutes earlier. The rest of his neurological examination is normal. What could be the problem?

5 .What do you think happened with this patient?

Case 3

A 38-year-old woman has not felt right since "twisting her lower back" two months previously. Her feet were numb and felt "cold like ice", and this numbness ascended up to her waist over 3-4 days. Her left hand became numb, and she

readily dropped utensils. At times her knees would tend to buckle when walking, at which time she also felt dizzy and "swaying." She was otherwise healthy.

On examination, there was a vague patch of visual loss in the inferior portion of her right eye. Visual acuity was 20/25 left, 20/40 right, with sluggish pupillary light reflex on the right. The optic discs were normal. There was a mild lateral nystagmus only when looking to the right. Other cranial nerves were normal. Her gait was wide-based and unsteady. Limb tone and strength were normal, although her left hand was clumsy. Reflexes were equal at 2+ in the upper limbs, and 3+ in the lower limbs without Babinski sign. Vibration sensation and position sense (proprioception) were impaired at the ankles and stereognosis was impaired in the left hand. No dysmetria was found.

1. What lesion could account for her visual symptoms and findings?

2. What lesion could account for her ataxic gait?

3. What lesion is suggested by her symptoms of numbness and "coldness" in the lower limbs, despite normal touch, pinprick (pain) and temperature sensation on clinical examination?

4. What lesion could account for the trouble with her left hand?

5. What disorder of the central nervous system could account for the lesion(s) noted in questions 1 through 4 above?

6. What diagnostic testing should be done?

7. What do you think happened to this patient?

Case 4

A 36 year-old woman has had 5 or 6 “spells" over the previous 8 months. Her aunt notes that she stares straight ahead, drools without responding, and has quivering lips for a few seconds. Thereafter she is confused for several minutes, has no recall of what happened, and asks bizarre questions. A similar spell happened once while she was watching TV, and her right arm” drew up" to her abdomen and her right foot was tapping. One month ago while driving alone, she was told that she crossed the median strip and struck a fire hydrant, but had no recollection of what had happened.

Her neurological examination was entirely normal. She was alert, attentive and had normal mental status and language.

1. What might these "spells" represent?

2. What are the possible causes of these "spells"?

3. What diagnostic testing should be done?

4. What do you think happened to this patient?

Study Questions

1. What are the component tracts of the superior, middle and inferior cerebellar peduncles?

2. What are cerebellar climbing fibers? …mossy fibers?

3. Are cerebellar symptoms ipsi- or contralateral after lateralized cerebellar lesions? Explain neuroanatomically?

4. What CNS structure is particularly associated with establishing new memories?

5. What is prosopagnosia?

6. What characteristics distinguish an astrocyte from a microglia?

7. What is a scotoma? How might it be caused?

8. Which cells from myelin in the CNS? …in the PNS?

9. What is the ascending MLF? …the descending MLF?

10. What is the anterior cerebral circulation? …the posterior circulation?….and where are the communicating vessels?

11. Which cranial nerve(s) innervates the salivary glands?

Small Group Session. Epilepsy (Dr. Merchut)

Types of Clinical Seizures

1. Partial seizures

Consciousness is not lost during a partial seizure. The epileptic discharge consists of the repetitive firing of a few cortical neurons, arising either spontaneously or after various provoking factors, but it remains confined to a specific cortical area or focus. Lesions of subcortical areas, brainstem, or spinal cord do not produce seizures. In a **simple partial seizure**, the clinical manifestations are functionally related to the cortical area involved by this neuronal discharge. For example, a simple partial seizure within the left frontal motor cortex may cause rhythmical contractions or jerking of the right face, arm, and leg for 1-2 minutes. Since this neuronal discharge does not spread or generalize diffusely to other cortical regions, the patient is fully aware of this event, remains conscious, and may even speak or follow commands during the spell. After the spell, the patient recalls the event and does not appear confused. Symptoms of simple partial seizures may also consist of localized sensory, visual, or autonomic (sweating, flushing, nausea) disturbances **without loss of consciousness.**

Complex partial seizures occur from bilateral neuronal discharges, usually in the medial temporal or hippocampal areas, causing **impaired consciousness.** These were previously named "psychomotor seizures." Although awake, the patient would be inattentive and unresponsive, "staring into space," as if in a trance (the "psycho" part of the seizure). Other psychic symptoms include emotional changes, hallucinations, and distortions of time and reality (déjà vu) which may also occur in simple partial seizures. If the seizure occurred while performing a task, the patient may continue the same motor activity, often repeatedly (the "motor" part of the seizure). Semipurposeful, stereotyped gestures or "automatic movements" (**automatisms**) may also occur, such as chewing, finger tapping, wandering about, or uttering short phrases. The patient is unable to follow commands during the 1 to 3 minute spell and after the event has **no recollection** of what happened, appearing confused for a brief period (**postictal phase**).

