Neuropathology:

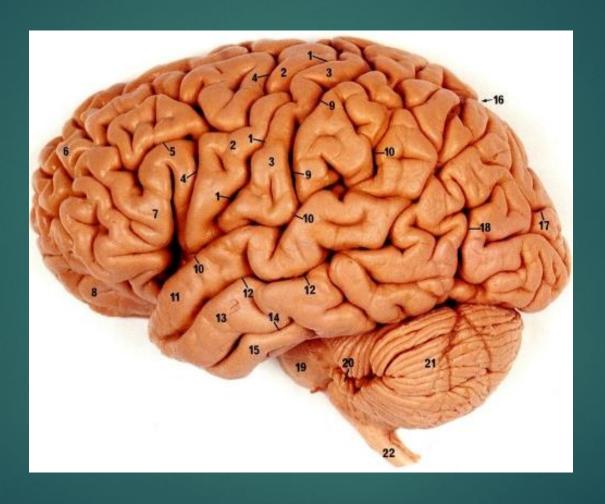
A visual alphabetic tour of what can go wrong with the brain

Charles J. Vella, PhD October 7, 2015

THANKS: FRANK NETTER, EVERETT AUSTIN

▶ 60 less for 90 minutes; ok for 2 hours

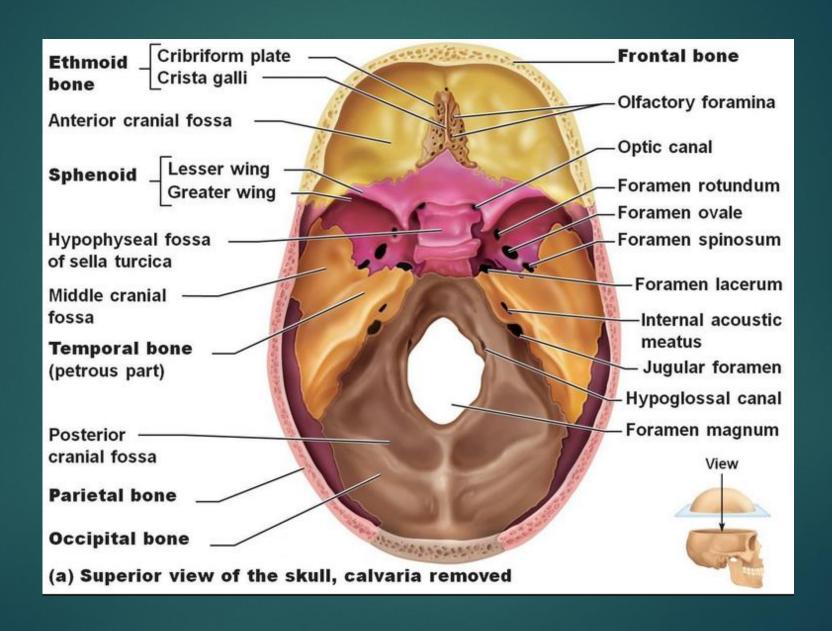
Normal Brain



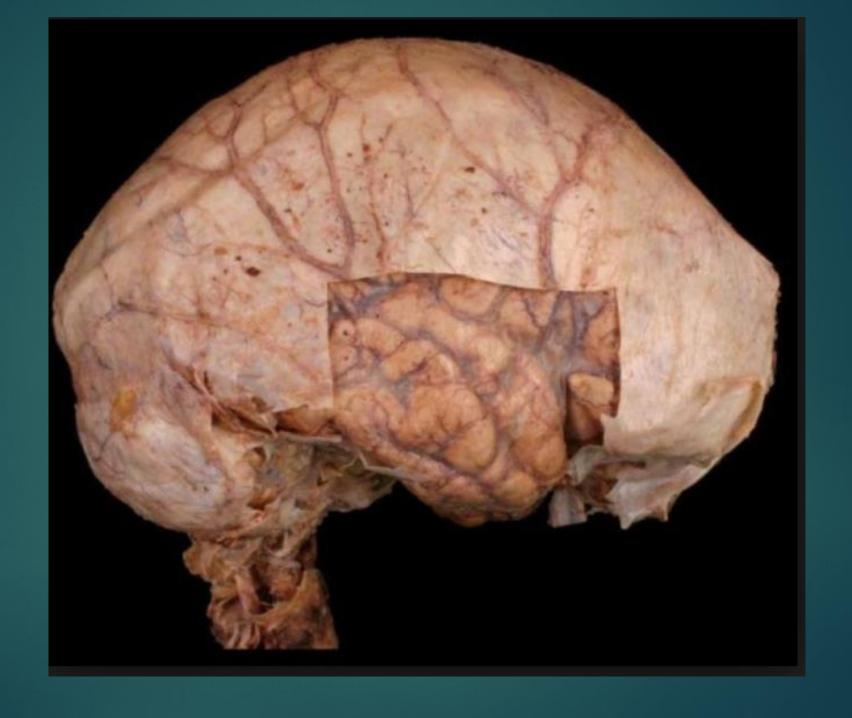
Medial View

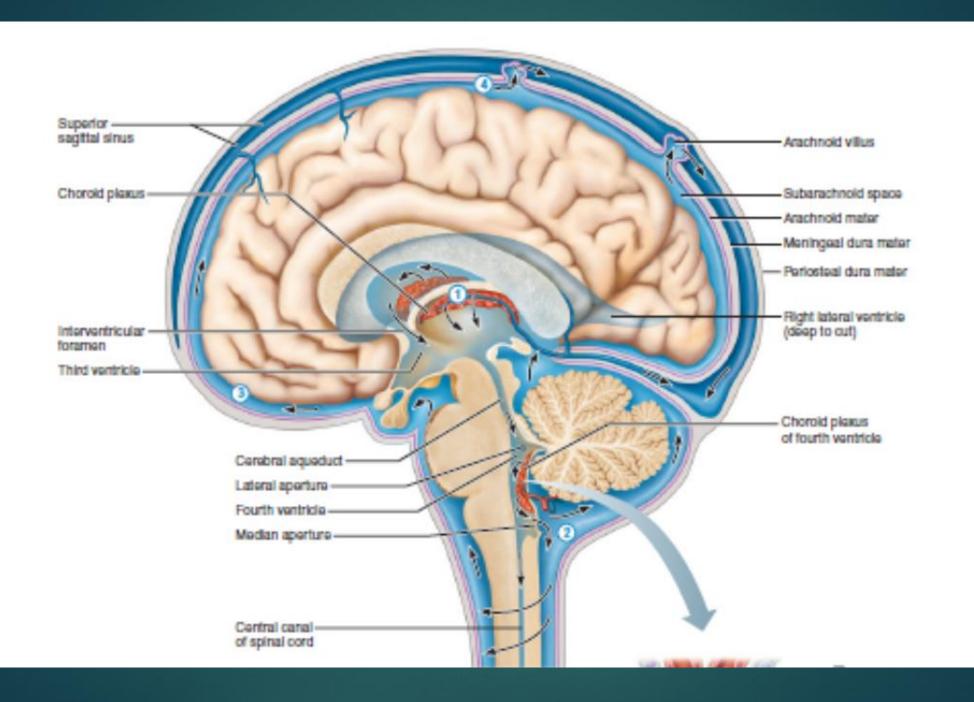


Anterior, Middle, Posterior Fossa

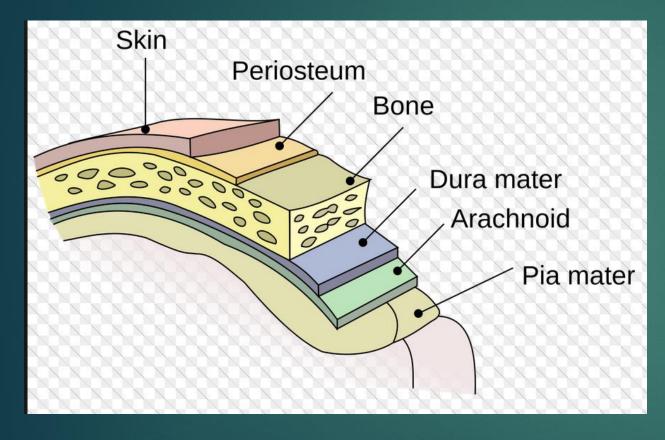


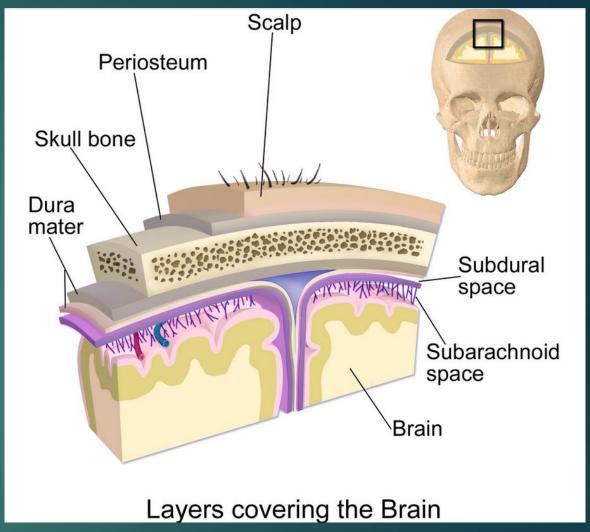
Dura



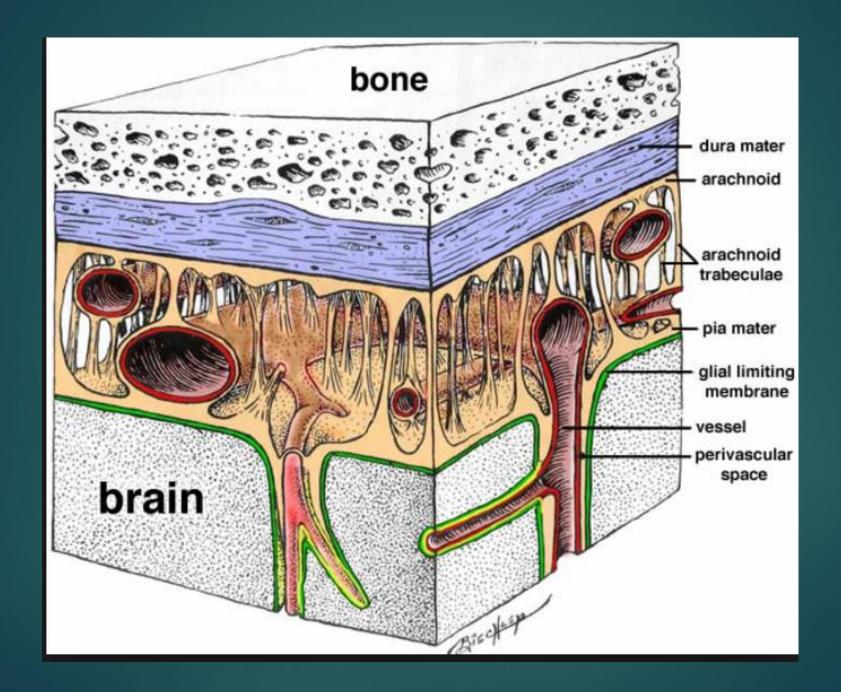


Dura: protection for your brain

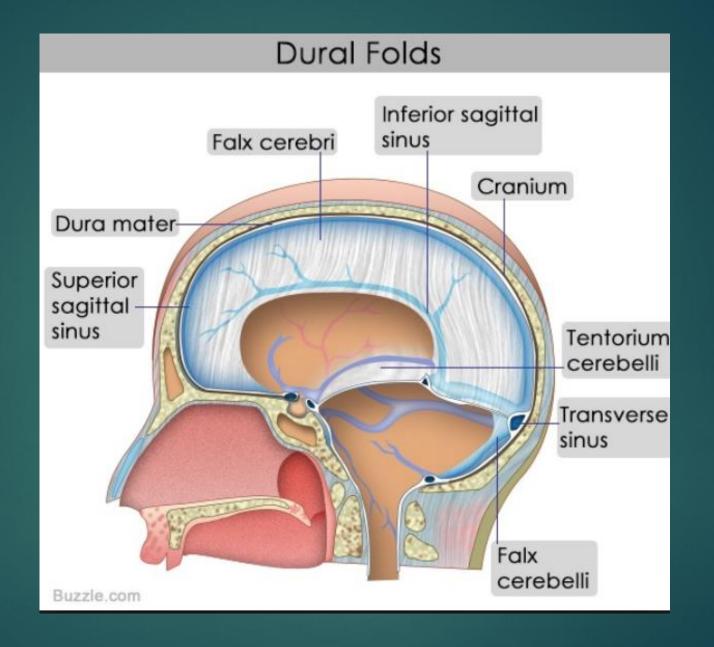




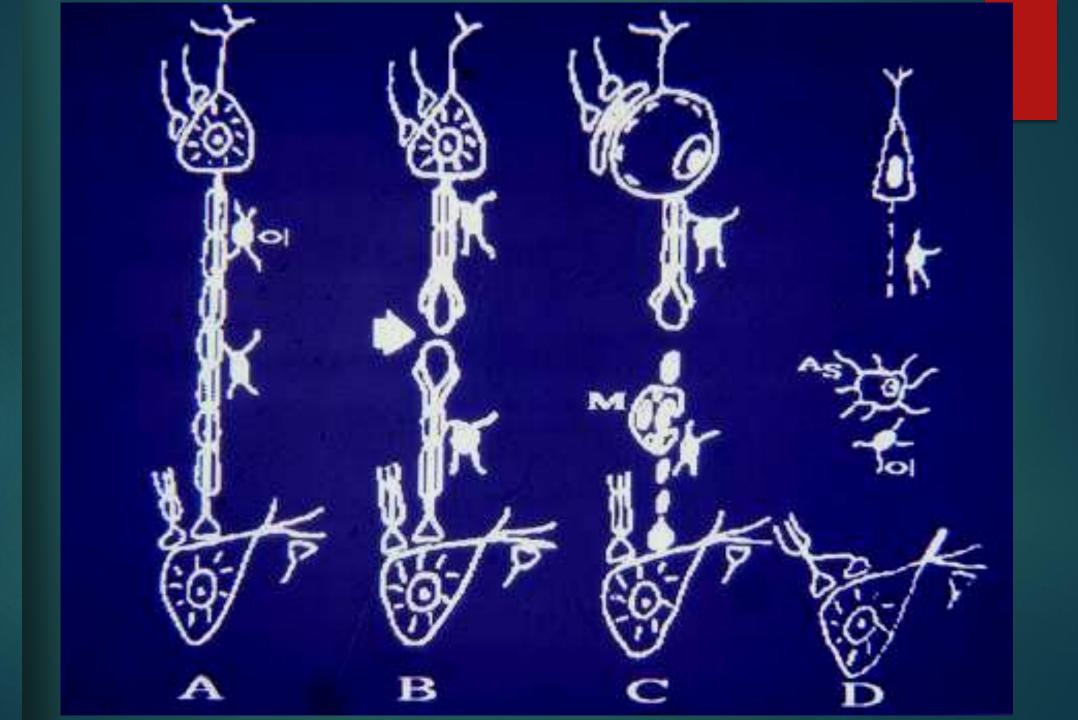
Dura

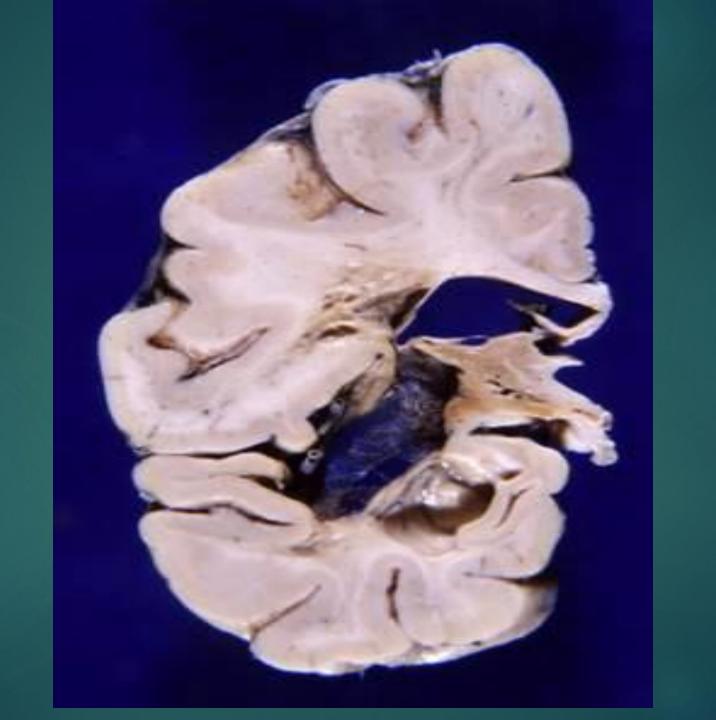


Dural Folds



Wallerian Degeneration



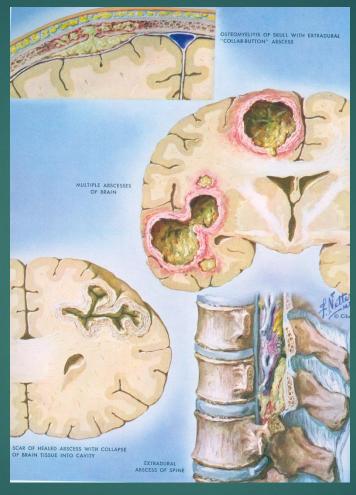


Cancer Tumors by Age

Age (years)	3–15	15–65	>65
Medulloblastoma	Pilocytic astrocytoma	Glioblastoma	Metastatic carcinoma
Pilocytic astrocytoma	Medulloblastoma	Anaplastic astrocytoma	Glioblastoma
Ependymoma	Ependymoma	Astrocytoma	Anaplastic astrocytoma
Choroid plexus tumours	Astrocytoma	Meningioma	Meningioma
Teratoma	Choroid plexus tumours	Pituitary tumours	Acoustic Schwannoma

CNS Tumors

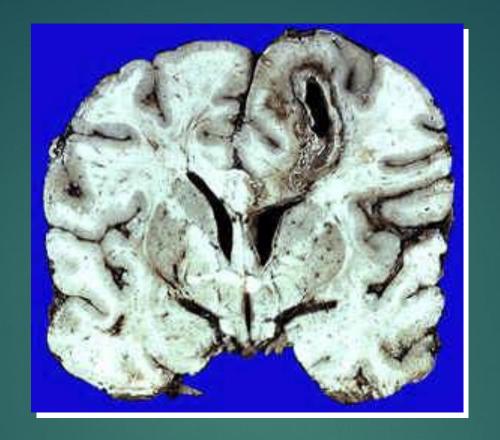
- Primary vs. metastatic
- Benign vs. malignant
- Focal vs. diffuse
- Above or below tentorum
- Not too common in adults
- About 20% of childhood malignancies
- Location is critical
- Cell type
 - None are of neuronal origin
 - Astocytoma, most
 - Oligodendrocytoma
 - Microgliomatosis
 - Ependymoma



Mortality – 20%

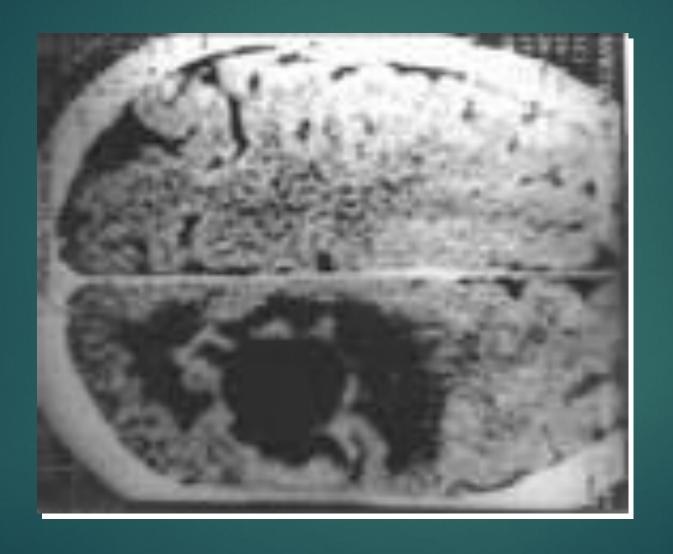
Morbidity with focal neurologic deficits or epilepsy (50%)

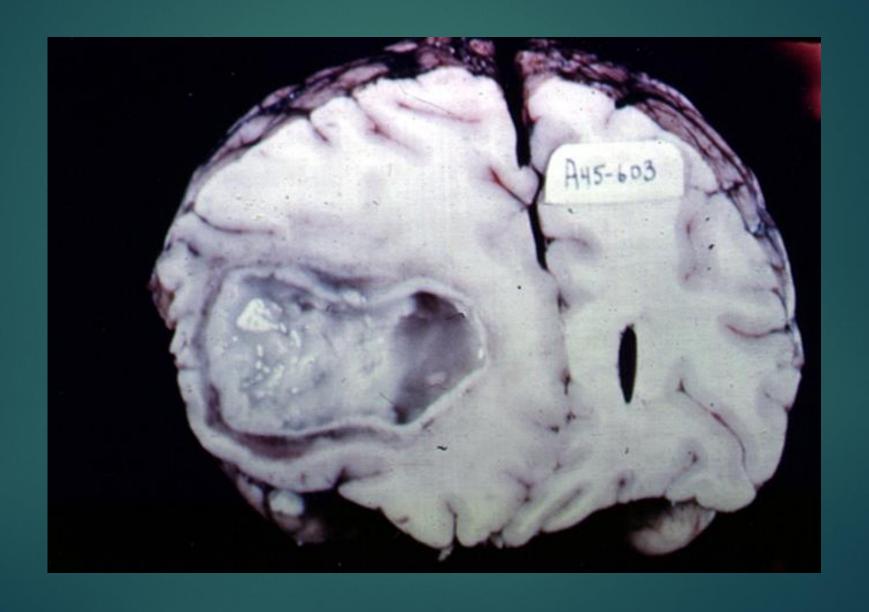
Need to surgically drain



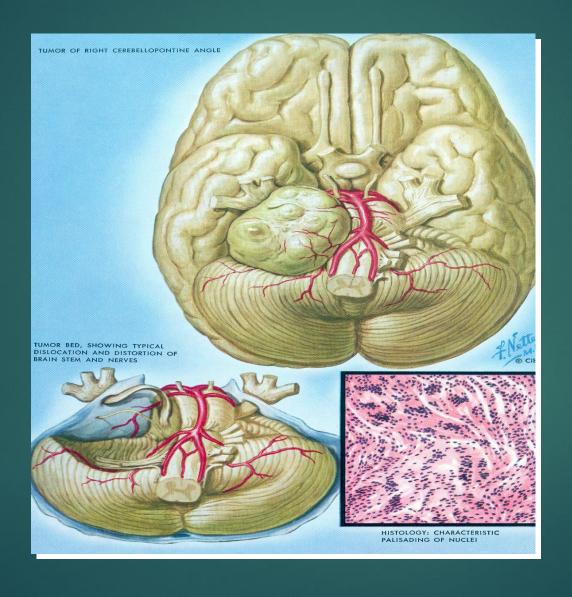
Etiology: *Streptococci milleri (most common) gram-bacilli, Staph. aureus, bacteriodes

