Sleep

We spend 1/3 of our lifetime doing this.

If we are sick, we do more.

If we don't do enough,our performance suffers.

If we don't do it at all, we die.

Yet we do not know its purpose.

Society for Neuroscience website

Sleep is:

- Dynamic
- Takes place in stages
- Controlled by specific factors & brain regions
- Linked to circadian rhythms
- Altered by age and physiological states
- Sleep disorders common

Organization of lecture

1. **Description of sleep stages and sleep across life cycle**
2. Factors and brain regions controlling sleep
3. Sleep disorders

Stages of sleep

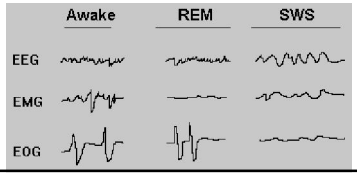
First discovered in 1950's; before, thought to be passive

Measured by:

- EEG Electroencephalogram (summation of brain activity)
- EMG Electromyogram
- EOG Electrooculogram

Major phases are:

- Non-rapid eye movement (NREM;slow wave sleep)
- Rapid eye movement (REM)



EEG patterns during sleep:wake cycles

Awake

Stage 1

Stage 2

Stage 3

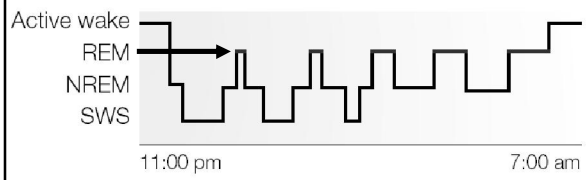
Stage 4

REM

EEG patterns during sleep:wake cycles

Stage	EEG Rate (Frequency)	EEG Size (Amplitude)	State
Awake	8-25 Hz	Low	Alert
1	6-8 Hz	Low	drowsy, easily aroused
2	4-7 Hz	Medium	deeper sleep
3	1-3 Hz	High	Slow wave sleep; deep
4	< 2 Hz	High	Slow wave sleep: Very deep; difficult to wake from external stimuli
REM	>than 10 Hz	Low	Deep sleep; dreaming; easy to awaken from internal, but not external, stimuli Very active, so referred to as paradoxical sleep, desynchronized sleep

Stages of sleep cycle throughout the night



Cycles are about 90 minutes in length
REM phase is longer as sleep episode progresses.

Adapted from Nature Reviews Neuroscience **3**; 679-693 (2002);

Slow-wave Sleep (SWS; NREM): restoration, growth, immunity

1. Blood to muscles is increased
2. Body temperature is lowered to conserve energy.
3. Metabolic activity decreased: tissue growth and repair.
4. Growth hormone secretion at its highest.
5. Immune system regulators elevated.
6. Rehearsal of activities, moving memories from short term storage in hippocampus to long term storage in prefrontal cortex.

REM sleep characteristics

Deep sleep; recallable dreams

Cortex is intensely active, so referred to as paradoxical sleep, desynchronized sleep

High O2 consumption

All voluntary muscle activity stops except for:
- muscles controlling respiration
- oculomotor muscles
- muscles that move the ear ossicles
- pupillary constrictors
- Controlled by ponto-geniculate-occipital spikes

Ability to maintain body temperature decreased

What does REM sleep do?

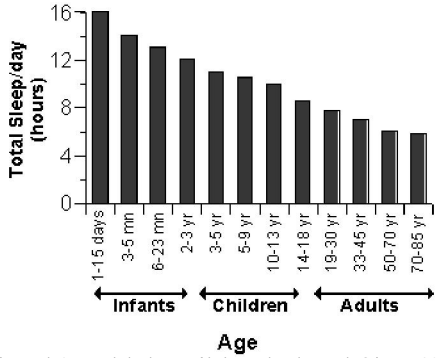
Physiologically important?
negative consequences of deprivation
REM rebound

Does not appear to improve memory, but rather the formation of associations essential for creative problem solving

Behavioural state		Wake	NREM	REM
Cognitive consequences		Acquisition of information	Iteration of information	Integration of information
Conscious experience	Sensation and perception	Vivid, externally generated	Dull or absent	Vivid, internally generated
	Thought	Logical progressive	Logical perseverative	Illogical bizarre
	Movement	Continuous voluntary	Episodic involuntary	Commanded but inhibited
Surface recordings	EMG			
	EEG			
	EOG			

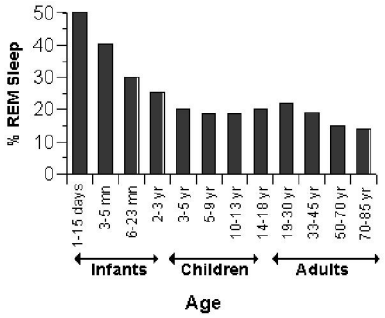
Adapted from Nature Reviews Neuroscience **3**, 679-693 (2002);
THE COGNITIVE NEUROSCIENCE OF SLEEP: NEURONAL SYSTEMS, CONSCIOUSNESS AND LEARNING

The total amount of sleep decreases with age.

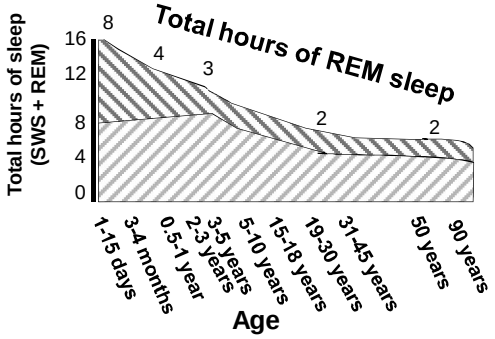


Roffwarg et al., Ontogenetic development of the human sleep-dream cycle, *Science*, 152:604-619, 1966

The % time spent in REM sleep changes with age.



Roffwarg et al., Ontogenetic development of the human sleep-dream cycle, *Science*, 152:604-619, 1966



1/2 total sleep time initially =REM

By age 10, 1/4 total sleep time = REM

Adapted from Dr. Robert Wurster

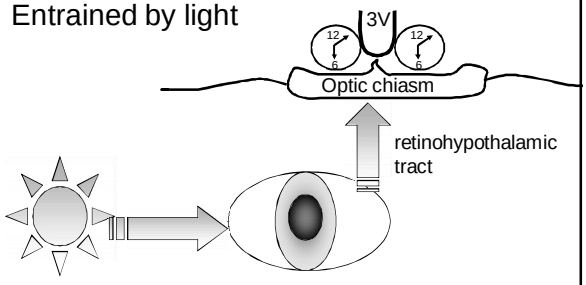
Organization of lecture

1. Description of sleep stages and sleep across life cycle
2. **Factors and brain regions controlling sleep**
3. Sleep disorders

Suprachiasmatic nucleus:

master clock

Entrained by light

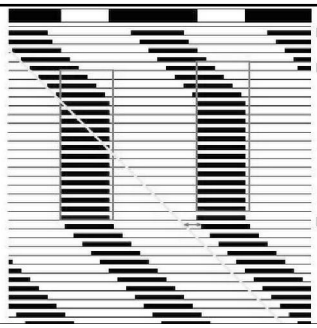


lldc

Control of Sleep:wake cycles by SCN

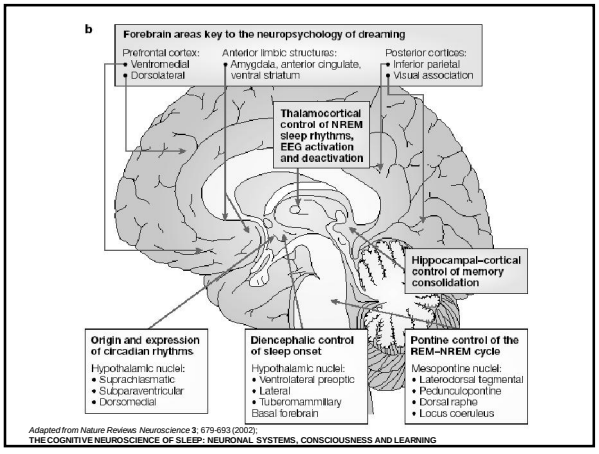
Lights on/off at same time everyday. Entrained.

Constant Darkness. No entrainment



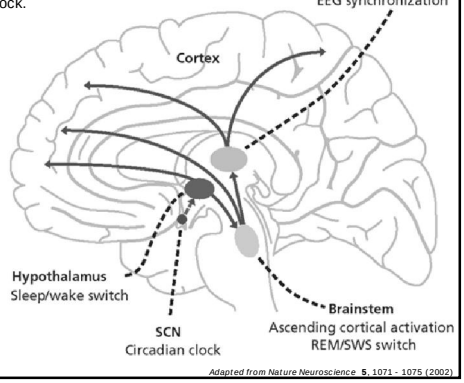
Actogram over two days:
Light = active, Dark = asleep
Shifts over time if no entrainment to cycle
Natural rhythm in constant dark = eventually about 25.3 days

adapted from 2005-2007 ScienceBlogs LLC



Adapted from Nature Reviews Neuroscience 3; 679-693 (2002);
THE COGNITIVE NEUROSCIENCE OF SLEEP: NEURONAL SYSTEMS, CONSCIOUSNESS AND LEARNING

Hypothalamus is the 'sleep switch' under the influence of the circadian clock.



Adapted from Nature Neuroscience **5**, 1071 - 1075 (2002)

The **ventrolateral preoptic area** inhibits the ascending arousal system via GABA-ergic connx.

The **lateral hypothalamus** activates the ascending arousal system via orexin-ergic (=hypocretin) connx.

The Ascending arousal systems excite cortical and subcortical targets. The Ascending arousal system includes:

adrenergic locus coeruleus (LC)

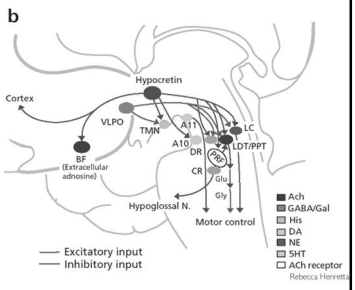
serotoninergic dorsal raphe (DR)

histaminergic tuberomammillary nucleus (TMN)

Cholinergic lateral dorsal tegmental n. and pedunculopontine n.

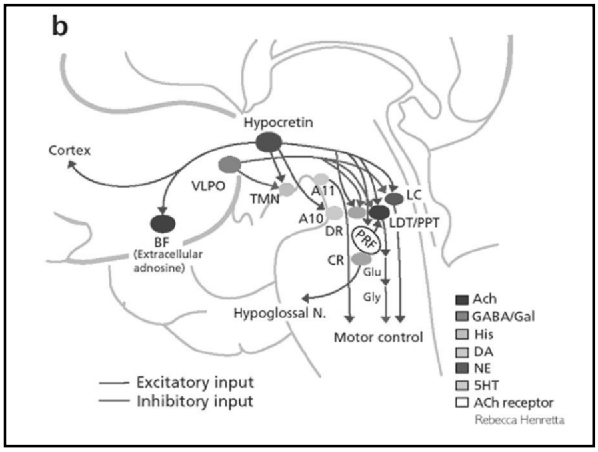
In addition:
Dopamine controls alertness and motor function.

Serotonin control of motor pathways, especially hypoglossal n., during sleep.



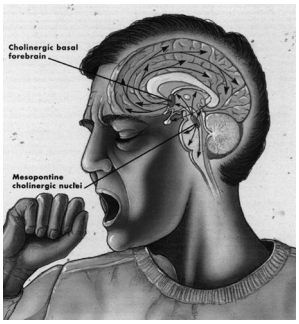
BF, basal forebrain cholinergic nuclei; LDT/ PPT, laterodorsal tegmental nuclei/pedunculopontine tegmental nuclei; CR, caudal raphe; PRF, pontine reticular formation; ACh, acetylcholine; NE, norepinephrine; GLY, glycine; GLU, glutamate.

Adapted from Nature Neuroscience **5**, 1071 - 1075 (2002)



Adenosine builds up during daily activity and decreases the activity of cholinergic arousal networks in the basal forebrain and brainstem. These cholinergic cell groups maintain alertness and arousal, therefore adenosine activates sleepiness.

What commonly used drug blocks the adenosine (A2a) receptor?



To summarize:

Arousal/waking regions and factors:
- Lateral hypothalamus- orexin/hypocretin
- Tuberomammillary- histamine
- Dorsal raphe- serotonin
- VTA- dopamine
- PPT-LDT- acetylcholine
- Locus coeruleus- norepinephrine
- Basal forebrain cholinergic region

Sleep region/factors:
- Ventrolateral preoptic area--GABA
- Adenosine inhibits cholinergic activity

Sleep Homeostat: preoptic area, basal forebrain, adenosine?

Organization of lecture
1. Description of sleep stages and across life cycle
2. Factors and brain regions controlling sleep

3. Sleep disorders

A yawn is quite catching you see.
Like a cough.
It just takes one yawn to
start other yawns off.

Dr. Seuss (in *Dr. Seuss's Sleep Book*, New York: Random House, 1962.)

Sleep disorders affect 70 million people in the US

- **Insomnia**
- **Sleep apnea**
- **Restless leg syndrome and other movement disorders**
- **Narcolepsy**
- Less common-- "sleeping sickness"
  - Trypanosomiasis (tse-tse fly)
  - Encephalitis lethargica
- Somnabulism (sleep walking); REM behavior disorder; night terrors

Sleep disorder	Prevalence	Common symptoms and pathophysiology
Insomnia	9–15%	Difficulty initiating and maintaining sleep; difficulty initiating sleep in adolescence is often a circadian phase maladjustment called 'delayed sleep phase syndrome'; can be associated with sleep-disordered breathing and other sleep disorders
Sleep-disordered breathing (obstructive sleep apnea)	10–20%	Snoring and breathing pauses causing sleep disruption and most often excessive daytime sleepiness; exacerbated by alcohol and sedatives Associated with airway anatomical abnormalities and/or central control of ventilation; multi-system disorder associated with obesity, hypertension, diabetes mellitus, hyperlipidemia
Restless legs syndrome (RLS)	2–5%	Parasthesias followed by akathisia (urge to move limbs, usually legs); often associated with periodic leg movements (PLM), brief, repetitive muscular jerks of the legs during sleep and wakefulness; pathophysiology possibly due to abnormalities in dopaminergic system and/or brain iron metabolism
REM sleep behavior disorder (RBD)	0.5%	Increased motor activity during REM sleep; multiple causes, often drug induced; frequently predates Parkinsonism
Narcolepsy	0.02–0.06%	Excessive daytime sleepiness, cataplexy (loss of muscle tone in response to emotions), short REM sleep latency; disturbed nocturnal sleep; often associated with PLM and RBD; HLA association and probable autoimmune etiology causing hypocretin deficiency

Adapted from Nature Neuroscience **5**, 1071 - 1075 (2002)

Insomnia

Inadequate or poor quality sleep characterized by one or more of the following:

- difficulty falling asleep
- difficulty maintaining sleep
- waking up too early in the morning
- nonrefreshing sleep

TYPES OF INSOMNIA

Acute Insomnia (1 night/week for <3w)

- Emotional or physical discomfort, stress
- Acute illness
- Environmental disturbances: noise, light, and temperature
- Perturbations in circadian rhythms (eg Jet lag)

Chronic Insomnia (3 nights/week for several weeks)

- In conjunction with other health problems.

Psychiatric disorders account for less than 50 percent of cases.

Consequences of Insomnia

Can be serious and ultimately fatal
Daytime sleepiness
Negative mood, irritability
Impairment of performance

Severity related to amount of sleep lost.

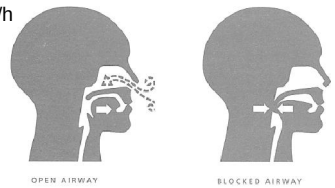
Chronic insomnia: fatigue, mood changes (eg, depression, irritability)
Difficulty concentrating, and impaired daytime functioning.

"The best cure for insomnia is to get a lot of sleep". WC Fields

Sleep apnea: another form of impaired sleep

- Obstructive-- most common, effort to breathe
- Central-- rare, poorly understood, no effort to breathe

Obstructive sleep apnea
snoring
unknowing arousal 5+/h
Progressive
4% men,2% women
Obesity/thick neck



From www.nhlbi.nih.gov/health/prof/sleep
Sleep apnea video: http://www.youtube.com/watch?v=nlFzQvHqihY

Who is at risk for sleep apnea?

- Upper body obesity
- Large neck girth
- Systemic hypertension
- Nasopharyngeal narrowing

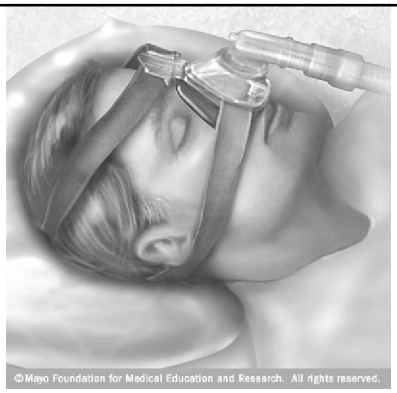
Serious consequences of sleep apnea

- Cardiovascular symptoms:
  - Systemic hypertension
  - Cardiac arrhythmias during sleep
  - Bradycardia common
  - tachycardia occasionally
  - myocardial ischemia/infarction

Treatment:

Continuous positive airway pressure (CPAP)

Surgical procedures



Continuous positive air pressure device

Restless Leg Syndrome

2-15% of population
Irresistable urge to move limbs.

The most common movement is a dorsiflexion of the ankles and flexion of the knees or hips.

Described as:
Creeping, Electric current-like,Crawling, Pulling, Restless, Itching, Drawing, Painful, Burning, Aching, Searing, Flowing, Tugging, Like worms or bugs crawling under the skin

Consequences: same as other forms of insomnia

Narcolepsy/cataplexy

- Sleep disorder, not insomnia but excess abnormal sleep
- Second leading cause of daytime sleepiness diagnosed by sleep centers (1/1,000 people overall)
- Underdiagnosed/ misdiagnosed
- Extremely disabling

Symptoms:

- **Sleepiness & muscle weakness triggered by excitement**
- Sudden, inappropriate emergence of REM sleep and atonia
- Hallucinations possible

Autoimmune disorder?

- Destruction of hypocretin/orexin neurons in lateral hypothalamus

Narcolepsy in dobermans

Mutation of hypocretin/orexin genes

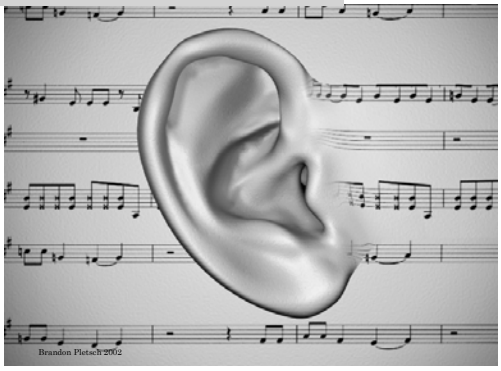
Orexin A and B
Multiple receptors

Narcoleptic are triggered by excitement
(play, food, eg)-- this is **not** normal sleep.
Atonia comes on abruptly.

Movies: *http://med.stanford.edu/school/Psychiatry/narcolepsy/movies/dog*
http://med.stanford.edu/school/Psychiatry/narcolepsy/movies/Blue.avi

To sleep, perchance to dream.
ay, there's the rub;
For in that sleep of death
what dreams may come
When we have shuffled off this
mortal coil, must give us pause---

The auditory System



Goals

- to know the routes of conduction to inner ear
- to know the role of the middle ear
- to understand how frequency separation occurs
- to know how sound transduction occurs
- to know the CNS auditory pathway
- to distinguish the different basic types of hearing loss

The auditory system *transforms* sound waves into electrical signals

- It preserves the temporary structure of the acoustic signal

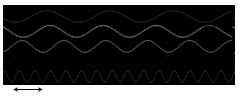
- It encodes changes in stimulus intensity

- It performs amplitude compression to encode stimulus intensities over 4 orders of magnitude.

- Highly optimized signal-processing capacity
  The mammalian cochlea can respond to sound-driven vibrations of 0.3 nanometers= the diameter of an atom…
- Ability to discern subtle differences in sound
  Trained musicians can detect between two tones at 1 kHz that differ in pitch by 1Hz (0.1% difference)
- Highly precise spatial location, can compare inputs from both ears with precision of 10 μs (birds, mammals)

Sound and the human hearing

- Sound waves travel superimposed on air
- range is 15 Hz to 20 KHz; sensitivity is optimized to the human voice range (between 1 to 5 KHz)

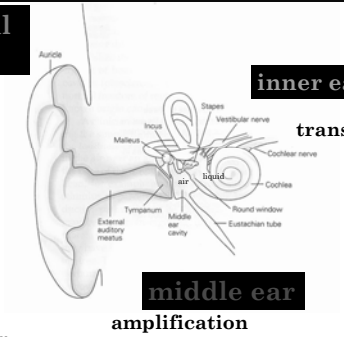


- the intensity of sound is related to the amplitude of oscillations

Functional Overview

External ear

Collection



inner ear

transduction

middle ear

amplification

From Neuroscience, Kandel 200

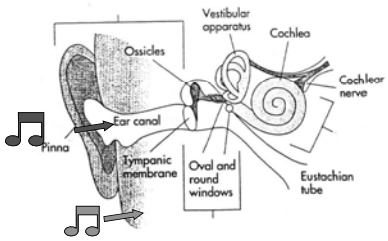
Function

- Collection.- The outer ear protects, funnels sound and performs spectral filtering for sound localization.
- Conduction.- The middle ear serves as an impedance matching device, allows for adequate transfer of energy from air-borne sound to the fluid-filled cochlea.
- Transduction.- The inner ear is the sensory transducer of sound-driven vibrations, gravity and acceleration into neuronal signals via inner hair cells

Sound Conduction Routes

✓ bone route

✓ ossicular route - most physiologically important

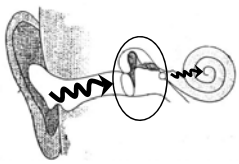


From Castro et al. Neuroscience outline textbook

Function of Middle Ear Ossicles

There is a significant energy loss when sound travels from gas to liquid due to impedance mismatch

AMPLIFY



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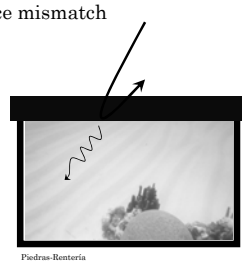
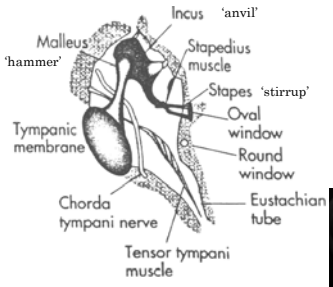


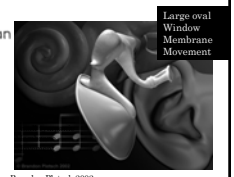
Piedras-Rentería

impedance ~ 3400 higher in water

Structures of the Middle Ear



Castro et al. Neuroscience outline



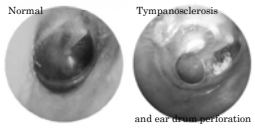
Brandon Pletsch 2002

20X

In the Clinic

Tympanosclerosis is a common problem causing conductive hearing loss accompanied by chronic otitis media.

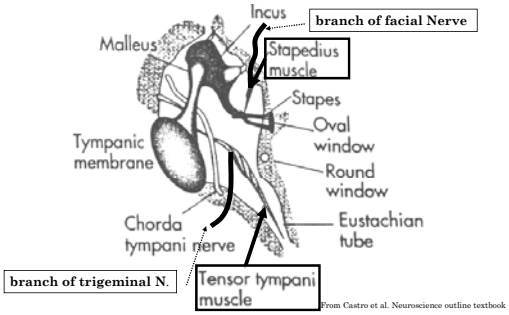
Tympanosclerosis usually appears on CT as ossicular thickening



and ear drum perforation

Modified from meweb.uwcm.as.uk/otoscopy

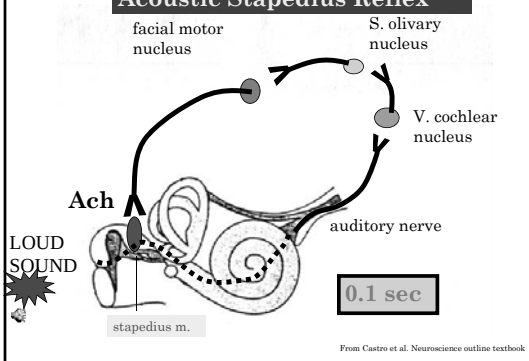
Middle Ear Muscles - stapedius and tensor tympani



From Castro et al. Neuroscience outline textbook

- contraction causes decreased amplification of the movements of the middle ear ossicles (increased impedance), especially of lower frequencies

Acoustic Stapedius Reflex

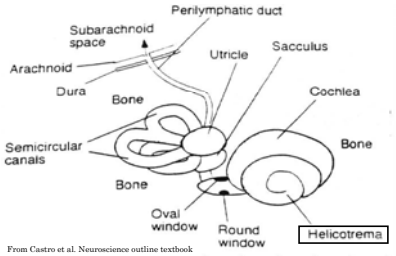


From Castro et al. Neuroscience outline textbook

- stapedius m. also activated before speaking

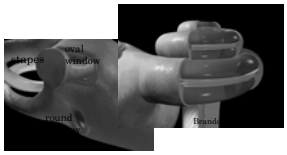
Inner Ear

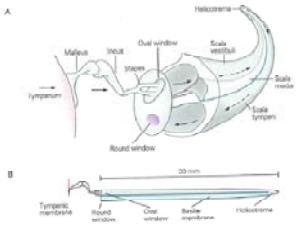
Bony Labyrinth



From Castro et al. Neuroscience outline textbook

Cochlea

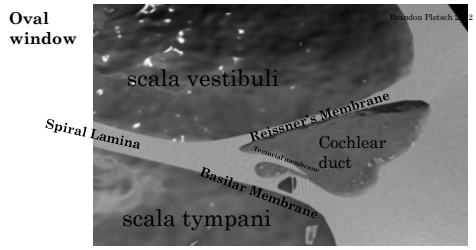




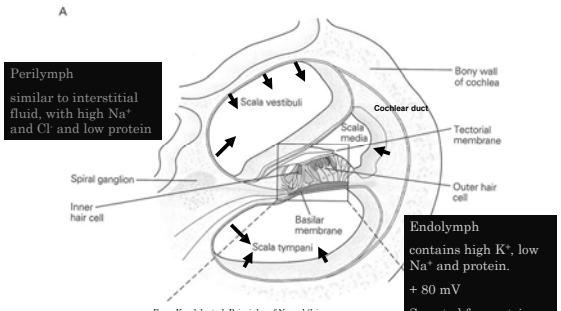
From Kandel et al. Principles of Neural Science

Cochlea

consists of 3 fluid-filled chambers, scala vestibuli, scala tympani, and scala media (or cochlear duct)



Fluids of the Inner Ear



From Kandel et al. Principles of Neural Science

Perilymph

similar to interstitial fluid, with high Na^+ and Cl^- and low protein

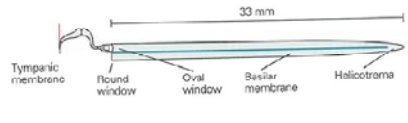
Endolymph

contains high K^+, low Na^+ and protein.