Either simple partial or complex partial seizures may secondarily spread or generalize diffusely to other bilateral cortical areas, causing loss of consciousness. Since the motor cortex is usually involved, rhythmical, vigorous jerking of the trunk and limbs occurs. Afterwards, the patient goes through a postictal phase and is amnestic for the generalized convulsion itself. Yet he or she may recall the symptoms of the initiating partial seizure (the **aura**), or an observer may notice the focal onset of a seizure, either of which provides a localizing clue for the seizure focus. In many secondarily generalized seizures, however, the focal discharge spreads so rapidly that the patient cannot recall a specific aura, and the seizure appears to be a generalized convulsion.

2. Generalized seizures

Primarily generalized seizures occur when an electrical discharge simultaneously arises from widespread, bilateral areas of cerebral cortex. An example of a non-convulsive primarily generalized seizure is the **absence seizures** of childhood, formerly

called "petit mal seizures." They last only several seconds, but may occur many times daily. There is a brief impairment of consciousness, where the child often suddenly stops what he or she was doing, "freezes" motionless, and may stare off with a flurry of eye blinking. Abruptly the child then resumes his or her previous activity without any postictal confusion or recall of the event. Usually these seizures cease when the child has grown to the teen years. An electroencephalogram (EEG) during an absence seizure typically shows a generalized, 3 Hertz (3 per second), spike-and-slow-wave electrical discharge.

Generalized, tonic-clonic (convulsive) seizures were previously known as "grand mal seizures." The convulsion involves violent jerking of the limbs and body with **loss of consciousness,** falling to the ground, and frequent injury. This could result from a primarily or secondarily generalized cortical discharge. Before a generalized tonic-clonic seizure begins, the patient may recognize vague, nonspecific symptoms of dizziness or nausea. A more specific **aura** may later be recalled, such as tingling or twitching of one arm, which is actually a simple partial seizure that subsequently generalizes. The **tonic phase** of the convulsion is a sudden stiffness from contraction of limb and trunk muscles which may cause the patient to fall and forcibly expel air ("cry"). Apnea leads to a cyanotic, dusky face and consciousness is lost. Seconds later the **clonic phase** begins, with rhythmic, forceful, synchronous jerking of the limbs and face, **tongue biting or other oral trauma**, and excessive salivation or drooling. During the **postictal phase** after the actual seizure ends, breathing resumes at a rapid rate and bladder incontinence may be noted. The patient is sleepy, confused and unable to recall what happened. This phase lasts about 5 to 15 minutes. **If the seizure itself was not observed, the postictal phase is an important clue that consciousness was lost from a preceding seizure and not from syncope or fainting.**

Etiology and Evaluation of Seizures

Depending on the circumstances, a single seizure may be a one-time event, never to occur again, or it may represent **epilepsy**, where there is a tendency or predisposition for seizures to recur. Although epileptic patients may be seizure-free on anticonvulsant medication, seizures may recur when provoked by sleep deprivation, systemic illness, stress, or drinking alcohol. **Primarily generalized seizures** are the result of a global, synchronous cortical discharge from diffuse cortical disinhibition. This disinhibition may be due to **diffuse, permanent brain injury** as occurs with anoxia, hereditary metabolic disorders, or congenital brain malformations. **Transient metabolic disorders** may also cause such cortical disinhibition, from drugs like cocaine, alcohol withdrawal, toxins such as tetanus, and electrolyte disturbances, particularly the rapid lowering of serum sodium or glucose. Recognition and correction of these treatable conditions is critical.

In **secondarily generalized seizures,** the cortical discharge begins at a focus, the site of an acquired lesion. This lesion may be due to recent or remote head trauma, viral encephalitis, stroke (hemorrhage or infarction), or tumor. The cortical spread of a secondarily generalized tonic-clonic seizure often occurs so rapidly that even an experienced observer would miss seeing any focal onset. Thus, even if an initial seizure clinically seems to be primarily generalized, that may not actually be the case and an evaluation for a focal lesion should be done. Even with thorough diagnostic testing,

however, the etiology of some seizures remains unknown. Non-epileptic **pseudoseizures** may appear as episodic jerking or thrashing movements without any spontaneous cortical discharge, and are a behavior noted in patients often with a history of depression and physical abuse in addition to real epilepsy. Needless to say, these are difficult diagnostic and therapeutic challenges.

Diagnostic testing often includes imaging of the brain. **Magnetic resonance imaging (MRI)** provides a far better scan than computed tomography (CT). An MRI brain scan may show congenital abnormalities causing primarily generalized seizures or a tumor or infarction causing partial or secondarily generalized seizures. In seizure patients suspected of having viral encephalitis, testing the cerebrospinal fluid by lumbar puncture is necessary. Another key diagnostic test is the **electroencephalogram (EEG)**, a scalp electrode recording of "brain waves," which are periodically firing electrical potentials from the summated synaptic activity of pyramidal neurons. The EEG may record brain wave slowing or irritable electrical activity over a focal area, such as the right temporal lobe. However, such focal findings may be found in patients who will never have seizures. A more helpful finding would be the actual EEG recording of a seizure, often a rhythmical spike or spike-wave discharge, but this rarely happens. Sleep deprivation, hyperventilation, photic stimulation (flashing lights), or prolonged EEG recording may increase the chance of recording an actual seizure, but some epileptics never have an abnormal scalp EEG. Clinical observations and eyewitness accounts thus remain very important for the diagnosis of seizures.