Direct spread from paranasal sinuses (50%)

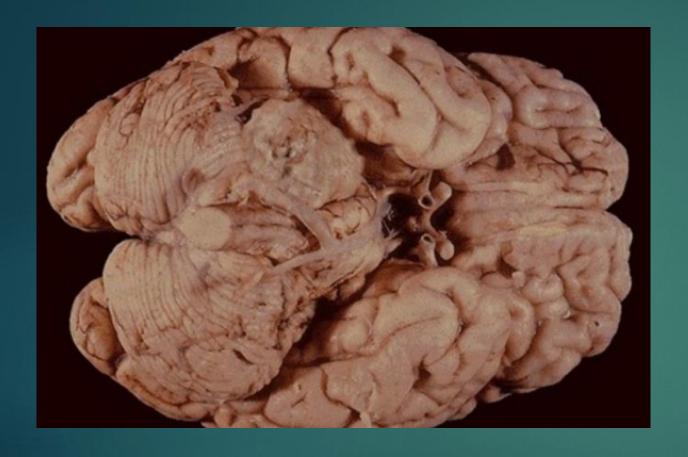


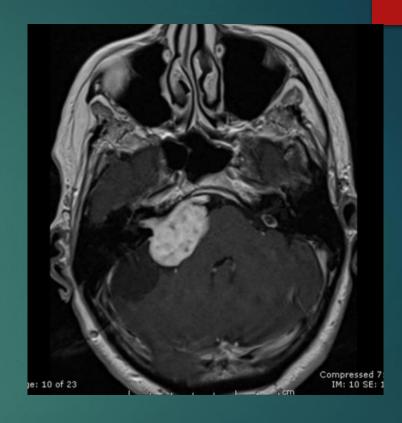


Acoustic Neuroma (tumor of a nerve)



Acoustic nerve Schwannoma



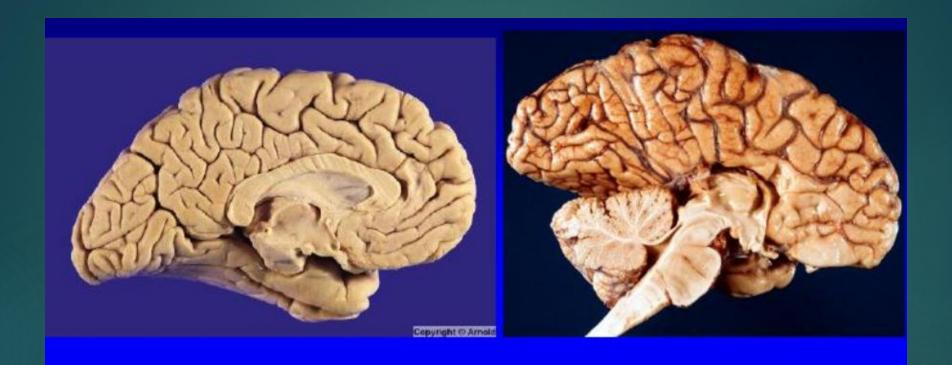


relatively common tumors that arise from the vestibulocochlear nerve (CN VIII). Bilateral acoustic schwannomas are strongly suggestive of neurofibromatosis type 2 (NF2).

What's missing?



Agenesis of Corpus Callosum

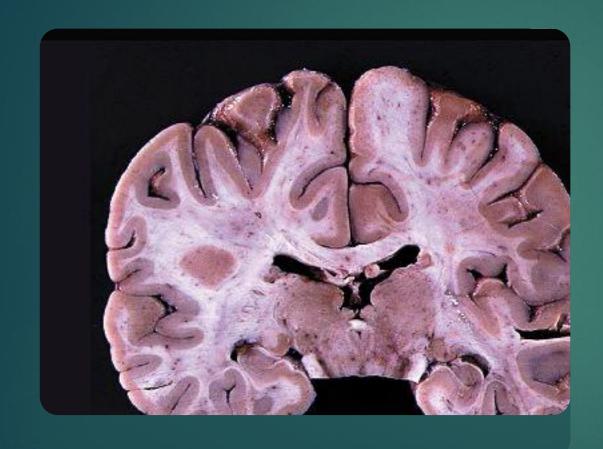


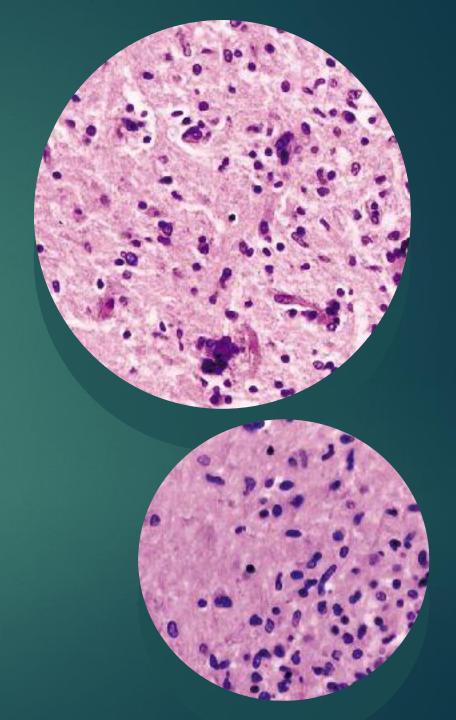
Forebrain anomaly: Agenesis of the corpus callosum.

Absence of white matter bundles connecting cerebral hemispheres.

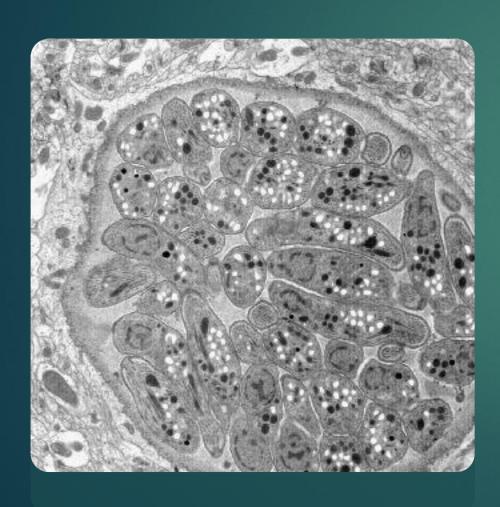
AIDS Dementia Complex: HIV

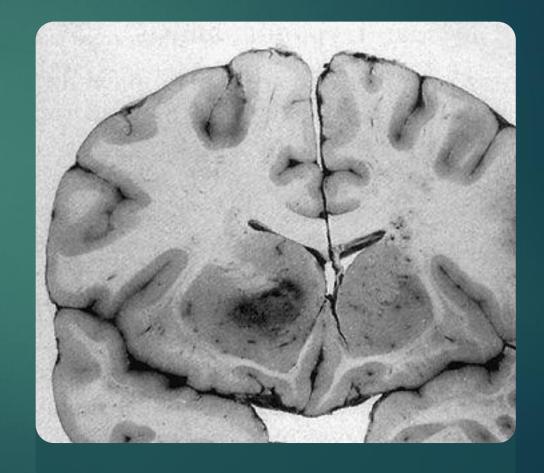




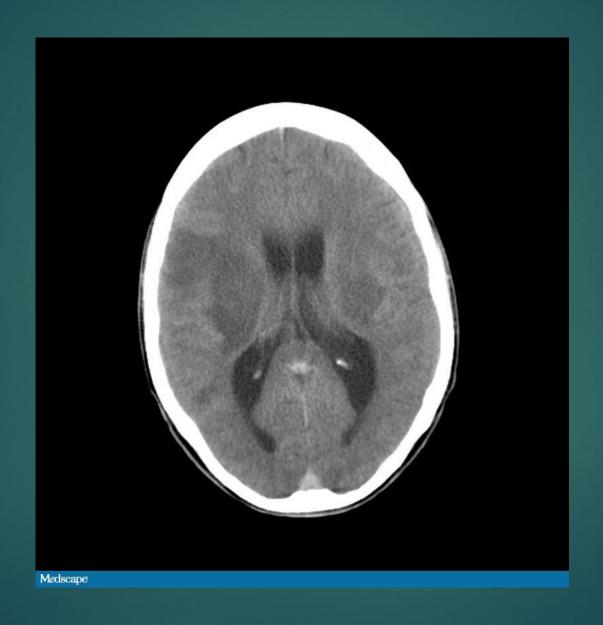


Toxoplasmosis

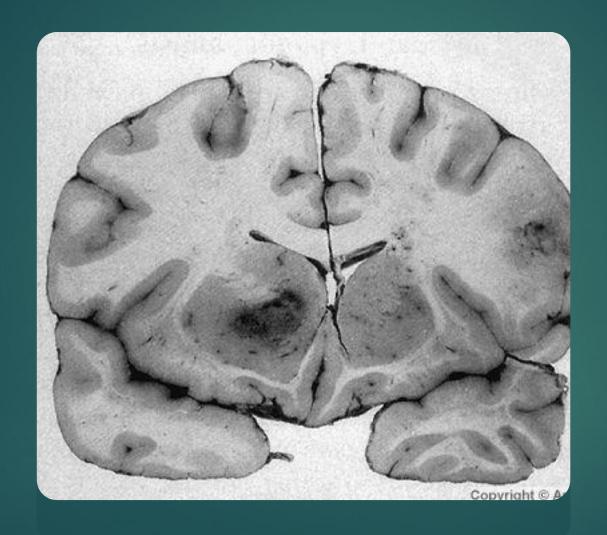




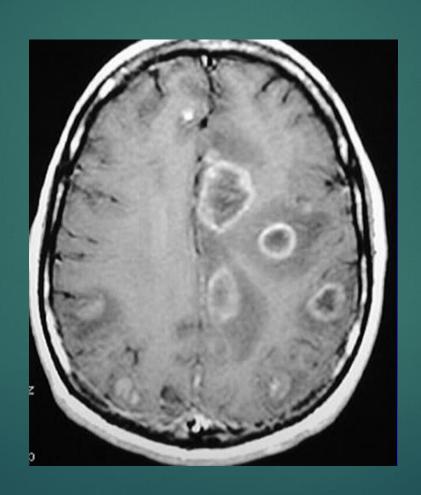
23 yo HIV Toxoplasmosis



HIV: Toxoplasmosis



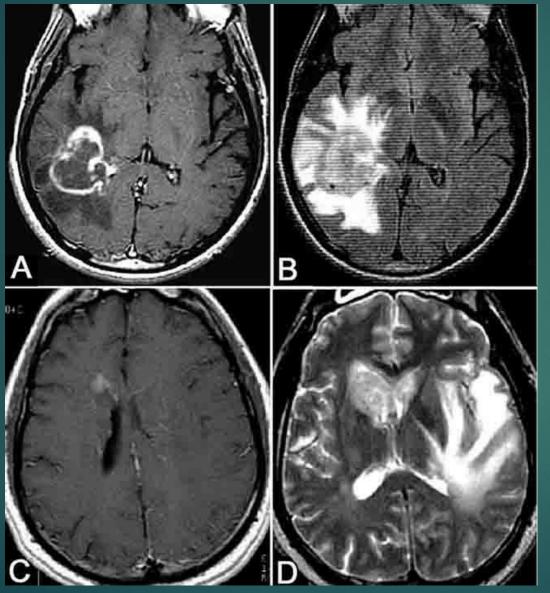
Toxoplasmosis



Parasites

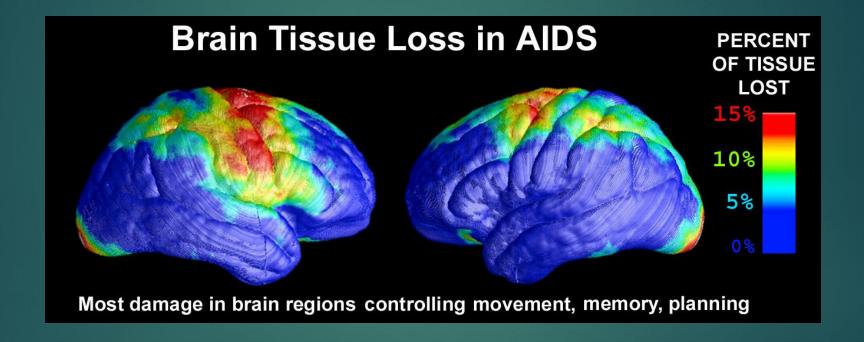
- Parasites that have been described to affect the central nervous system (CNS), either as the dominant or as a collateral feature, include
- ▶ Cestodes (Taenia solium (neurocysticerciasis), Echinococcus granulosus (cerebral cystic echinococcosis), E. multilocularis (cerebral alveolar echinococcosis), Spirometra mansoni (neurosparganosis)), nematodes (Toxocara canis and T. cati (neurotoxocariasis), Trichinella spiralis (neurotrichinelliasis), Angiostrongylus cantonensis and A. costaricensis (neuroangiostrongyliasis), Gnathostoma spinigerum (gnathostomiasis)), trematodes (Schistosoma mansoni (cerebral bilharziosis), Paragonimus westermani (neuroparagonimiasis)), or protozoa (Toxoplasma gondii (neurotoxoplasmosis), Acanthamoeba spp. or Balamuthia mandrillaris (granulomatous amoebic encephalitis), Naegleria (primary amoebic meningo-encephalitis), Entamoeba histolytica (brain abscess), Plasmodium falciparum (cerebral malaria), Trypanosoma brucei gambiense/rhodesiense (sleeping sickness) or Trypanosoma cruzi (cerebral Chagas disease)).
- ▶ Adults or larvae of helminths or protozoa enter the CNS and cause meningitis, encephalitis, ventriculitis, myelitis, ischemic stroke, bleeding, venous thrombosis or cerebral abscess, clinically manifesting as headache, epilepsy, weakness, cognitive decline, impaired consciousness, confusion, coma or focal neurological deficits.

CNS Lymphoma

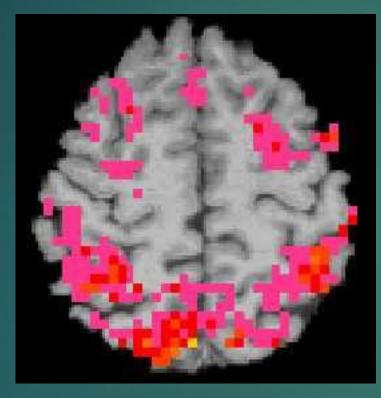


Mostly in patients with severe immunosuppression (typically patients with AIDS

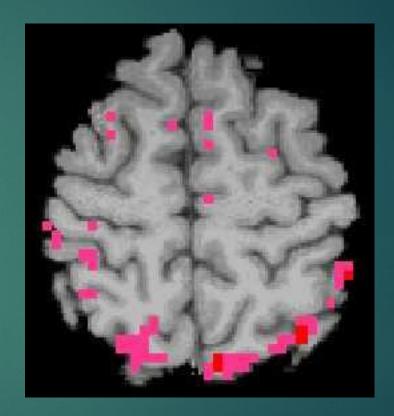
AIDS 2



Alcoholism 2: Lack of spatial WM activation

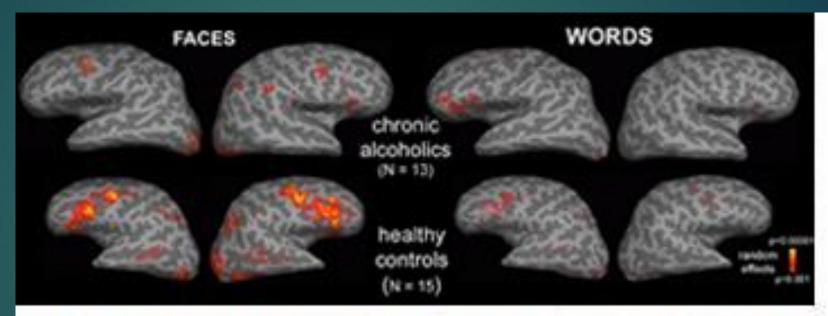


This shows a 20-year old female nondrinkers response to the spatial working memory task. Brain activation is shown in bright colors.



This shows an alcohol-dependent 20-year old female's response to the spatial working memory task. Brain activation is shown in bright colors.

Alcoholism 3: no bilateral frontal activation in deep encoding



This figure shows a comparison between the fMRI activations observed in chronic alcoholics (n=13) vs. healthy controls (n=15) during "deep" encoding of words and faces. The data were analyzed with a stringent random effect model. The most striking differences between the alcoholic patients and healthy controls were in prefrontal brain regions. Face stimuli in particular reliably evoked a bilateral prefrontal activation in healthy controls but not in the alcoholic group. The activation to words had a different pattern in both subject groups. As expected, these differences are particularly obvious in the "deep" encoding condition, as it evoked prefrontal activation.