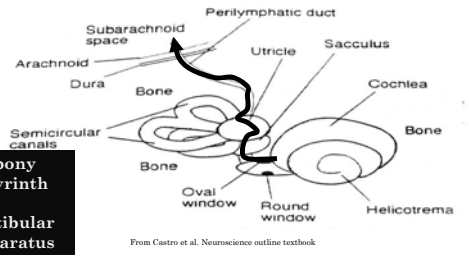
+ 80 mV

Secreted from stria vascularis via Na/K ATPase

Perilymph Flow



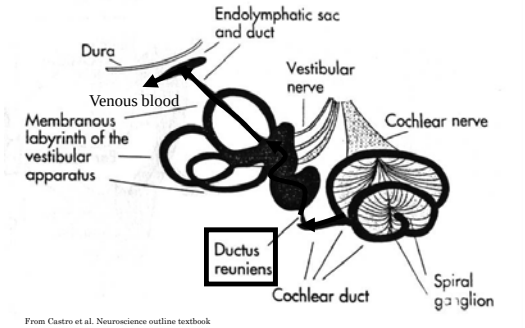
From Kandel et al. Principles of Neural Science



To bony labyrinth of vestibular apparatus

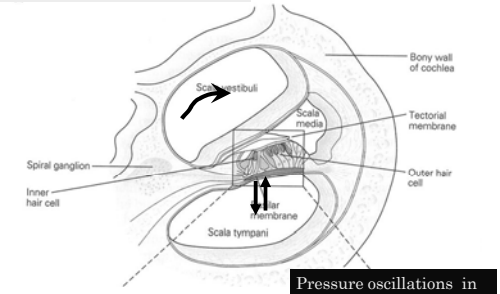
From Castro et al. Neuroscience outline textbook

Flow of Endolymph



From Castro et al. Neuroscience outline textbook

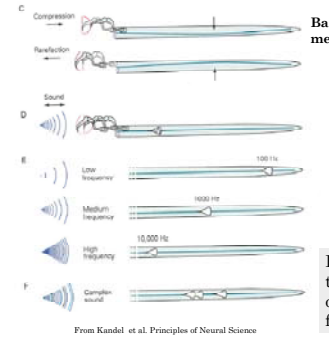
Sound Transduction



From Kandel et al. Principles of Neural Science

Pressure oscillations in the cochlea induce movement, vibration of the organ of corti, the site of mechano-electrical transduction

Sound Transduction

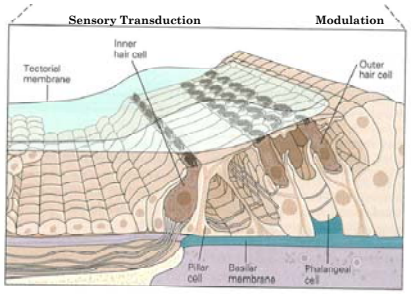


Basilar membrane

From Kandel et al. Principles of Neural Science

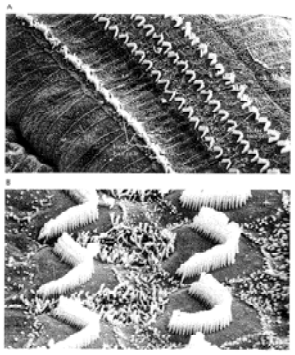
Different portions of this membrane move optimally at different frequencies of sound

Organ of Corti



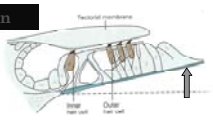
From Kandel et al. Principles of Neural Science

Spiral ligament

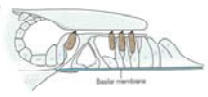


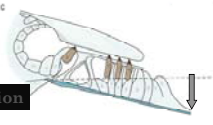
From Kandel et al. Principles of Neural Science

Excitation

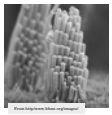


Resting Position





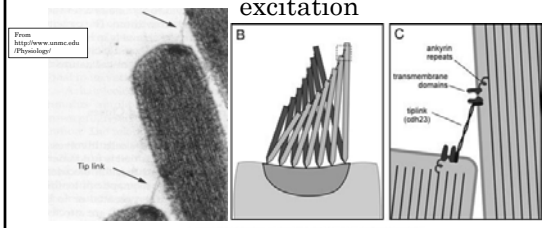
Inhibition



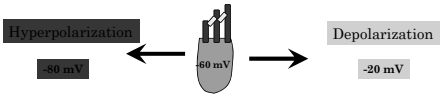
When the basilar membrane moves up and down, it causes the organ of Corti to slide in and out relative to the tectorial membrane, which causes the cilia to bend in and out.

From Kandel et al. Principles of Neural Science

The 'Trapdoor' Theory of Hair Cell excitation

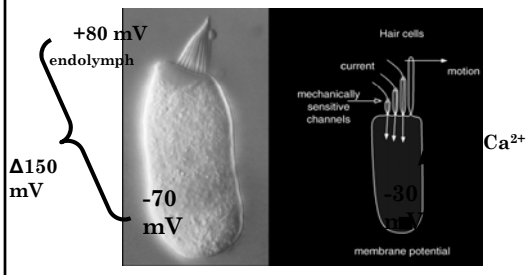


Theoretical and Computational Biophysics Group
Beckman Institute
University of Illinois at Urbana-Champaign



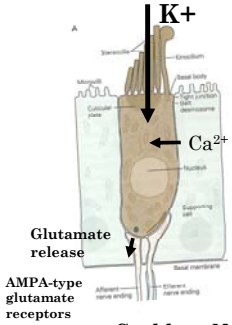
Membrane Potential of Hair Cells

Large gradient for the movement of K+ from the endolymph into the hair cell



Modified from umech.mit.edu

Inner hair cell transduction



From Kandel et al. Principles of Neural Science

Cochlear Nerve Fiber

In the Clinic

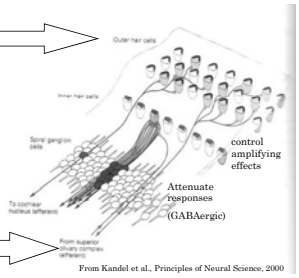
Science News
_ Share _ Blog _ Cite
_ Print _ Email _ Bookmark

New Stem Cell Therapy May Lead To Treatment For Deafness
ScienceDaily (Mar. 23, 2009) — Deafness affects more than 250 million people worldwide. It typically involves the loss of sensory receptors, called hair cells, for their "tufts" of hair-like protrusions, and their associated neurons. The transplantation of stem cells that are capable of producing functional cell types might be a promising treatment for hearing impairment, but no human candidate cell type has been available to develop this technology.

Outer hair cells & the Olivocochlear Efferent System control inner hair cell output

Activate contractile elements, enhance the movements of the inner hair cells

"tunable amplifier" the selected activation of efferent fibers can help frequency discrimination



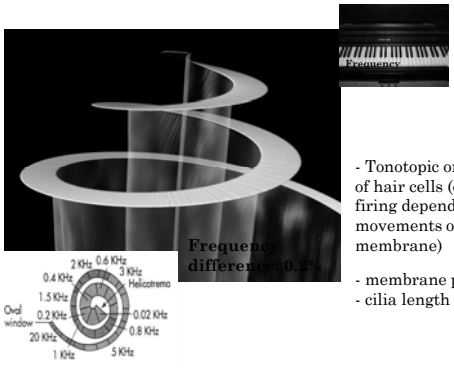
Can attenuate responses of selective hair cells or auditory nerve fibers

From Kandel et al., Principles of Neural Science, 2000

BREAK

- Review
- Frequency coding, masking effects
- Auditory pathway
- Hearing Tests
- Hearing Loss: common causes

Frequency-discrimination



From Castro et al. Neuroscience outline textbook

- Tonotopic organization of hair cells (optimal firing depending on the movements of the basilar membrane)

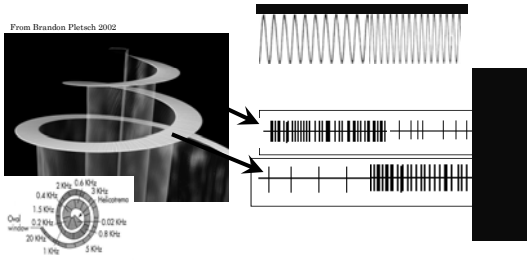
- membrane potential
- cilia length

Coding Sound Frequencies

How are different frequencies of sound coded?

• Place theory - the ***place*** along the basilar membrane where the optimal hair cell discharge is attained.

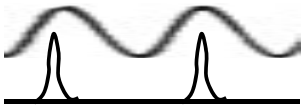
From Brandon Pletsch 2002



From Castro et al. Neuroscience outline textbook

Coding Sound Frequencies

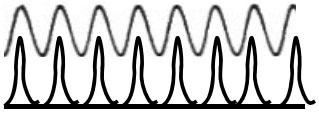
• **Phased locked coding** - probability of a cochlear afferent fiber to discharge is increased with the phase of the sound wave which causes the cilia to move toward the spiral ligament (limited to < 2 KHz)



Low Frequency Sound

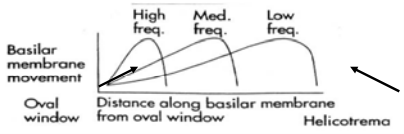
Cochlear Nerve Fiber Activity

Medium Frequncy Sound



Masking Effects of Low Frequency Sound

• loud, low frequency sounds decrease the ability to hear high frequencies

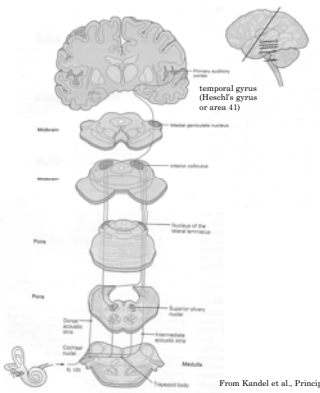


From Castro et al. Neuroscience outline textbook

• low frequency sound waves cause basilar membrane movements and hair cell activation throughout of the cochlea

• counteracted, in part, by the contraction of the stapedius muscle which affects more the low frequency amplitudes

Auditory Pathway



From Kandel et al., Principles of Neural Science, 2000

- Varying degrees of deafness affect almost 30 million Americans
- Costs $56 billion annually
- Greater economic impact than epilepsy, MS, spinal injury, stoke, HD & PD *combined*

We perceive sound in ~ equal increments of loudness for each 10-fold increment in the amplitude of sound waves

Sound intensity level $L = 20 \times \log_{10} (P/P_{ref})$
Measured in decibels

Decibel loss = $-20 \log_{10}$ (pressure$_{patient}$/pressure$_{normal}$)

Noise levels	
A quiet room at night	20 decibels
An ordinary spoken conversation	60 decibels
A busy street	70 decibels
A pneumatic drill	100 decibels
Some personal music players (at high volume)	105 decibels
Aircraft taking off	110 decibels

- Conduction Deafness
- Sensorineural Deafness
- "Neural" Deafness
- Central Deafness
- Genetic Deafness

Testing hearing with a tuning fork

Rinne's test

Modified from edinfo.med.nyu.edu/.../cranials.html

Testing hearing with a tuning fork

Rinne's Test

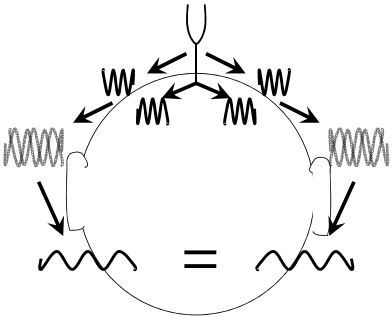
1. Bone Conduction
2. Ossicular Conduction + 15 sec

NO = Sensorineural loss

YES → NO = Conduction loss

YES → Normal

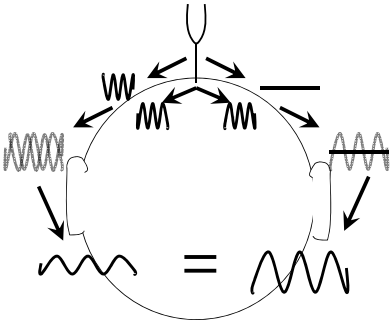
Normal Weber's Test



Modified from edinfo.med.nyu.edu/.../cranials.html

Sound level is the same in both ears

Weber's Test: Right Conductive Hearing loss



bone conduction is better than air conduction

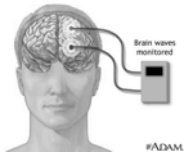
Louder sound in affected ear

*muted sound indicates Sensorineural loss

BAER
(Brain Stem Auditory Evoked Response)

Computer driven analysis of auditory responses recorded with electrodes placed on the scalp. Used to assess auditory function in infants, and in general in patients not able to respond.

www.nlm.nih.gov/medlineplus/ency/



From uconnmagazine.uconn.edu

Audiometry

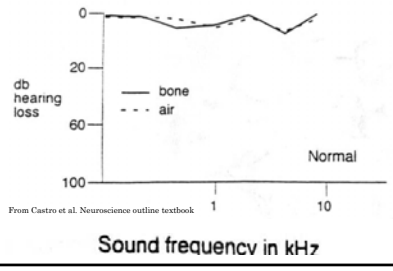
- different tones are presented separately to each ear
- intensity is increased until threshold is reached
- Hearing ability at a given frequency is given as threshold pressure compared to that of a normal population of young adults and is represented as hearing loss in decibels

Testing Hearing using Audiometry

Decibel loss = $-20 \log_{10} (\text{pressure}_{\text{patient}}/\text{pressure}_{\text{normal}})$

e.g., if patient's threshold pressure is 1000 x normal, it would be 60 dB loss.

> - 20 dB loss is abnormal

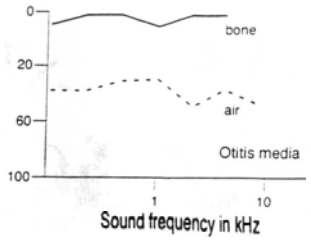


From Castro et al. Neuroscience outline textbook

Conduction Deafness

- decreased vibrations to the basilar membrane
- decreased air conduction but bone conduction OK

- broad range of frequencies affected but especially low frequencies

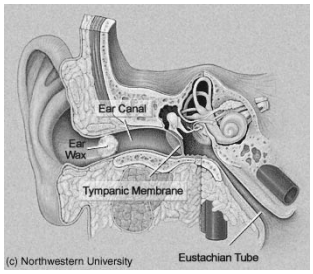


From Castro et al. Neuroscience outline textbook

Conduction Deafness

- Some causes:
  foreign object, wax

- Treatment : remove cause

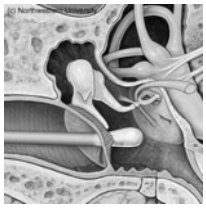


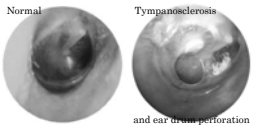
Conduction Deafness

- Otitis media,

- Otosclerosis (overgrowth of temporal bone around oval window, limiting stapes movement

- Treatment : remove cause, surgery, hearing aids

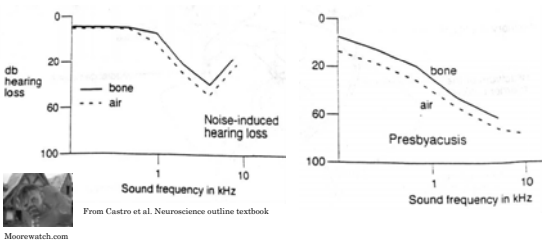




Modified from meweb.uwcm.ac.uk/otoscopy

Sensorineural Deafness

• loss of both air and bone conduction, especially higher frequencies



From Castro et al. Neuroscience outline textbook

Moorewatch.com

Sensorineural Deafness

Causes:

chronic loud sounds,

aminoglycoside antibiotics* (parenteral use of streptomycin, neomycin, gentamicin, especially long duration use),

quinine,

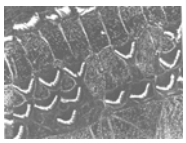
prolonged high doses of aspirin,

vaccines (e.g., rubella)

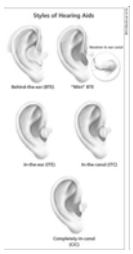
old age (presbyacusis)

Sensorineural Deafness

Can be associated with hair cell loss



(From Meyerhoff, 1984)



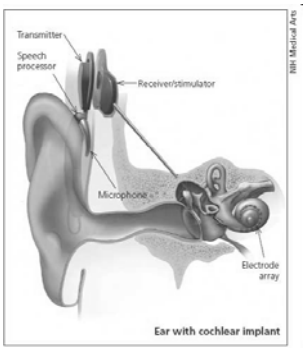
✓ Treatment

Hearing aids (microphone-amplifier-speaker) are limited to hear loss less than 60 dB.

Sensorineural Deafness

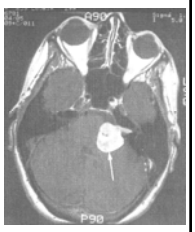
Cochlear implants are an important option for severe and complete hearing loss

multi-channel stimulatory device placed in the cochlear duct



"Neural" deafness

- sometimes considered as part of sensorineural deafness
- unilateral hearing loss
- most common cause is a Schwannoma or acoustic neuroma of the auditory nerve in the internal auditory canal



(from Kingsley, Concise Text of Neuroscience, 2000)

Central Deafness

- lesion in CNS causing abnormal processing of auditory signals
- very rare

- bilateral brainstem injury (inferior colliculus)

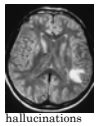
- pure word deafness: pure tone OK, words X (Heschl transverse gyrus-medial geniculate

- auditory agnosia: pure tone OK, non-verbal sound X (amusia, right hemisphere)

- cortical deafness: PWD + AA (bilateral embolic stroke Heschl's gyri

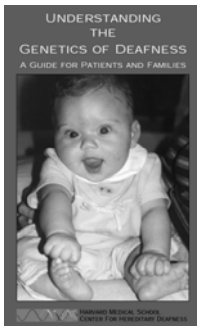
-Auditory hallucinations (schizophrenia, brain damage injury to the superior temporal auditory association areas, temporal lobe seizures

www.radpod.org



Cortical-auditory hallucinations

Genetic Deafness

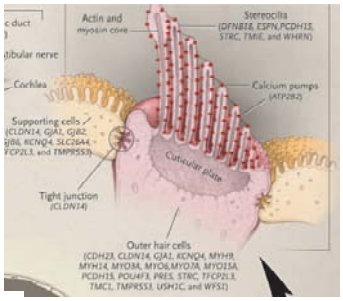


Prevalence: 1/1,000

Newborn hearing test: early detection affects educational outcome

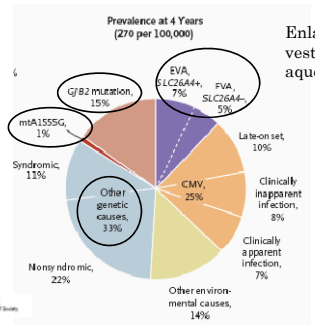
Connexins 26, 30
SLC26A4
Mitochondrial Genes
COCH Gene test

DFNA3	13q11–q12	GJB2	Connexin 26	Dominant; changes with PPK, KID, or Vohwinkel's syndromes and deafness	Moderate-to-profound, prelingual deafness, K^+-recycling defect, may be some hearing at birth	601544



Connexins

Mitochondrial



Enlargement of vestibular aqueduct

Total genetic contribution 60%

Brain Tumors
Sept 26, 2008

Note: this lecture is abridged - some figures are lacking to refrain from copyright infringement

Henry G. Brown, MD PhD

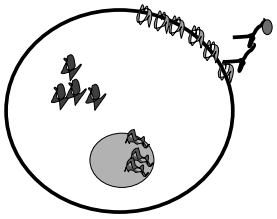
Preview

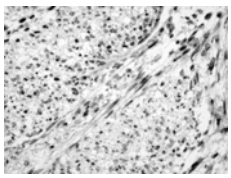
- Immunoperoxidase
- The world of tumors
- Brain tumors
  - Demographics
    - Patient age
    - Tumor location
    - Etiology
    - Genetics

Preview # 2
Nine specific tumors

- Gliomas
  - Pilocytic astrocytoma
  - Astrocytoma/GBM
  - Oligodendroglioma
  - Ependymoma
- Medulloblastoma
- Meningioma
- Schwannoma
- Pituitary adenoma
- Metastatic tumors

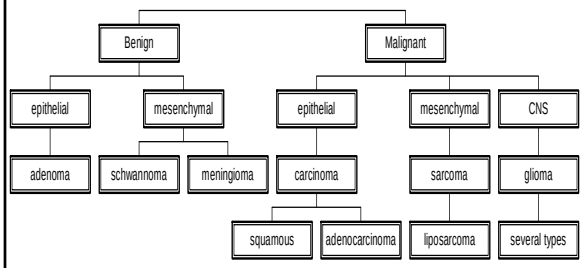
Immunoperoxidase





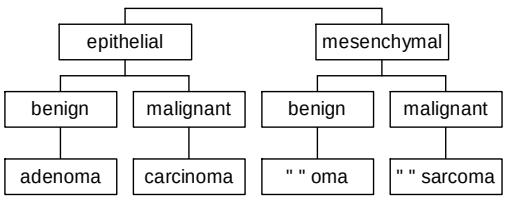
Henry Brown, MD PhD

Neoplasms



Henry Brown, MD PhD

Another way



Henry Brown, MD PhD

Quiz 1

- Benign epithelial tumors are called?
- Adenomas
- Malignant epithelial tumors are called?
- Carcinomas
- Malignant mesenchymal lesions are called?
- Sarcomas
- Primary (glial) brain tumors are called?
- Gliomas

Henry Brown, MD PhD

Primary CNS neoplasms

- 2% of all cancers
- 15 – 20% of pediatric cancers
- Presentations:
  - Headache, seizures, cognitive changes, focal deficits, ICP, hydrocephalus, nausea/vomiting
- Death is usually caused by increased ICP causing brain herniation

Henry Brown, MD PhD

Breakdown by age and location

- Pediatric
  - Usually in the posterior fossa
    - Medulloblastoma - high grade
    - Ependymoma - intermediate
    - Pilocytic astrocytoma (PA) - low grade
  - Cerebral tumors are rarer
    - Optic glioma (PA) - low grade
    - Ganglioglioma - low grade
    - PNET - high grade

Henry Brown, MD PhD

Breakdown, continued

- Adults
  - Usually Supratentorial
    - Glioma (mostly astrocytoma/GBM)
    - Meningioma
    - Lymphoma
    - Metastatic cancer
  - Posterior fossa
    - Schwannoma
    - Meningioma
    - Hemangioblastoma

Henry Brown, MD PhD

Central nervous system tumors are unique

- The distinction between a "benign" and "malignant" tumor is less evident than in other sites, (eg. glial tumors with benign histology will infiltrate the brain and are fatal, when located in an area where surgical resection is not possible).
- Surgical resection is restricted because of the functional anatomic considerations, (e.g. removal of a lesion in the motor area will leave the patient paralyzed).
- Benign lesions can have fatal outcome because of the location.

Henry Brown, MD PhD

Etiology

- Mostly unknown
- Post radiation
  - usually sarcomas
  - Can be glioma or nerve sheath tumor
- Virus
  - EBV in lymphoma
  - Papova virus can cause astrocytoma experimentally (also causes PML)
  - Other?
- Genetic factors
  - SEX
    - astros 3:2 in men
    - meningioma 2:1 women

Henry Brown, MD PhD

More Genetics

Syndrome	CNS findings
Neurofibromatosis 1 Chromosome 17 Incidence 1:4000	Neurofibromas, pilocytic (optic) astrocytomas, MPNST
Neurofibromatosis 2 Chromosome 22 Incidence 1:50,000	Bilateral acoustic schwannomas, meningiomas, ependymomas, astrocytomas
Tuberous sclerosis Chromosome 9 OR 16 Incidence 1:10,000	SEGA, tubers, etc…
Von Hippel Lindau Chromosome 3 Incidence 1:30,000	Hemangioblastomas, RCC, etc…

Henry Brown, MD PhD

Quiz 2

- True or False: children and adults get similar kinds of tumors, and tumors in similar locations?
- **False:**
  - Children usually have infratentorial tumors like medulloblastomas, pilocytic astrocytomas and ependymomas;
  - adults have supertentorial tumors like gliomas (astrocytoma, oligodendroglioma), meningiomas, and pituitary adenoma.