Treatment of Seizures

In general, a convulsing patient should be rolled onto his or her side to help maintain an adequate airway. Since the jaw muscles are vigorously contracting during the seizure, insertion of any object into the mouth would be more injurious than helpful. If possible, nearby furniture or other objects should be pushed aside from the patient. After stabilization and transport to the nearest emergency room, the patient should be checked for fractures or other acute injuries in addition to evaluation and management of the seizure. It is critical to recognize and urgently treat any life-threatening metabolic problems causing the seizure, especially hypoglycemia, central nervous system infections, or uncontrolled hypertension. Prompt correction of these conditions alone may prevent further seizures, but in patients having multiple seizures or at great risk for recurrence, anticonvulsant medication is indicated.

It is usually best to use one anticonvulsant drug at a time, increasing the dosage to either achieve seizure control or limiting side effects. These drugs essentially enhance cortical inhibition by affecting sodium or calcium channels, acting as GABA analogues, or a combination of actions. Valproate, lamotrigine, and benzodiazepines treat many seizure types, including primarily generalized convulsive or nonconvulsive (absence) seizures as well as partial or secondarily generalized seizures. An older drug, ethosuximide, is effective for absence seizures. The other anticonvulsants are used primarily to treat secondarily generalized or partial seizures, and include phenytoin, carbamazepine, oxcarbazepine, gabapentin, pregabalin, levetiracetam, and topiramate. It is often helpful to monitor the serum levels of anticonvulsants when adjusting the doses for patients. Epileptic patients with persistent seizures despite multiple anticonvulsant

trials may benefit from epilepsy surgery. Intraoperative EEG monitoring is often needed to clearly identify the seizure focus, which ideally should be surgically resected with little to no residual neurological deficit. Functional brain imaging is also helpful here. Intractable epileptics with severe neurological deficits or mental retardation may be candidates for more extensive surgery, such as extensive removal of cortex or resection of the corpus callosum to prevent seizure generalization.

Generalized tonic-clonic (convulsive) status epilepticus is defined as a continuous, **unabated seizure or series of repeated seizures** from which the patient does not recover, for a period of **30 minutes or longer.** Some experts feel that continued seizures for even 10 minutes represent status epilepticus. In either case, status is a neurological emergency. In addition to any injuries or metabolic disorders caused by prolonged muscle contractions and apnea, brain damage may result from the persistent cortical electrical discharges. When status epilepticus persists or takes a long time to control, survivors are apt to have permanent deficits of memory or cognition. Patients in status epilepticus require emergent life support measures, including mechanical ventilation and oxygenation with immediate correction of any hypoglycemia. Control of seizures here takes precedence over investigating seizure etiology. The anticonvulsants of choice for status are the benzodiazepines, such as diazepam or lorazepam, because of their rapid onset of action. Longer-acting anticonvulsants are added thereafter. More complicated treatment protocols are tried in patients with status refractory to these initial measures.

Gait, Cerebellar Function, and Movement Disorders (Dr. Merchut)

Gait

1. Essentials for normal walking

Obviously, **strength** in the lower limbs and trunk is required to walk, which is dependent on functioning upper and lower motor neurons, neuromuscular junctions and muscles. The cerebellar and extrapyramidal systems help provide the **coordination** and **postural control** of gait. Intact **sensation**, especially proprioception, is needed to walk safely in the dark. The **memory or concept of walking** is required to execute or perform this learned motor activity "on command." Patients with gait apraxia have adequate strength, coordination, postural control, and sensation to walk, but are immobile when asked to walk.

Standing up is the first action prior to actual walking. Patients with significant weakness, dizziness, or pain may be unable to stand up on their own. In other cases, the **Romberg sign** is present, where a patient can stand steadily with the feet together, but sways and breaks stance or topples if the eyes are closed. The Romberg sign suggests a problem with impaired proprioception, either from involvement of the posterior or dorsal column pathways or their afferent sensory nerves. It should be noted however that elderly patients may readily sway or lose balance when standing with closed eyes, often due to dizziness or other factors, and the Romberg sign may not truly be present. Other patients may stand up, but spread the feet apart widely to keep balance, swaying or falling over if the feet are placed together. This finding suggests a cerebellar problem since intact vision cannot compensate for this type of imbalance.

2. Types of gait abnormalities

In the **broad-based ataxic gait** (Fig. 1A), the feet are spread apart for greater stability when standing or walking. Unsteadiness worsens when the patient tries to walk tandem "on a straight line" or "heel to toe." This may occur with lesions of the posterior columns or proprioceptive sensory nerves, where it is worse with eyes closed, or may be due to cerebellar dysfunction. The **hemiplegic gait** (Fig. 1B) is often seen with stroke patients. The affected lower limb is stiffly extended and swung or circumducted when walking while the ipsilateral upper limb is flexed at the elbow and wrist with decreased armswing. The **tabetic gait** occurs with tabes dorsalis from neurosyphilis, and has a "foot slapping" characteristic. The patient compensates for impaired sensation in the feet by forcibly planting the feet down to "feel" the floor. **Steppage gait** (Fig. 1C) occurs in a patient with foot drop or weak dorsiflexion of the foot. To prevent tripping over the toes when walking, the hip is flexed or pulled up even higher to elevate the drooping foot, which is then lowered to the floor toe first. Unilateral foot drop may occur from a lesion of the peroneal nerve or L5 root. Bilateral foot drop may be seen with severe polyneuropathy, motor neuron disease or bilateral L5 root lesions.