Alcoholism: Atrophy due to Korsakoff's

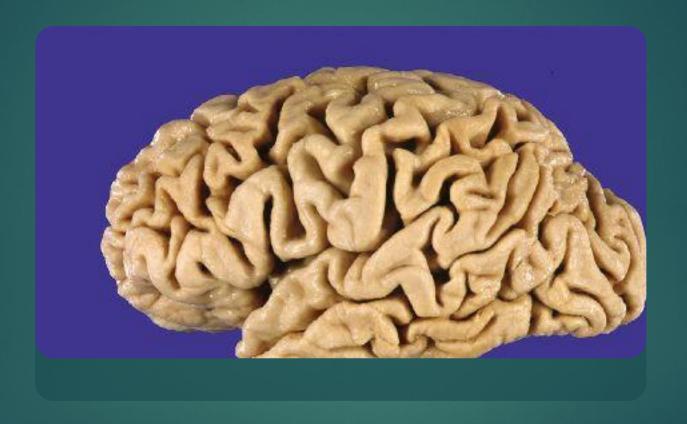


Cerebral atrophy and severe atrophy of mammillary bodies and thalami

Alzheimer's: atrophy

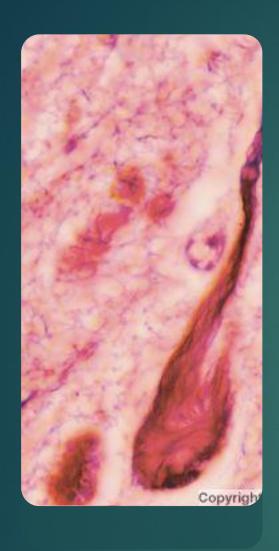


Cortical atrophy in Alzheimer disease

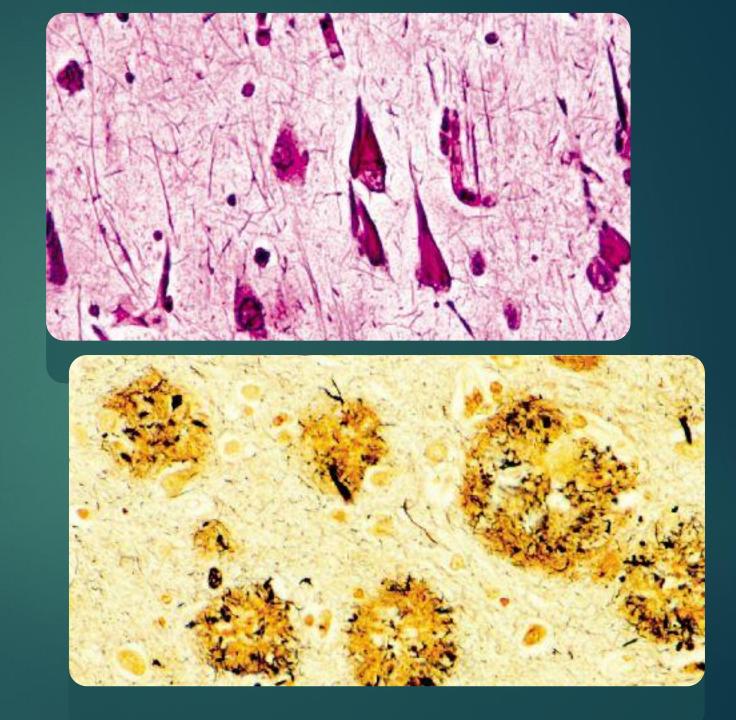


Hippocampal atrophy in Alzheimer's



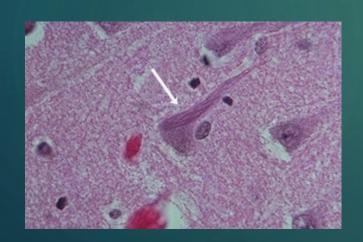


Alzheimer: tangles and plaques

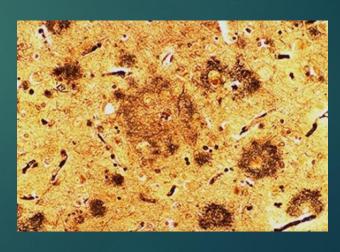




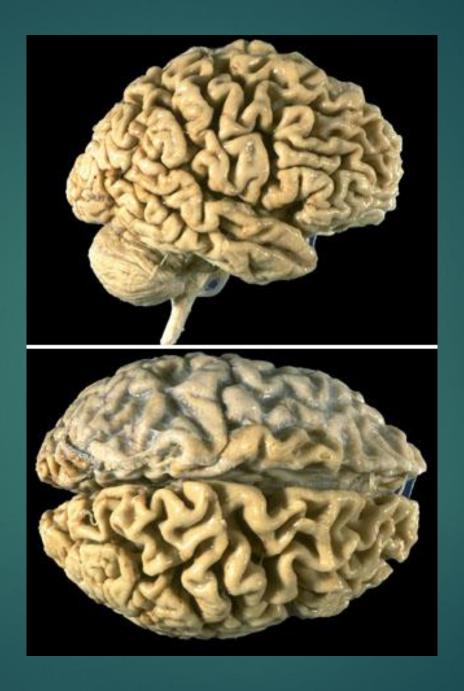




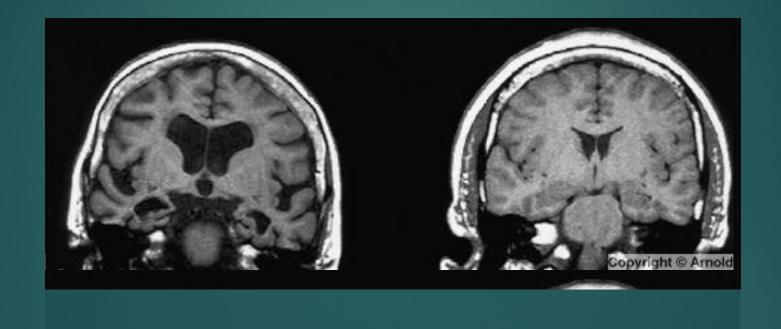
Alzheimer's



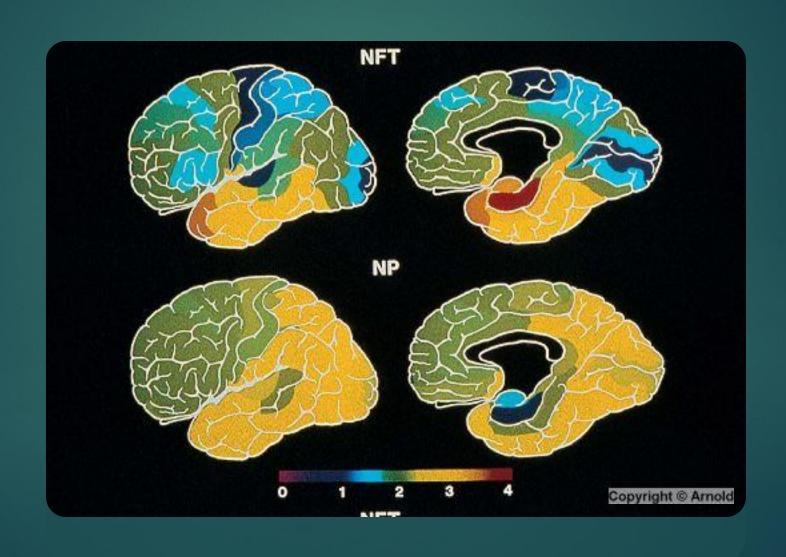
Alzheimer 2



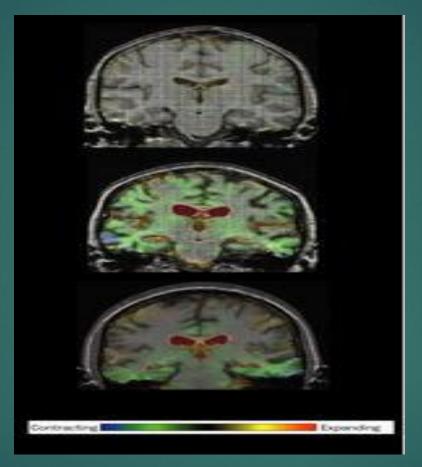
Alzheimer's vs. Control



Topography of NF Tangles and N Plaques in Alzheimer's



Alzheimer's vs. Frontal Dementia



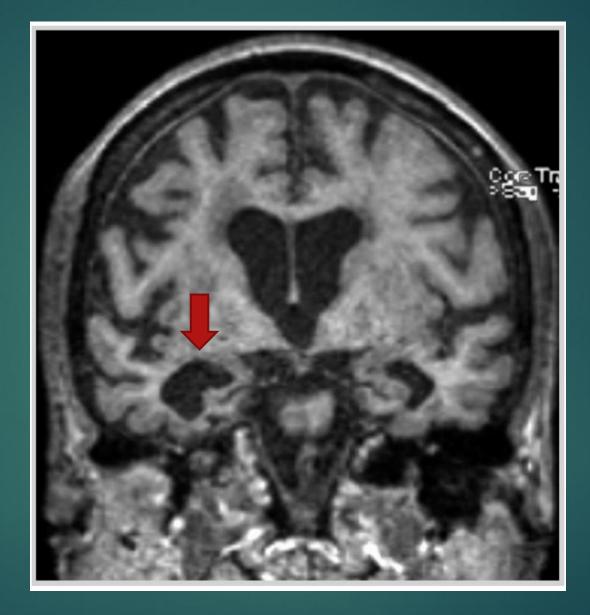
Normal

Alzheimer's

FTD

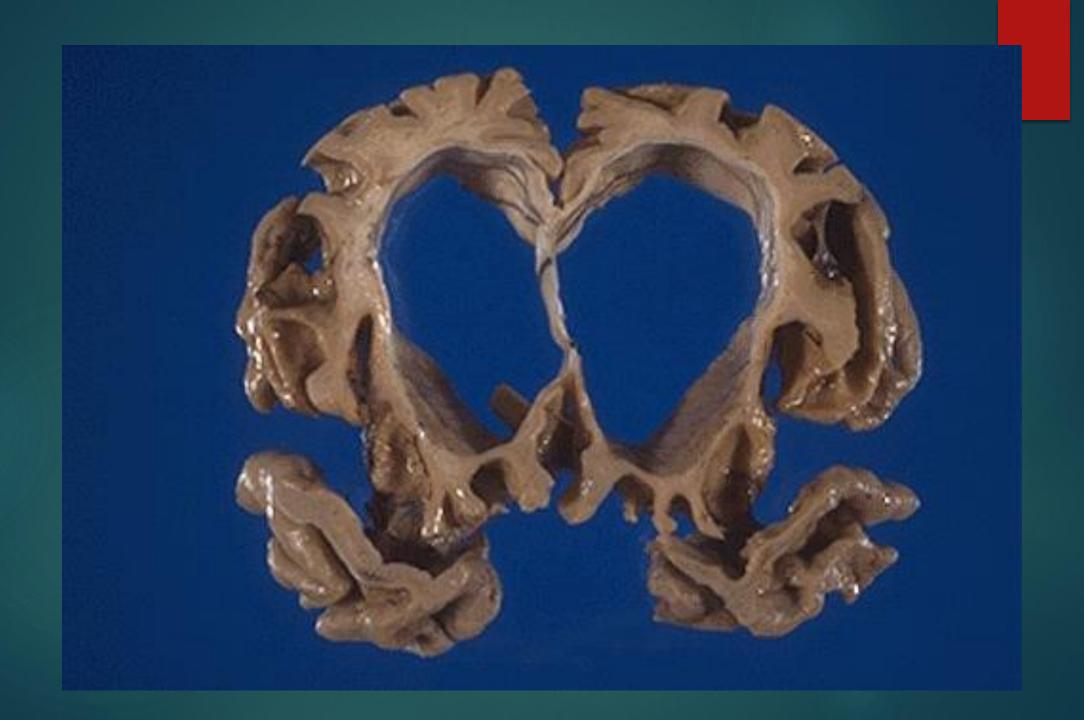
Top: Change over 11 months in healthy control. Middle: change over 14 months in an individual with Alzheimer's disease. Bottom: change over 15 months in an individual with frontotemporal dementia. Blue-Green = atrophy.

Alzheimer's



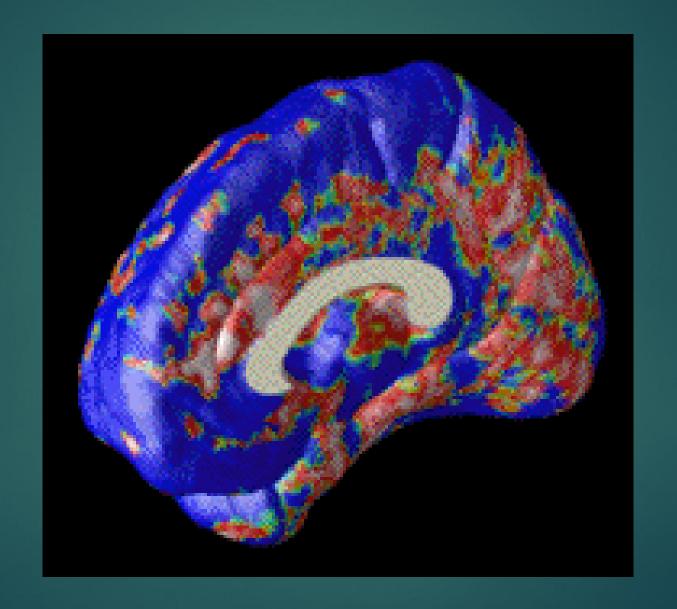
Note hippocampal reduction, R > L



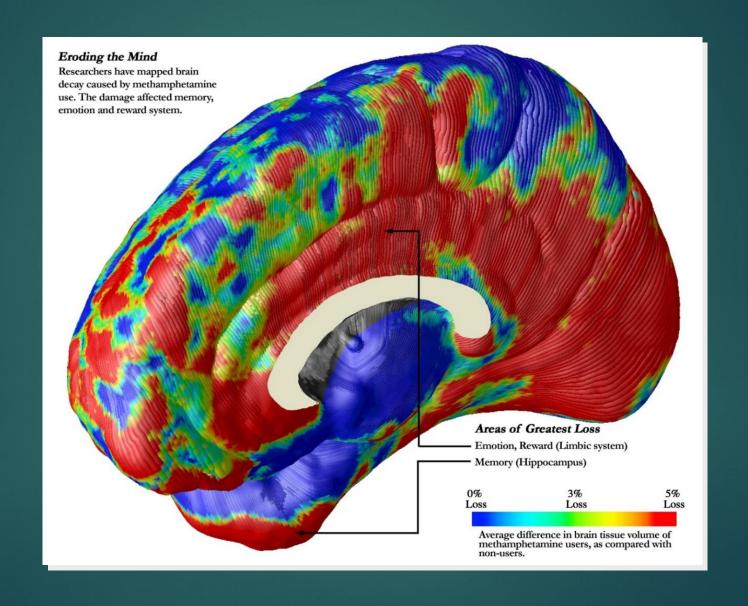




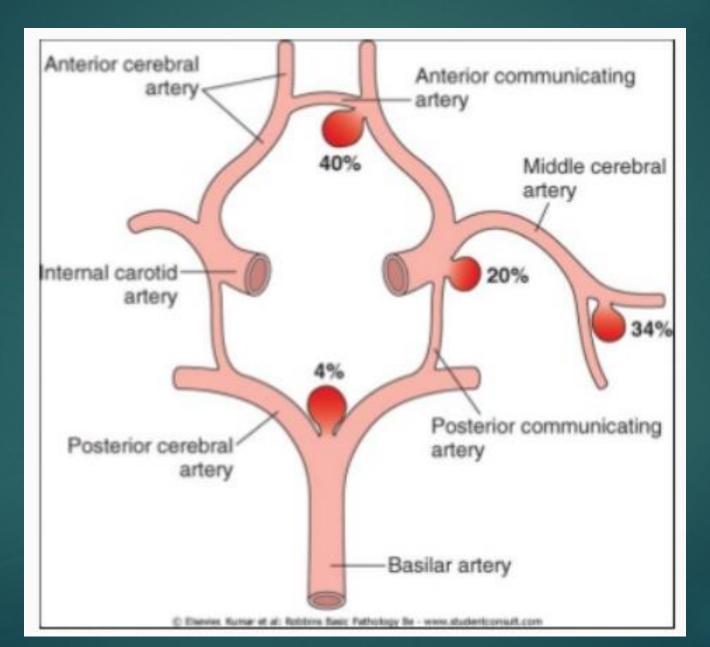
Alzheimer's: 18 months



Amphetamine use atrophy

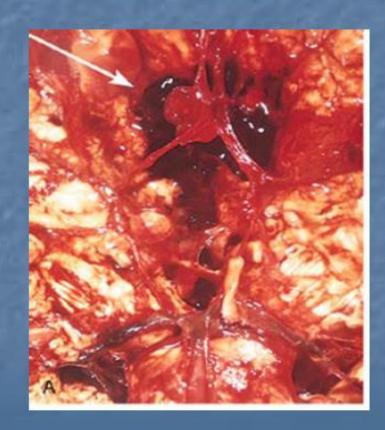


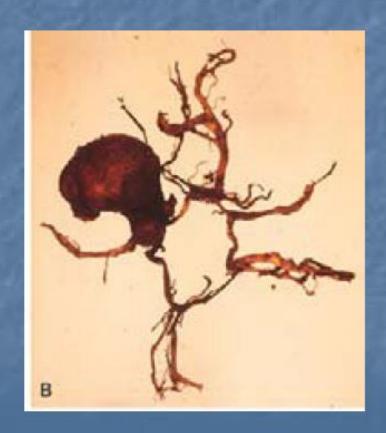
Aneurysm Sites



Berry Aneurysm

Saccular aneurysms, also known as berry aneurysms, appear as a round outpouching and are the most common form of cerebral aneurysm

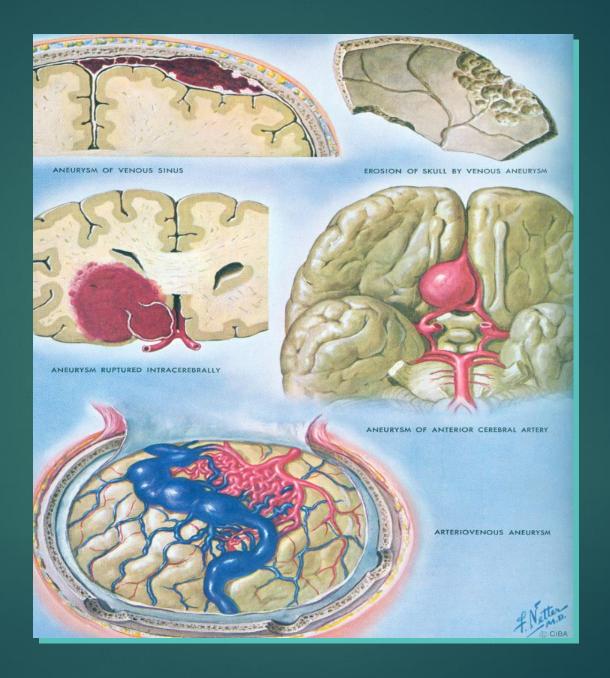






Berry aneurysms

Aneurysm



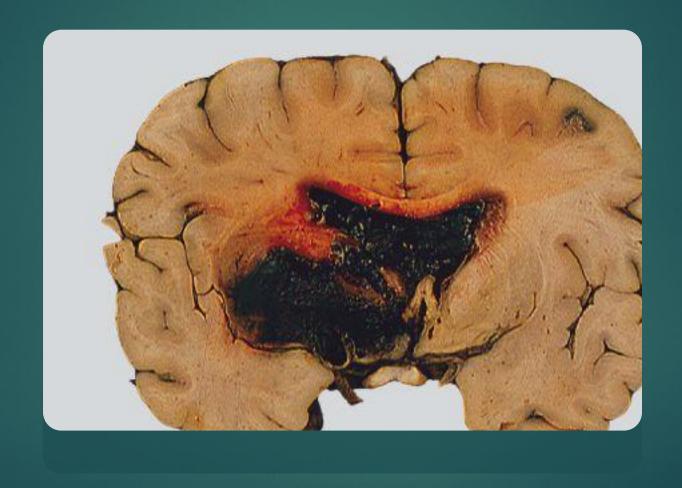
ACA Aneurysm Rupture

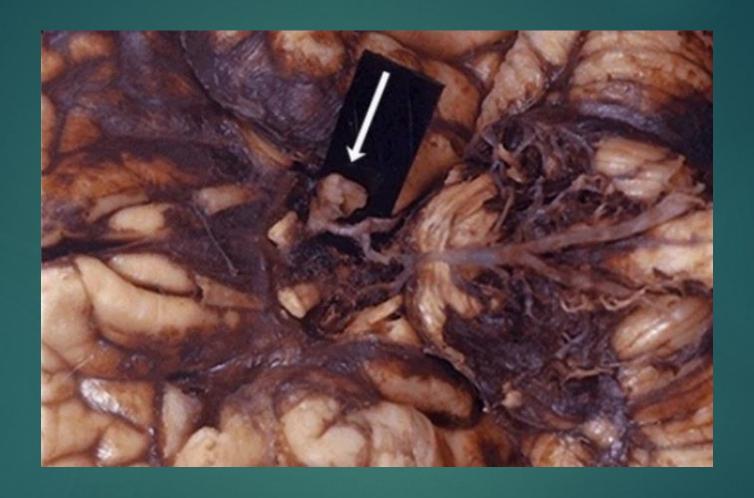


Aneurysm of Basil Artery



Ruptured aneurysm



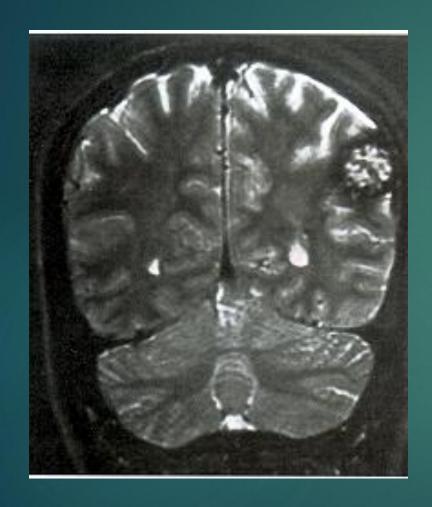


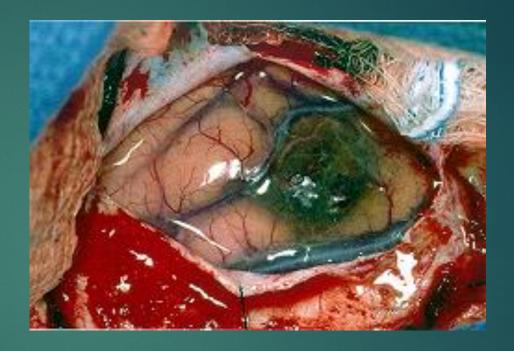
Ruptured PCOM aneurysm

Angiomas (tumors made up of blood vessel)



Cavernous Angioma

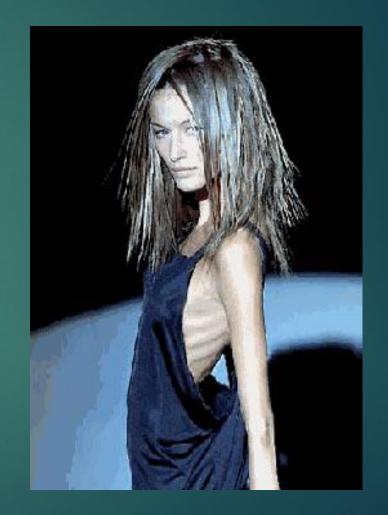




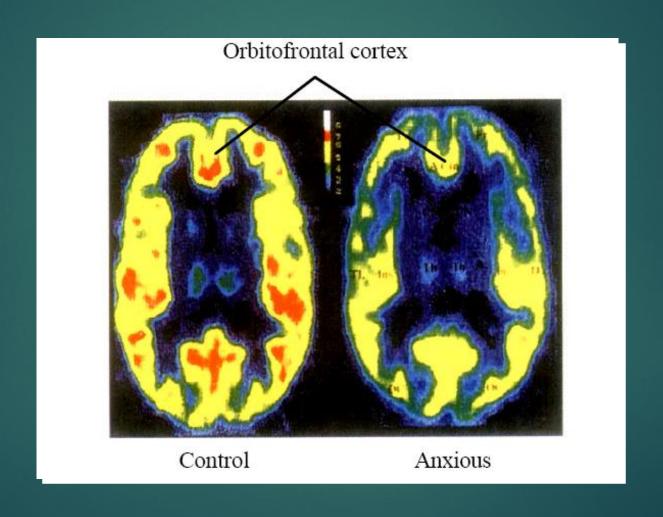
blood vessel abnormality characterized by large, adjacent capillaries with little or no intervening brain.

Anorexia

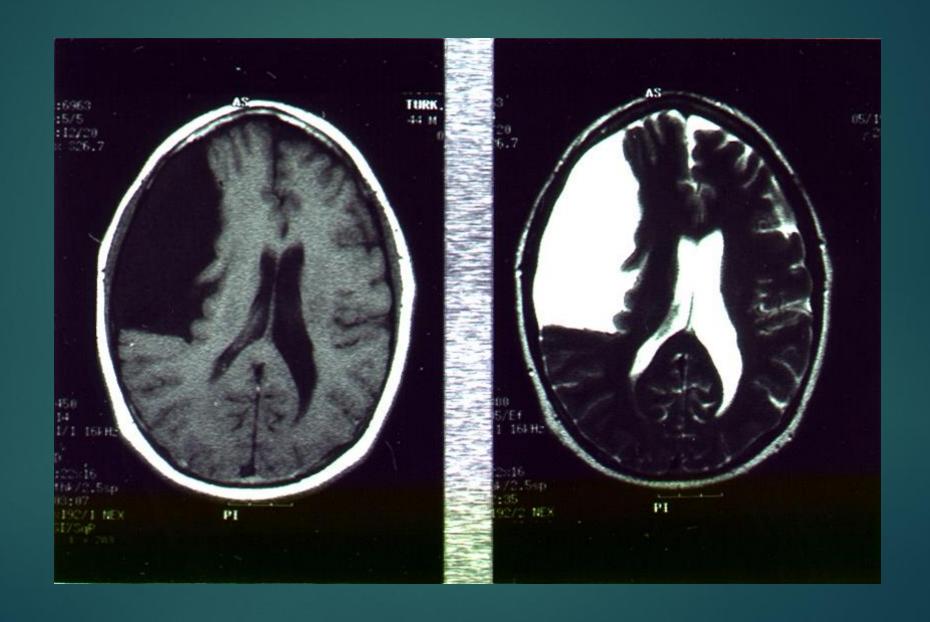
► Underweight adult patients with AN have reduced grey and white matter volumes that reverse with short-term weight restoration.