Henry Brown, MD PhD

Specific tumors

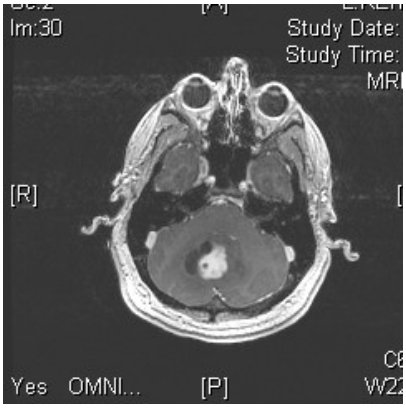
- Gliomas
  - Pilocytic astrocytoma
  - Astrocytoma/GBM
  - Oligodendroglioma
  - Ependymoma
- Medulloblastoma
- Meningioma
- Schwannoma
- Pituitary adenoma
- Metastatic tumors

Henry Brown, MD PhD

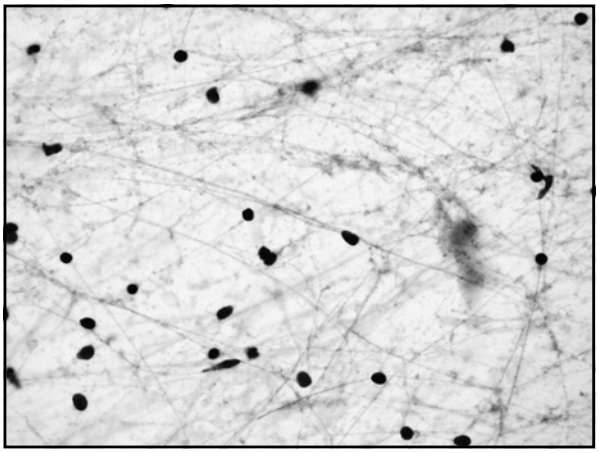
Pilocytic astrocytoma

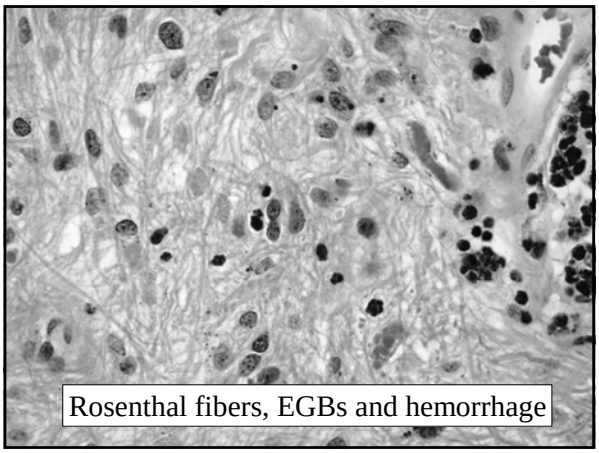
- WHO grade I
- Mostly kids
- Cerebellum, optic nerve, chiasm/hypothalamus.diencephalon (thalamus), temporal lobe
- Cerebral location tend to be older patients
- Associated with NF1 (esp. optic)

Henry Brown, MD PhD

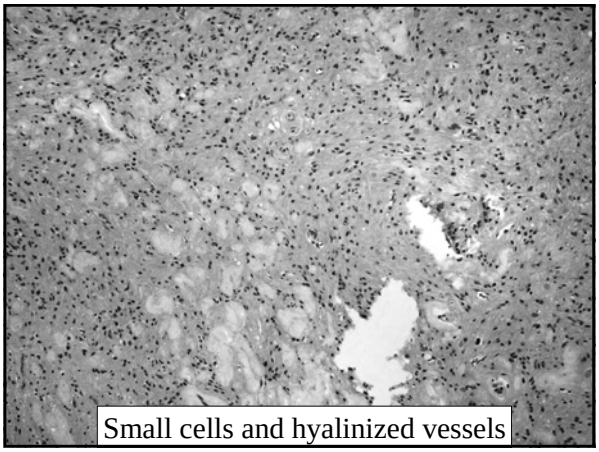


Henry Brown, MD PhD





Rosenthal fibers, EGBs and hemorrhage



Small cells and hyalinized vessels

‘Fibrillary’ Astrocytoma

- At least 1/3 of all intracranial tumors
- Cerebrum in adults and brainstem in kids
- 50% of adult astros are high grade (GBM)
- Low grade astro tends to transform to high grade in 5 –10 years (“secondary” GBM).

Henry Brown, MD PhD

Benign Astrocyte

17p (p53) loss
PDGFR overexpression
Hypermethylation of p14

Astrocytoma

19q loss

Anaplastic astrocytoma

Chromosome 10q loss
Hypermethylation of RB

"Secondary" Glioblastoma

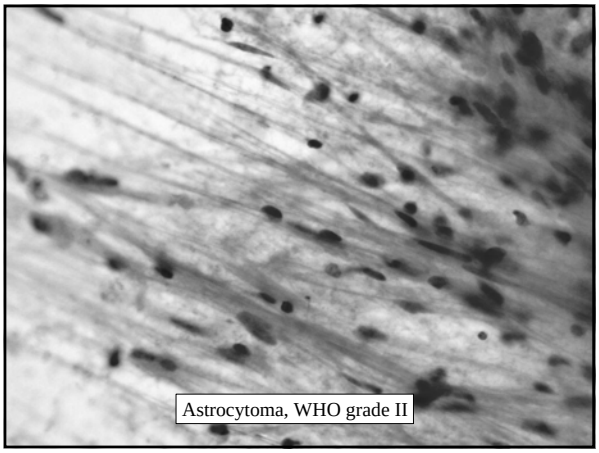
Gene transformations from low grade astrocytoma to secondary GBM

Henry Brown, MD PhD HGB

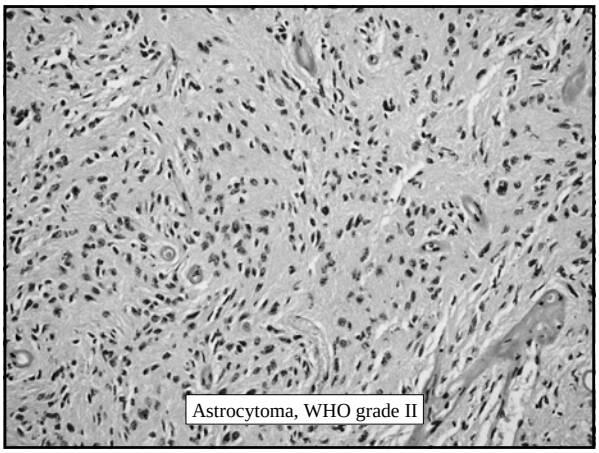
Genetic differences between primary and secondary GBM

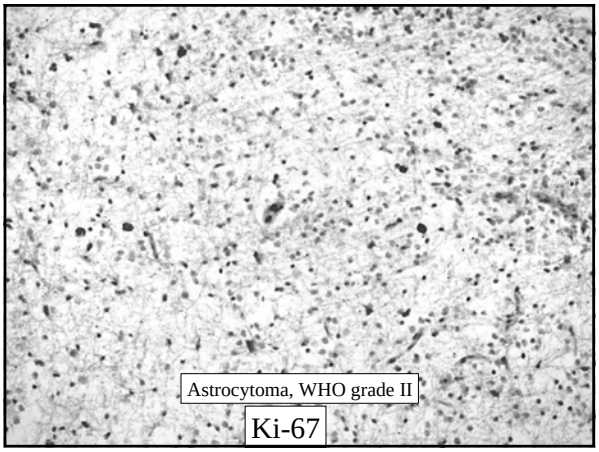
	Primary	Secondary
EGFR Overexp	**Common**	rare
MDM2 "	**Common**	rare
PTEN mutation	**Frequent**	rare
P53 mutation	rare	**Common**
Loss of 19q	rare	**Common**
RB1 hypermeth	rare	**Common**

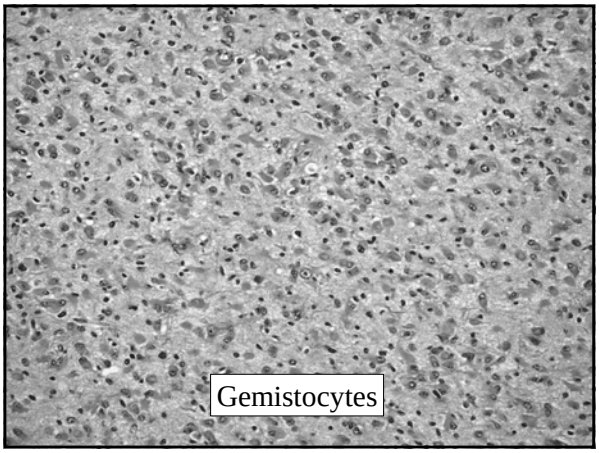
Henry Brown, MD PhD HGB

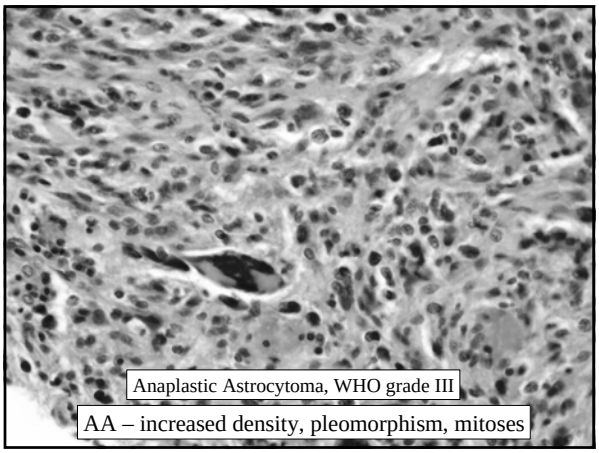


Astrocytoma, WHO grade II


Astrocytoma, WHO grade II

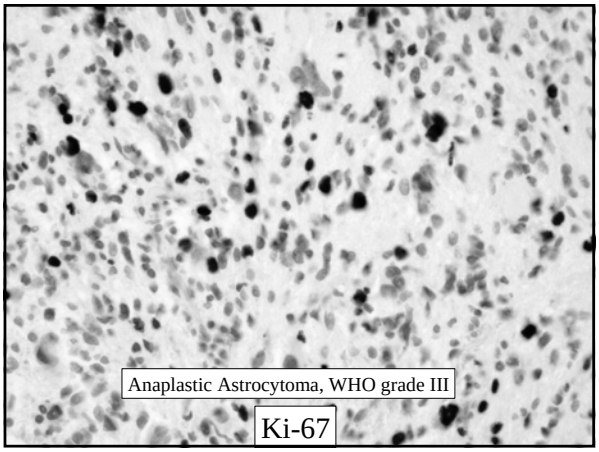

Astrocytoma, WHO grade II
Ki-67


Gemistocytes



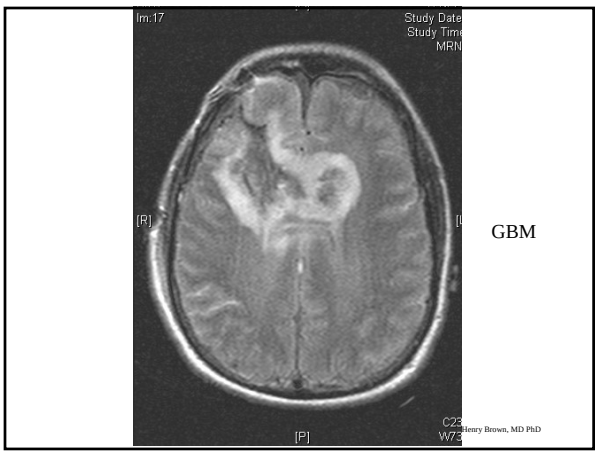
Anaplastic Astrocytoma, WHO grade III

AA – increased density, pleomorphism, mitoses

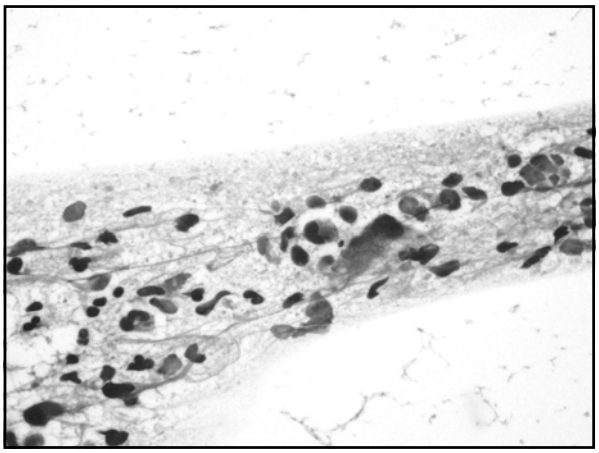


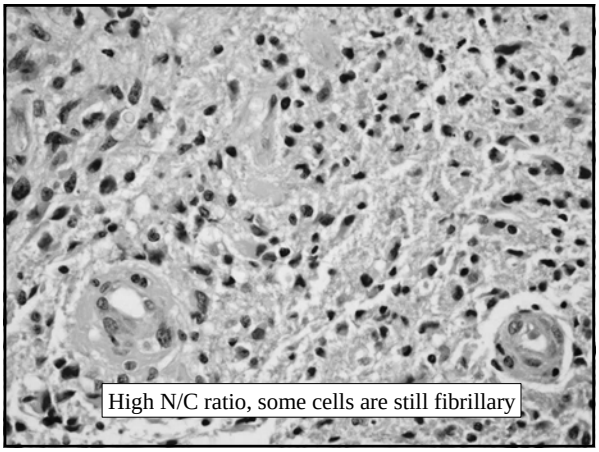
Anaplastic Astrocytoma, WHO grade III

Ki-67

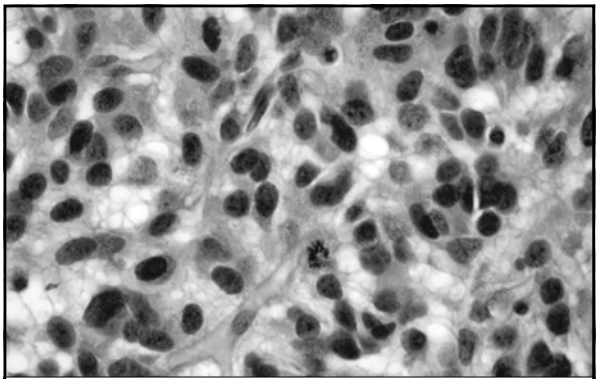


GBM

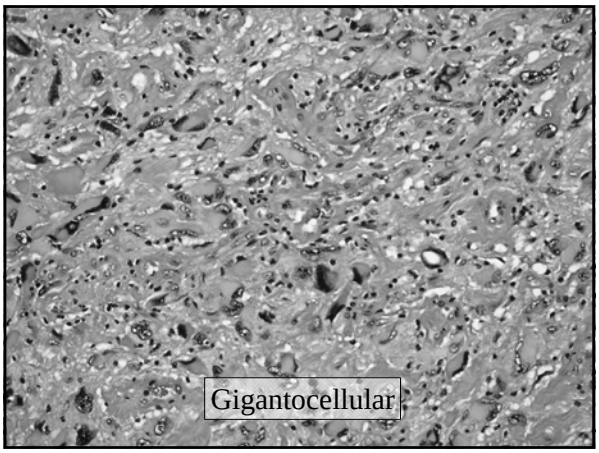


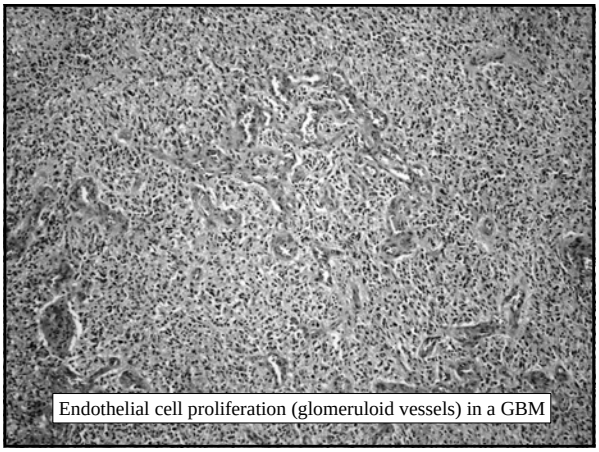


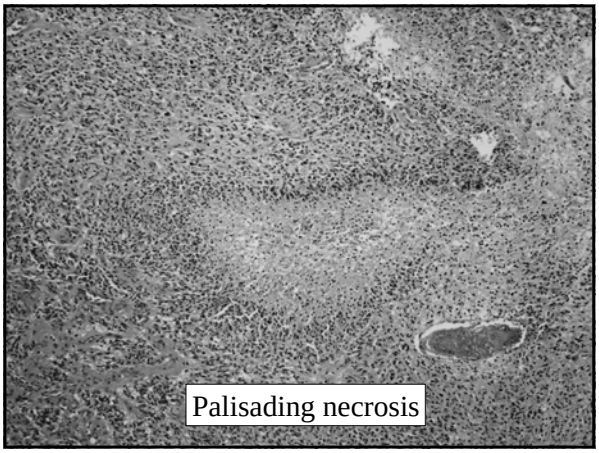
High N/C ratio, some cells are still fibrillary



Small cell variant, usually a primary GBM, often EGFR +, often does not show necrosis


Gigantocellular


Endothelial cell proliferation (glomeruloid vessels) in a GBM


Palisading necrosis

Quiz 3

- What features are characteristic of GBM?
  - Palisading necrosis
  - Vascular endothelial proliferation
- Which genetic mutations are more common in primary GBM? A) EGFR, MDM2 and PTEN; or B) p53, RB1 and –19q?
  - A
- The most significant prognostic factor in astrocytomas is?
  - Age

Henry Brown, MD PhD

Oligodendroglioma

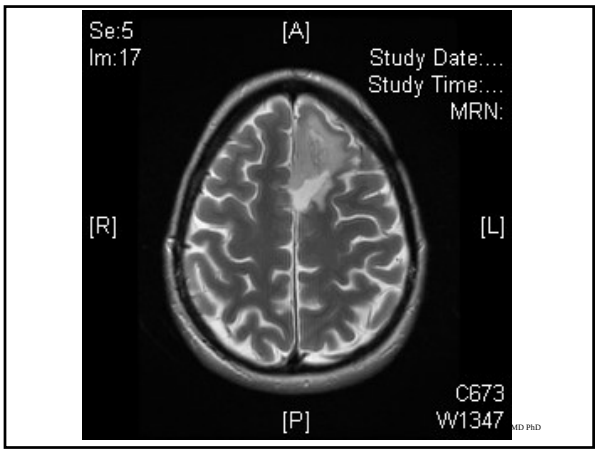
- 7-10% of primary CNS tumors
- M:F 1:1
- 30-50 years
- Frontal lobe
- Often present with seizures
- Prone to hemorrhage
- More sensitive to chemotherapy

Henry Brown, MD PhD

Genetic analysis of ‘oligoid’ tumors

- Loss of 1p on ~80%, early event
- Loss of 19q also ~80%, strong linkage to 1p loss
- p53 mutation (17p) uncommon

Henry Brown, MD PhD


Se:5
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[A]
Study Date:...
Study Time:...
MRN:
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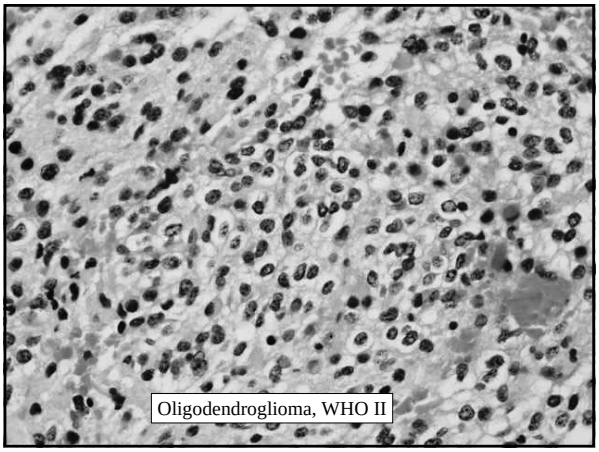
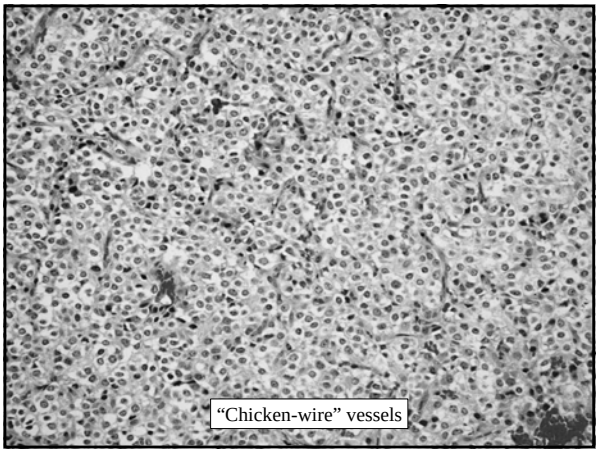
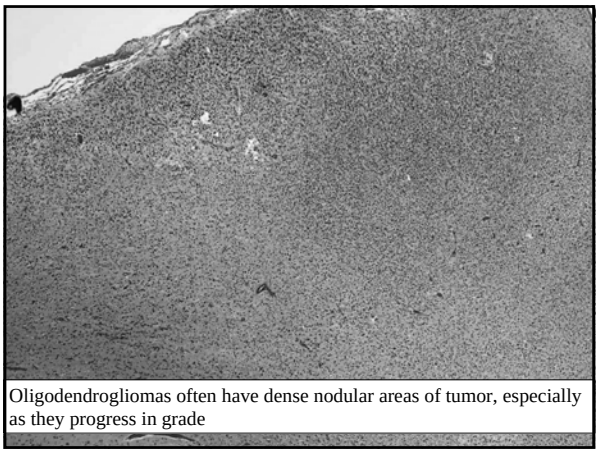
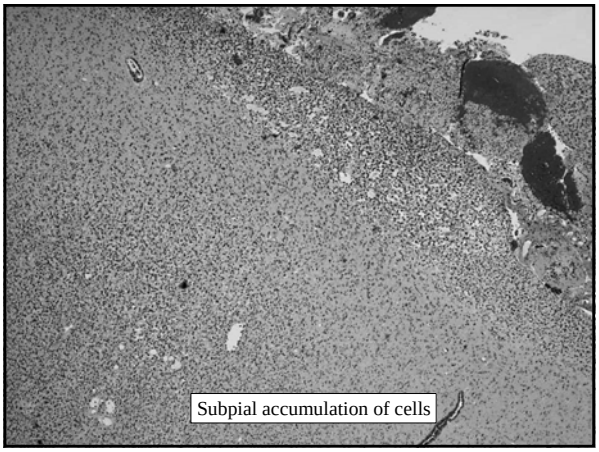
C673
W1347

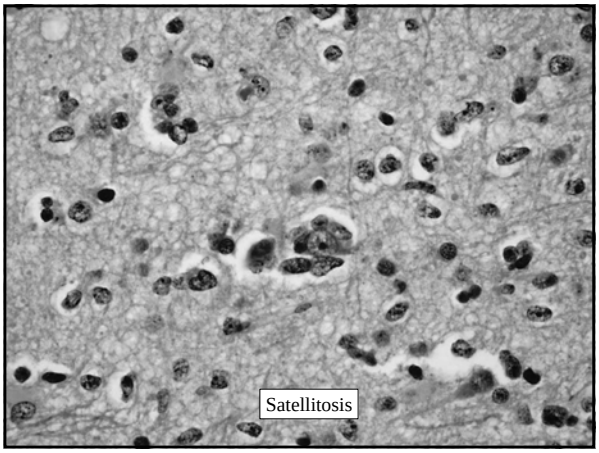

Oligodendroglioma, WHO II


“Chicken-wire” vessels



Oligodendrogliomas often have dense nodular areas of tumor, especially as they progress in grade





Quiz 4

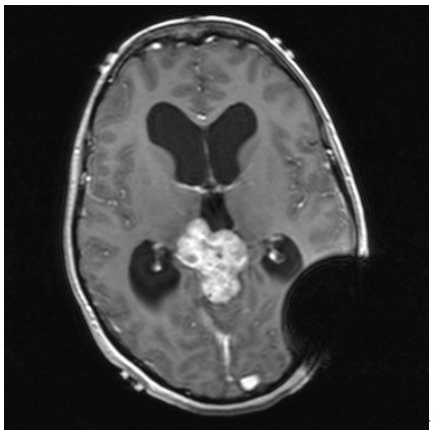
- Oligodendrogliomas are characterized by?
  - Chicken wire vessels
  - Perinuclear clearing (fried egg cell)
- A frequent genetic change in oligodendroglioma that also indicates response to treatment is
  - deletion of 1p and 19q

Henry Brown, MD PhD

Ependymoma

- 6-9% of primary CNS lesions
- Usually children (30% of pediatric primary)
- Often infratentorial
- Spinal:
  - Usually myxopapillary, 20-40 years old
  - Associated with NF-2