The **duck waddle or waddling gait** occurs from weakness of the hip girdle muscles, usually seen in muscle disease (myopathy). Hip and pelvic muscles support the weight of the patient "on one leg" when the other leg is elevated while walking. The

patient may topple over if these muscles are weak. To compensate for this, the patient leans or bends the trunk to the left as the right foot is raised, and vice versa when lifting up the left foot, alternately tilting the pelvis and hips side to side like a walking duck. In the **scissors gait** (Fig. 1D), the advancing leg or foot tends to cross over the opposite lower limb, similar to the closing blades of a scissors. This usually occurs from upper motor neuron (corticospinal tract) lesions affecting the lower limbs, as in spastic paraparesis. The increased spastic tone and tightness in the adductor muscles of the thighs tends to force the lower limbs together when walking. The **parkinsonian gait** (Fig. 1E) is slow and shuffling, with decreased armswing and a "stooped forward" or "bent over" posture. Patients with Parkinson's disease may exhibit festination of gait, having to lean forward in order to walk, followed by uncontrollable running to "catch up" with the center of gravity.

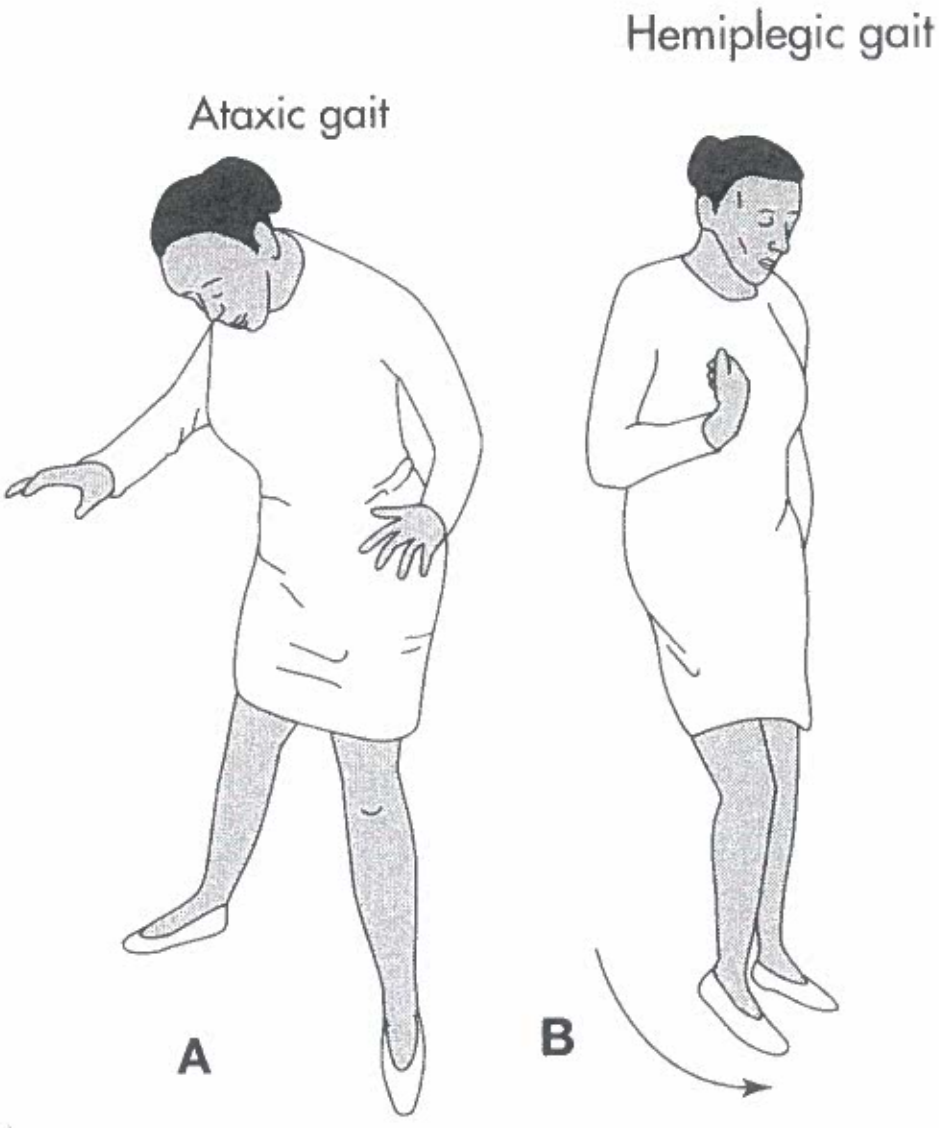


Fig. 1 Gait abnormalities

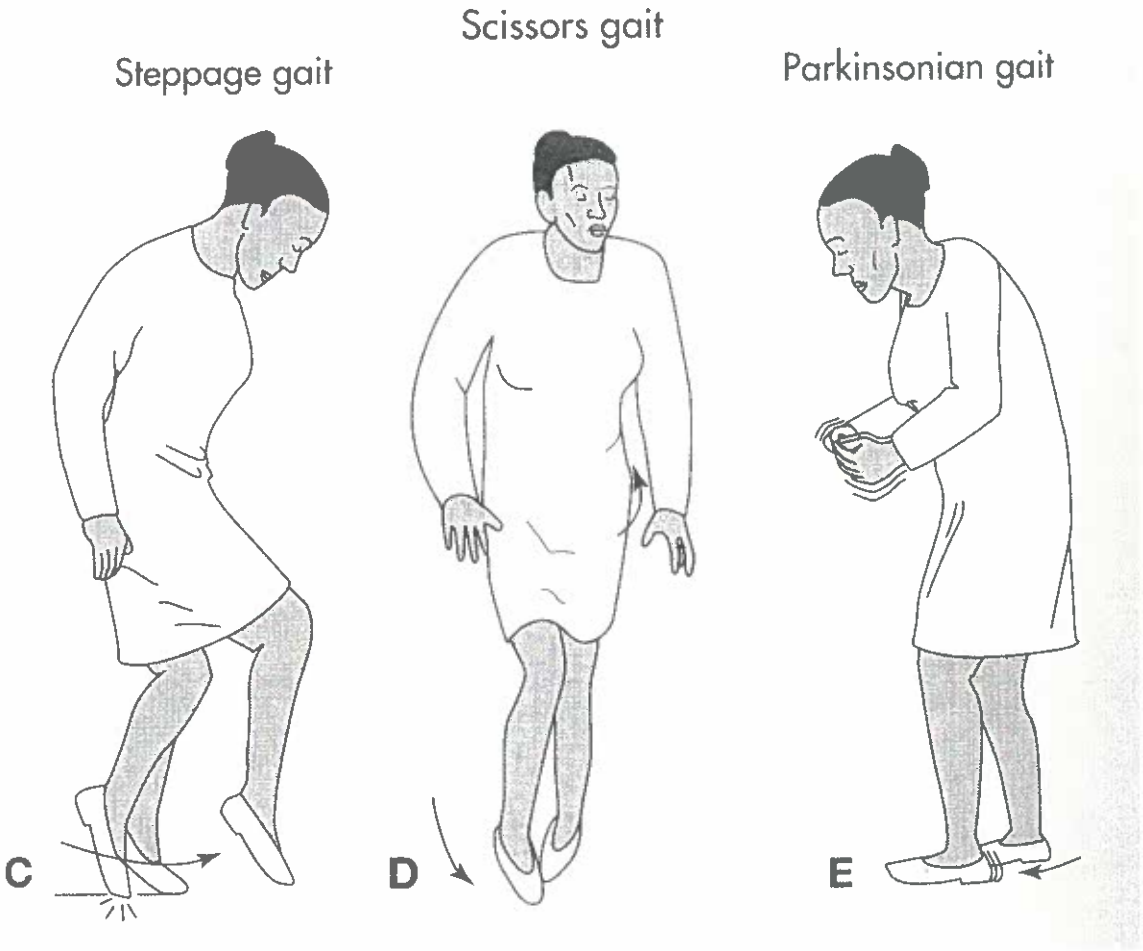


Fig. 1 (continued) Gait abnormalities

Cerebellar Function

1. Clinical cerebellar deficits