Anxiety: Reduced GABA Receptors

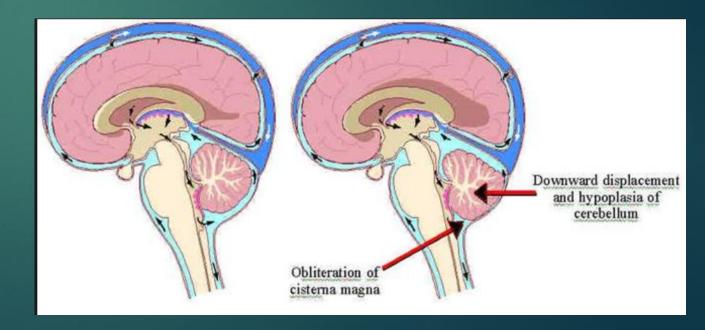


Arachnoid Cyst



Arnold-Chiari malformation

- ► The Arnold-Chiari malformation (Chiari type II malformation) consists of: a small posterior fossa
 - a misshapen midline cerebellum with downward extension of vermis through the foramen magnum
 - almost invariably, hydrocephalus and a lumbar myelomeningocele.

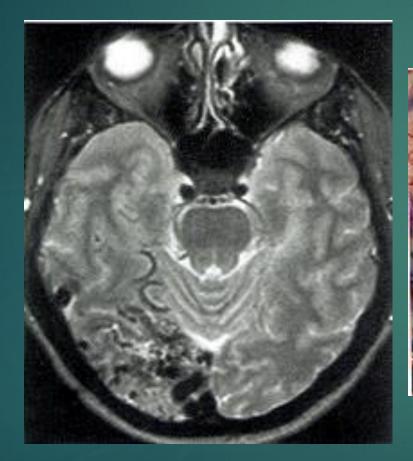




Posterior fossa abnormality:
Arnold-Chiari malformation
(Chiari type II malformation)

- Small posterior fossa
- Downward extension of cerebellar vermis through foramen magnum
- Caudally displaced medulla
 Often associated with:
- Aqueductal stenosis
- Hydrocephalus
- Lumbar myelomeningocele
- Hydromyelia

Arteriovenous Malformation

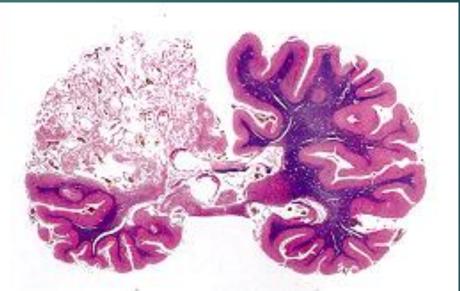




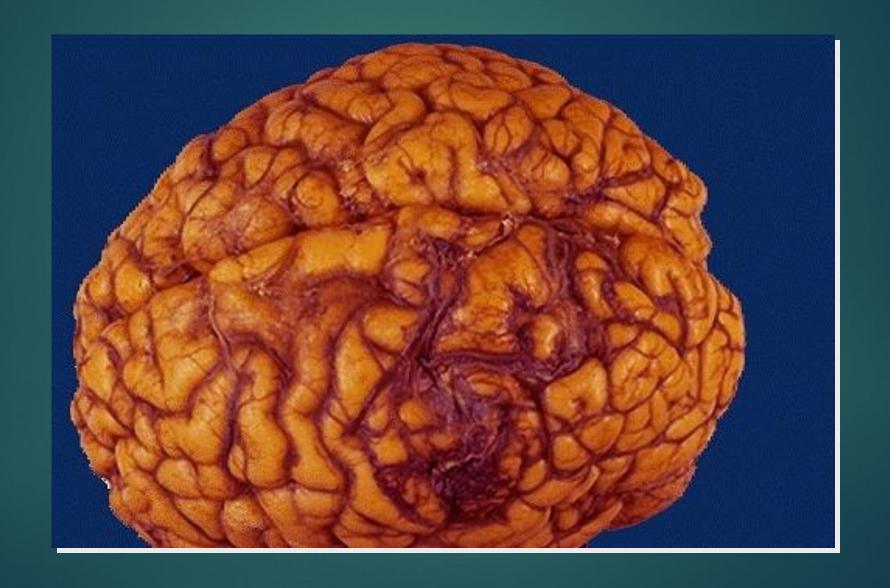
Burger et al., Surgical Pathology of the Nervous System and its Coverings, 4th Ed, 2002

Arteriovenous Malformation

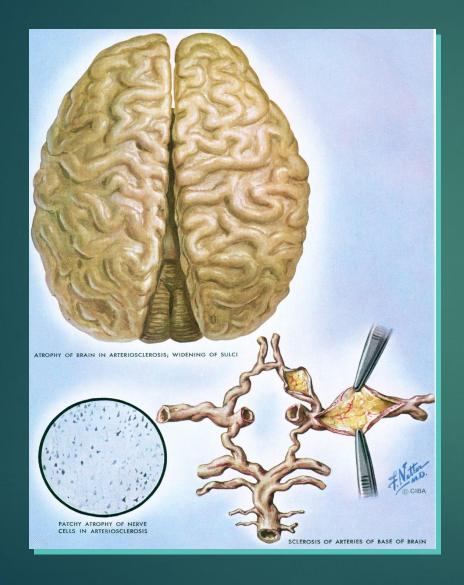


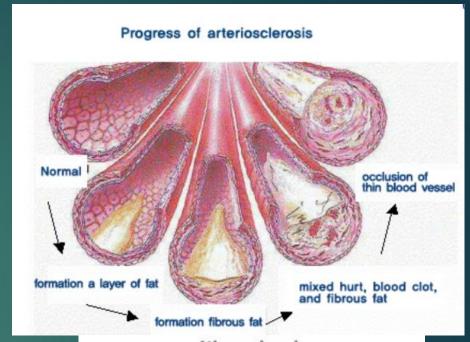


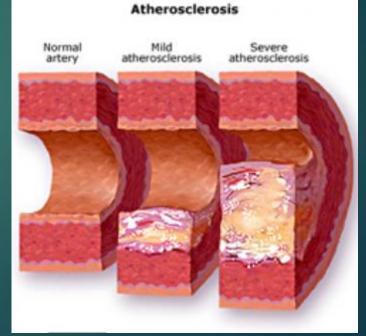
Vascular Malformation



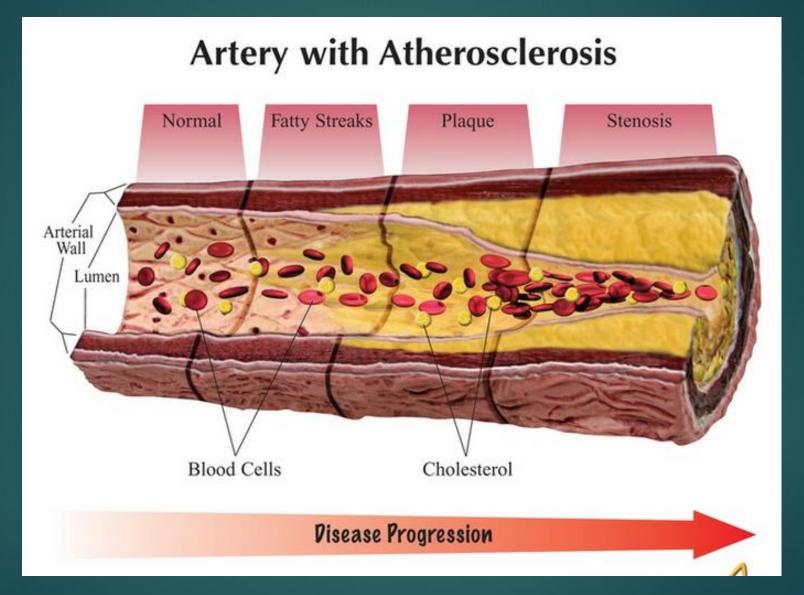
Arteriosclerosis (wall thickening)



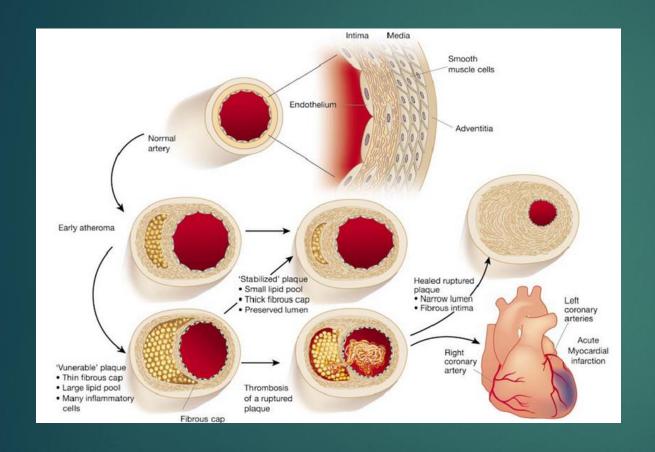




Atherosclerosis

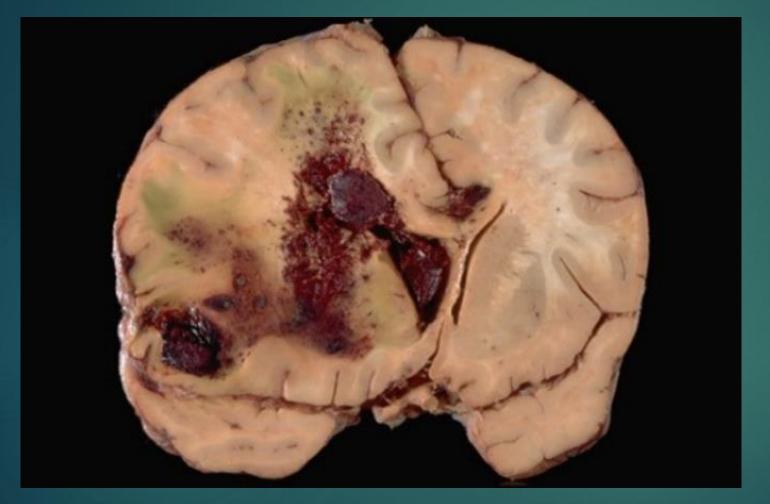


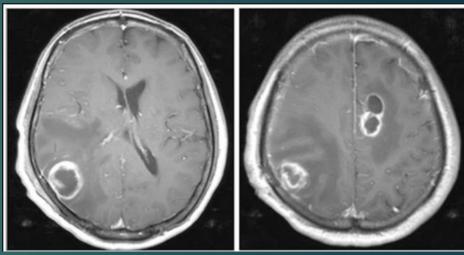
Fairly marked atherosclerosis





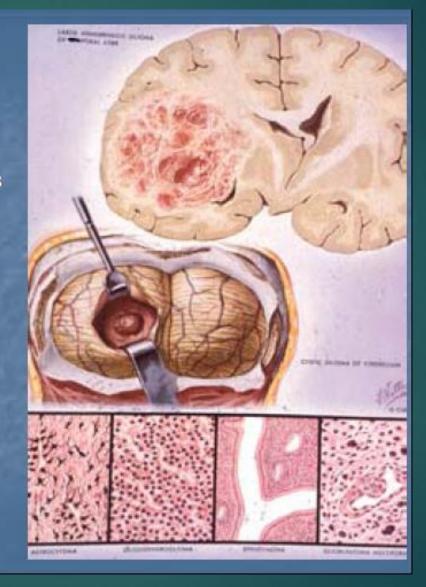
Aspergillis: a mold fungus infection



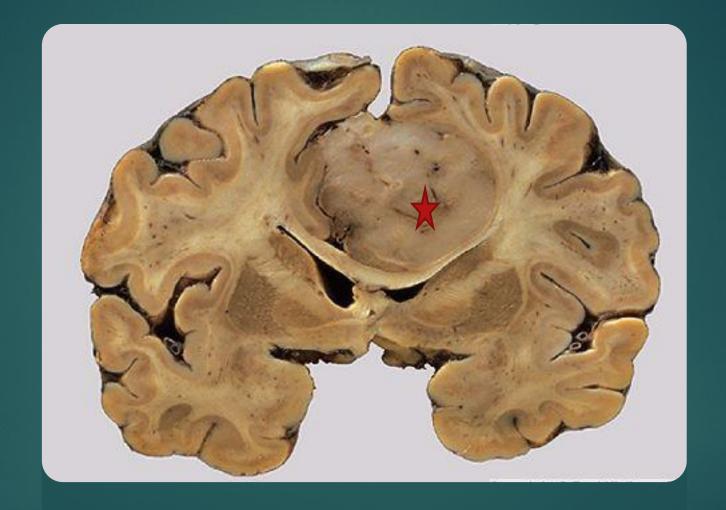


Astrocytoma

- Astrocytic origin
 - Above tentorum most times in adults
- Multiple grades
- Compresses surrounding tissue
- Hemorrhage and necrosis
- With higher grade malignant tumors,
 - Look for vascular growth

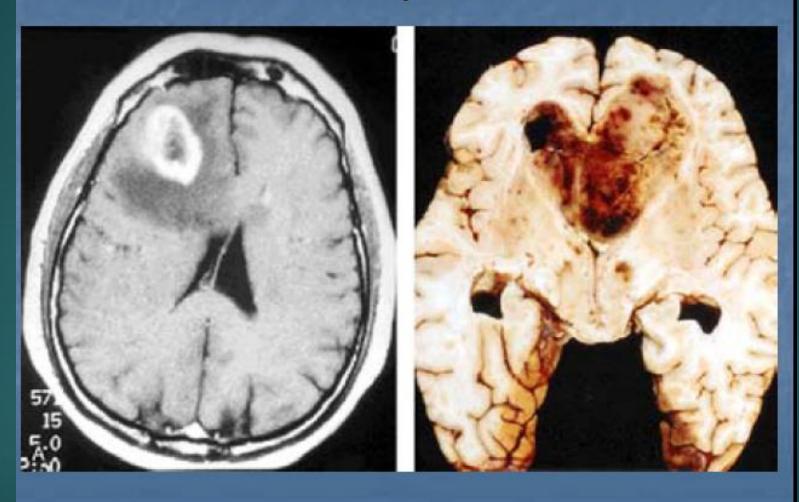


Astrocytoma

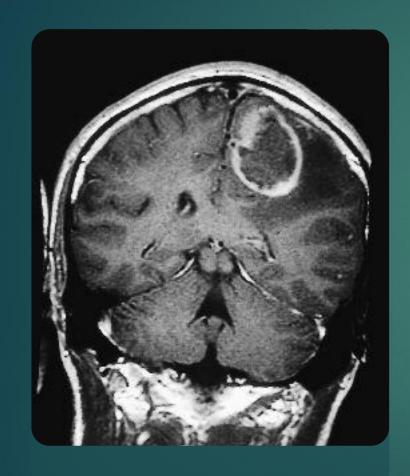


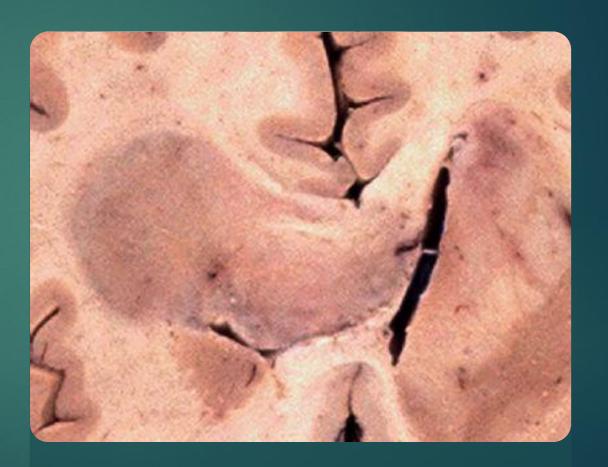
Astrocytomas are the most common glioma; originate in astrocytes

Astrocytoma



Anaplastic astrocytoma



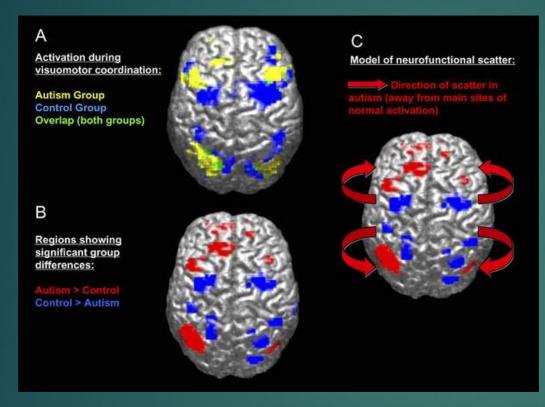


Anaplastic: cancer cells that divide rapidly and have little or no resemblance to normal cells.

Auditory Hallucinations: 3 steps

- ► Auditory hallucinations in schizophrenia are:
 - ▶ Present in 70-80% of schizophrenics
 - ▶ 1 Internally generated speech mis-representations
 - ► Lateralized to the left hemisphere superior temporal gyrus and sulcus,
 - ▶ 2 Not cognitively suppressed due to enhanced parietal attention to the "voices" and
 - ▶ 3 Failure of prefrontal & anterior cingulate mediated executive inhibition & response suppression functions
 - Reduction of grey matter density and volume and reduced activation in the same temporal areas

Autism: Variety of Brain Differences

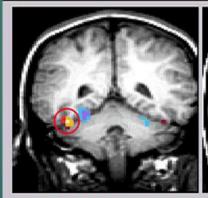


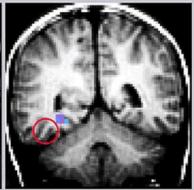
Also known differences in Amygdala \, Cerebellum, Prefrontal \, Corpus Callosum, Fusiform Gyrus \



Larger brain in 1st year

Healthy Control vs Autism FFA activation





Healthy Control

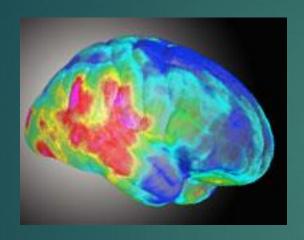
Person with Autism

Notes

- Areas in red show where brain areas that are significantly more active during perception of faces; areas in blue show where brain was more active during perception of nonface objects.
- 2. The right side of the brain is shown on the left side of the image, as if you were looking at the person face on.

Autism vs. Williams Syndrome: over social vs social impairment

Williams Syndrome





Autism



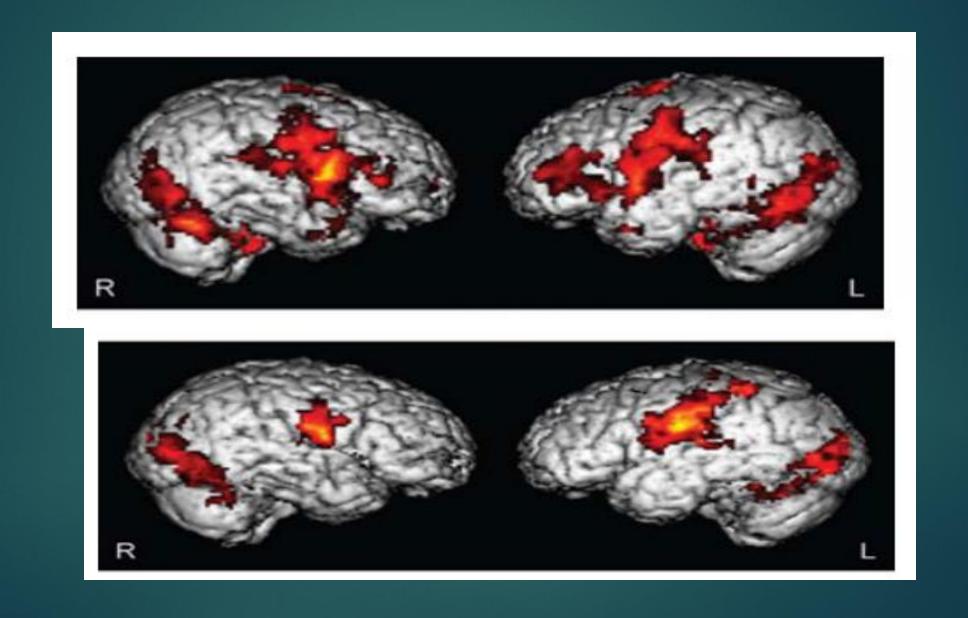


Autism vs. Williams Syndrome: Eye Tracking

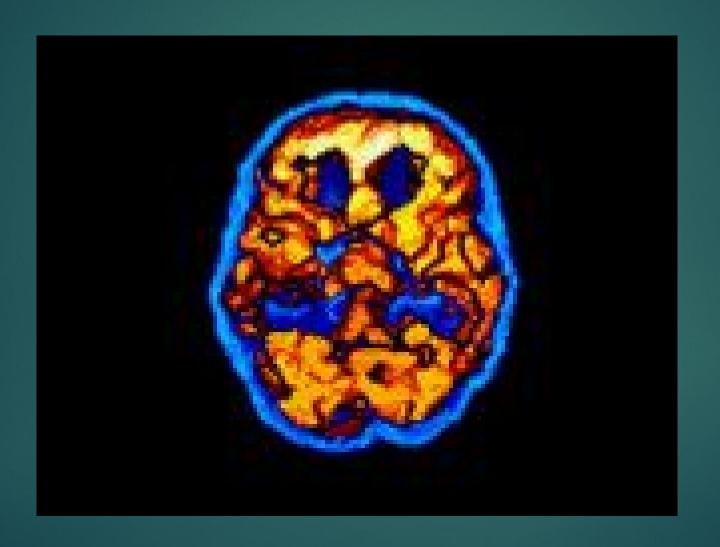
► A <u>lack of attention to eyes</u> in autism, and <u>a contrasting abundance of attention in Williams syndrome</u>, may help explain why people with Williams syndrome tend to be so <u>much better than those with autism in understanding gaze cues and expressions</u>.