Henry Brown, MD PhD

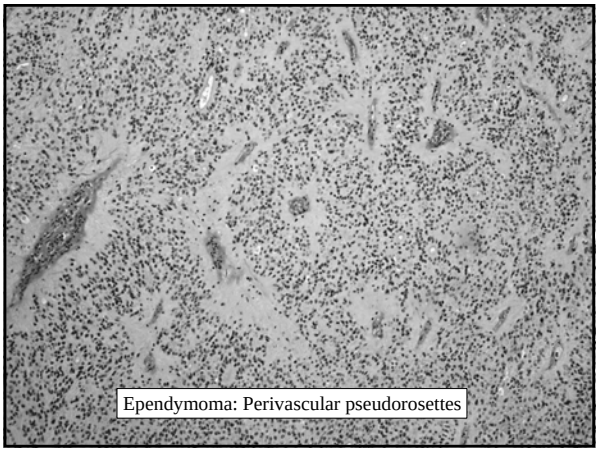


, MD PhD

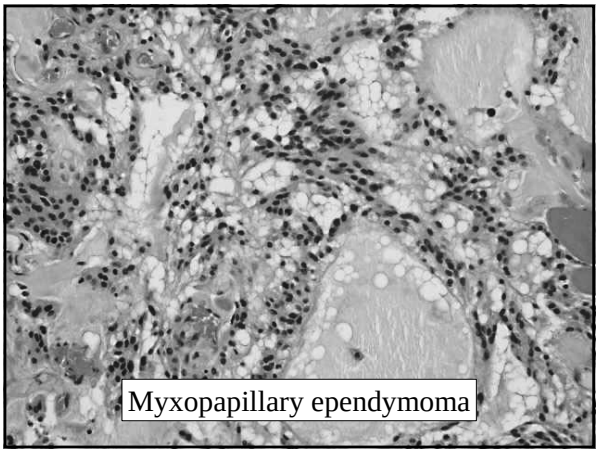
Variants

- Ependymoma
  - Cellular
  - Papillary
  - Tanycytic
- Anaplastic (prognosis may not be worse)
- Myxopapillary (typically indolent)
- Subependymoma

Henry Brown, MD PhD



Ependymoma: Perivascular pseudorosettes

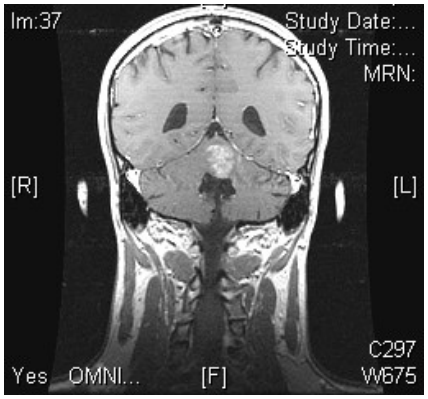


Myxopapillary ependymoma

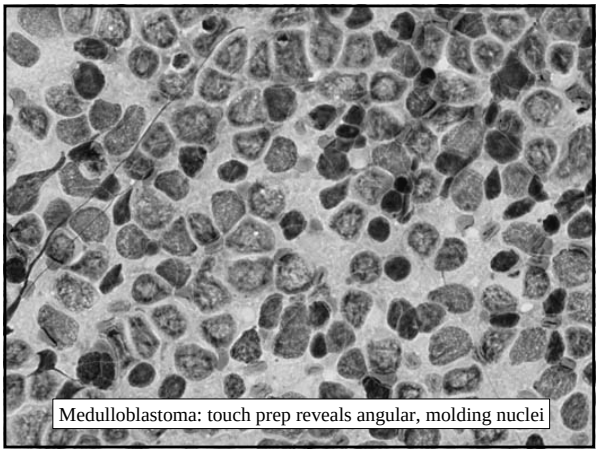
Medulloblastoma

- 5% of CNS neoplasms
- 20% of pediatric CNS neoplasms
  - Bimodal (peaks at ~3-4 and young adult (older more often lateral)
- 90% of pediatric 'PNET'
- Usually arise from vermis/4th ventricle
- Patients require craniospinal radiation and chemotherapy
  - About 70% survive

Henry Brown, MD PhD



Henry Brown, MD PhD

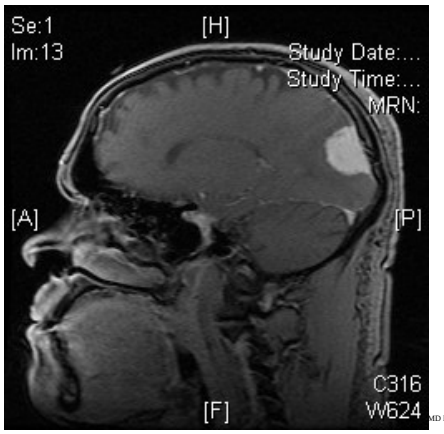


Medulloblastoma: touch prep reveals angular, molding nuclei

Meningioma

- Incidence increase with age, can be asymptomatic
- 15% of intracranial, 25% intraspinal lesions
- 10% have multiple meningiomas
- Most are supratentorial
- Intracranial 3:2 F:M; intraspinal 10:1 F:M
- Associated with:
  - Radiotherapy
  - Estrogenic neoplasms (i.e. breast, endometrial CA)
  - Castleman's (chordoid and lymphocyte-rich var.)
  - Polyclonal gammopathies (lymphocyte-rich var.)

Henry Brown, MD PhD

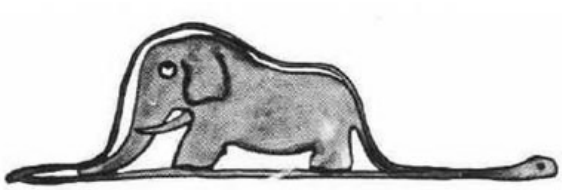


MD PhD

QUIZ 5

What is this object?

A Hat?



An elephant swallowed by a boa constrictor! (The Little Prince)

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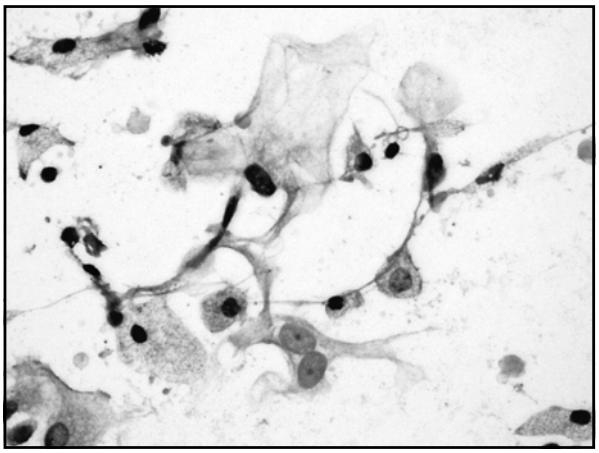
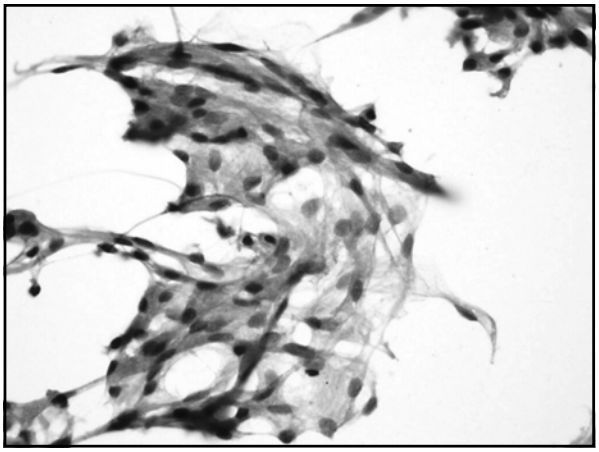
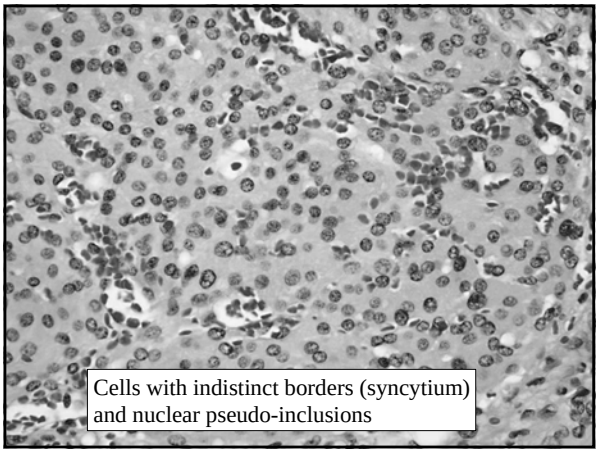
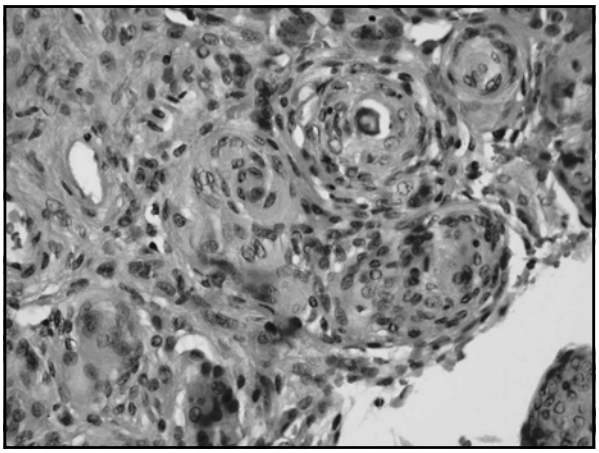
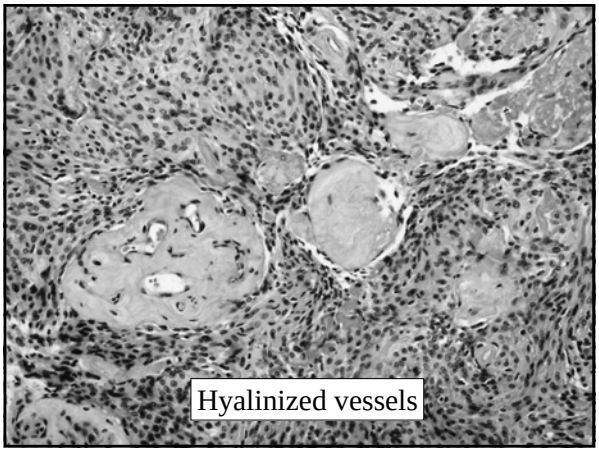
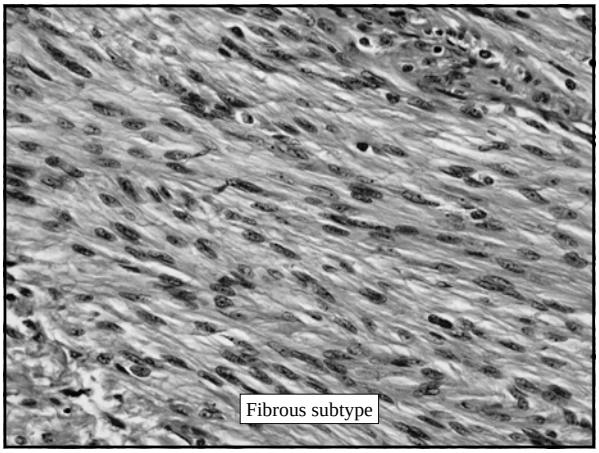


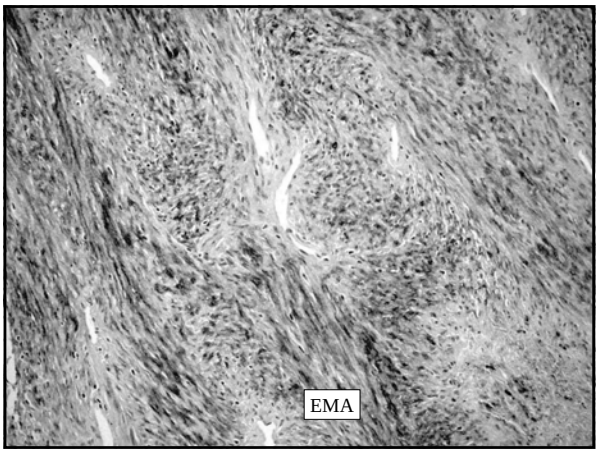


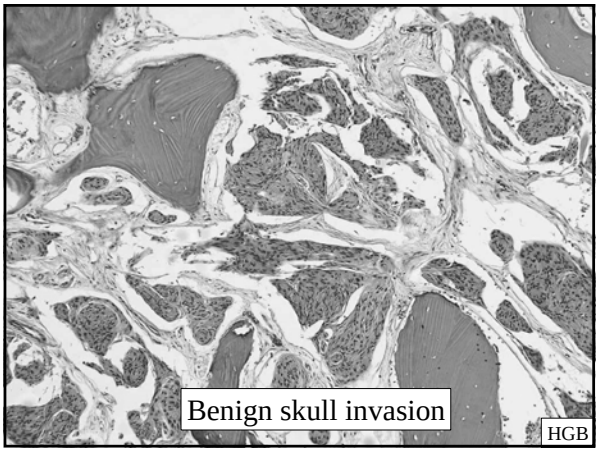

Cells with indistinct borders (syncytium)
and nuclear pseudo-inclusions




Hyalinized vessels


Fibrous subtype

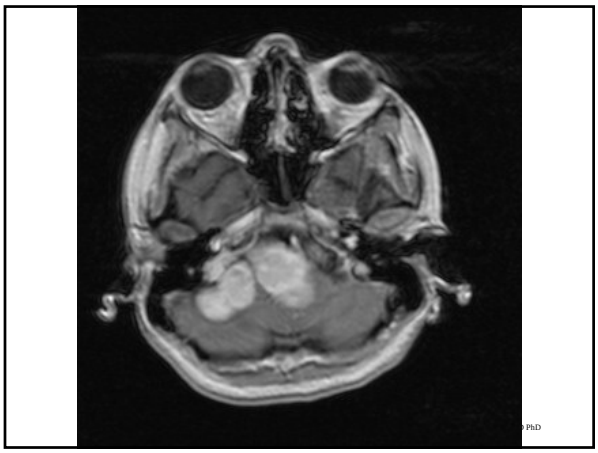


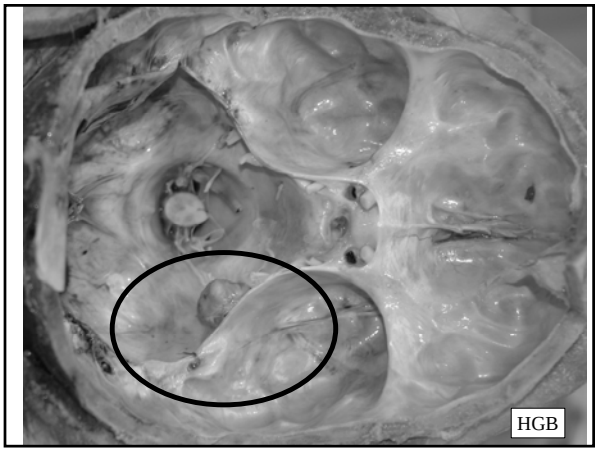


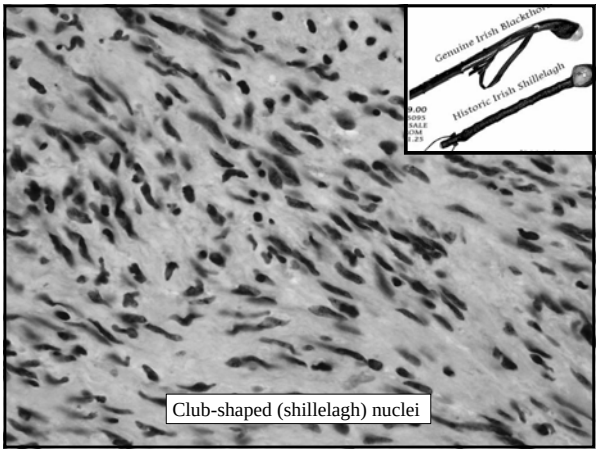
Schwannomas

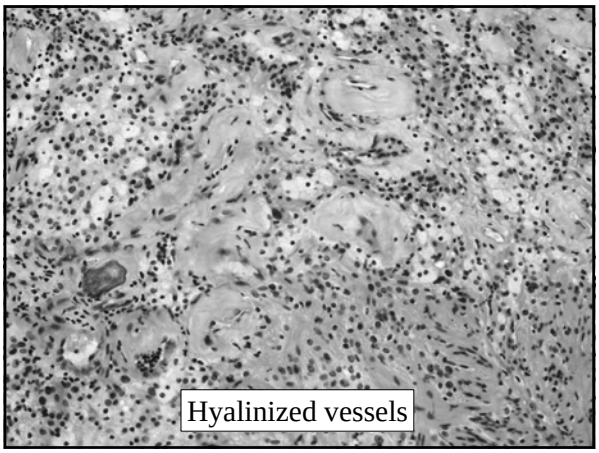
- 8% of intracranial neoplasms
- 4th and 5th decade
- Vestibular portion of 8th N
  - If bilateral, strongly consider NF2
- Sometimes 5th N
- Spinal are usually sensory roots, lumbosacral
- Intradural and extramedullary

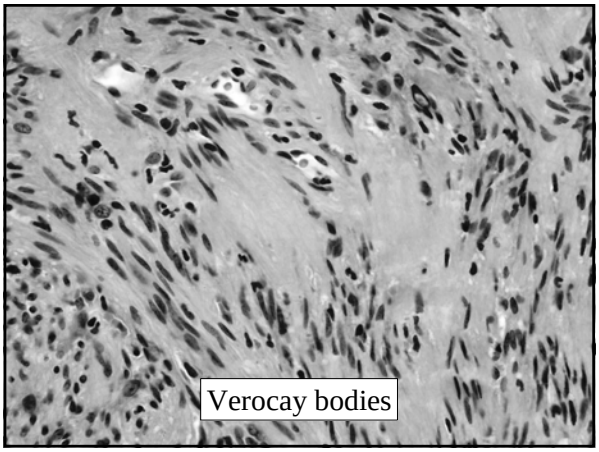
Henry Brown, MD PhD

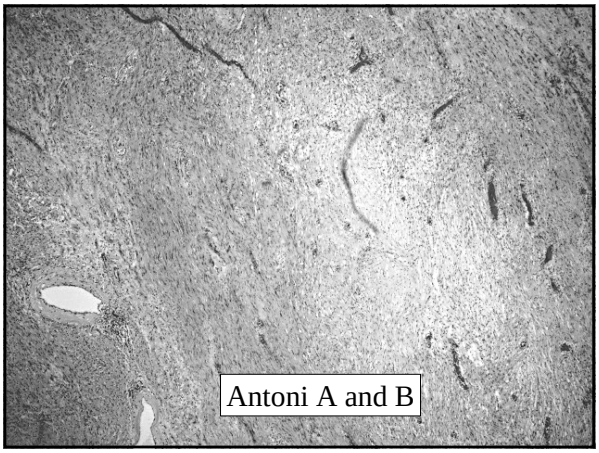


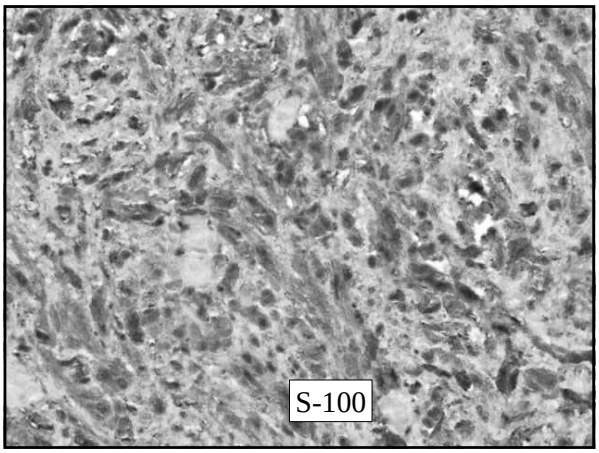

HGB


Genuine Irish Blackthorn
Historic Irish Shillelagh
Club-shaped (shillelagh) nuclei


Hyalinized vessels


Verocay bodies


Antoni A and B



Quiz 6

- Which type of vessel is associated with malignancy?
  - A) hyalinized vessels;
  - B) vessels with endothelial proliferation;
  - C) vessels with perivascular pseudorosettes?

  - B, as seen in GBM. Hyalinized vessels are seen in low grade tumors like pilocytic astrocytoma and schwannoma. Perivascular pseudorosettes are seen in ependymomas.

Henry Brown, MD PhD

Pituitary fossa neoplasms

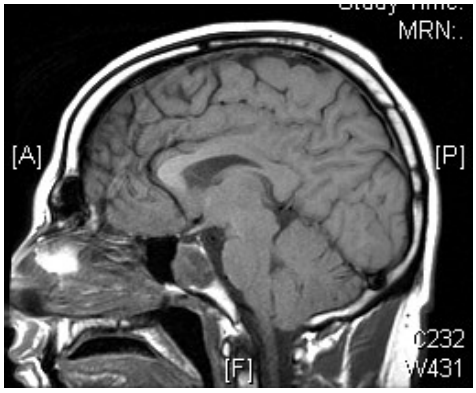
- Most common:
  - pituitary adenomas and meningioma
- Others:
  - Craniopharyngioma, germ cell tumor, astrocytoma, metastases

Henry Brown, MD PhD

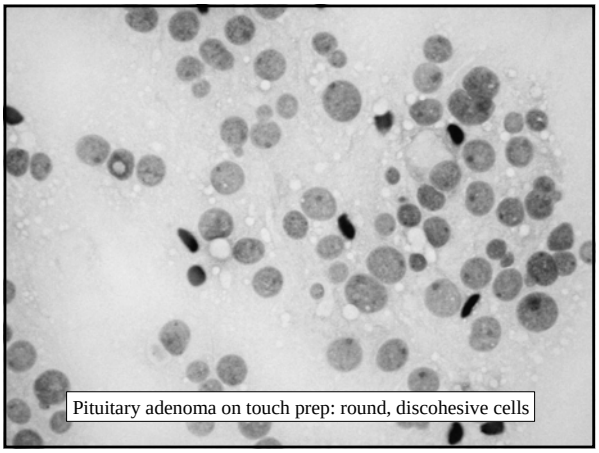
Pituitary adenomas

- Genetics: MEN 1 (pancreas, parathyroid)
- 10-15% of intracranial neoplasms
- 3rd-6th decade
- F:M 3:1, incidental prolactinomas not uncommon
- Hormone symptoms (can also be peptide deficiencies) or mass effects

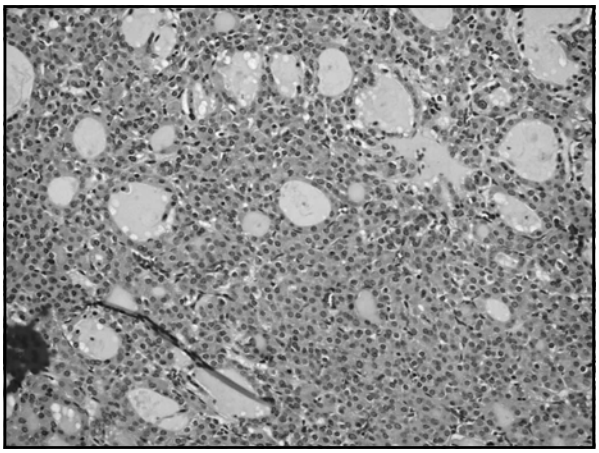
Henry Brown, MD PhD

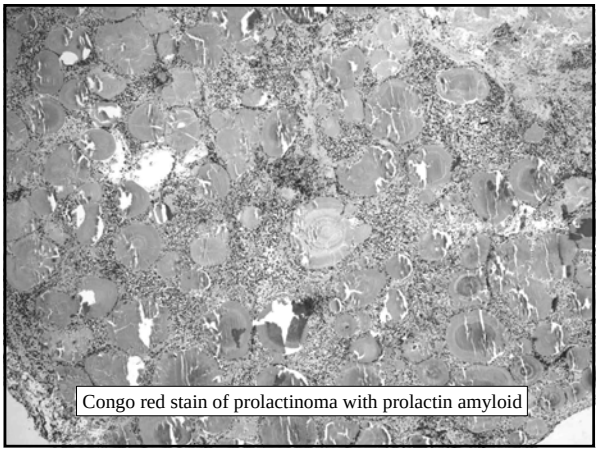


Henry Brown, MD PhD

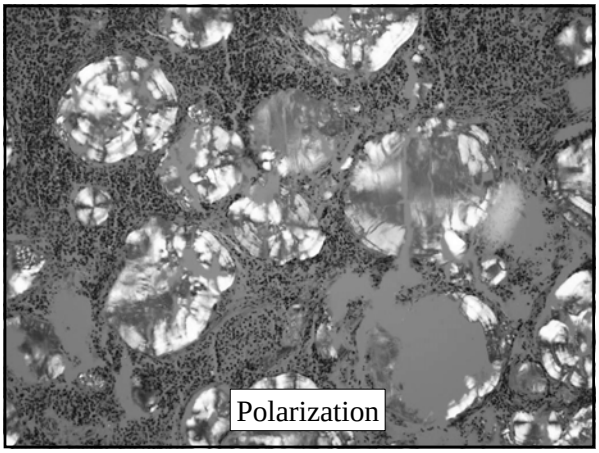


Pituitary adenoma on touch prep: round, discohesive cells





Congo red stain of prolactinoma with prolactin amyloid



Polarization

Quiz 7

- Which of these tumors can have rosette-like structures?
- A) ependymoma
- B) medulloblastoma,
- C) schwannoma,
- D) pituitary adenoma?
  - All of them can!