The cerebellum helps maintain the smoothness and precision of movements for the limbs, trunk, eyes, and voice. Deficits may be obvious by merely observing the patient or demonstrated by various bedside neurological tests. The **finger-nose-finger** test consists of the patient using the index finger to alternately touch his or her own nose and then the extended finger of the examiner (Fig. 2A). In the **heel-shin-knee** test (Fig. 2B), the supine patient places the heel on the opposite knee and slides it up and down the shin. Jerky, "broken down," imprecise, or off-target movements are typical of cerebellar deficits in the absence of significant weakness. While performing these tests, a patient may show a **kinetic or action tremor** consisting of rhythmic oscillations of the hand or foot while it is moved. **Dysmetria** is the term used to describe the overshooting or undershooting of the target by the hand or foot. **Rapid alternating movements** are also tested, such as a patient quickly slapping his or her own knee (or contralateral palm) with

alternating pronation and supination of the hand (Fig.2C). Cerebellar dysfunction may create uncoordinated, nonrhythmic, sloppy hand movements termed as **dysdiadochokinesia**. A **rebound phenomenon** or abnormal "check reflex" may be found in an upper limb with cerebellar deficits creating an imbalance between agonist and antagonist muscles (Fig. 2D). The patient is asked to contract the biceps muscle against the examiner's efforts. If the examiner suddenly "lets go," normally the patient's triceps (antagonistic muscle) should reflexively contract to "check" or stop the unopposed elbow flexion by the biceps. In the presence of cerebellar disease, the persisting elbow flexion may cause the patient to strike his or her chest or face unless protected by the examiner.