► People with <u>Williams syndrome</u> find it <u>difficult to disengage their</u> attention from faces.

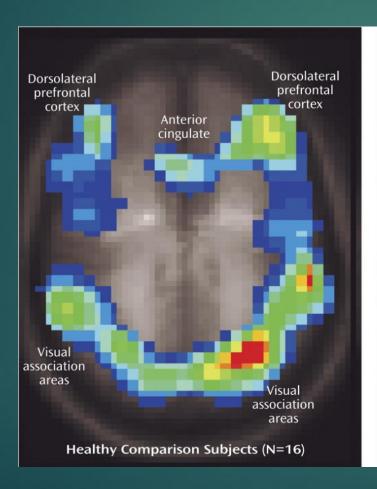
Mirror Neuron Activity: Normal Top; Autism Bottom

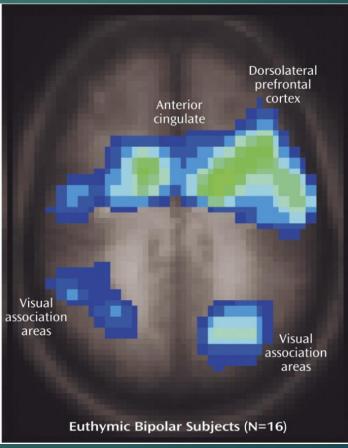


Bipolar Disorder, Mania: Hyperactivation

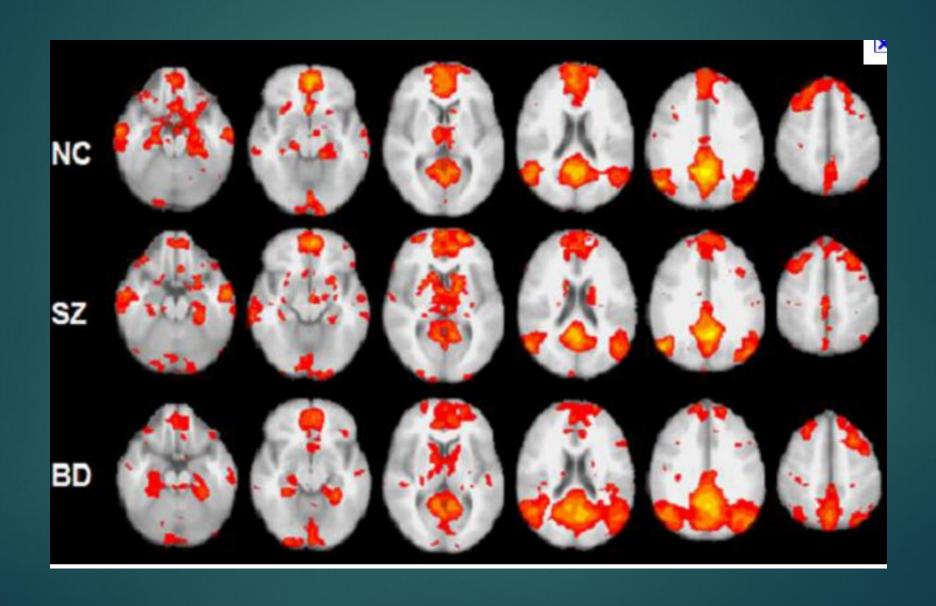


Normal v Euthymic on Stroop test

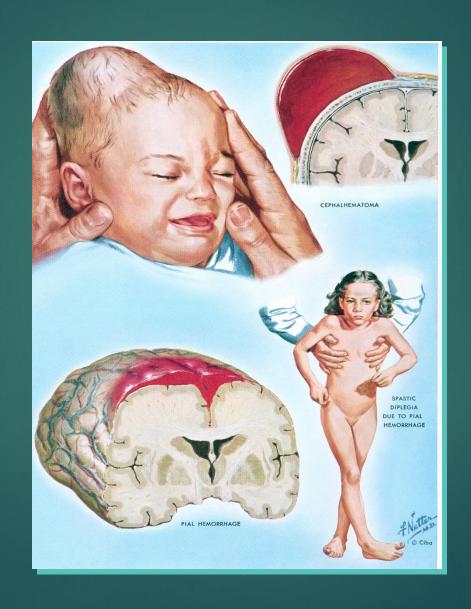




Default Network: Schizophrenic v Bipolar



Birth Injuries



Body Dysmorphic Disorder: Left Hemisphere overactivation: details!

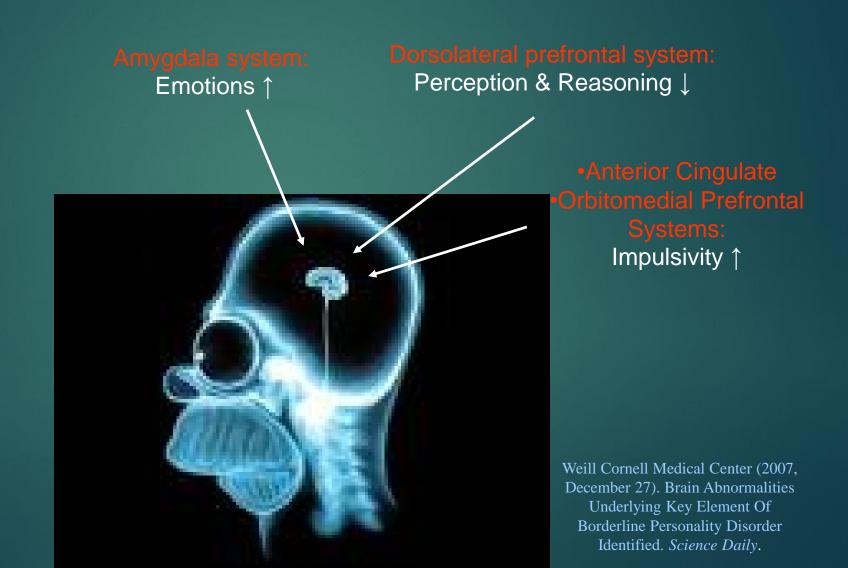
- ▶ People suffering from body dysmorphic disorder (BDD) <u>perceive themselves</u> as ugly and <u>disfigured</u>; Individuals with BDD <u>fixate on an imagined flaw in appearance or a slight physical abnormality</u>.
- ► To fix their "problem," they tend to pursue plastic surgery -- sometimes repeatedly. They often feel ashamed, depressed and anxious, increasing their risk of suicide. Thirty percent of people with BDD suffer from eating disorders
- Brains of people with BDD look normal, but <u>function abnormally when processing visual details.</u>
- ▶ BDD patients more often <u>used their brain's left side -- the analytic side</u> <u>attuned to complex detail -- even when processing less intricate, low-frequency images</u>
- ► The more severe the BDD patient's symptoms, the more strongly the brain's left side activates during visual processing

 Feusner, 2007

Borderline Personality Disorder

- Driessen, 2000: The patients with BPD had nearly 16% smaller volumes of the hippocampus and 8% smaller volumes of the amygdala than the healthy controls.
- Ventromedial prefrontal cortex was key to people's ability to restrain behaviors in the presence of emotion; subgenual anterior cingulate cortex and the medial orbitofrontal cortex areas—were relatively less active in patients versus controls; and amygdala was more active

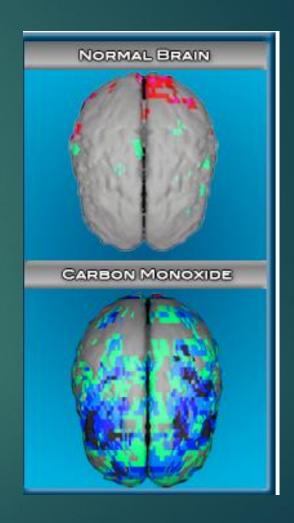
Neuroanatomy of BPD



Carbon Monoxide Poisoning: petechial hemorrhages



A **petechial hemorrhage** is a tiny pinpoint red mark that is an important sign of asphyxia How Walt Disney killed his mother.



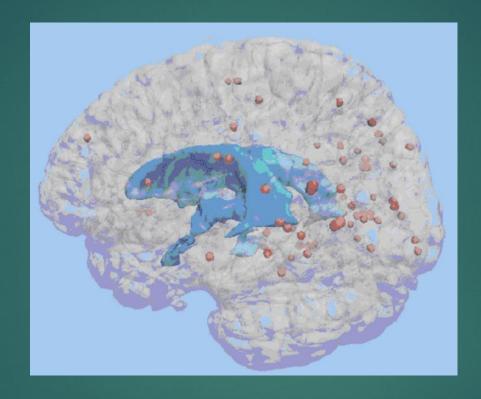
Pet Scan: atrophy

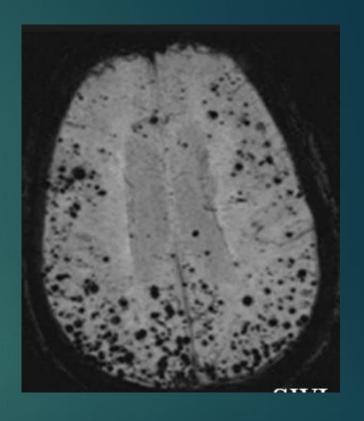
Cardiac Arrest: Late Effects



Cerebral Amyloid Angiopathy

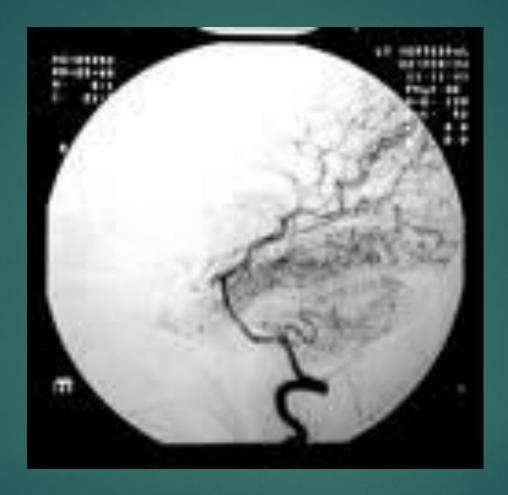
Form of **angiopathy** in which **amyloid** deposits form in the walls of the blood vessels of the central nervous system.





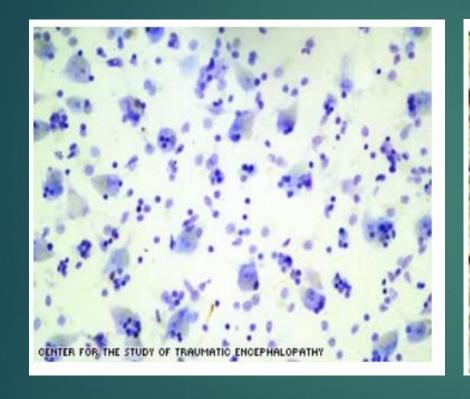
Vascular disease that commonly affects the elderly. Hemorrhages tended to cluster in a single lobe

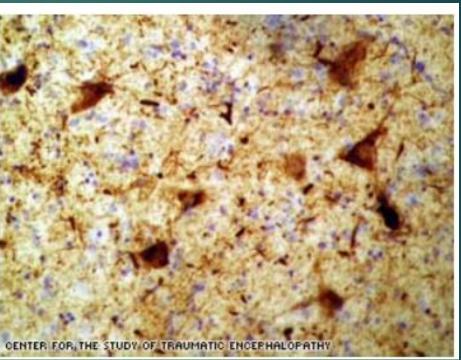
Cerebral Vasculitis



Inflammation of blood vessel walls

Chronic Traumatic Encephalopathy





Contusion (hematoma)

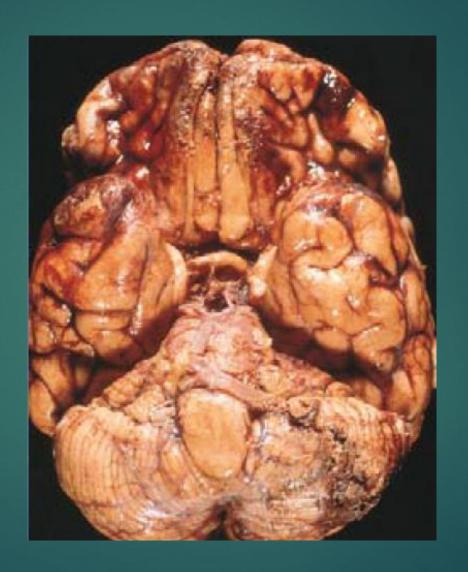
A contusion is a type of hematoma in which blood has escaped from ruptured capillaries and is interspersed into surrounding tissue, usually due to trauma.

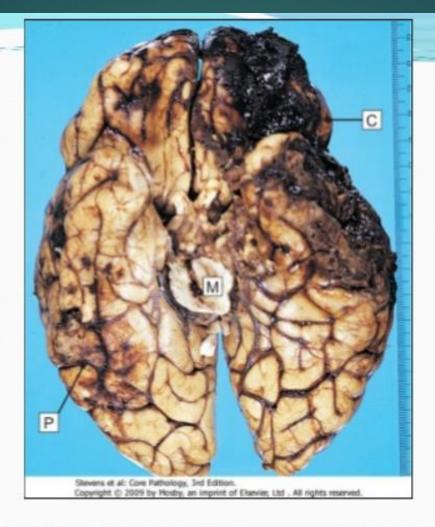


Contusions



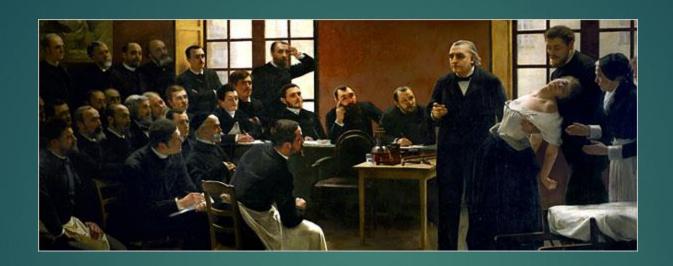
Contusion





Cerebral contusions. Primary impact damage has caused severe hemorrhagic contusion of the left frontal lobe (C) - coup lesion, with smaller contusions on the right parietal lobe (P) - contrecoup lesion. Swelling of the left side of the brain has caused cerebral herniation with compression of the midbrain

Conversion Disorder: Hysterical Paralysis

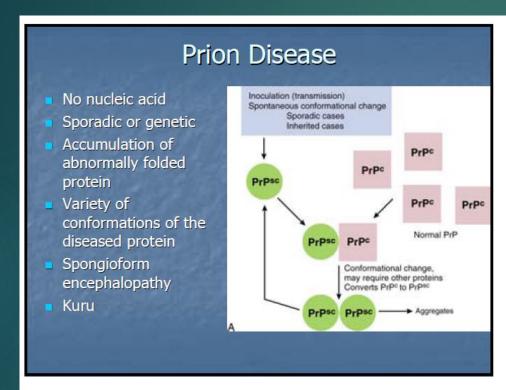


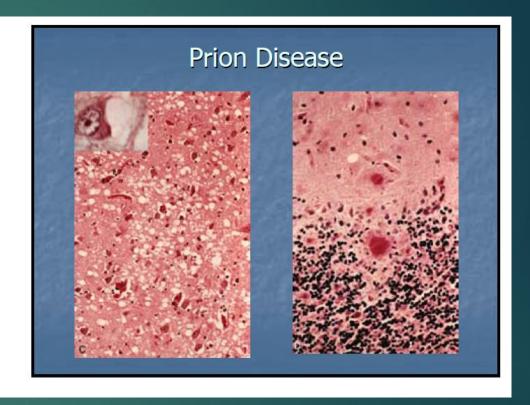
But...

- 1997 Cognition, Halligan & Marshall: <u>woman with left hemiparesis</u>. No organic lesion; if she tried to move "paralyzed leg", <u>motor cortex did not activate</u>
- Right orbitofrontal and right anterior cingulate cortex activated instead
- Emotions suppress motor activation
- Disconnected crosstalk between anterior cingulate and the prefrontal cortex: neuroscientific basis for the psychodynamic dissociation hypothesis

Transmissible Spongiform Encephalopathies (Prion Diseases)

- they are predominantly characterized by "spongiform change" caused by intracellular vacuoles in neurons and glia.
- ► Clinically, most of these patients develop progressive dementia.
- ► The most common clinical presentation is CJD. Creutzfeldt-Jakob disease

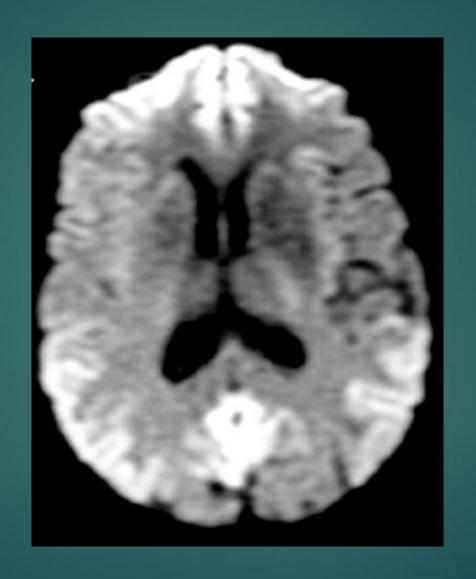




Creutzfeldt-Jakob Disease



CJD



Transmissible Spongiform Encephalopathies

▶ Prion Deseases:

- *Creutzfeldt-Jakob disease(CJD)
- *Gerstmann-Strausler-Scheinker dis.(GSS)
- *Fatal familial insomnia(FFI)
- *Kuru

Common features:

- -Accumulation of abnormal cellular protein
- -Transmission: Sporadic(85%), familial(15%), iatrogenic CJD(inoculation, tissue transplant), endocannibalism(kuru)
- -Epidemiology: CJD incidence 1-2/million

age of onset 55-75 M=F

Prion diseases of humans and animals

<u>Disease</u> Host

Scrapie Sheep, goats

 Transmissible mink encephalopathy (TME)

Mink

Chronic wasting disease
 Revine spengiform

Mule deer, elk

 Bovine spongiform encephalopathy (BSE)

Cattle

 Feline spongiform encephalopathy (FSE)

Cats

• Kuru

Humans

Creutzfeldt-Jakob disease (CJD)

Humans

New variant CJD (nvCJD)

Humans

 Gerstmann-Straussler syndrome (GSS)

Humans

Fatal familial insomnia (FFI)

Humans

Characteristics of prion diseases and agents

- Prolonged incubation period of months to years
- Progressive course of weeks to months to death
- No host immune response (except astrocytosis)
- Pathologic lesions confined to the central nervous system
- Similar histopathology
- No specific treatment

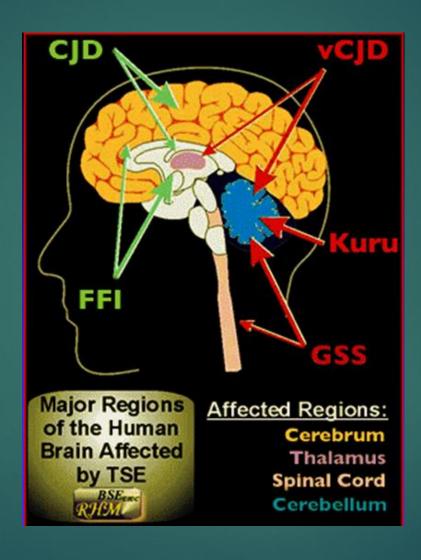
Causative agents (prions) have specific properties:

- No detectable nucleic acid
- Resistant to alcohol, formalin, heat, ultraviolet (UV) irradiation, nucleases*
- Susceptible to proteolytic enzymes, denaturing agents, organic solvents**

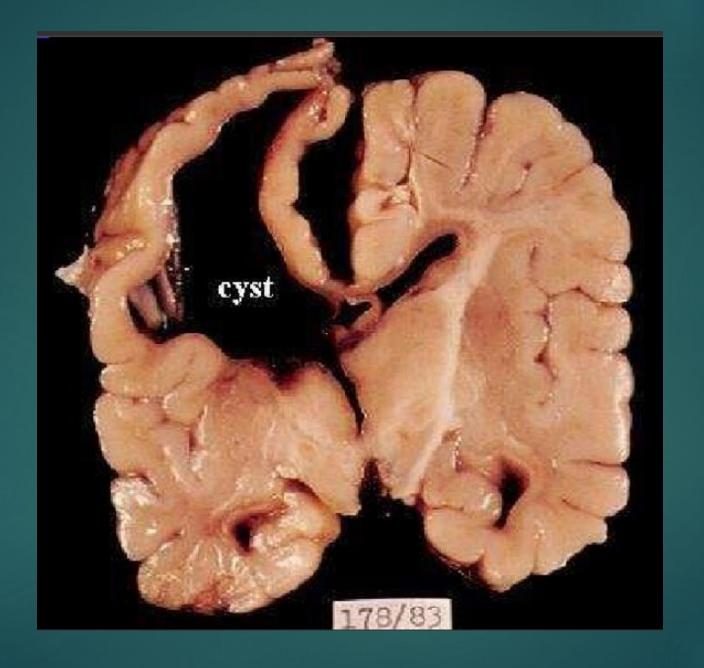
Sterilized by:

- Steam autoclaving 1 hour at 132°C
- Immersion in 1N NaOH for 1 hour at room temperature
 - *Agents that hydrolyze or modify nucleic acids.
 - **Agents that digest, denature, or modify proteins