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Metastases

- 40-50% of intracranial neoplasms
- About 15% of patients with disseminated CA will have brain mets.
- 6^{th}-7^{th} decade
- Solitary met about 50% of the time ?treatable
- About 50% are from lung
- Initial presentation about 15% of the time

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	% of CNS metastases	Frequency this tumor mets to brain
Lung	50	35
Breast	15	20
Melanoma	10	**50**
Kidney	5	10

Lung is most common, and frequently goes to the brain, but melanomas appear somewhat brain 'trophic', and is found in the brain out of proportion to its incidence

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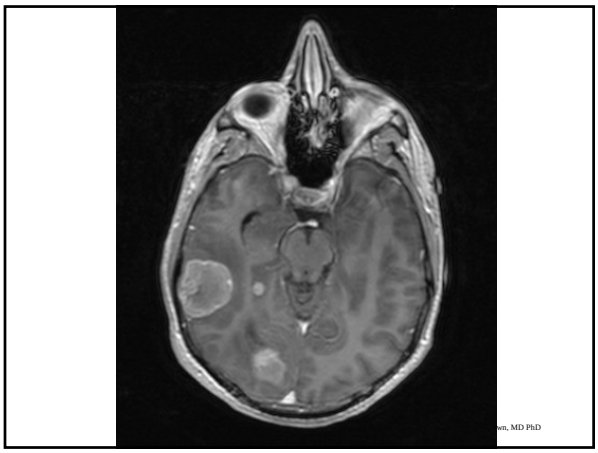
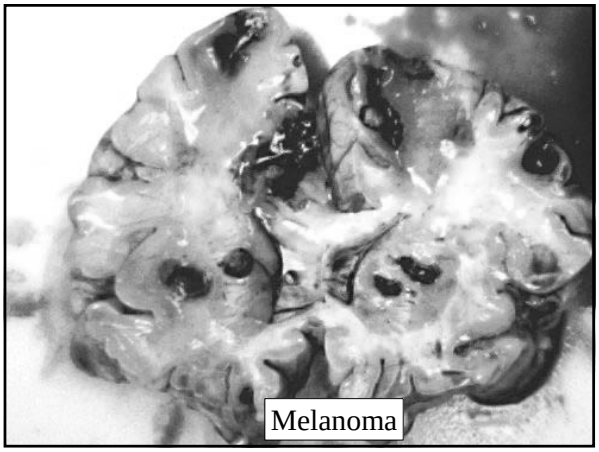
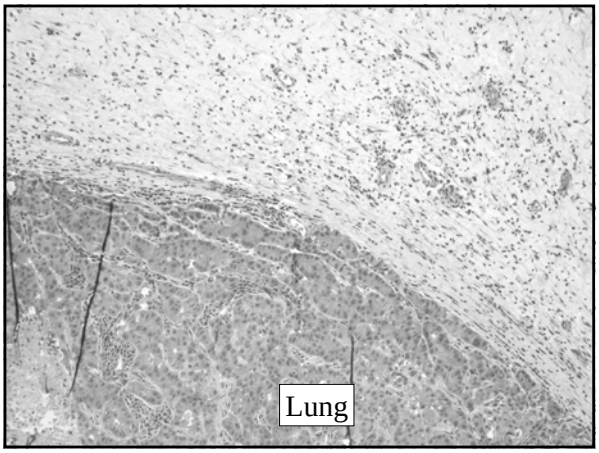
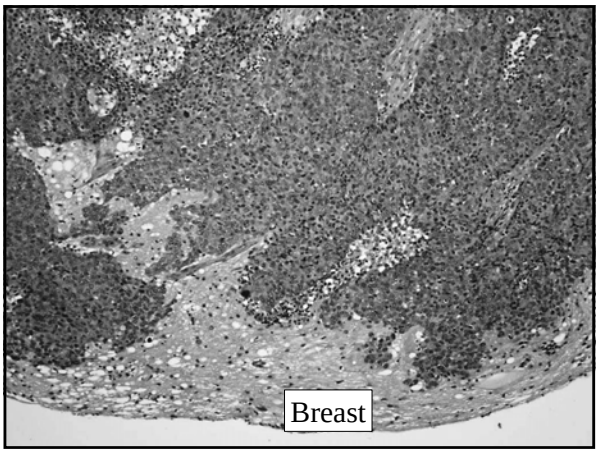
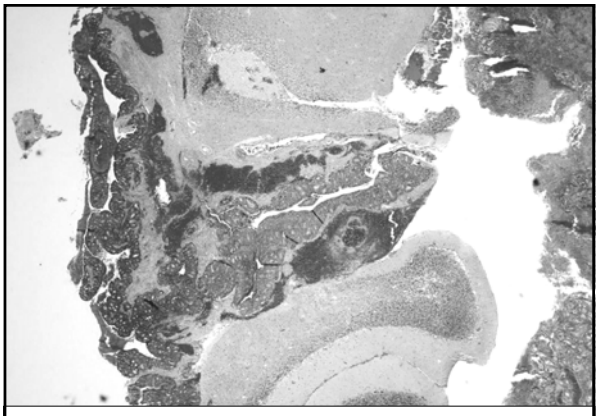



Melanoma

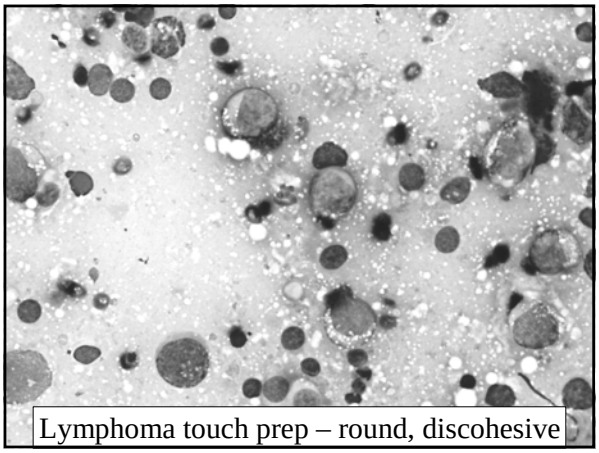

Lung



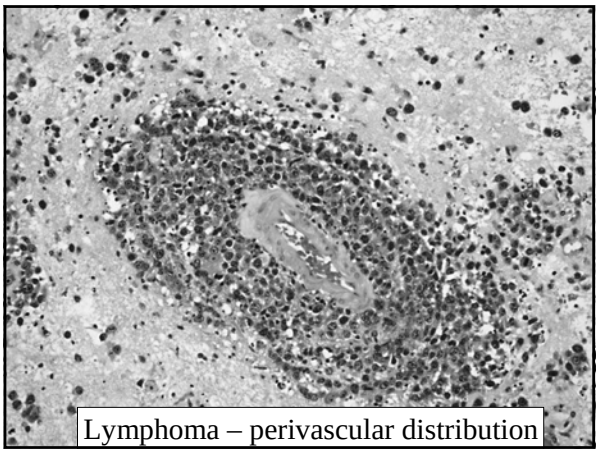
Breast



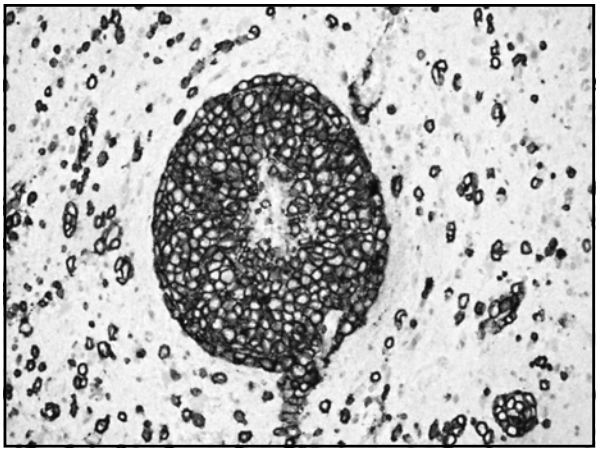
Invasion into leptomeninges (carcinomatosis)



Lymphoma touch prep – round, discohesive



Lymphoma – perivascular distribution



Take home

- There are no truly ‘benign’ CNS neoplasms, just more or less aggressive ones
- Past childhood, age is a bad prognostic factor
- Some specific mutations are associated with tumors, e.g. deletion of 1p and 19q in oligos.
- Metastases account for about ½ of all brain tumors
- The most common primary CNS tumors in adults are astrocytomas and meningiomas - cerebral
- In children the most common are medulloblastomas and pilocytic astrocytomas - cerebellar

Henry Brown, MD PhD

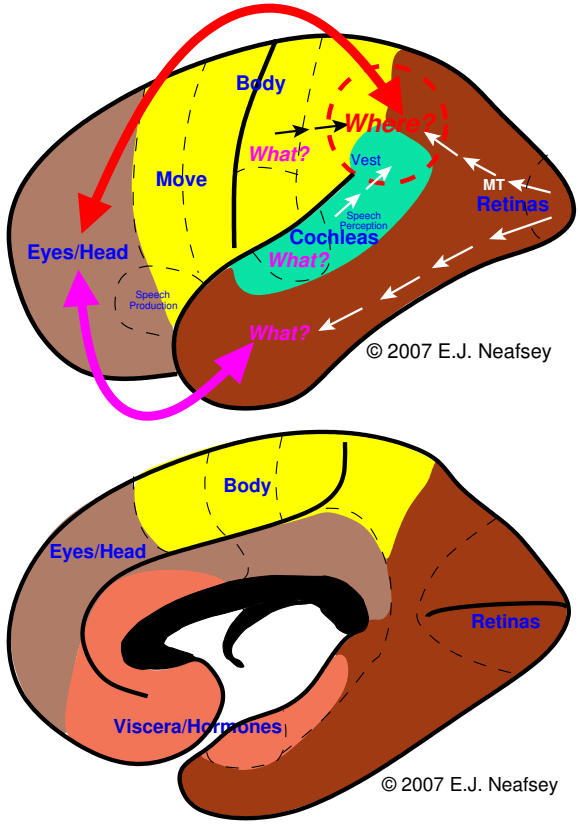
Auditory and Visual Cortex; Hemispheric Specialization

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

Outline

1. Review of 5 Major Functional Regions of Cortex
2. Retina Cortex: Visual Cortex
3. Inner Ear Cortex: Auditory and Vestibular Cortex
4. Hemipheric Specialization (Left vs. Right Brain)

The Five Major Functional Regions of Cortex

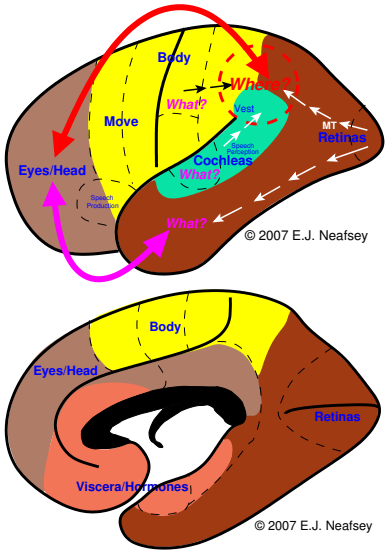


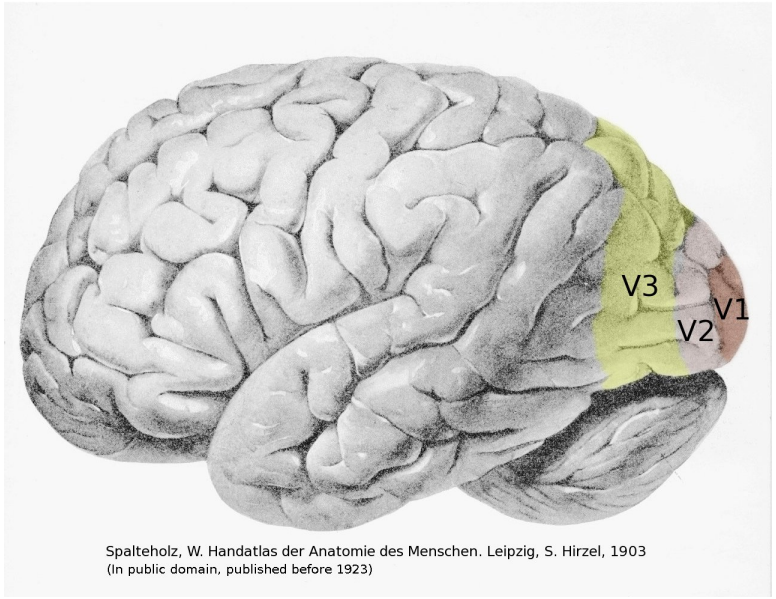
Only Five Major Functional Areas:

Sensory Input	Thalamic Relay	"Motor" Output	Function
Retinas	LG, PUL-LP, ANT-LD	Superior Colliculus	Seeing
Inner Ears	MG	Inferior Colliculus, Superior Olive	Hearing, Balance
Body	VP, VL, VA	Spinal Cord, Brain Stem	Feeling, Moving
Eyes-Head	MDl-ILN	Superior Colliculus	Looking, Attending
Viscera-Hormones	MDm-Mid	Hypothalamus, PAG, ANS	ANS arousal, Emotions

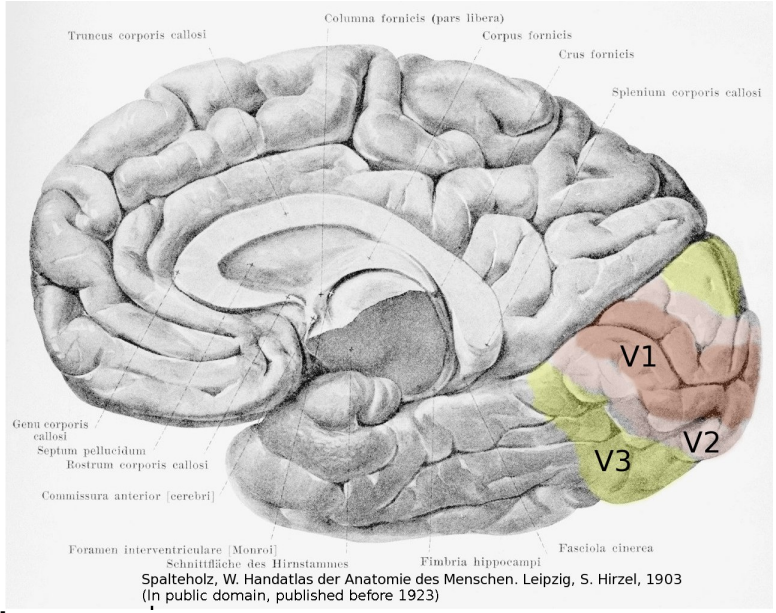
Retinas (Visual) Cortex

Retinas: Primary Visual Cortex (V1) = BA17





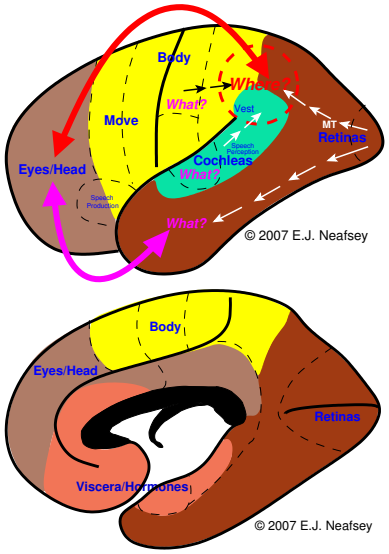
Spalteholz, W. Handatlas der Anatomie des Menschen. Leipzig, S. Hirzel, 1903
(In public domain, published before 1923)

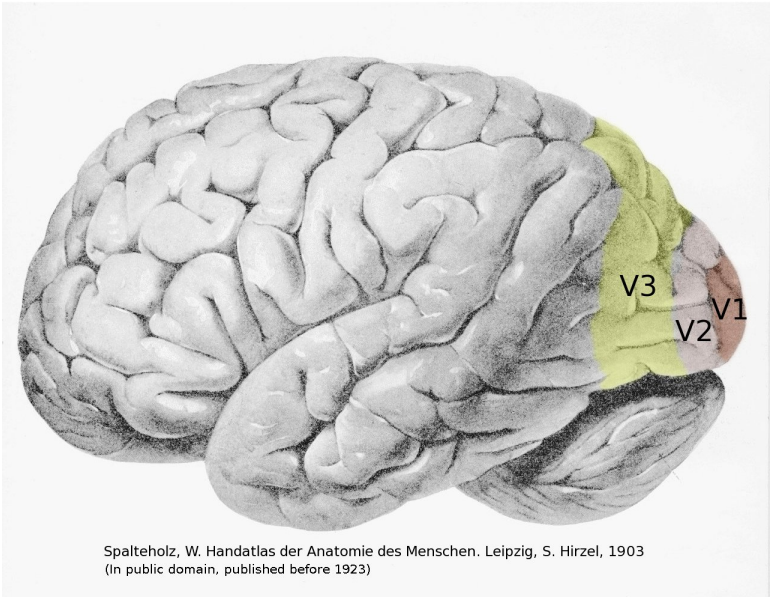


Spalteholz, W. Handatlas der Anatomie des Menschen. Leipzig, S. Hirzel, 1903
(In public domain, published before 1923)

- upper and lower banks of calcarine sulcus
- aka striate cortex or calcarine cortex or V1
- afferents from lateral geniculate of thalamus
- complete map of contralateral visual hemifield
- macular retina projects to posterior third of calcarine cortex
- efferents to superior colliculus (tectum) and pretectum are involved in generating eye movements in visual tracking by projections to brain stem (occipital eye field)
- complete unilatateral lesions cause "contralateral homonymous hemianopsia" (complete blindness in contralateral visual field)

Retinas: Secondary Visual Cortex (V2, V3) = BA18,19





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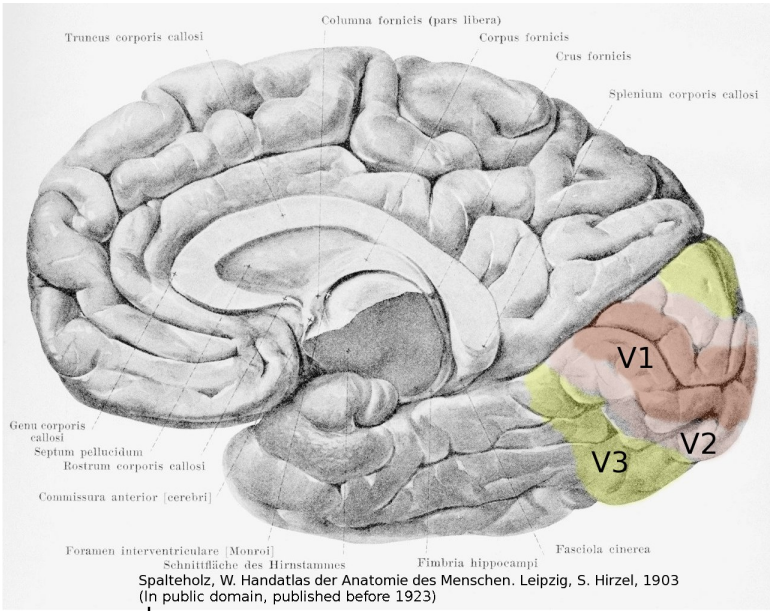
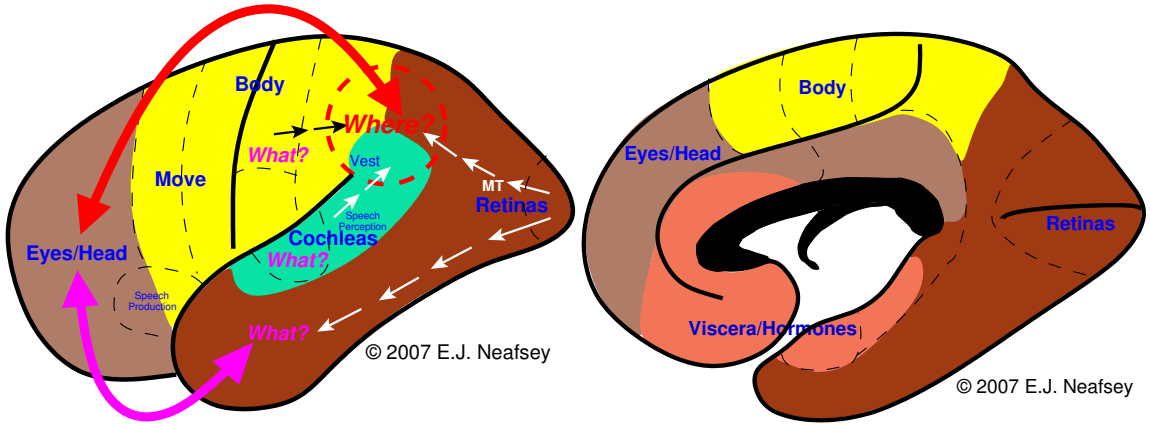
(In public domain, published before 1923)



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

- aka peristriate cortex or V2 and V3
- afferents from V1 and from thalamic lateral geniculate and pulvinar
- contain additional maps of contralateral visual hemifield
- efferents to superior colliculus (tectum) and pretectum that generate visual tracking
- lesions can cause inability to recognize familiar objects or persons although no visual field defects are found
- prosopagnosia: inability to recognize familiar faces

Retinas: "What and Where" Ventral and Dorsal Streams

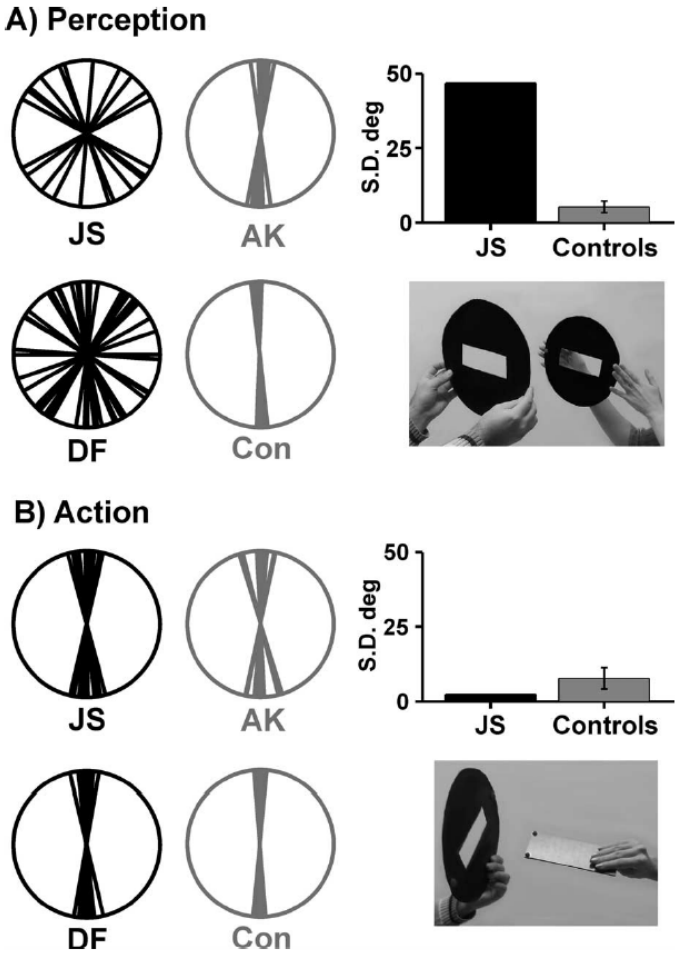


- "What" pathway passes through multiple areas into temporal lobe and processes information from *high resolution* retinal and lateral geniculate **parvo** ("P") system; it leads to identification of complex objects, recognition of faces, etc.

- "Where" pathway passes through multiple areas into parietal lobe and processes information from *low resolution but movement sensitive* retinal and lateral geniculate magno ("M") system; it leads to awareness of where stimulus is, how fast it is moving, whether it is coming towards me or away from me, etc.