Cerebellar disorders may also cause a characteristic type of slurred speech or **cerebellar dysarthria**, most often associated with involvement of the left cerebellar hemisphere. Here, the speech is less distinct, "thick," erratic, jerky, or explosive. Syllables are often "broken down" or "hyphenated" with nonrhythmic or unequal emphasis or force. Eye movements may appear jerky or erratic with cerebellar disease, sometimes exhibiting multidirectional **nystagmus** (which may also occur with lesions of the vestibular system and brain stem).

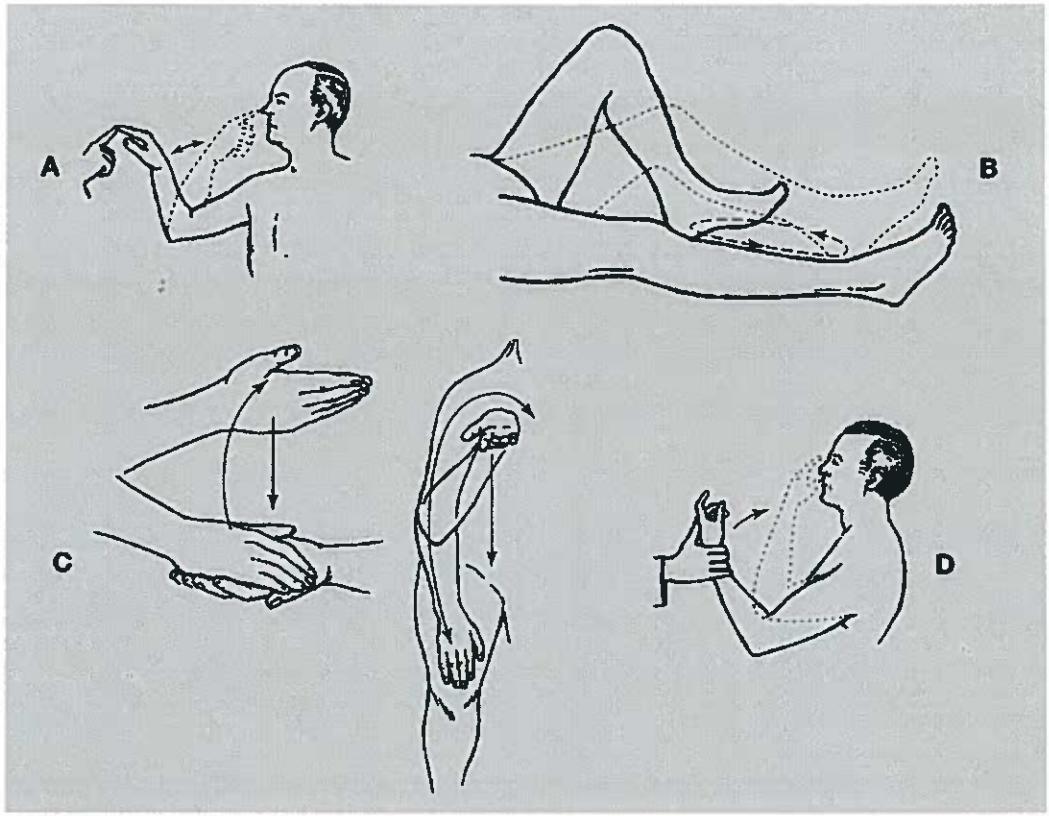


Fig. 2

Limb movement tests. A, Finger-nose-finger; B, heel-shin-knee; C, rapid alternation; D, rebound. (From Lindsay KW, Bone I, Callander R: *Neurology and neurosurgery illustrated*, ed 2, New York, 1991, Churchill Livingstone; Swartz MH: *Textbook of physical diagnosis*, New York, 1989, WB Saunders.)

2. Cerebellar syndromes

A lesion of a cerebellar hemisphere predominantly affects the ipsilateral limbs, causing kinetic tremor, limb dysmetria, dysdiadochokinesia, and rebound phenomenon. Common examples of unilateral cerebellar hemispheral lesions include ischemic infarction, hemorrhage, tumor, and multiple sclerosis. Bilateral involvement of the cerebellar hemispheres may be seen with various degenerative or toxic diseases. **A midline lesion of the cerebellar vermis predominantly affects the trunk**, causing truncal unsteadiness while standing or walking, with impaired balance and gait ataxia. Common causes include hemorrhage, tumor, multiple sclerosis, and degenerative or toxic disorders. **Alcoholic cerebellar degeneration** is an example of the latter, where chronic alcoholism leads to atrophy of the anterior-superior vermis, where the trunk and lower limbs are represented (Fig. 3). Deficits here include gait ataxia, truncal unsteadiness, and lower limb dysmetria.