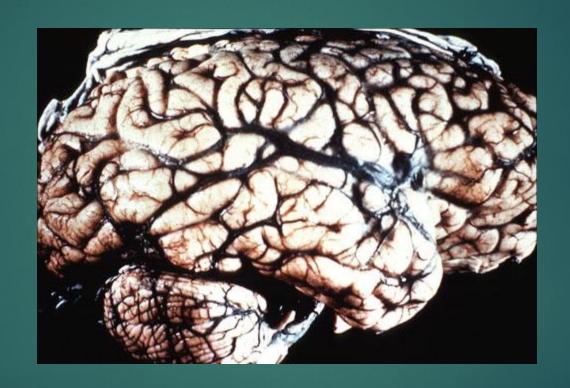
Prion Diseases Encephalopathies



Cyst



Kuru: Prion Disease via Cannibalism

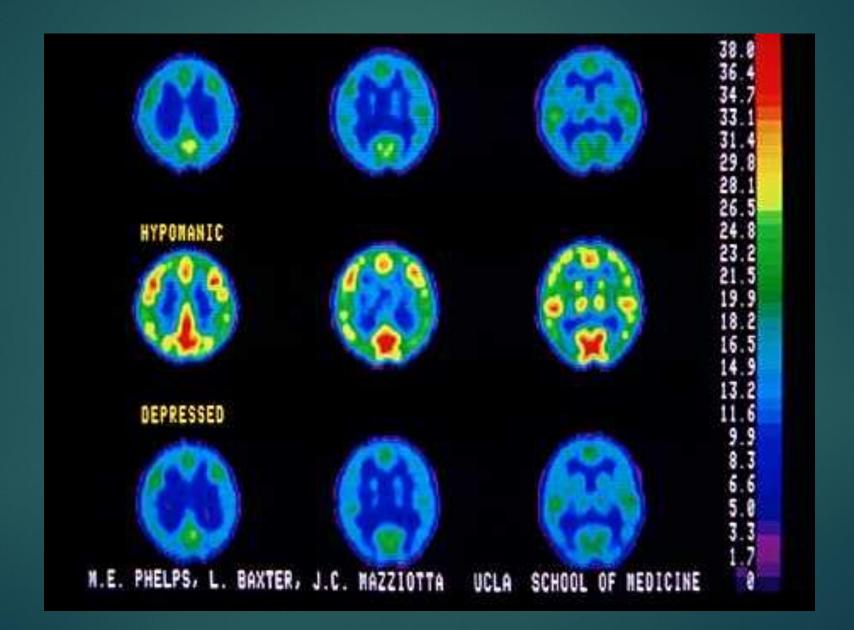


Dandy Walker Syndrome

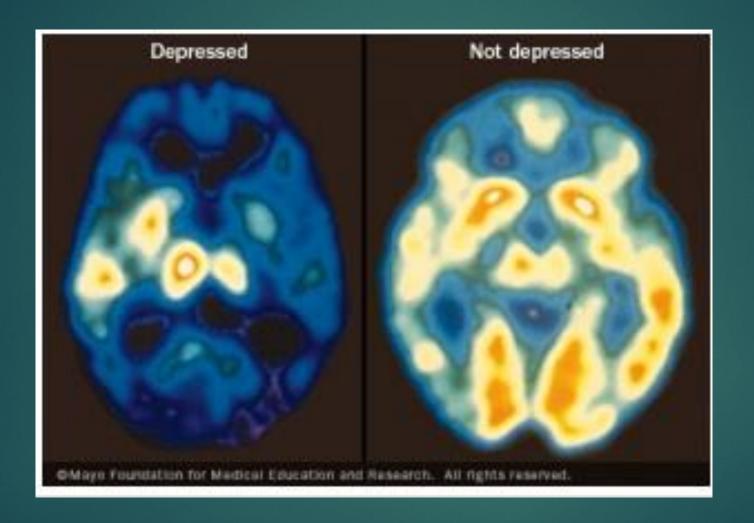


Enlargement of the 4th ventricle or complete absence of the *cerebellar vermis* and cyst formation near the internal base of the skull

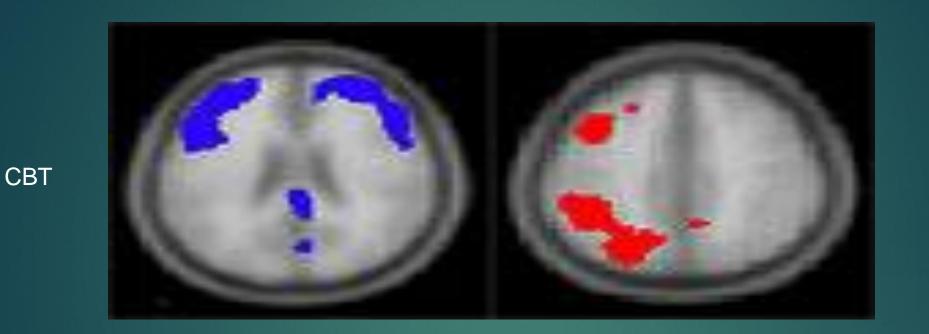
Depression



Pain Symptoms in Depression



Depression: Cognitive Behavior Therapy vs. SSRIs

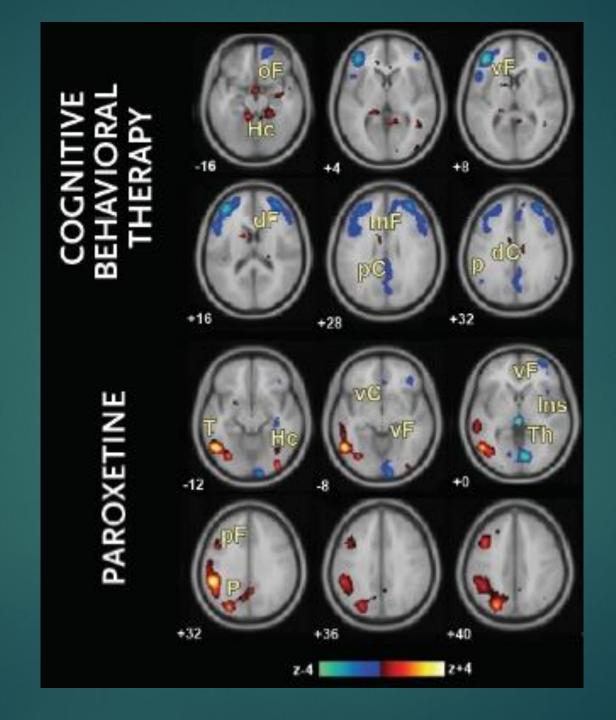


Effexor

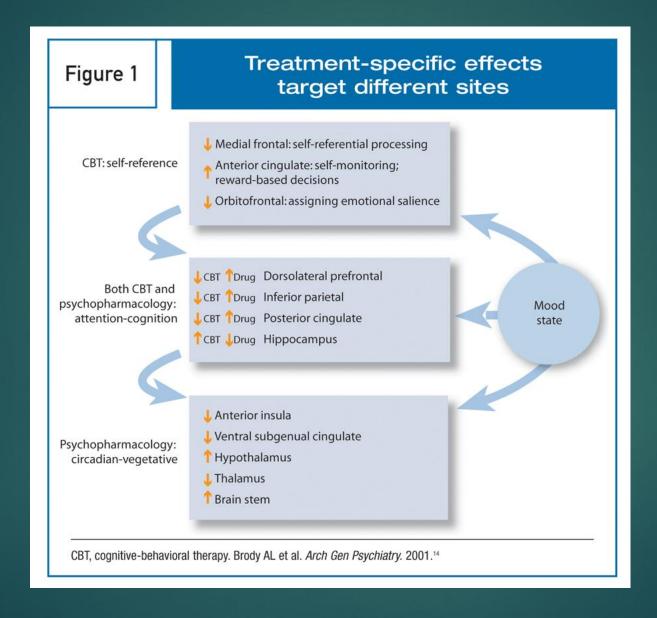
Dr. Mayberg:

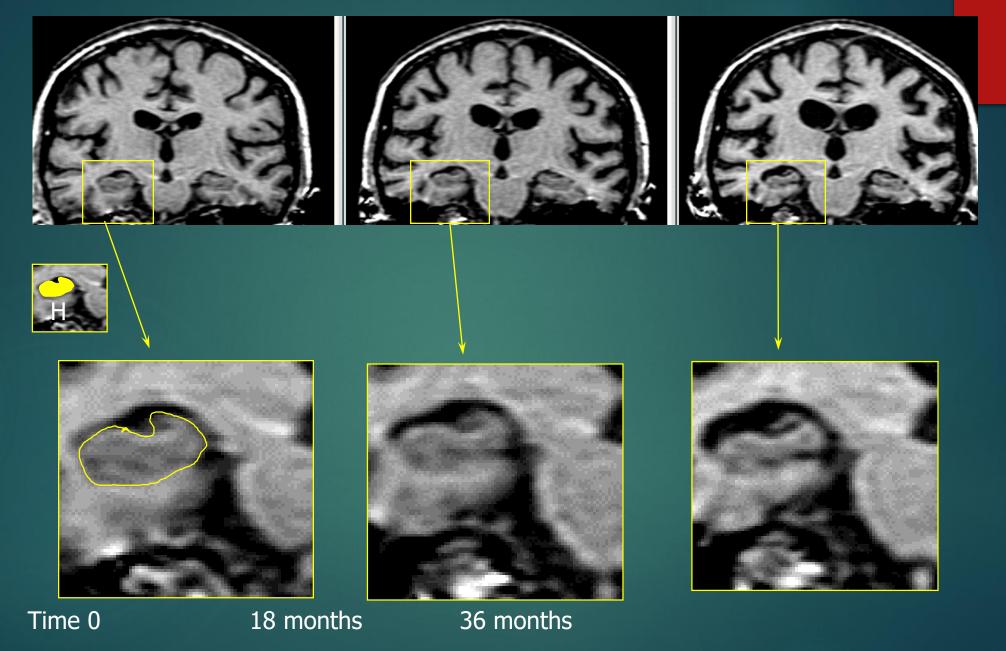
Response to either treatment modality was associated with decreased glucose metabolism bilaterally in the orbitofrontal cortex and left medial prefrontal cortex, along with increased metabolism in the right occipital-temporal cortex. Changes in metabolism in the anterior and posterior parts of the subgenual cingulate cortex and the caudate differentiated CBT and Effexor responders.

CBT vs Paxil



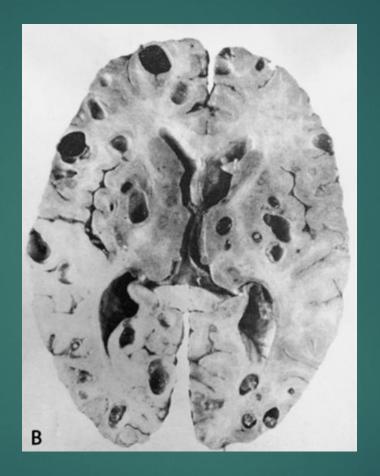
Depression: CBT and Medications affect different brain areas





Hippocampal Atrophy: Serial coronal MRI of an individual with initially mild AD

Eat only cooked Pork: Cysticercosis

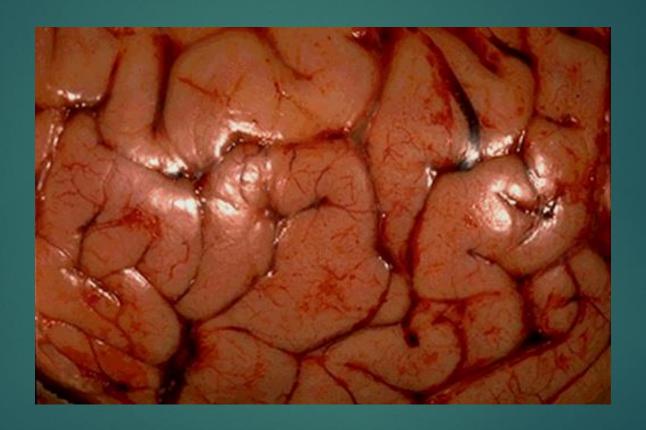


Acquired after ingestion of larval stage of pig tapeworm in unhygienic pork meat

Dissociative Identity Disorder

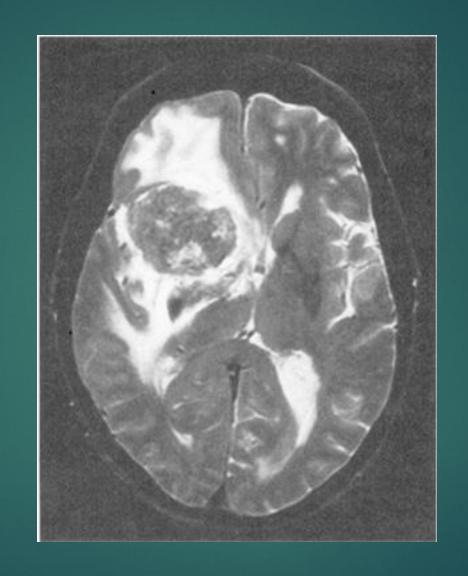
- ► Eric Vermetten, 2006:
 - ► Hippocampal volume was 19% smaller
 - ► Amygdalar volume was 32% smaller in the patients with dissociative identity disorder.

Edema



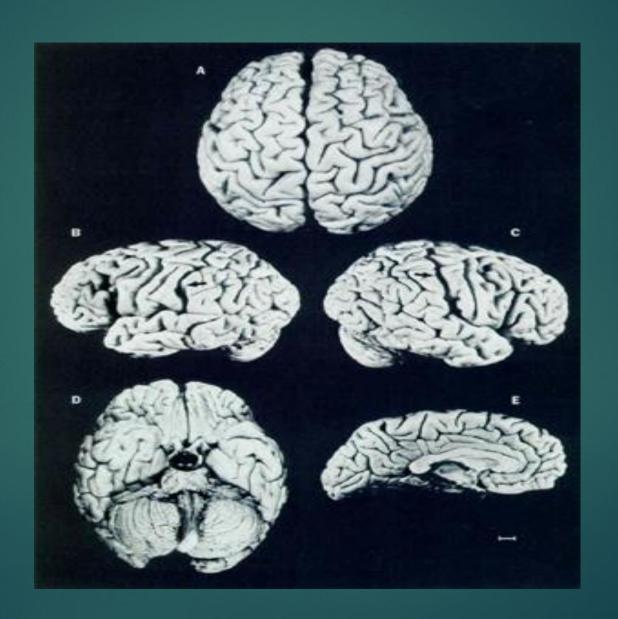
Abnormal accumulation of fluid; old term: dropsy

Edema and Right Frontal Tumor

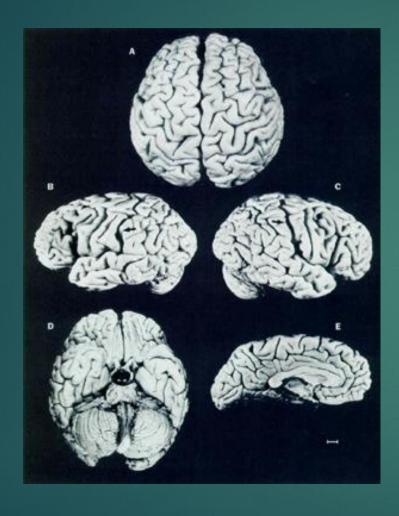


Extensive vasogenic edema in the white matter surrounding the frontal lobe mass.

Einstein's Brain



Einstein's Brain



Thomas Harvery did autopsy and kept it.

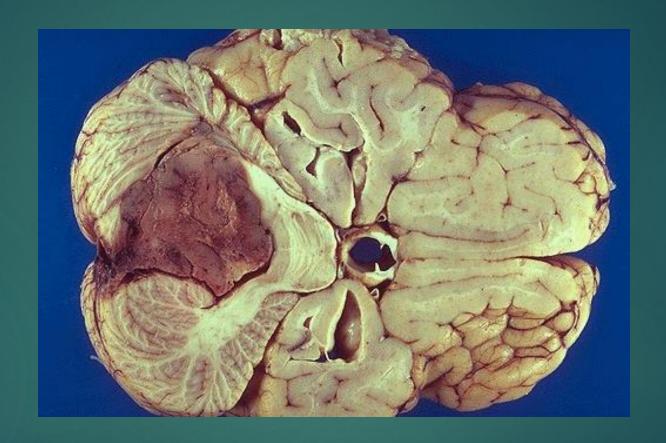
Absent:

- parietal operculum region in the inferior frontal
- part of lateral sulcus (Sylvian fissure).

The inferior parietal was 15 percent wider than normal. The inferior parietal region is responsible for mathematical thought, Visuospatial cognition, and imagery of movement.

Einstein's brain also contained 73 percent more glial cells than the average brain.

Ependymoma (glioma) of 4th Ventricle



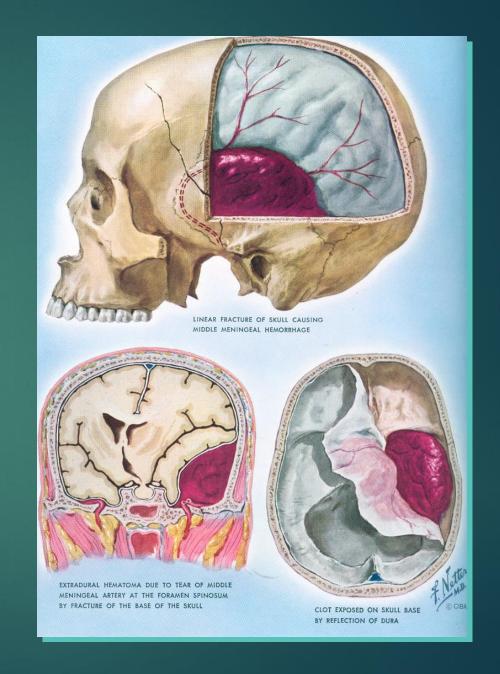
Rare type of <u>glioma</u>. They develop from the <u>ependymal cells which line the ventricles</u> and from the central canal of the spinal cord. Particularly common in the cerebellum They are the second most common spinal cord tumor.

Epidural Hematoma

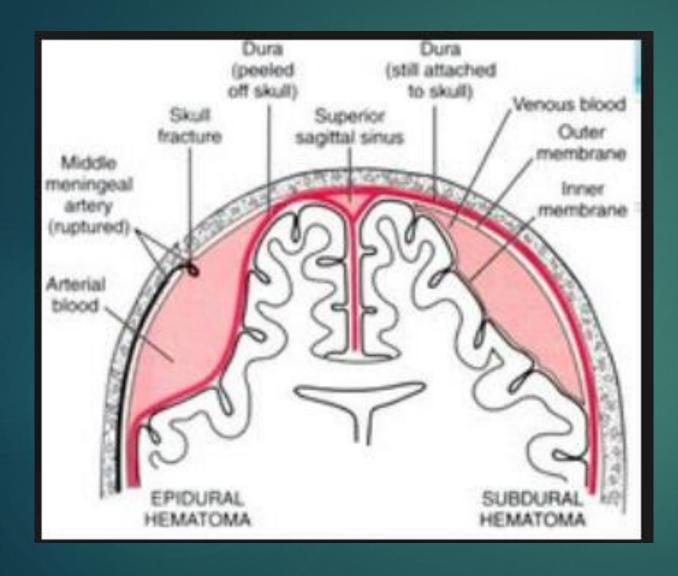
Trauma with skull fracture

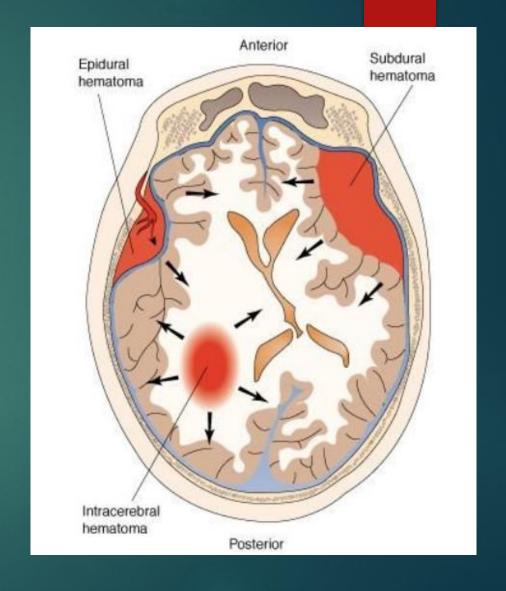
Middle Meningeal artery

Hemorrhage compresses brain



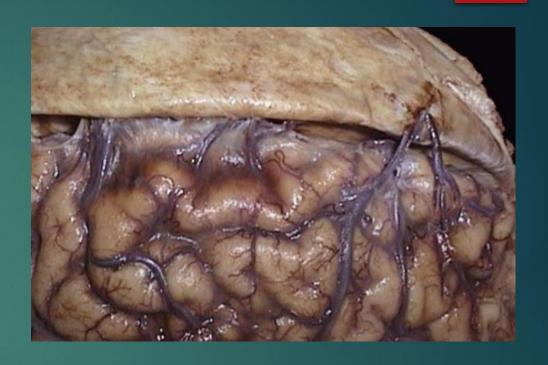
Epidural (above Dura) vs Subdural (below Dura)





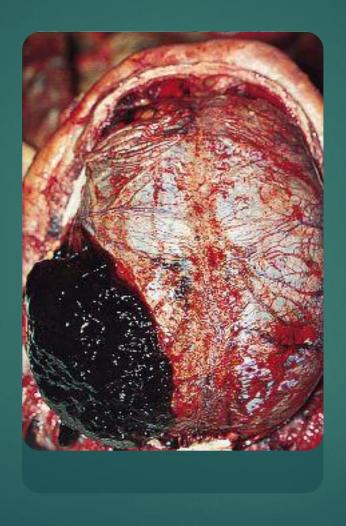


Middle Meningeal Artery



Bridging veins

► Epidural (extradural) hematoma



Epidural hematoma: Flattening of the cerebral convexity (now concave!)