- This illustrates "parallel processing" of different features or aspects of a stimulus at the same time through different sequences of cortical regions

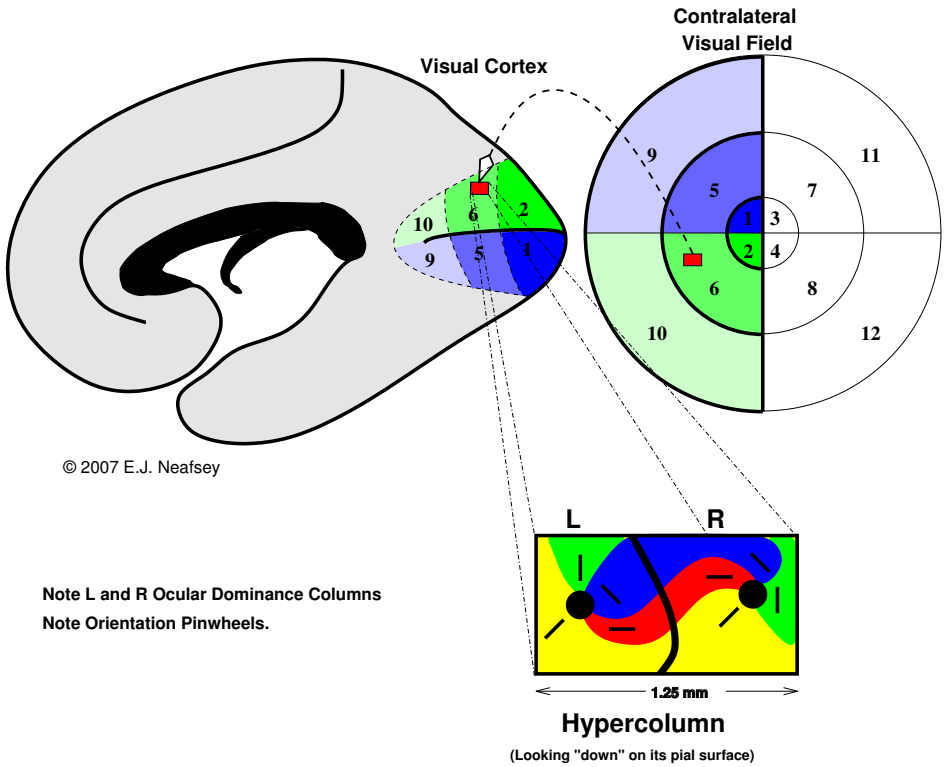
What and Where in a Human Subject

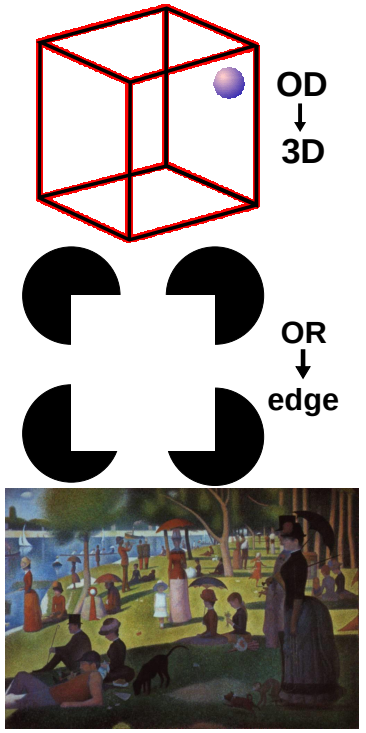


Polar plots illustrating perceptual orientation judgements (A) and orientation adaptation in reaching movements (B). The photo inlays illustrate the respective tasks. The different orientations of individual trials have been normalized to the vertical. The polar plots therefore show difference values to the vertical, representing a difference to the target orientation of 0°. Black data plots indicate the data of our patient J.S. and the data of VFA patient D.F. reported by Milner and Goodale (1995). Gray polar plots indicate an exemplary control of our study (A.K.) and the control subject reported by Milner and Goodale (1995) (Con). Bar plots illustrate SDs of J.S.'s responses in either task and average SDs in our group of healthy controls (error bars denote 1 SD).

From: Karnath *et al.*, *J Neurosci* 29:5854 Âŋ5862, 2009

Retinas: Primary Visual Cortex (area 17, V1) is a retinotopic map of contralateral visual field



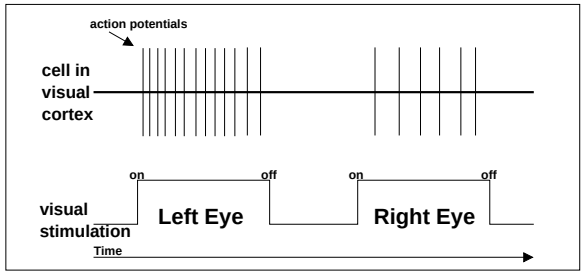


Seurat: A Sunday Afternoon on the Island of La Grande Jatte

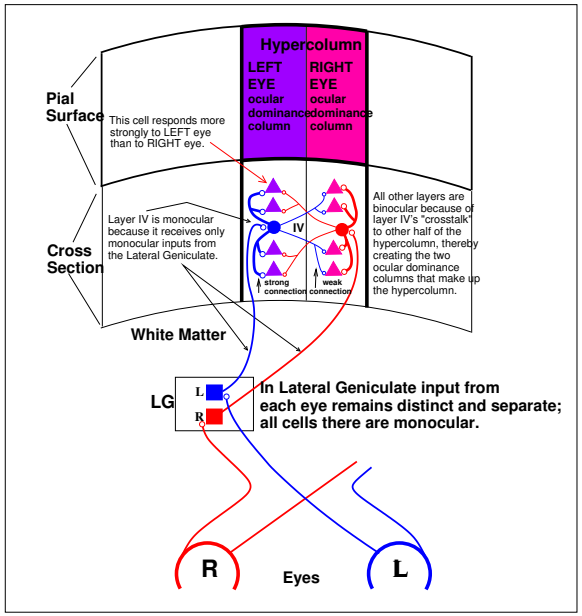
- Each small region of contralateral visual field (red rectangle) maps to a small "retinotopic" patch of primary visual cortex (red rectangle) that is termed a hypercolumn; its surface area is about 1 mm^2.
- Each hypercolumn is divided into two ocular dominance columns about .5-1mm wide (L, R) where cells respond more strongly to left or right eye; this is the beginning of stereoscopic depth perception.
- Each hypercolumn is also subdivided into two orientation pinwheels where cells respond most strongly to a particular orientation of a visual stimulus (only 4 orientations are shown, but many more exist; this edge detector makes us perceive edges even when they are not really there.
- Primary visual cortex connects retinal "dots" into "lines," allowing us to see Seurat's pointillist painting.

Retinas: Ocular Dominance in Visual Cortex

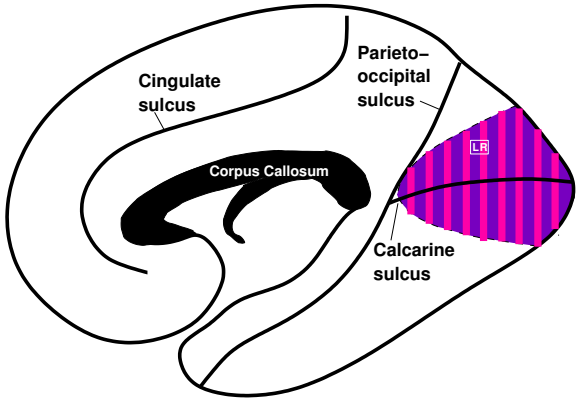
Half the Cells and Half of V1 (BA17) Cortex Respond More to One Eye than the Other



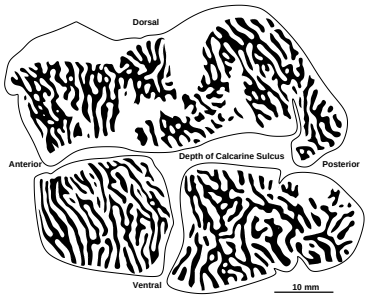
Note that this cell in visual cortex, like most cells, is "binocular" and fires action potentials when visual stimuli are presented in its receptive field with either eye open. However, this cell fires more action potentials with stimuli presented with left eye open than it does with stimuli presented with right eye open. Thus, for this cell the left eye is "dominant."



Neuroanatomical explanation of ocular dominance.

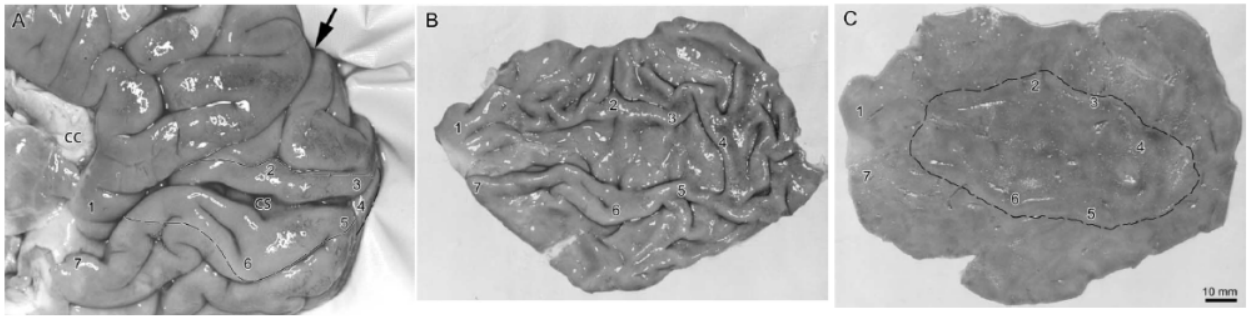


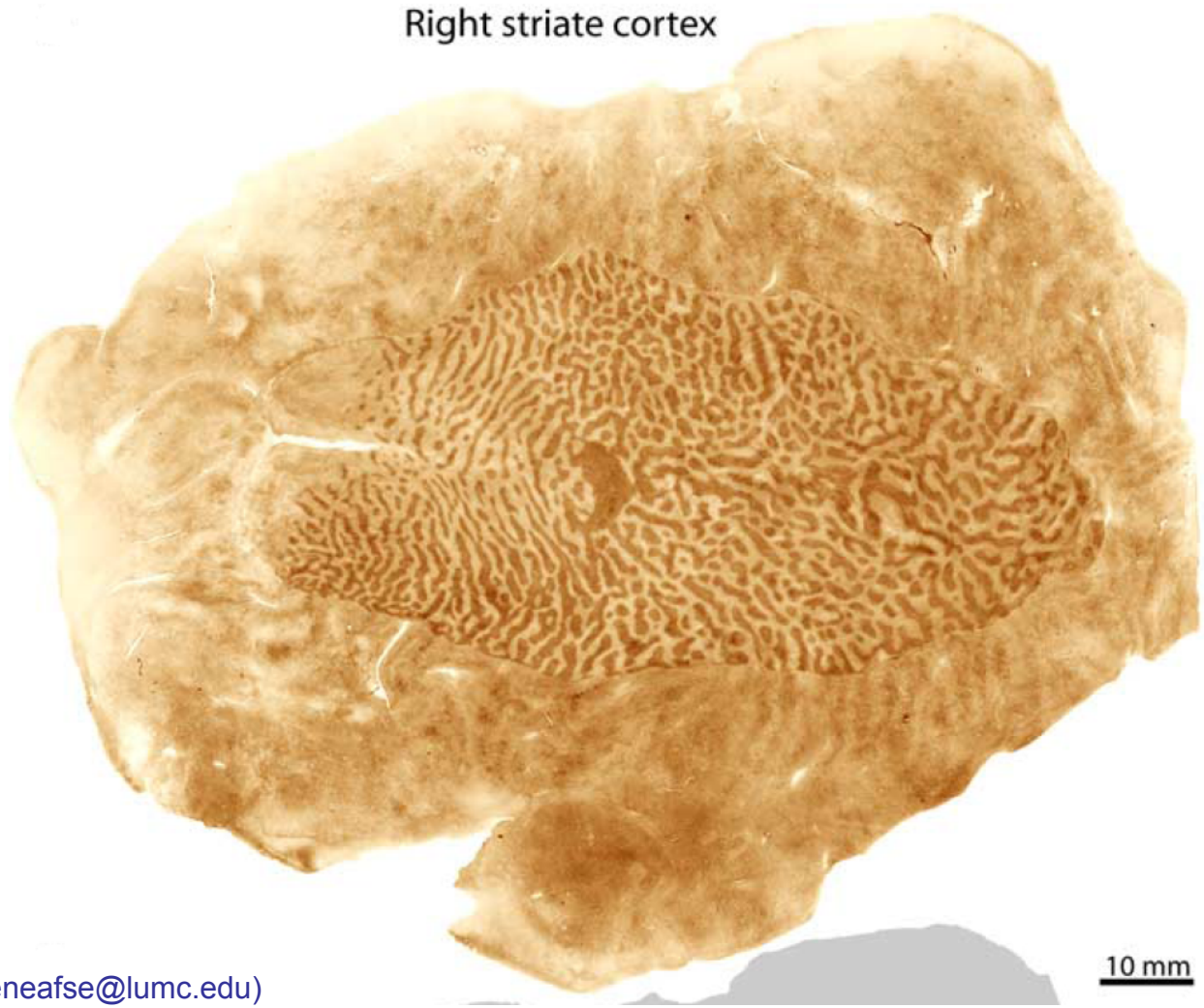
Ocular dominance columns are organized into an overall pattern of ocular dominance stripes in primary visual cortex. Purple band represents LEFT eye (L) dominance, and magenta band represents RIGHT eye (R) dominance. Small white rectangle corresponds to hypercolumn on previous figure. Actual pattern of ocular dominance stripes is more complex and looks like a fingerprint or zebra stripes.



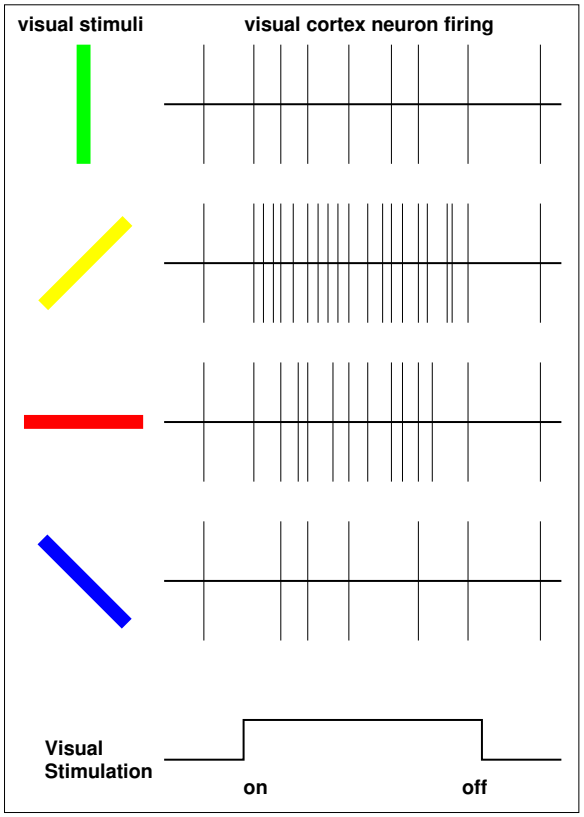
Ocular Dominance Complete

Adams et al.,Complete Pattern of Ocular Dominance Columns in Human Primary Visual Cortex. Journal of Neuroscience (2007) 27:10391–10403





Retinas: Orientation Sensitivity in Visual Cortex



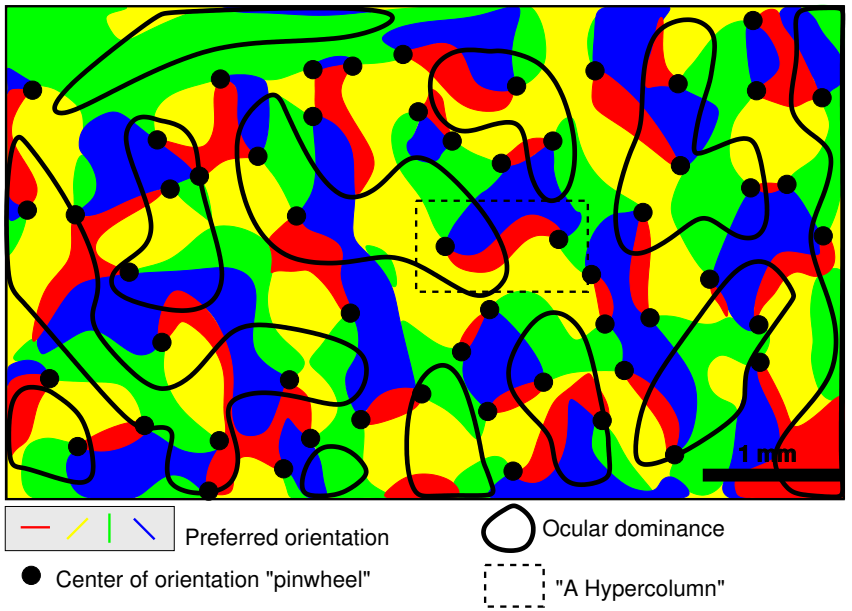
Note that this cell fires more action potentials to oblique visual stimuli in its visual field. This defines its preferred orientation.

Hubel and Weisel Simple Cell

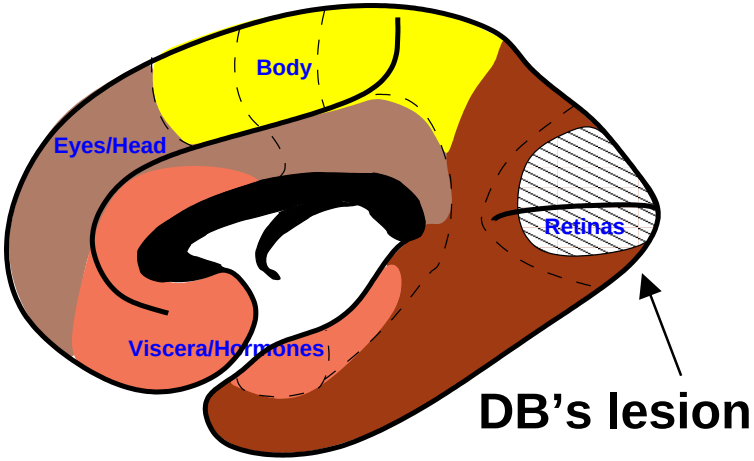
Hubel and Weisel Complex Cell

Pial surface view (looking down on cortex) of overall pattern of orientation sensitivity has been described as "orientation pinwheels." (Hubener et al., *J Neurosci* 17:9270, 1997)

Orientation Pinwheels in Primary Visual Cortex (after Hubener)

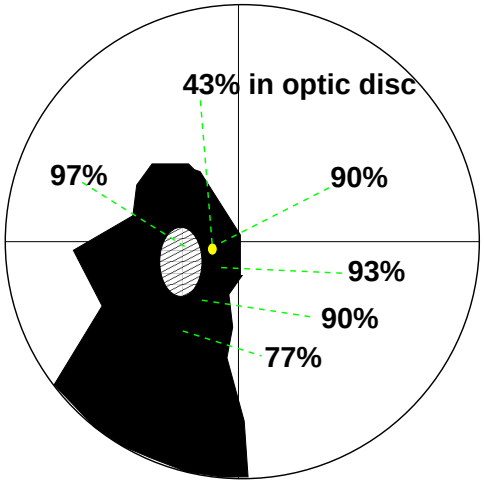


Retinas: "Blindsight" After Damage to Primary Visual Cortex



DB's lesion

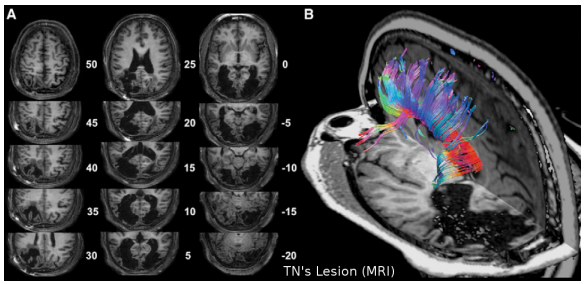
(caused by surgical removal of AVM)



DB couldn't "SEE" anything inside his scotoma, as seen in right side figure. However, when forced to GUESS, he could very accurately look or point to stimuli located inside the scotoma. He was even able to guess if stimulus was an "X" or an "O." Figure at right contains results of optic disc experiment. Numbers show per cent correct in 30 trials for forced-choice detection (chance = 50%) at different locations, including the optic disc (small shaded region), for a 0.5° target. The hatched area estimates the area in which D.B. had a 'feeling' of stimulus presentation. Note that his accuracy was only 43% in the optic disc, close to chance value of 50%.

Weiskrantz L, *Blindsight: A Case Study and Implications*, Clarendon Press, Oxford, 1986

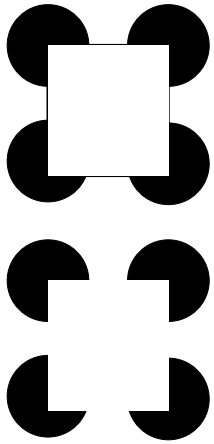
New Blindsight patient TN:



From: de Gelder B, Tamietto M, van Boxtel G, Goebel R, Sahraie A, van den Stock J, Stienen BM, Weiskrantz L, Pegna A. Intact navigation skills after bilateral loss of striate cortex. Curr Biol. 2008 Dec 23;18(24):R1128-9.


Blindsight video of new patient TN from http://www.beatricedegelder.com/documents/Filmato.wmv

Retinas: MM . . . Blind But Now I See?



MM sees edge.

MM can't see edge.

At three and half years of age MM lost his left eye and was blinded in the right eye due to extensive corneal damage that only allowed him to distinguish light from dark. At age 43 MM received a corneal transplant in his right eye. His retina showed no evidence of degeneration, and his ERG responses were normal. However, even two years after surgery his spatial frequency contrast sensitivity was only 1.3 cycles/degree, compared to 30-40 in controls. He was able to distinguish simple forms or shapes but was unable to distinguish complex, 3D shapes or see the edges in a Kanisza figure. In addition, faces and objects evoked little fMRI activity in his lingual and fusiform gyri, in contrast to controls who had strong responses. His fMRI responses in area MT were of normal amplitude.

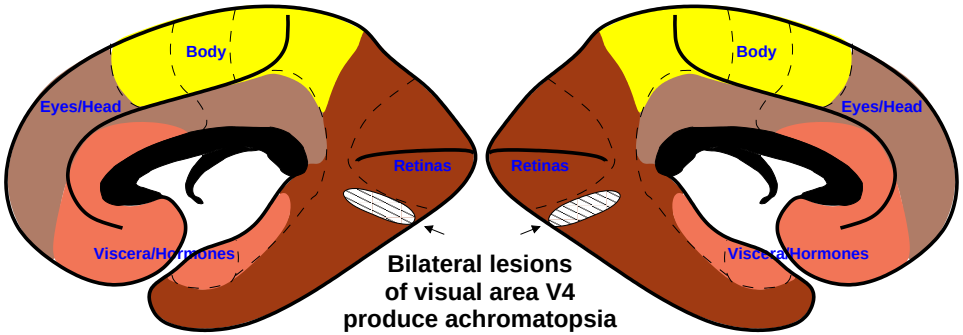
MM was an expert skier as a blind person, but immediately after his operation he closed his eyes while skiing because the visual information gave him a frightening sense of imminent collision. MM now makes significant use of vision in everyday life but states:

> "The difference between today and over 2 years ago is that I can better guess at what I am seeing. What is the same is that I am still guessing."

Fine I, Wade AR, Brewer AA, May MG, Goodman DF, Boynton GM, Wandell BA, and MacLeod DIA. Long-term deprivation affects visual perception and cortex. *Nature Neuroscience* 6:915–916 (2003).

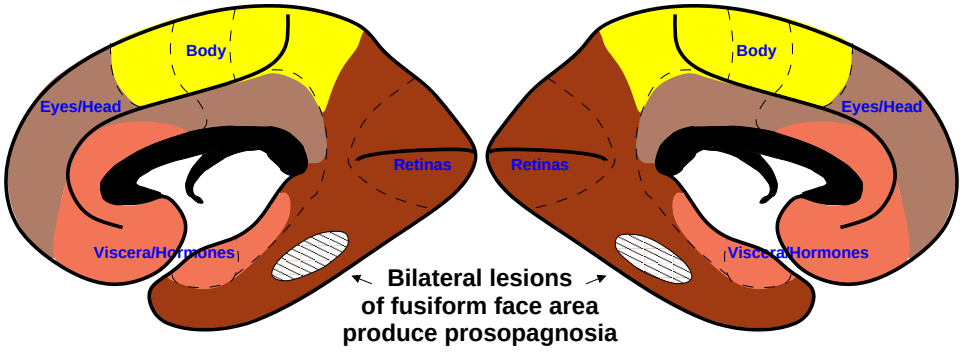
Retinas: Achromatopsia

"Olive harvest" by Jessica Neafsey



- Bilateral damage to visual area V4 produces achromatopsia in which COLOR perception is lost.
  Bartels and Zeki. The architecture of the colour centre in the human visual brain: new results and a review. *Eur J Neurosci* 12:172-193, 2000.

Retinas: Prosopagnosia

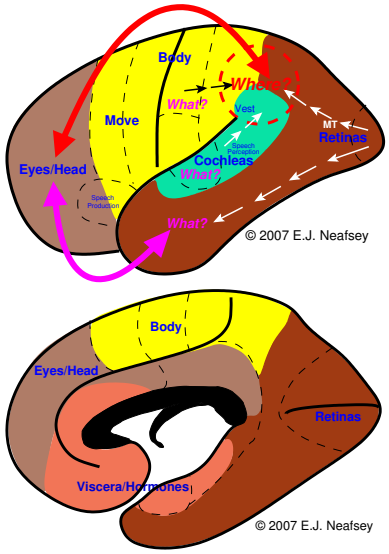


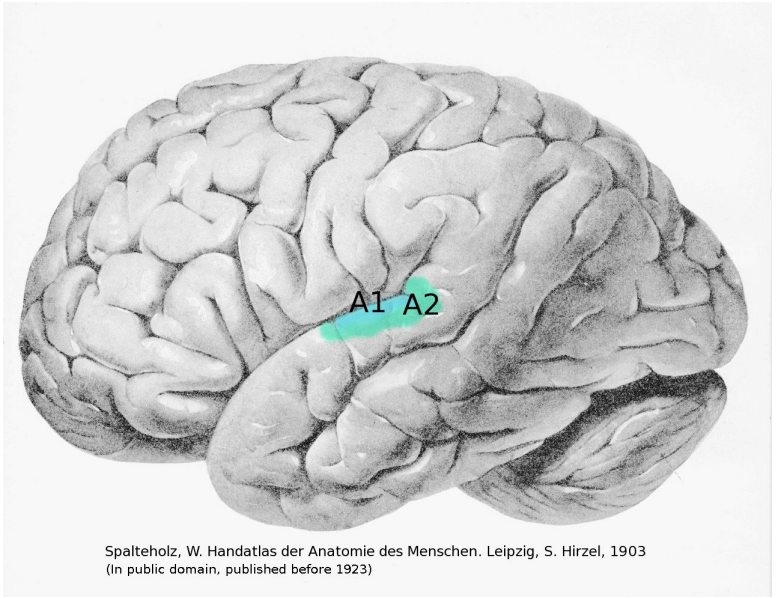
- Bilateral fusiform face area damage (FFA) in the fusiform gyrus (aka occipito-temporal gyrus) produces prosopagnosia in which FACES are seen but not recognized.