Other degenerative cerebellar diseases are the **spinocerebellar degenerations or ataxias**, a group of several hereditary disorders with unknown cause and no curative treatment. Specific nuclei and tracts of the spinal cord and cerebellum are affected in progressive fashion, such that older patients become wheelchair-dependent. The most common type is **Friedreich's ataxia**, an autosomal-recessive disorder which begins in school-age children and gradually worsens. Although the cerebellum is affected, most signs and symptoms here are related to lesions in the dorsal or posterior spinal cord. Spinocerebellar tract lesions, with patchy loss of cerebellar Purkinje cells, lead to limb dysmetria, gait ataxia, and dysarthria. Corticospinal tract lesions produce weakness and Babinski signs. Lesions of the dorsal root ganglia and dorsal or posterior columns initially affect the lower limbs, causing loss of vibration, position sense, and absent reflexes. Non-neurological features include scoliosis, pes cavus (high-arched feet), cardiac hypertrophy, and potentially fatal cardiac arrhythmias. The clinical diagnosis is confirmed by a blood test revealing multiple trinucleotide repeats from a defect in chromosome 9.

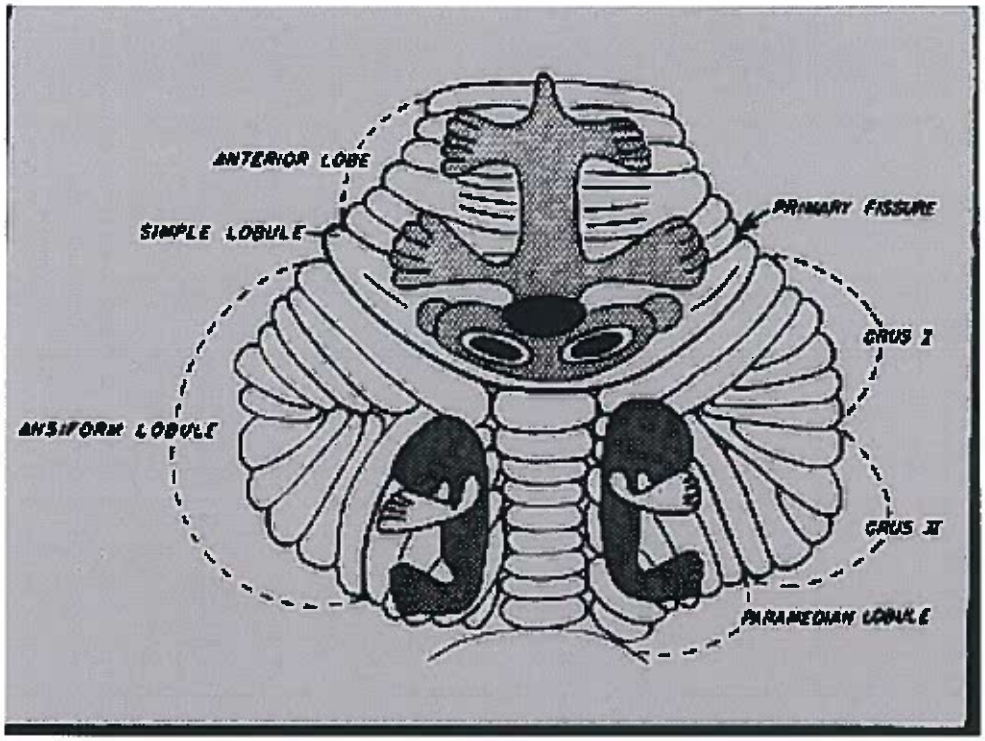


Fig. 3 Cerebellar afferents mapped out in an animal model, with ipsilateral limbs represented in each hemisphere and the trunk represented in the vermis.

Movement Disorders (Hyperkinesias)

1. Types of hyperkinesia

Hyperkinesias are spontaneous, involuntary movements with characteristic clinical features. Some of these abnormal movements are associated with specific anatomical lesions or disorders while the underlying lesion or etiology of other movement types is unknown. **Tremor** is a spontaneous, rhythmic, oscillatory movement of hands, limbs, head, or voice, and is fairly common. A **resting tremor** of the limbs or head, primarily noticeable during restful sitting or reclining, is typical of **Parkinson's disease**. A **postural tremor** is more obvious when the limbs are maintained in various positions, such as holding an object or extending an arm or leg. Postural (and kinetic) tremor without other neurological signs or symptoms is often due to **familial essential tremor,** the lesion and etiology of which remains unknown**.** The voice and head may also be affected in essential tremor. **Kinetic tremor** primarily occurs in a limb moving towards a target or performing a task. It may accompany other signs and symptoms of **cerebellar disease**.

Athetosis is the term for slow, writhing, fairly continuous movements of the distal limbs. It often coexists and blends in with chorea, which consists of purposeless, random, nonrhythmic movements of the limbs, face, neck, and trunk. **Choreoathetosis** is the combination of these brief, irregular movements that flow together in dancelike fashion (the Greek *choreía* means "dance"). Choreoathetosis patients (Fig. 4) appear

somewhat restless, fidgety and "antsy." This abnormal movement is produced by lesions in the **caudate nucleus or its connecting pathways**. A well-known example is Huntington's disease, which is further discussed in "Disorders of the Basal Ganglia."