Epidural Hematoma: Calcification

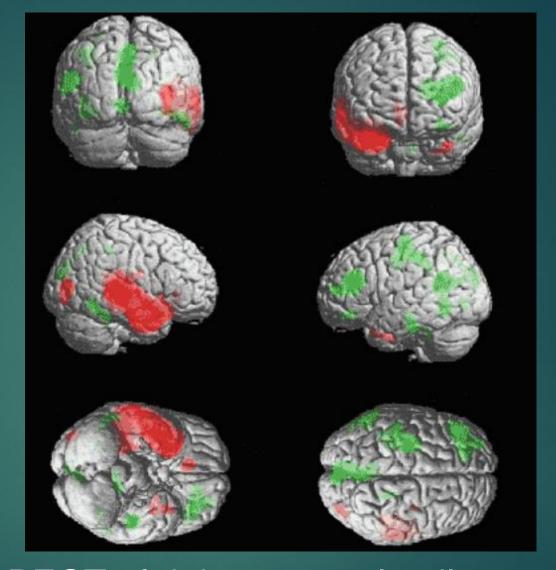


► Brain deformation due to epidural hematoma



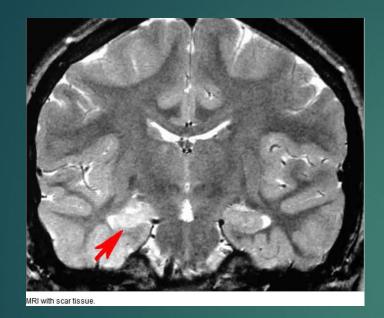
Epilepsy

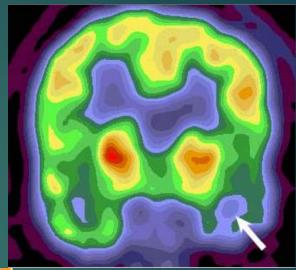
Red = ictal Green = interictal

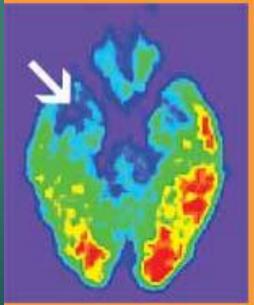


Ictal and Intraictal SPECT of right temporal epilepsy: perfusion increases in ictal SPECT and perfusion decreases in interictal SPECT in patients with epilepsy

Epilepsy: MRI & PET hypometabolism







Epilepsy: Hippocampal Atrophy





- ▶ Pt with longstanding epilepsy: periventricular nodular heterotopiasand prior left temporal lobectomy
- ► Overall, left hemisphere appears smaller

FAS, Foreign Accent Syndrome: In ear of the listener

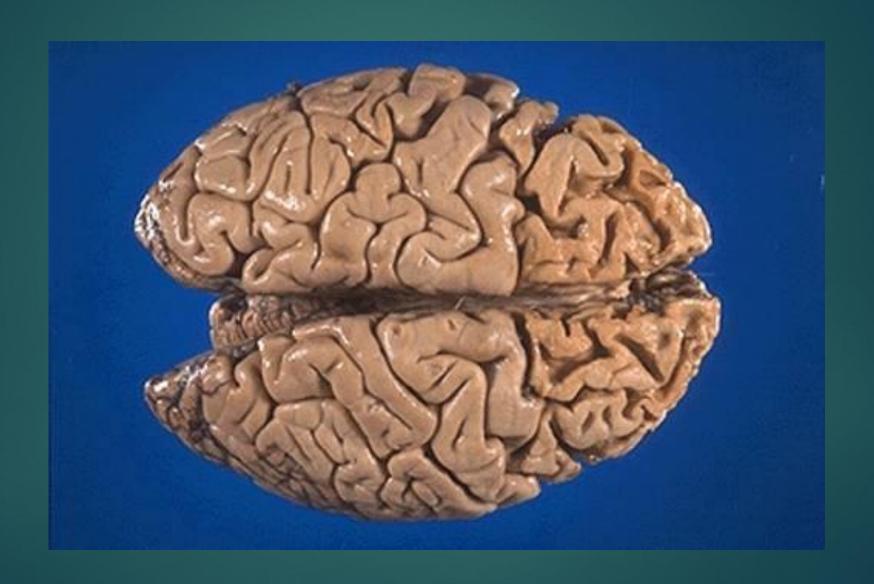
- Foreign Accent Syndrome (FAS) is a relatively rare motor speech disorder in which the pronunciation of a patient is perceived by listeners of the same language community as distinctly foreign.
- ► FAS has been well documented in adult patients with etiologically heterogeneous, though mostly vascular brain lesions affecting the motor speech network of the language dominant hemisphere.
- ▶ In addition, reports exist of adult patients in whom FAS was due to a psychiatric illness.

Frontal Atrophy

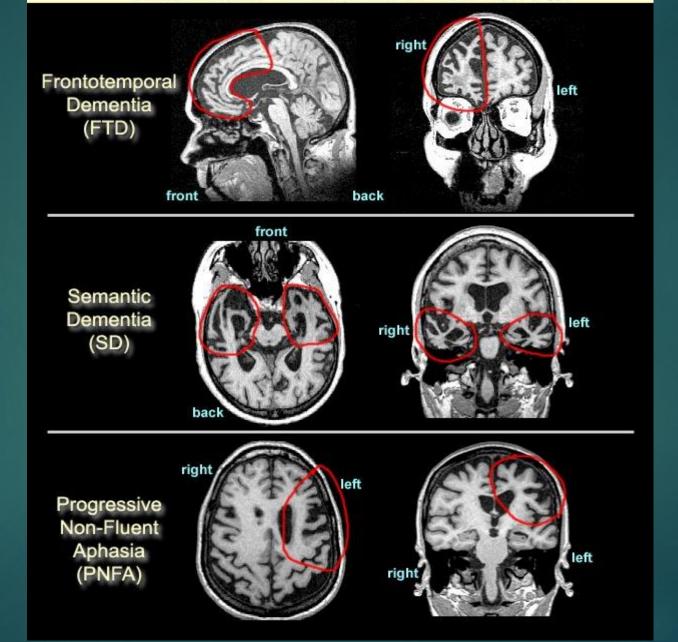


Social and language disorder

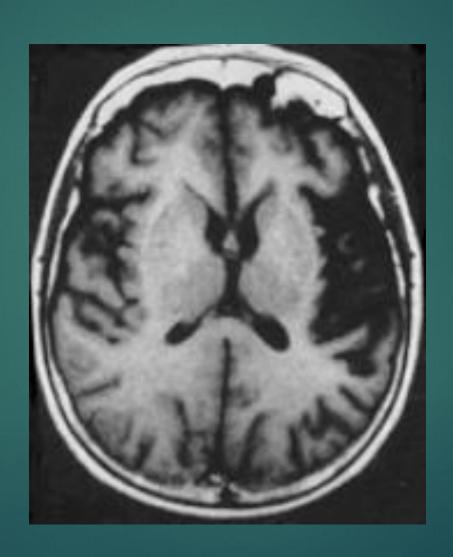
Frontal Atrophy 2



Notice that the areas circled in red have less white area compared with the other areas. This indicates loss of brain tissue (atrophy).



Primary Progressive Aphasia



Semantic Aphasia in FTD

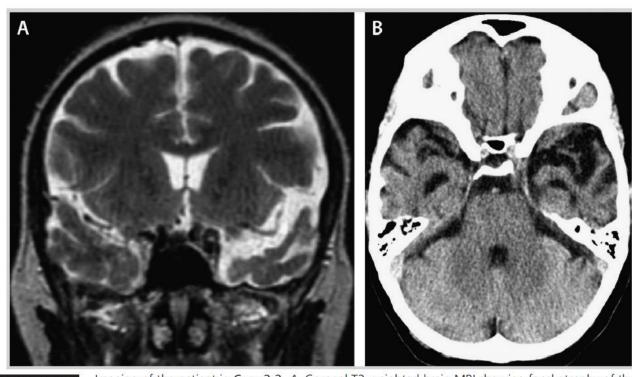
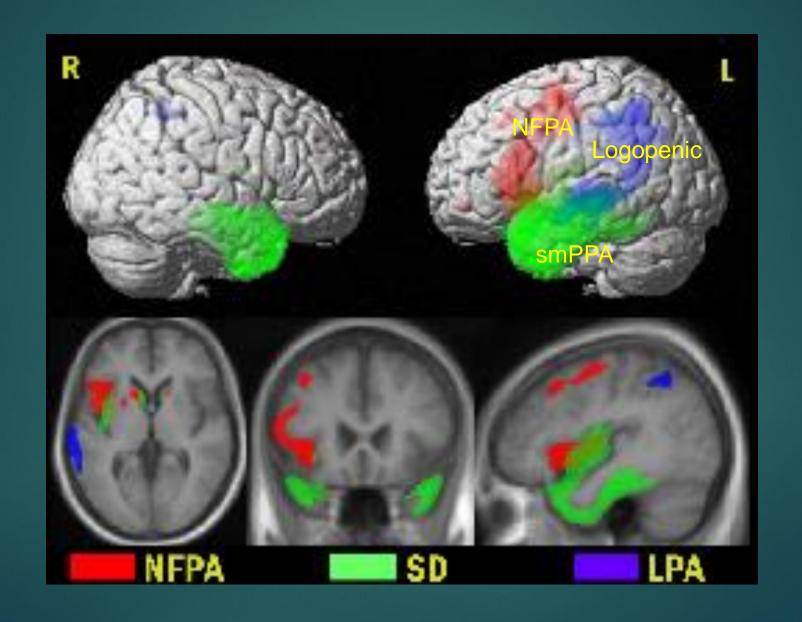


FIGURE 2-4

Imaging of the patient in Case 2-2. A, Coronal T2-weighted brain MRI showing focal atrophy of the left anterior temporal lobe. B, Axial head CT with bilateral anterior and inferior temporal lobe atrophy.

Comment. This patient initially had a mild deficit of semantic memory that predominantly affected her naming ability with relative sparing of her episodic memory. As the neurodegenerative illness progressed, her episodic memory was affected with relative preservation of her procedural memory (her golf game actually improved) and increasingly prominent behavioral features.

FMRI: NFPA, Sem var PPA, LPA



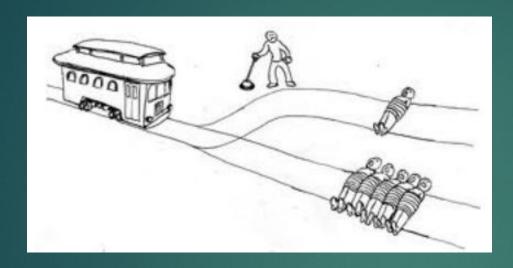
Gambling: Near Win = Win

► Winning, Near Winning, & Addiction:

► A <u>near-win in gambling</u> stimulates a large portion of the win-related circuitry in the brain and boosts a person's motivation to gamble

Significant activation of the ventral striatum and anterior insula, areas that were also activated by wins.

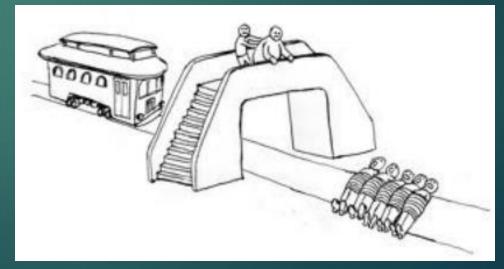
Trolley Problem and VM FC



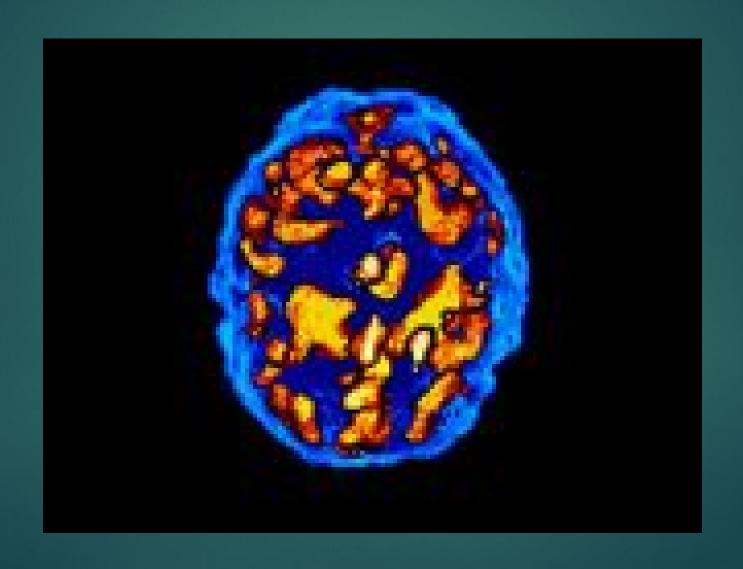
Choice 1: most vmFC sacrifice 5

Choice 2: most hesitate at active pushing to death

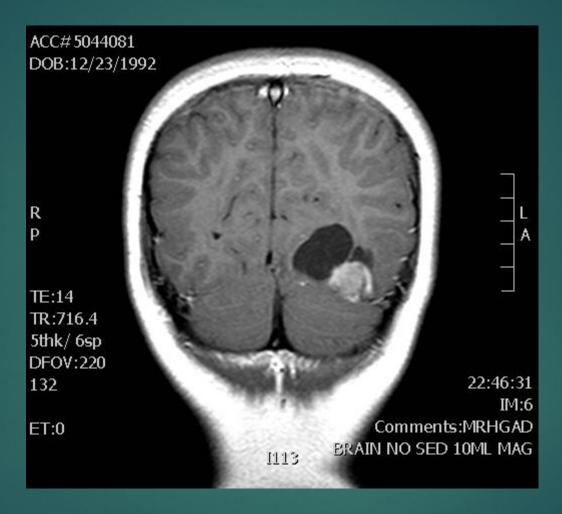
Except for VMFC lesioned pts



Gille de la Tourette's: Frontal overactivation Motor tics, echolalia, coprolalia

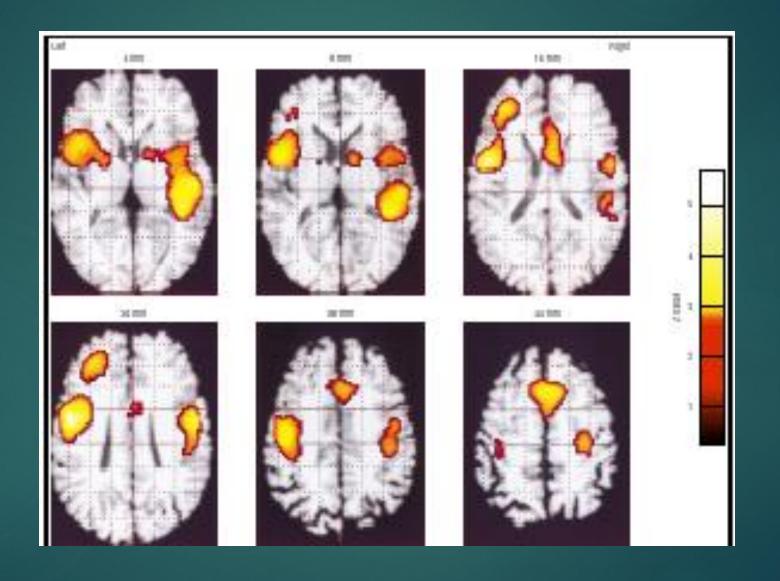


Ganglioglioma

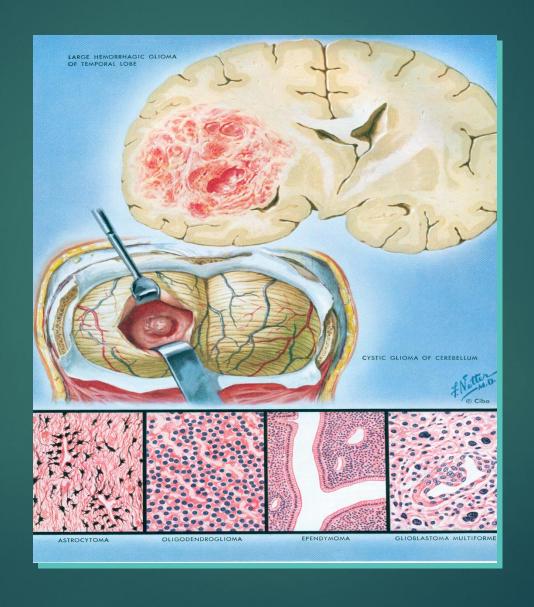


rare, slow-growing primary central nervous system (CNS) tumor which most frequently occurs in the temporal lobes of children and young

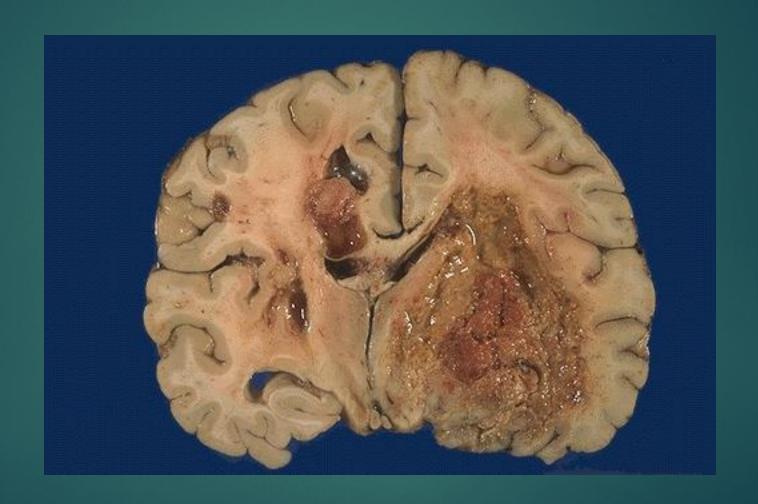
Gille de la Tourette's: Activation of the brain during tics



Gliomas: originate in glial cells



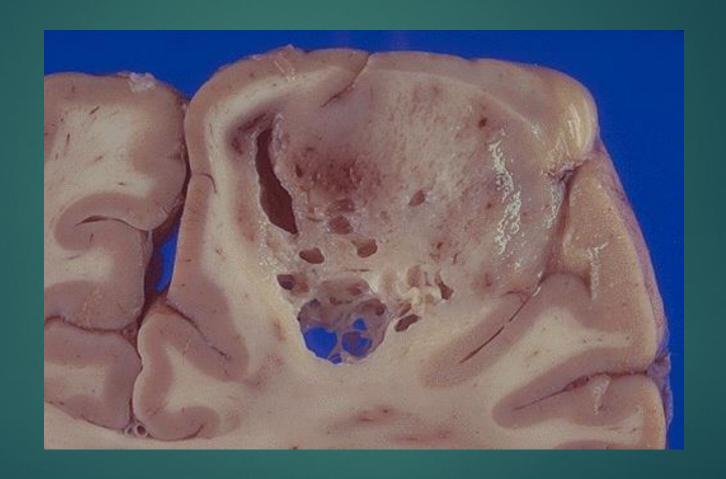
Glioma: Glioblastoma Multiforme



Glioma 2



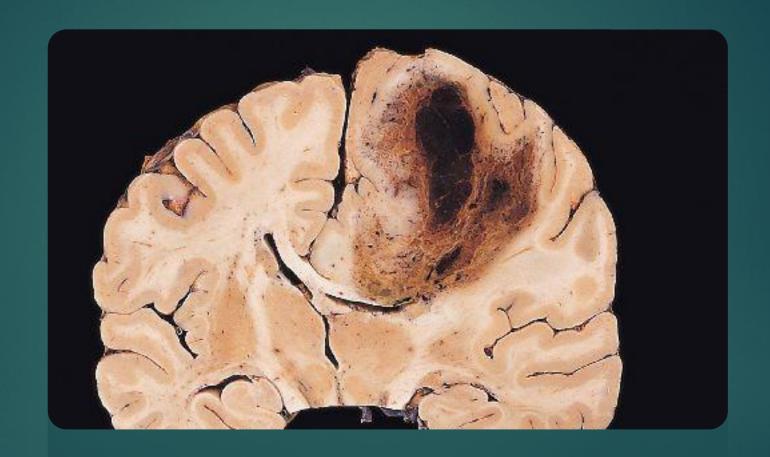
Glioma 3



Glioblastoma Multiforme



Hemorrhagic glioblastoma multiforme with subfalcine herniation



Subfalcine herniation: most common cerebral herniation pattern, is characterized by displacement of the brain (typically the cingulate gyrus) beneath the free edge of the falx cerebri due to raised intracranial pressure.