- A few cases have been reported in which unilateral damage to RIGHT fusiform gyrus only also produced prosopagnosia (Uttner *et al*. Prosopagnosia after unilateral right cerebral infarction. *J Neurol* 249:933–935, 2002).

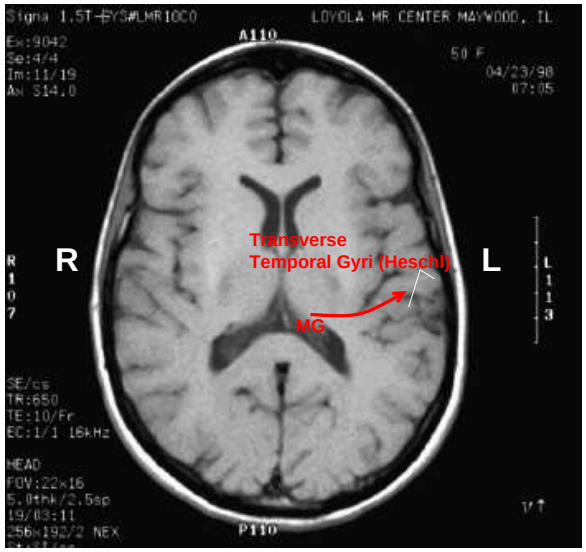
Inner Ears (Auditory and Vestibular) Cortex

Inner Ears: Primary Auditory Cortex (A1, A2) = BA41,42





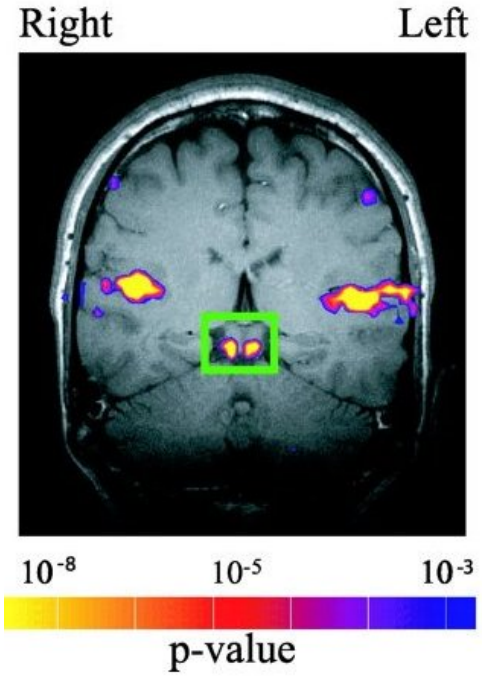
Spalteholz, W. Handatlas der Anatomie des Menschen. Leipzig, S. Hirzel, 1903
(In public domain, published before 1923)



- mostly "buried" inside Sylvian fissure on surface of superior temporal gyrus on what is known as tranverse temporal gyrus (of Heschl)
- afferents from medial geniculate nucleus of thalamus relay auditory signals from both ears
- "Tonotopic" frequency maps are found in which cells are tuned to different frequency ranges, with low frequencies found rostrally and high frequencies caudally
- Unilateral lesions or strokes affecting the auditory cortex may produce only a slight hearing loss and a small defect in localizing sounds because the auditory pathway from each ear projects so extensively to both sides of the brain.

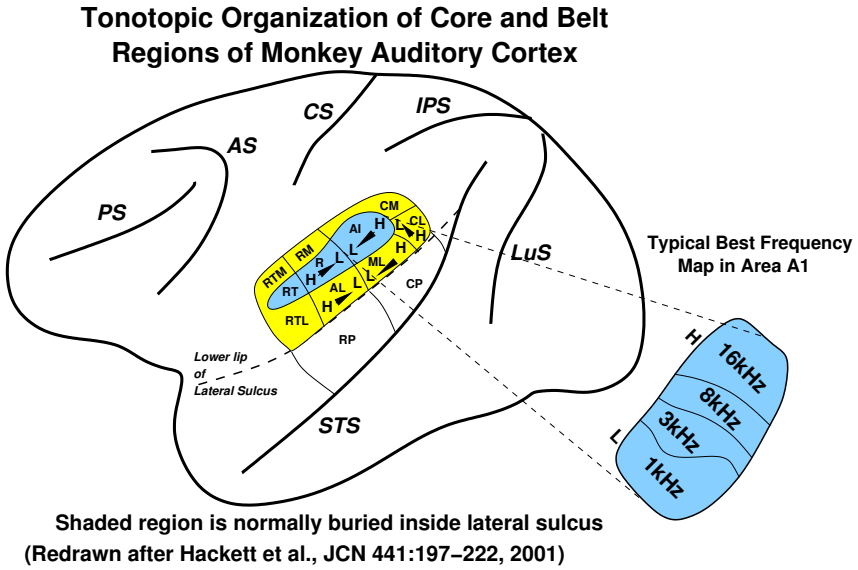
LOYOLA MEDICINE
Loyola University Chicago Stritch School of Medicine

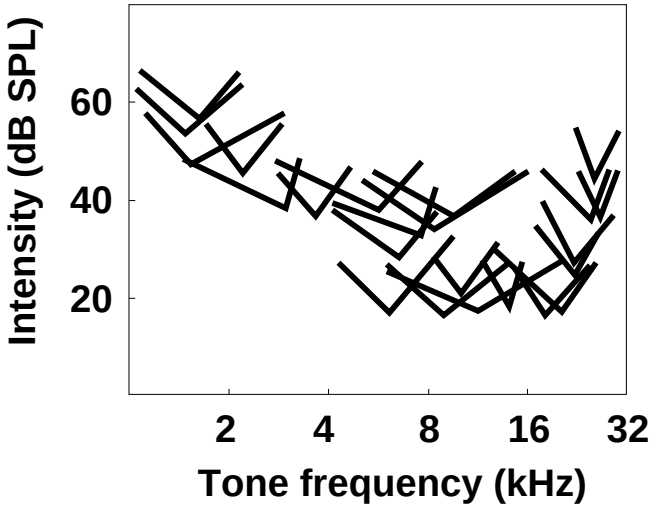
Inner Ears: Primary Auditory Cortex fMRI



fMRI showing activation of inferior colliculus and auditory cortex by sound stimuli.
Adapted from Figure 4 of of Penagos H, Melcher JR, and Oxenham AJ. A Neural Representation of Pitch Salience in Nonprimary Human Auditory Cortex Revealed with Functional Magnetic Resonance Imaging. *J Neuroscience* 24 :6810-6815 2004.

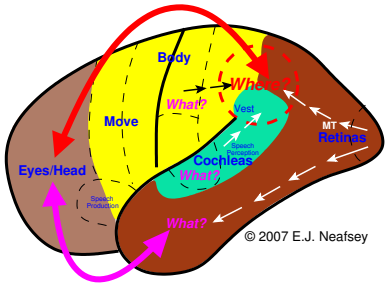
Inner Ears: Auditory Cortex Frequency Tuning

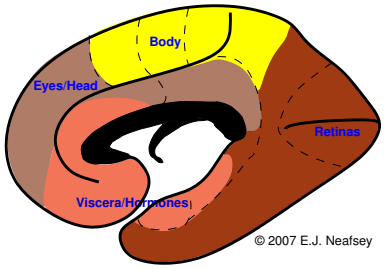


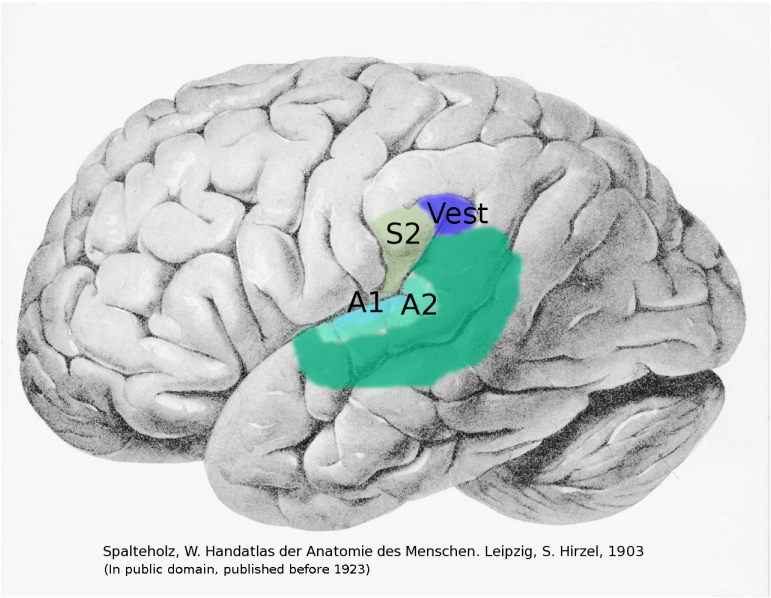


Tuning curves of neurons in auditory cortex.
Adapted from Chang and Merzenich *Science* 300:498–502, 2003.

Inner Ears: Vestibular Cortex







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

- fMRI studies have found that the posterior portion of the lateral sulcus and adjacent temporal and insular cortex are strongly activated by vestibular stimulation.

  Fasold *et al.*, Human Vestibular Cortex as Identified with Caloric Stimulation in Functional Magnetic Resonance Imaging. *NeuroImage* 17:1384-1393, 2002.

- Vestibular area is part of "Where" system.

"The Hard Problem"

- How does the brain's neuronal activity (action potentials, synaptic potentials, etc.) produce our conscious, subjective experience?

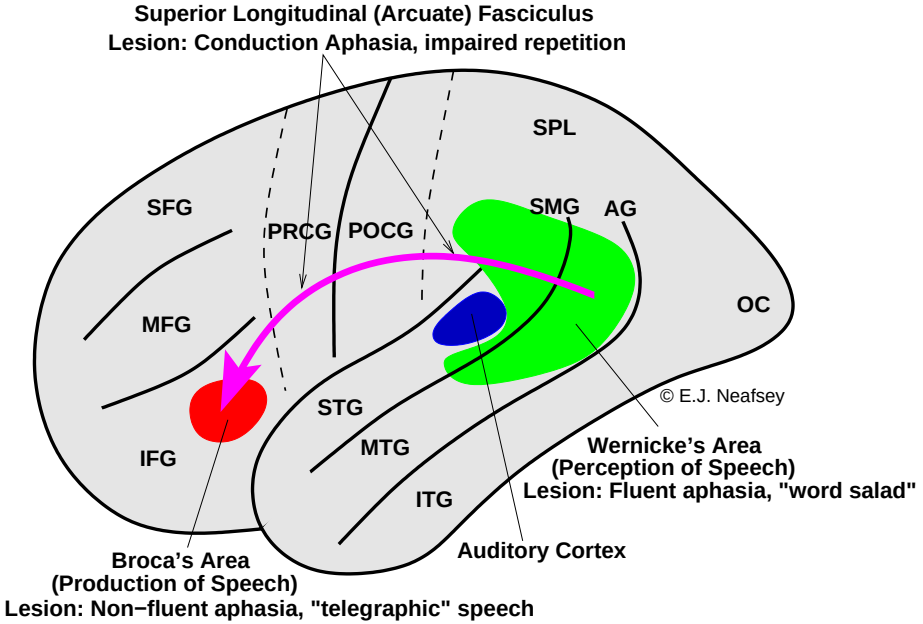
- This question is known as the "hard problem" because the answer is not obvious at all.
  - *Some feel the answer is close. (Crick F and Koch C. The problem of consciousness. Sci Am 1992 Sep;267(3):152-9)*
  - *Some feel the answer is far away. (Chalmers DJ, The puzzle of conscious experience. Sci Am 1995 Dec;273(6):80-6.)*

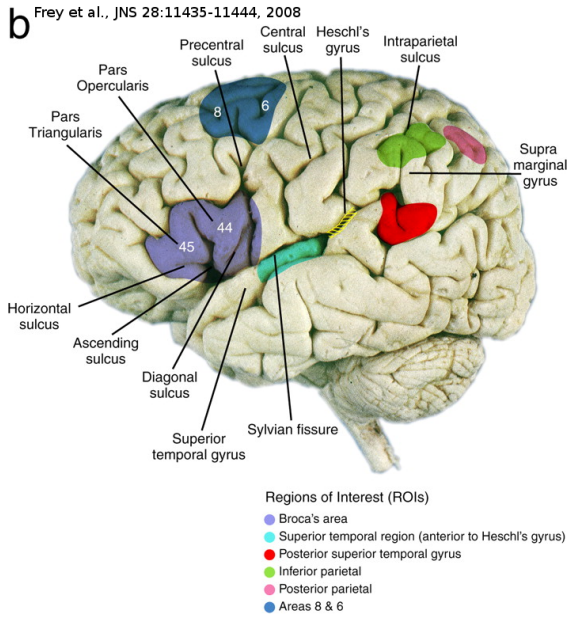
Hemispheric Specialization

Brief History of Hemispheric Specialization

1836	Marc Dax	L hemisphere	speech production
1864	Paul Broca	L inf frontal	speech production
1870	Carl Wernicke	L temporal	speech perception
1905	Hugo Liepmann	L hemisphere	alexia, agraphia, apraxia
1930s	psychologists	R hemisphere	neglect, navigation, flat affect, facial agnosia
1939	Kurt Goldstein	L hemisphere	"catastrophic reaction" after LH but not RH damage
1960s	Roger Sperry	L/R hemispheres	split brain cats and humans
1960s-present	Michael Gazzaniga	L/R hemispheres	humans

LEFT: Language and Aphasia Plus the "Catastrophic Reaction"

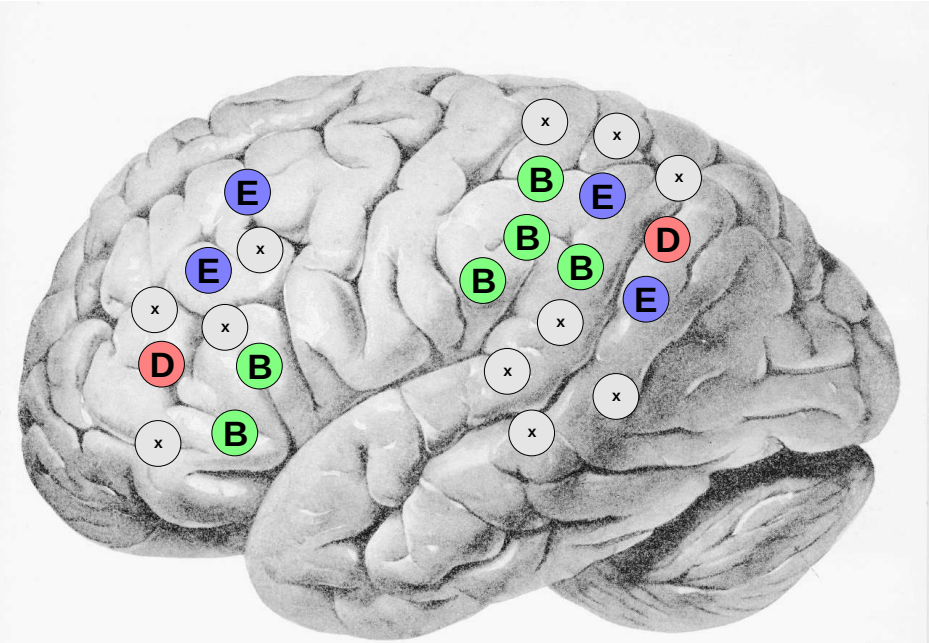




- Some patients with LEFT hemisphere lesions and aphasia also show the **"catastrophic reaction"**: great anxiety, worry, fear of loss of control, avoidance of situations where their disability makes them unable to perform, etc. (cf. *The Organism* by Kurt Goldstein).

- In contrast, patients with RIGHT hemisphere lesions often are inappropriately cheerful, making light of the severity of their deficits.

LEFT: Language and Bilingual Naming Interference

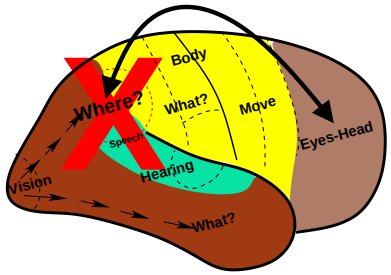


Spalteholz, W. Handatlas der Anatomie des Menschen. Leipzig, S. Hirzel, 1903
(In public domain, published before 1923)

Cortical stimulation interferes with naming in a bilingual patient (D=Dutch, E=English, B=Both, x=neither).

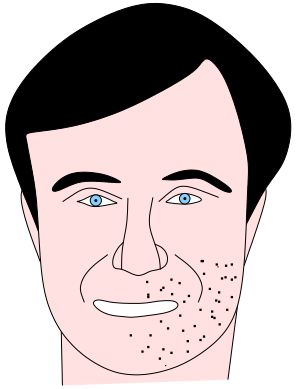
Adapted from *Conversations with Neil's Brain* by G. Ojeman and W. Calvin.

RIGHT: Neglect and RIGHT Parietal Cortex



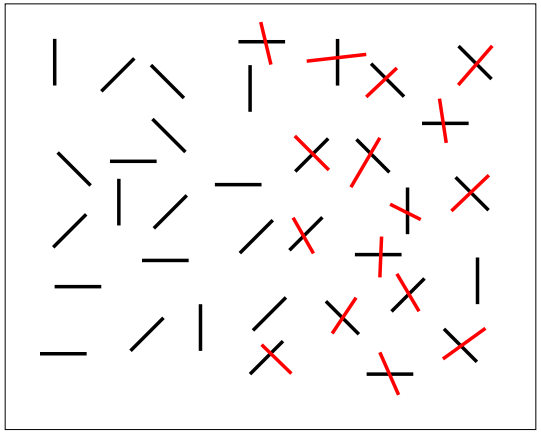
RIGHT posterior parietal cortex damage to the "Where?" region produces PROFOUND NEGLECT of the left side of space and the left side of the person's own body.

LEFT parietal cortex damage can produce a much milder neglect of right side.

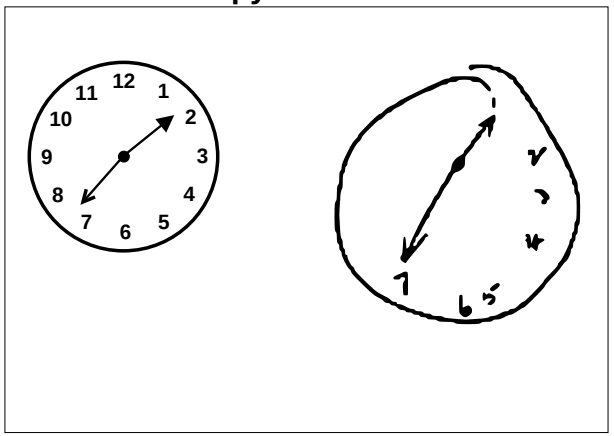


Of course I shaved this morning!

Cross the lines.



Copy the clock.



- Recovery from neglect can occur over about a year's time.

- Interestingly, neglect not only occurs to what you see but also to what you imagine you see. Patients with neglect fail to see things on the left as they visualize places they know well. When they change position so the things missing on the left are now on the right, they "see" them again as they re-visualize the scene.

RIGHT: Neglect and Recovery

Anton Raderscheidt's self–portraits following right parietal cortex damage.

2mo

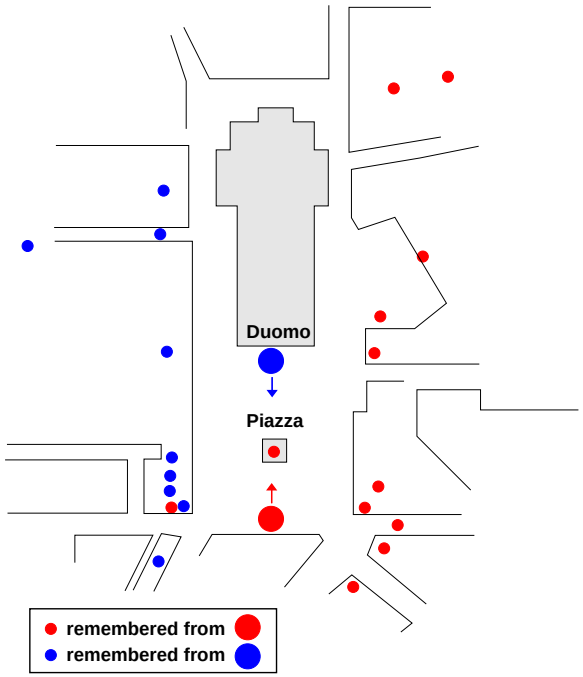
3.5mo

6mo

9mo

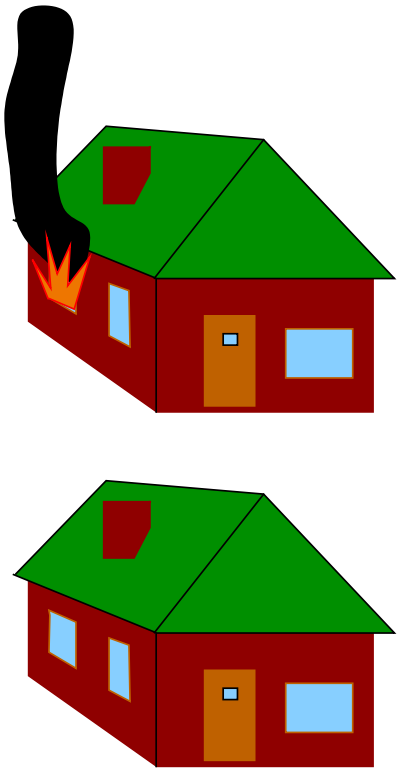
RIGHT: Neglect Can Include Impaired Remembering and Imagining

Image of the Piazza del Duomo in Milan from the Wikipedia article on "Milan."



Adapted from Bisiach E, Luzzatti C. Unilateral neglect of representational space. *Cortex* 1978;14:129-133

RIGHT: Neglect—BUT Emotion Gets Through!



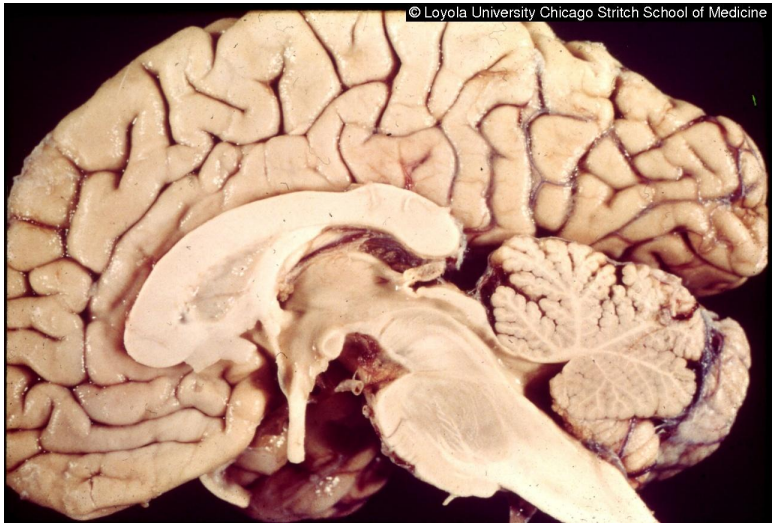
Are houses the same or different?

P.S.— the same.

Which house would you prefer to live in?

P.S.— the one on the bottom.

LEFT/RIGHT: Split Brain Surgery for Epilepsy



- In the 1960s a series of patients with epilepsy had the corpus callosum and anterior commissure sectioned to prevent spread of epilepsy from one hemisphere to the other. This group of "split brain" patients has been extensively studied to learn more about hemispheric specialization.

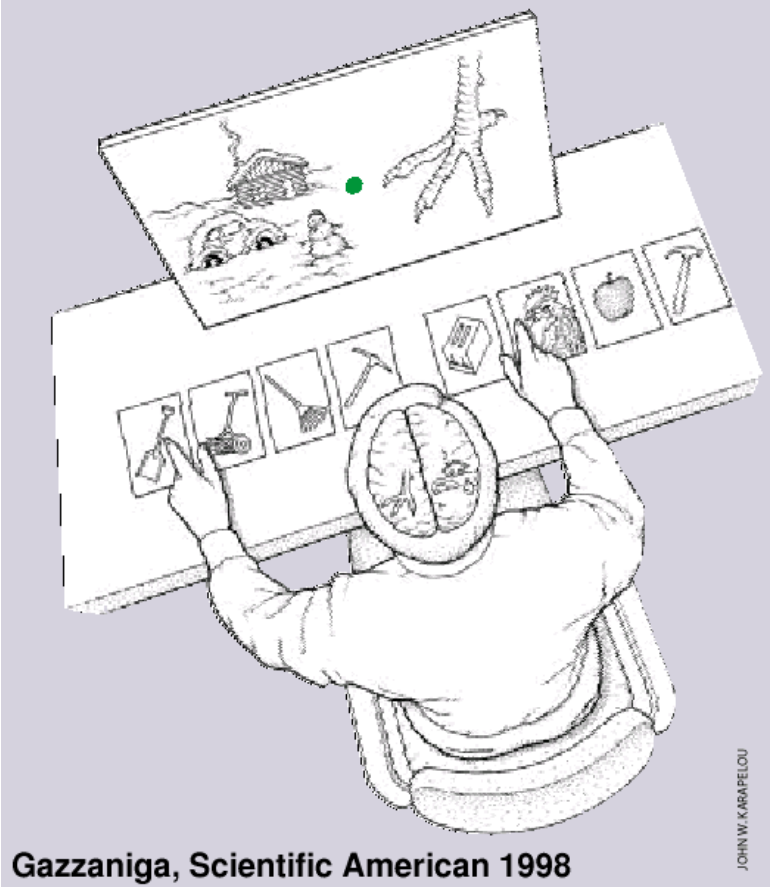
LEFT/RIGHT: Split Mind?