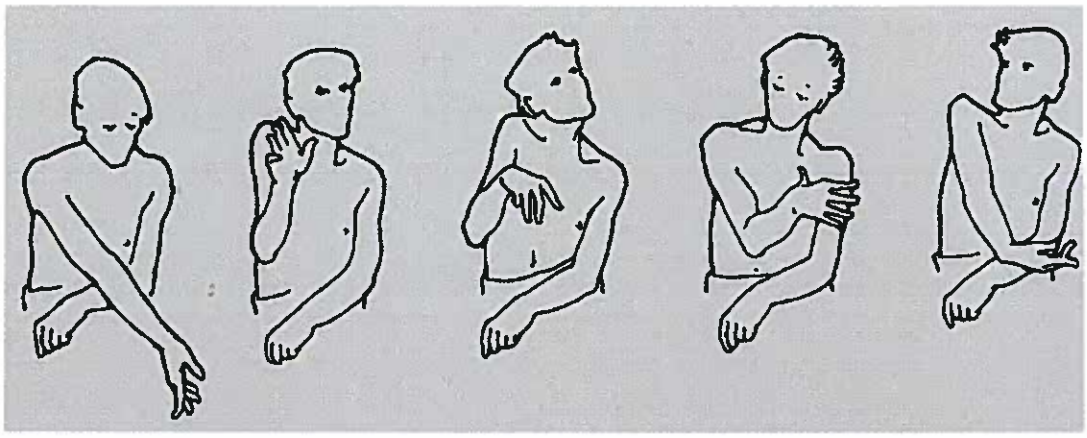


Fig. 4

Choreoathetosis. Sequential abnormal movements of the right arm and neck. (From Mumenthaler M *Neurologic differential diagnosis*, New York, 1992, Thieme Medical.)

Hemiballismus consists of rapid, violent, flinging movements of the proximal limbs on one side. (The Greek *bállein* means "throw" and is the root for "ballistics," the study of projectile movements, which aptly describes the "throwing" characteristics of this hyperkinesia.) A lesion in the contralateral subthalamic nucleus, usually an ischemic infarction, causes hemiballismus, which may improve or disappear over time. **Dystonia** is the continual, sustained, often painful contraction of muscles leading to spasms, turning, and twisting of the limbs, neck, head, or trunk into unnatural positions or fairly fixed postures. It can be **focal**, confined to muscles in the neck or shoulder (cervical dystonia or torticollis) or it may be a **generalized** dystonia which is often hereditary and progressively disabling. Its anatomical substrate or lesion is uncertain.

Tics (not to be confused with "ticks," which are blood-sucking insects) are brief, stereotyped, often repetitive, focal muscle contractions that appear semipurposeful, such as an eyeblink, facial twitch, or sniff. After the patient tries suppressing these movements for a period of time, there may be an irresistible urge or "need" for the tics to occur. Such motor tics occur with vocal tics (grunts, growls, or vocalizations) in **Tourette's syndrome**, a hereditary condition more commonly seen in boys and often accompanied by attention deficit and behavioral disorders. It has been suggested that decreased motor inhibition in the basal ganglia causes tics, but the specific anatomical lesion or pathology underlying Tourette's syndrome is still unclear.

A diffuse encephalopathy occurs when a toxic, metabolic, infectious, or inflammatory disorder affects the brain as a whole. Systemic illnesses such as renal failure or liver dysfunction thus indirectly impair several functions of the brain, which are further discussed in "Behavior, Cortical Function, and Alzheimer's Disease." Movement disorders which accompany encephalopathy include myoclonus (myoclonic jerks) and asterixis. **Myoclonus** refers to the rapid, shocklike, lightning movements or jerks of the

limbs and trunk, which is usually bilateral but asynchronous and irregular. It may also be observed in patients with Creutzfeldt-Jakob disease, which is discussed later. **Asterixis** is the semirhythmic loss of postural control of hands and feet, so that the extended hands or feet appear to have a "flapping tremor." This movement resembles bouncing a ball or tapping the foot to music. When occurring unilaterally it is due to structural brain disease such as an ischemic infarction.

2. Pharmacotherapy for hyperkinesias

Some of these medications were found helpful in reducing or lessening these abnormal movements by coincidence, while other drugs were the result of directed research. The **resting tremor** of Parkinson's disease is treated with **anticholinergic drugs** if it is more of an isolated or predominant symptom, while **levodopa and dopamine agonist drugs** are used if other troubling parkinsonian symptoms accompany the resting tremor. **Essential tremor** may improve with **beta-adrenergic blocker drugs** or **barbiturates**. **Choreoathetosis, hemiballismus, and tics** may improve with **dopamine antagonist** drugs. **Dystonia** is treated with **anticholinergic drugs, benzodiazepines and botulinum toxin injections** into the affected muscles. For medically refractory, severe cases, advanced neurosurgical techniques now allow the implantation of "deep brain stimulators" to inhibit areas in the thalamus and subthalamic nucleus to help patients with essential tremor and Parkinson's disease, respectively.