Pick two pictures below, one to “match” each picture above.

Why my picture matches the left picture:_____

Why my picture matches the right picture: _____

LEFT/RIGHT: Split Brain = Split Mind?



Gazzaniga, Scientific American 1998

Gazzaniga's famous split brain subject (whose corpus callosum was sectioned to prevent spread of epilepsy) saw a picture of a snowy winter scene in his left visual field (right hemisphere) and a picture of a chicken claw in his right visual field (left hemisphere). When asked to match what he saw to a set of pictures, the left hand (right hemisphere) picked a snow shovel and the right hand (left hemisphere) picked a chicken. When asked to VERBALLY explain the two choices, the speaking left hemisphere said:

"The chicken claw goes with the chicken. The reason you need a shovel is to clean out the chicken shed."

- Gazzaniga postulates the LEFT hemisphere acts as the **interpreter** that explains behavior and experience. When the LEFT hemisphere interpreter saw the left hand pointing to the shovel, it had to create an explanation based on what it knew.

LEFT/RIGHT: Split Brain But Still One Mind?

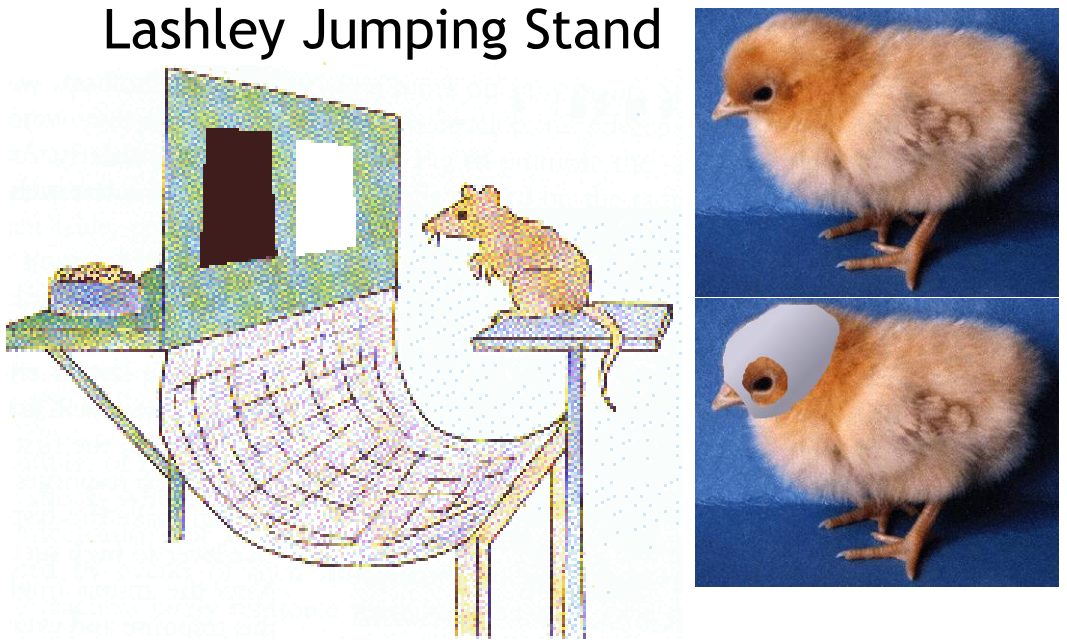
Split Brain Patients CAN:

- **Verbally** state (LH) **race** of face shown to LVF/RH with **95%** accuracy
- **Verbally** state (LH) **gender** of face shown to LVF/RH with **100%** accuracy
- Use **either hand** to indicate whether numbers in LVF and RVF are both odd or both even with **70%** accuracy (50% is chance level).
- Use **either hand** to indicate which of two numbers (one in LVF, other in RVF) is higher with **95%** accuracy

LVF, RVF = left, right visual field; LH, RH = left, right hemisphere
Sergent, J. 1990. Furtive incursions into bicameral minds. *Brain* 113:537–568.

Thus, at some level the verbal left hemisphere "interpreter" appears to "know" about things like race, gender, numerical size, etc., even though it cannot verbally state who it saw or what the number was. This suggests that the mind is not completely split in the split brain subjects.

LEFT/RIGHT: Chicks with One Eye Open

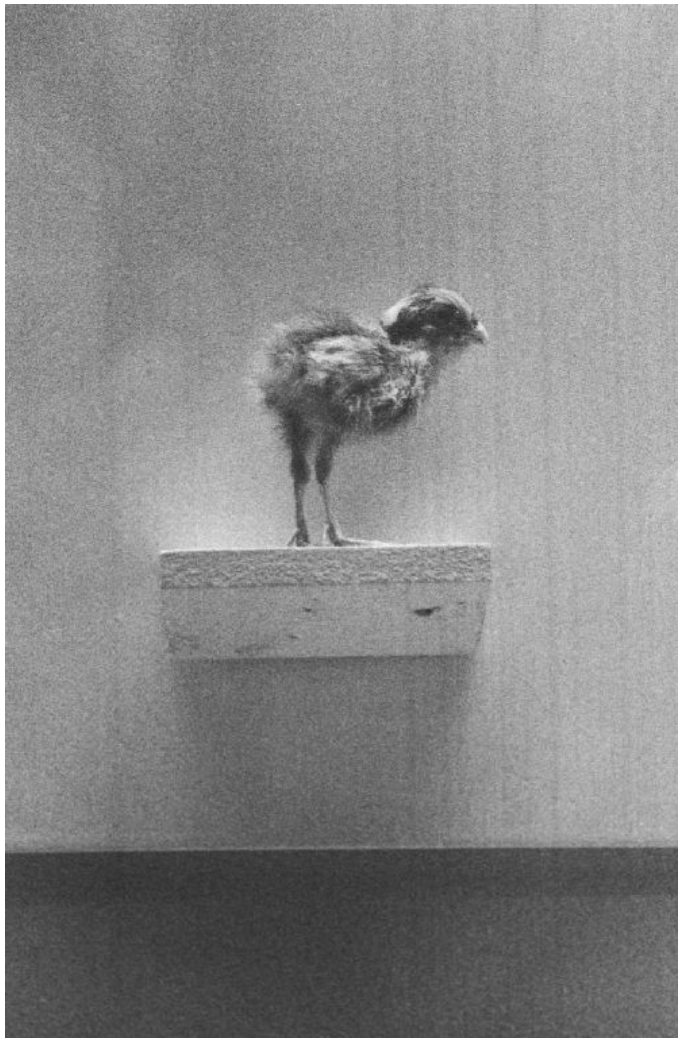


- In chickens there is complete crossing at optic chiasm, so left brain only gets input from right eye and *vice versa*. In addition, there is very little interconnection between left and right sides of brain, so chick is a natural "split-brain" subject.

- One week old baby chicks can easily learn to jump through white door or black door to get to food and other chicks.

- By covering one eye, chicks can learn to go through white door with left eye open and through black door with right eye open, similar to what is seen in Gazzaniga's split brain patients.

Two Gray Doors
What the ...?



Used with permission of Jessica Neafsey

Jill Bolte Taylor: Stroke and Left/Right Brain

http://www.ted.com/talks/view/id/229

Evidence Based Neurology 2010
Dr. Michael Schneck

Goals

- To review a clinical case scenario involving possible **cerebrovascular symtoms** and use your knowledge of anatomy and physiology to make **a clinical decision** about whether or not you should recommend a **Carotid Endarterectomy (CEA)** treatment based on the **medical literature**.

The Relevant Medical Literature

These papers are available on the LUMEN Medical Neuroscience course website EBN link:
`http://www.lumen.luc.edu/lumen/meded/Neuro/`

Required

- NASCET Collaborators. Beneficial effect of carotid endarterectomy in symptomatic patients with high grade stenosis. *N Engl J Med* 325:445-453, 1991.
- NASCET collaborative Group. The final results of the NASCET trial. *N Engl J Med* 339:1415-25, 1998.
- ACAS Study Group. Carotid endarterectomy for patients with asymptomatic internal carotid artery stenosis. *JAMA* 273: 1421-28, 1995.

Optional

- ECST Collaborative Group. (European equivalent of NASCET) *Lancet* 351:1379-1387, 1998.
- Halliday et al. (European equivalent of ACAS) *Lancet* 363:1491-1502, 2004.
- Chaturvedi *et al.* An evidence-based review Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology*65:794801, 2005.

The Hierarchy of Evidence

- Meta-Analysis
- Systematic Review (Chaturvedi et al., 2005)
- Randomized Controlled Trials (ACAS, NASCET, and European trials)
- Cohort Studies
- Case-Control Studies
- Case Series
- Case Reports
- Basic Science/Animal Research

Limits of the studies

- Studies are old
  - Not clear if data applies to stenting vs surgery
    - New technologies as well
  - Benefits of modern medical therapy may change the risk benefit profile
- Not generalizable
  - May not apply to community
    - Surgeons were selected
    - Neurological oversight in studies
  - Defined inclusions/exclusions
    - i.e., older patients excluded
    - Patients with atrial fibrillation, high risk surgery, other ailments

CASE SCENARIO

- A 79 year old woman presented to her primary physician with complaints of **visual blurring** starting that morning. She thought it was on the left side.
- No other neurological abnormalities were found on exam.
- Her medical history included well-controlled hypertension and hyperlipidemia with no other medical issues.
- She was sent for a CT scan that was unremarkable and a carotid ultrasound.
- The ultrasound described 50-74% carotid stenosis on the left side and $>$75% stenosis on the right side.
- She was also seen by an ophthalmologist.

- **What is the severity of her stenosis on the left side, based on the literature?**
- **What is the severity of her stenosis on the right side, based on the literature?**

Three Variations

- Assume the following three variations for analysis of your case in terms of whether these symptoms are **symptomatic** or **asymptomatic** of carotid artery disease with **moderate or severe stenosis** as defined in the medical literature.
  1. The ophthalmology exam revealed a left retinal artery infarct (ophthalmic a. "stroke" of the eye).
     - **Symptomatic or asymptomatic of carotid artery disease?**
     - **Is there relevant moderate or severe stenosis?**
     - **What study supports this conclusion?**
  2. Alternatively, the ophthalmology exam revealed a left visual field cut in both the right and left eyes (possible occipital lobe infarct).
     - **Symptomatic or asymptomatic of carotid artery disease?**
     - **Is there relevant moderate or severe stenosis?**
     - **What study supports this conclusion?**
  3. Other alternative: the exam revealed a 'macular hole' in the left eye (non-neurologic cause of blurring).
     - **Symptomatic or asymptomatic of carotid artery disease?**
     - **Is there relevant moderate or severe stenosis?**
     - **What study supports this conclusion?**

Other important factors to consider in your recommendation

- Sex
- Age
- Type of event
- Other comorbidities
- Which surgeon? How experienced? What hospital?

Your Group's Recommendations

Variation	Grade of Relevant Stenosis?	Symptomatic? Why?	Any Other Relevant Patient Variables?	CEA or not? Supporting Data? Reference?	Other Factors?
1					
2					
3					

Dr. Schneck's Recommendations

Variation	Grade of Relevant Stenosis?	Symptomatic? Why?	Any Other Relevant Patient Variables?	CEA or not? Supporting Data? Reference?	Other Factors?
1					
2					
3					

Evidence-Based Neurology

Application of Clinical trials literature with clinical-anatomic correlations

Michael J. Schneck, MD
Associate Professor of Neurology and Neurosurgery

Goals Of This Module

- To review an abbreviated clinical case scenario and ask you to use your knowledge of anatomy, physiology etc to make a clinical decision based on the literature
- To review how to understand that literature, its strengths and weaknesses, in particular disease states.

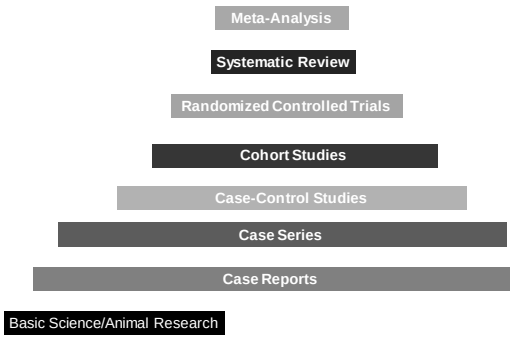
What is Evidence-Based Medicine?

- See a patient
- Ask a question
- Seek the best evidence for that question
- Appraise that evidence
- Apply the evidence
- Monitor the change

Types of Studies

- Primary
  - Observational
    - Cohort studies
      - Retrospective cohort with prospective follow-up
      - Prospective cohort
    - Case control studies
    - Case series/case reports
  - Experimental
    - Randomized controlled trials (RCT)
    - Other clinical trials
- Secondary
  - Meta-analysis
  - Systematic reviews
  - Practice guidelines
  - Consensus reports
  - Decision analyses
  - Commentaries and topic reviews

The Hierarchy of Evidence



How to Evaluate a Question:

Clinical Issue	Best Type of Study

Evidence-Based Medicine

"A system of belief that requires prospectively collected objective evidence of everything except its own utility."

- Proposed Alternative Approach
  - Class 0 — Things I believe
  - Class 0 a — Things I believe despite the available data
  - Class 1 — Randomized controlled clinical trials that agree with what I believe
  - Class 2 — Other prospectively collected data
  - Class 3 — Expert Opinion
  - Class 4 — Randomized controlled clinical trials that don't agree with what I believe
  - Class 5 — What you believe that I don't

Dr. Thomas Bleck, University of Virginia

National Health and Medical Research Council EBM Levels

Grade	Definition
I	Evidence obtained from a systematic review of all relevant randomised controlled trials.
II	Evidence obtained from at least one properly-designed randomised controlled trial.
III – 1	Evidence obtained from well-designed pseudo-randomised controlled trials (alternate allocation or some other method).
III – 2	Evidence obtained from comparative studies with concurrent controls and allocation not randomised (cohort studies), case-control analytic studies, or interrupted time series with a control group.
II – 3	Evidence obtained from comparative studies with historical control, two or more single-arm studies, or interrupted time series without a parallel control group.
IV	Evidence obtained from case series, either post-test or pre-test and post-test.

Oxford Centre for Evidence-based Medicine Levels of Evidence (May 2001)

Level	Therapy/Prevention, Aetiology/Harm	Prognosis	Diagnosis	Differential diagnosis/symptom prevalence study	Economic and decision analyses
1a	homogeneity*	homogeneity* CDR†	homogeneity* CDR†	homogeneity*	homogeneity*
1b	Confidence Interval‡	CDR†	good††† CDR†		
1c	All or none§		Absolute SpPins and SnNouts††		

Oxford Centre for Evidence-based Medicine Levels of Evidence (May 2001)

	homogeneity*	homogeneity*	homogeneity*	homogeneity*	homogeneity*
		CDR†	good††† CDR†		

Oxford Centre for Evidence-based Medicine Levels of Evidence (May 2001)

	homogeneity*		homogeneity*	homogeneity*	homogeneity*
	poor quality cohort and case-control studies§§	poor quality prognostic cohort studies***			

Hills Criteria of Causation

(Causality and Strength of Association)

1. Temporal relationship: Exposure always precedes the outcome. If factor "A" is believed to cause a disease, then it is clear that factor "A" must necessarily always precede the occurrence of the disease. This is the only absolutely essential criterion.
2. Strength of association (statistical correlation): The stronger the association, the more likely it is that the relation is causal.
3. Dose-response relationship: An increasing amount of exposure increases the risk. If a dose-response relationship is present, it is strong evidence for a causal relationship. However, as with specificity, the absence of a dose-response relationship does not rule out a causal relationship.

Hills Criteria of Causation

(Causality and Strength of Association)

4. Consistency: The association is consistent when results are replicated in studies in different settings using different methods. That is, if a relationship is causal, we would expect to find it consistently in different studies and in different populations.
5. Plausibility: The association agrees with currently accepted understanding of pathological processes. However, studies that disagree with established understanding of biological processes may force a reevaluation of accepted beliefs.
6. Consideration of alternate explanations: In judging whether a reported association is causal, it is necessary to determine the extent to which researchers have taken other possible explanations into account and have effectively ruled out such alternate explanations.

Hills Criteria of Causation

(Causality and Strength of Association)

7. Experiment: The condition can be altered (prevented or ameliorated) by an appropriate experimental regimen.
8. Specificity: when a single putative cause produces a specific effect. When specificity of an association is found, it provides additional support for a causal relationship. However, absence of specificity in no way negates a causal relationship.
9. Coherence: The association should be compatible with existing theory and knowledge. In other words, it is necessary to evaluate claims of causality within the context of the current state of knowledge within a given field. As with the issue of plausibility, research that disagrees with established theory and knowledge are not automatically false. They may, in fact, force a reconsideration of accepted beliefs and principles. Thomas Kuhn has referred to such changes in accepted theories as "Paradigm Shifts".

The CONSORT Statement

http://www.consort-statement.org

- The CONSORT Statement is intended to improve the reporting of a randomized controlled trial (RCT), enabling readers to understand a trial's design, conduct, analysis and interpretation, and to assess the validity of its results. It emphasizes that this can only be achieved through complete transparency from authors.
- Investigators and editors developed and revised the CONSORT (CONsolidated Standards of Reporting Trials) Statement to help authors improve reporting of two-parallel design RCTs by using a checklist and flow diagram. Extensions of the CONSORT Statement have been developed for other types of study designs, interventions and data.
- The STROBE (Strengthening of Observational Studies in Epidemiology) Statement extends the CONSORT concept to observational/epidemiologic studies- see Annals of Internal Medicine, PLOS Medicine, or Epidemiology Websites

CONSORT Statement 2001 - Checklist

Items to include when reporting a randomized trial

PAPER SECTION And topic	Item	Descriptor	Reported on Page #
TITLE & ABSTRACT	1	How participants were allocated to interventions (e.g., "random allocation", "randomized", or "randomly assigned").	
INTRODUCTION Background	2	Scientific background and explanation of rationale.	
METHODS Participants	3	Eligibility criteria for participants and the settings and locations where the data were collected	
Interventions	4	Precise details of the interventions intended for each group and how and when they were actually administered	
Objectives	5	Specific objectives and hypotheses	
Outcomes	6	Clearly defined primary and secondary outcome measures and, when applicable, any methods used to enhance the quality of measurements (e.g., multiple observations, training of assessors).	
Sample size	7	How sample size was determined and, when applicable, explanation of any interim analyses and stopping rules.	
Randomization – Sequence generation	8	Method used to generate the random allocation sequence, including details of any restrictions (e.g., blocking, stratification)	
Randomization – Allocation concealment Randomization – Implementation	9 10	Method used to implement the random allocation sequence (e.g., numbered containers or central telephone), clarifying whether the sequence was concealed until interventions were assigned. Who generated the allocation sequence, who enrolled participants, and who assigned participants to their groups.	
Blinding (masking)	11	Whether or not participants, those administering the interventions, and those assessing the outcomes were blinded to group assignment. If done, how the success of blinding was evaluated.	
Statistical methods	12	Statistical methods used to compare groups for primary outcome(s); Methods for additional analyses, such as subgroup analyses and adjusted analyses	
RESULTS Participant flow	13	Flow of participants through each stage (a diagram is strongly recommended). Specifically, for each group, report the numbers of participants randomly assigned, receiving intended treatment, completing the study protocol, and analyzed for the primary outcome. Describe protocol deviations from study as planned, together with reasons.	
Recruitment	14	Dates defining the periods of recruitment and follow-up.	
Baseline data Numbers analyzed	15 16	Baseline demographic and clinical characteristics of each group Number of participants (denominator) in each group included in each analysis and whether the analysis was by "intention-to-treat". State the results in absolute numbers when feasible (e.g., 10/20, not 50%).	
Outcomes and estimation	17	For each primary and secondary outcome, a summary of results for each group, and the estimates' effect size and its precision (e.g., 95% confidence interval).	
Ancillary analyses	18	Address multiplicity by reporting any other analyses performed, including subgroup analyses and adjusted analyses, indicating those pre-specified and those exploratory.	
Adverse events	19	All important adverse events or side effects in each intervention group.	
DISCUSSION Interpretation	20	Interpretation of the results, taking into account study hypotheses, sources of potential bias or imprecision and the dangers associated with multiplicity of analyses and outcomes.	
Generalizability	21	Generalizability (external validity) of the trial findings.	
Overall evidence	22	General interpretation of the results in the context of current evidence.	

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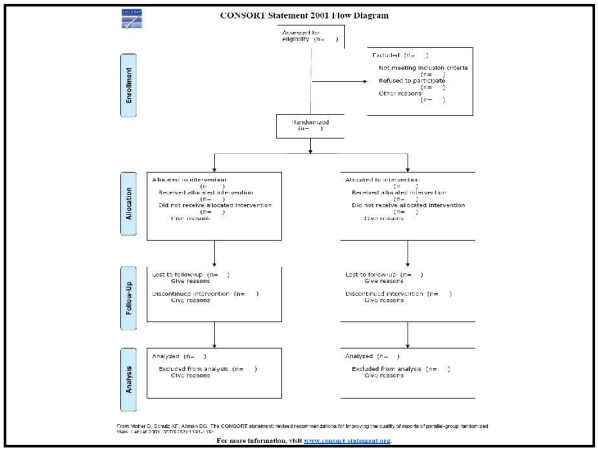
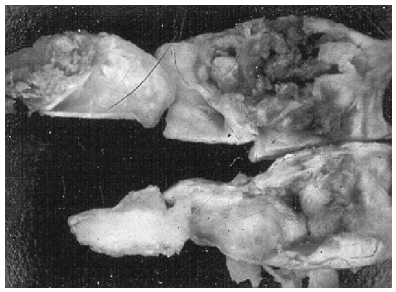


Case Scenario: Carotid Artery Disease



A surgical endarterectomy specimen!

Case Scenario

- A 79 year old **woman** presented to her primary physician with complaints of **visual blurring** starting that morning. She thought it was on the **left** side.
- No other neurological abnormalities were found on exam.
- Her medical history included well-controlled hypertension and hyperlipidemia with no other medical issues.
- She was sent for a CT scan that was unremarkable and a carotid ultrasound. **The ultrasound described 50-74% carotid stenosis on the left side and >75% stenosis on the right side.**
- She was also seen by an ophthalmologist.

Case Scenario

- Assume the following alternatives for analysis of your case
  1. The ophthalmology exam revealed a **left retinal artery infarct** (ophthalmic artery 'stroke' of the eye)
  2. Alternatively, the ophthalmology exam revealed a left visual field cut in the right and left eyes (**possible occipital lobe infarct)**
  3. Other alternative: the exam revealed a 'macular hole' in the left eye. **(non-neurologic cause of blurring**)

Literature References

1. ***NASCET Collaborators. Beneficial effect of carotid endarterectomy in symptomatic patients with high grade stenosis. N Engl J Med; 1991; 325: 445-453***
2. ***NASCET collaborative Group. The final results of the NASCET trial. N Engl J Med 1998; 339:1415-25***
3. ***ACAS Study Group. Carotid endarterectomy for patients with asymptomatic internal carotid artery stenosis JAMA 1995; 273: 1421-28***
4. **ECST Collaborative Group. (European equivalent of NASCET) Lancet 1998; 351: 1379-1387**
5. **Halliday et al (European equivalent of ACAS) Lancet 2004; 363: 1491-1502**

Literature References

- Review papers for this exercise:
  1. ***Chaturvedi S et al Carotid endarterectomy: an evidence based review. Neurology 2005; 65: 794-801***
  2. **Alamowitch S et al. The risk and benefit of carotid endarterecomy in women with symptomatic internal carotid artery disease Stroke 2005; 36: 27-31**
  3. **Rothwell PM, et al. Analysis of pooled data from the randomized controlled trials of endarterectomy for symptomatic carotid stenosis. Lancet 2003: 361: 107-116**

Literature References

Additional readings for interest:

- Yadav JS. Wholey MH. Kuntz RE. et al Cutlip DE. Firth BG. Ouriel K. Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy Investigators. Protected carotid-artery stenting versus endarterectomy in high-risk patients.*New England Journal of Medicine. 351(15):1493-501, 2004.*
- Mas JL, Chatellier G, Beyssen B, et al; EVA-3S Investigators. Endarterectomy versus stenting in patients with symptomatic severe carotid stenosis. *N Engl J Med.* 2006;355:1660–1671.
- SPACE Collaborative Group. 30 day results from the SPACE trial of stent-protected angioplasty versus carotid endarterectomy in symptomatic patients: a randomised non-inferiority trial*Lancet. 368(9543):1239-47, 2006*

Questions In Formulating Your Analysis

- What is the data for or against carotid endarterectomy in this patient for the various case scenario variations?
  - How does this correlate with your knowledge of neuroanatomy/vascular anatomy
- What is the quality of evidence to support your clinical decisions?
- What additional data, based on the literature, would you want before making your decision?