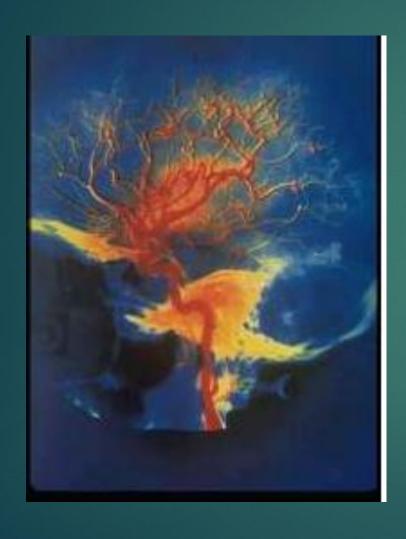


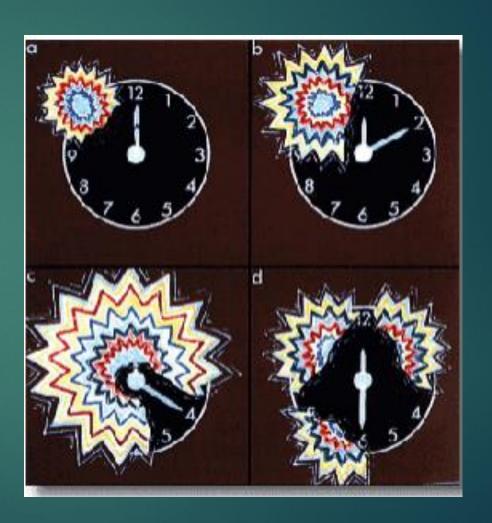
Glioma of the brainstem (midbrain)

Headaches

- The brain itself has no pain receptors and is not a source of head pain.
- Pain sensitive structures in the <u>head and face include the skin, bone and structures in the eyes, ears, nose and mouth</u>. Also, the <u>large blood vessels of the head are exquisitely sensitive and these are the principal organs causing pain in vascular headaches, such as migraines</u>. The jaw hinge (called the temporomandibular joint) and the teeth can also generate headache.
- ► The most common type of headache is the tension or muscle contraction type, which is frequently caused by spasms in the neck muscles and the muscles of mastication (chewing). This type of headache is usually treated easily by over-the-counter medications

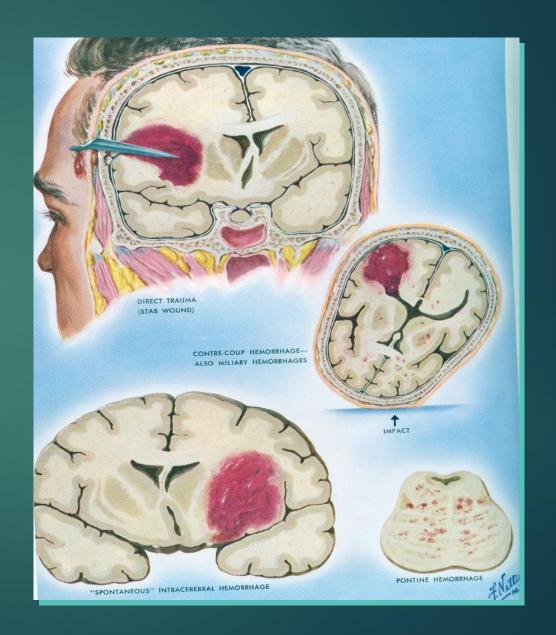
MRI & Fortification Spectra





Hematomas: Bleeds in brain

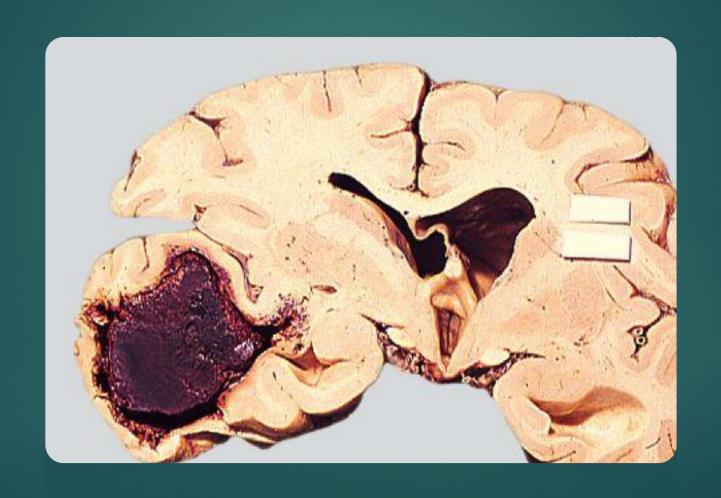
A hematoma is a pathologic collection of blood in body tissues, outside of blood vessels.



Traumatic intracerebral hematomas

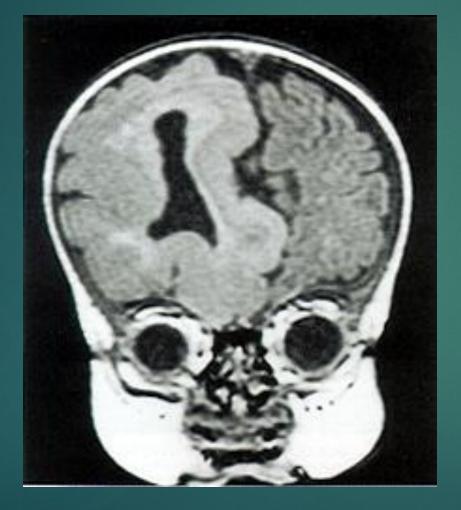


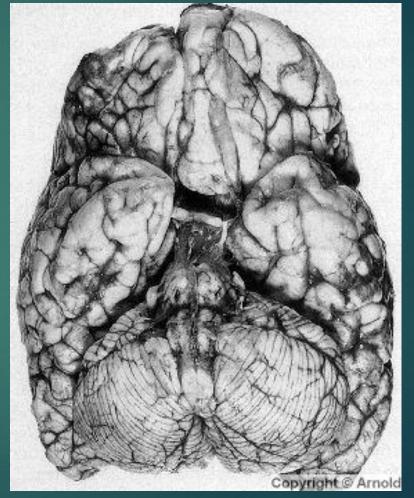
Traumatic temporal lobe hematoma: may occur in a delayed fashion a day or two after injury



Hemimegalencephaly

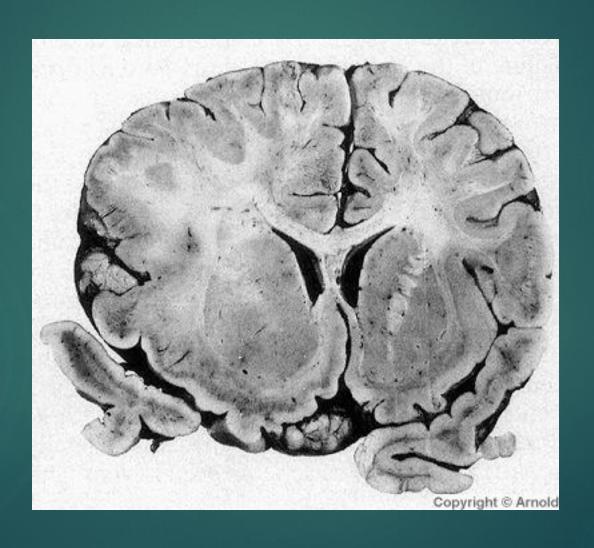
Enlargement of one cerebral hemisphere associated with intractable seizures May lead to hemispherectomy



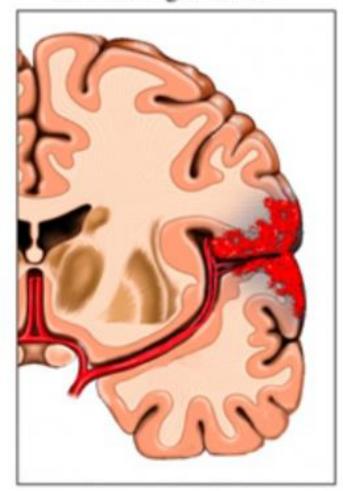


Burger et al., Surgical Pathology of the Nervous System and its Coverings, 4th Ed, 2002

Hemimegalencephaly

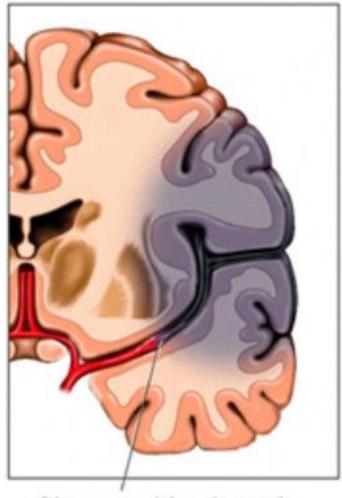


Hemorrhagic Stroke



Hemorrhage/blood leaks into brain tissue

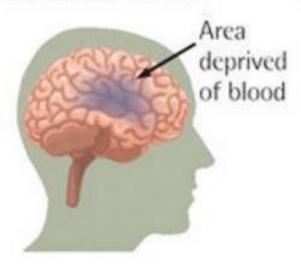
Ischemic Stroke

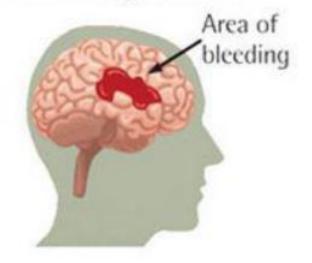


Clot stops blood supply to an area of the brain

Ischemic Stroke

Hemorrhagic Stoke





Blood Deprivation

Obstruction blocks blood flow to part of the brain

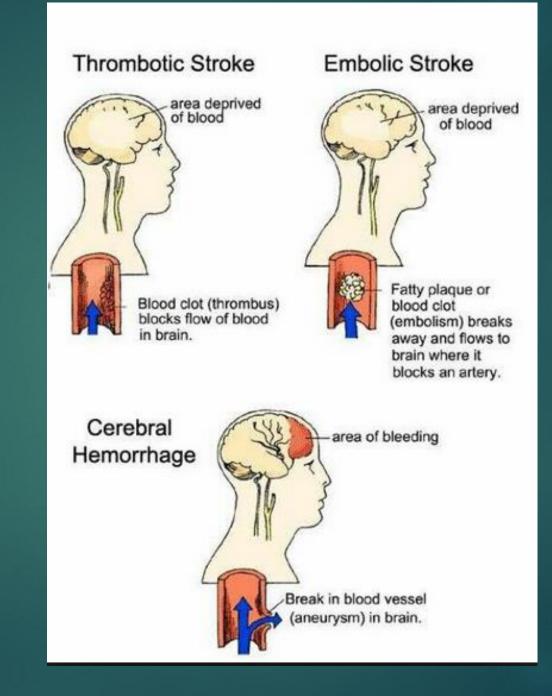


Weakened vessel wall ruptures, causing bleeding in the brain

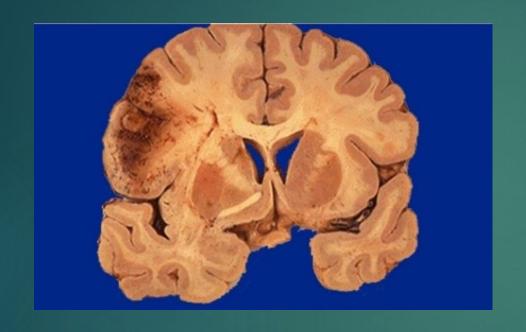


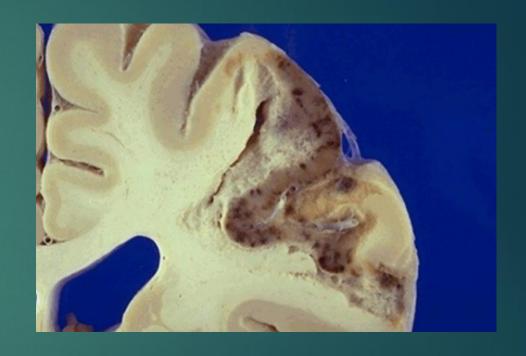
Blood Excess

Thrombotic vs Embolic Strokes



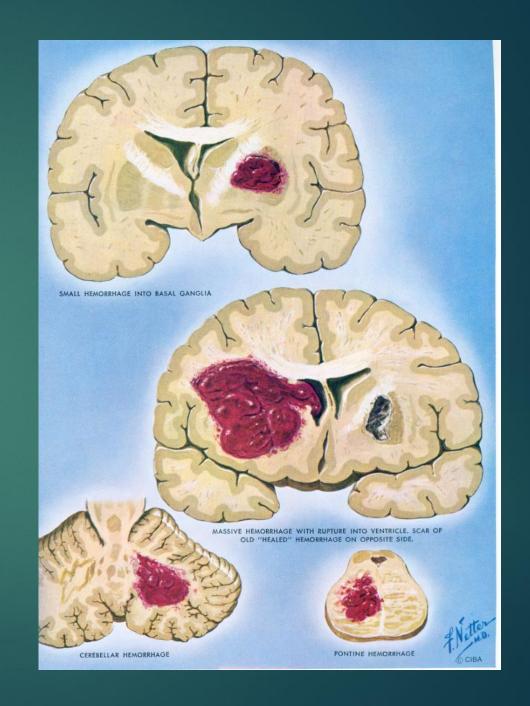
Embolic stroke with edema





Hemorrhages

Hemorrhage is active or ongoing bleeding.



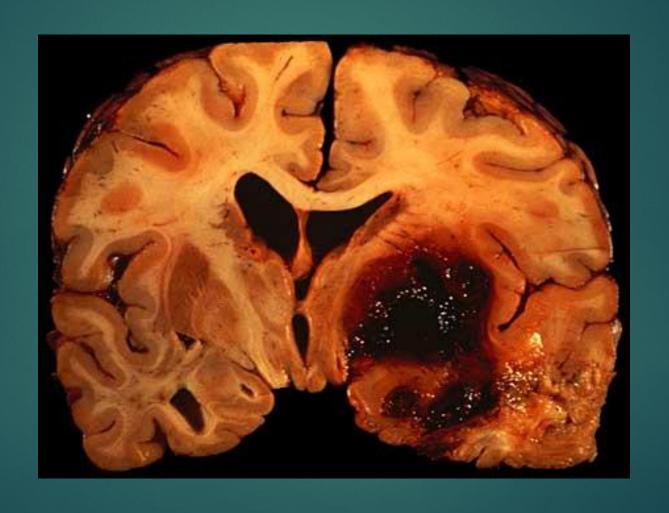
Infarct

focal tissue necrosis owing to insufficient local blood supply

= Ischemia



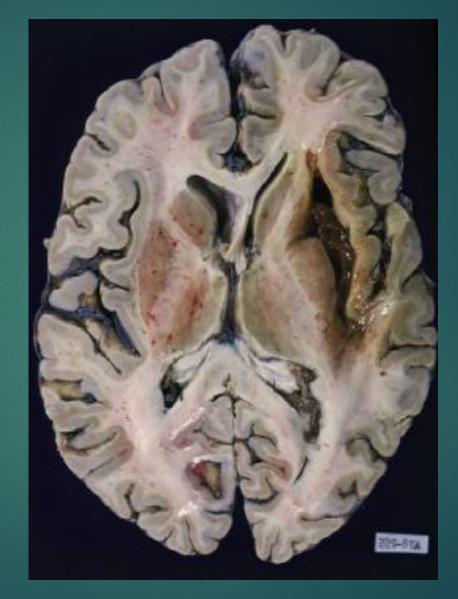
Hemorrhagic Stroke



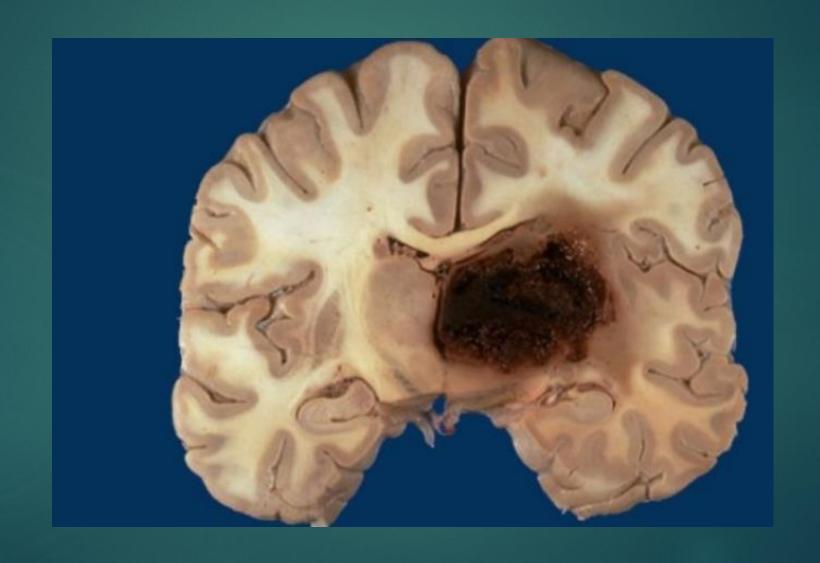
Hemorrhagic Stroke due to Cocaine use



Hemorrhage: Hypertensive



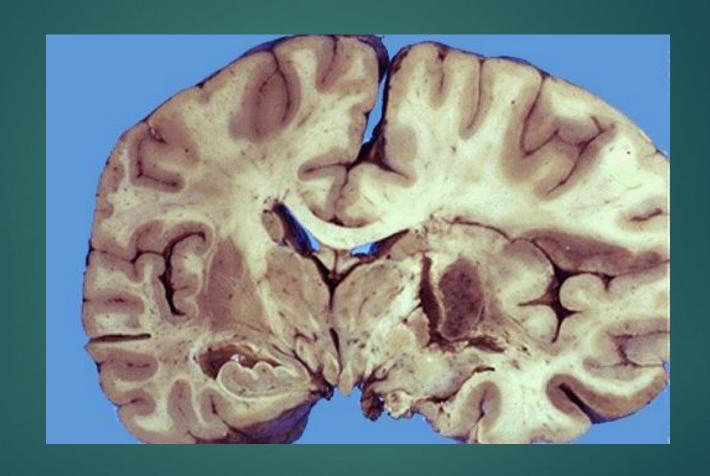
Basal Ganglia Hemorrhage due to hypertension



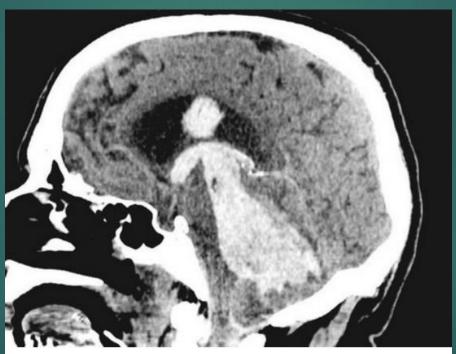
MCA stroke



Hemorrhage: Thrombotic (obstructive)



Ghost in the Machine: A strange shaped hemorrhage



A hemorrhage in an elderly man's brain revealed itself in a startling way. (The *New England* Journal of Medicine (c)2009)

Viral Encephalitis

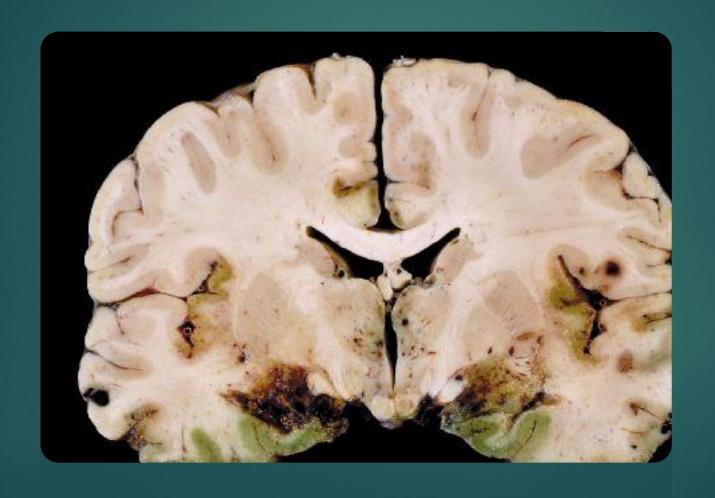
Infectious causes of chronic meningitis

- Tuberculosis
- Cryptococcosis
- Coccidioidomycosis
- Histoplasmosis
- Candidiasis
- Blastomycosis
- Syphilis
- Brucellosis
- Toxoplasmosis
- Nocardiosis
- Lyme disease
- Actinomycosis

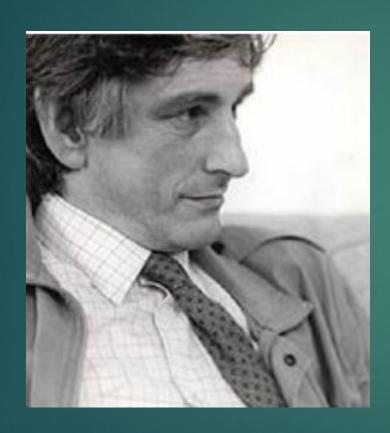
Herpes Simplex Viral (HSV) Encephalitis



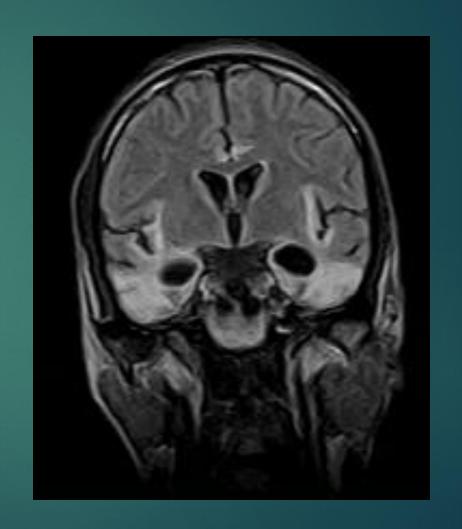
Herpes encephalitis (note jaundice also)



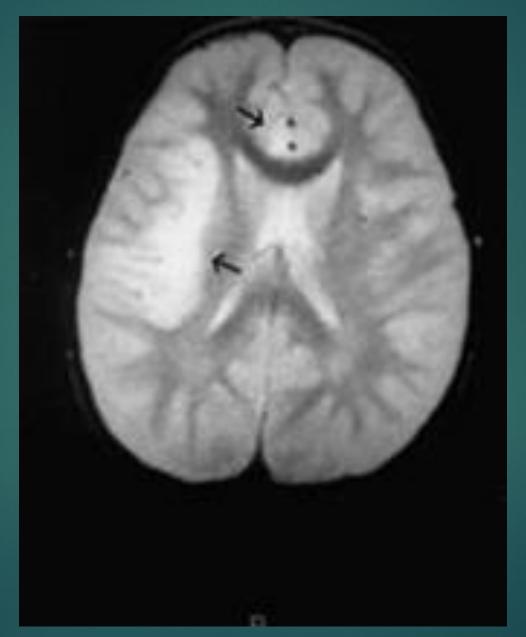
Herpes Encephalitis: MRI



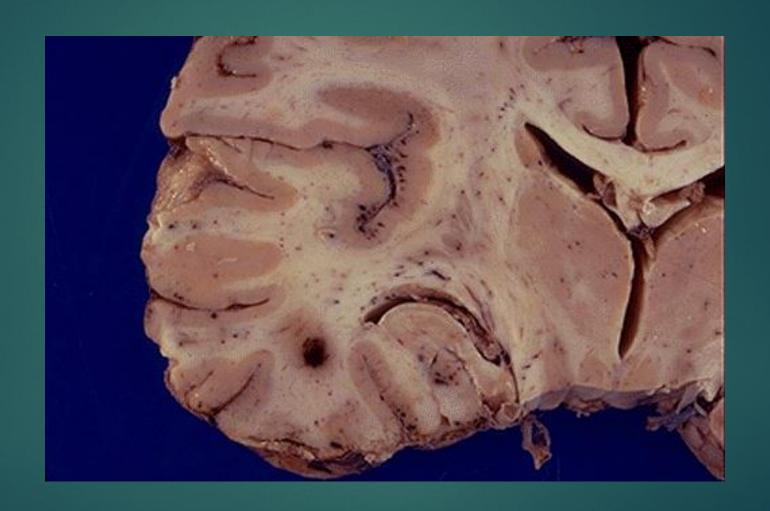
Clive Wearing



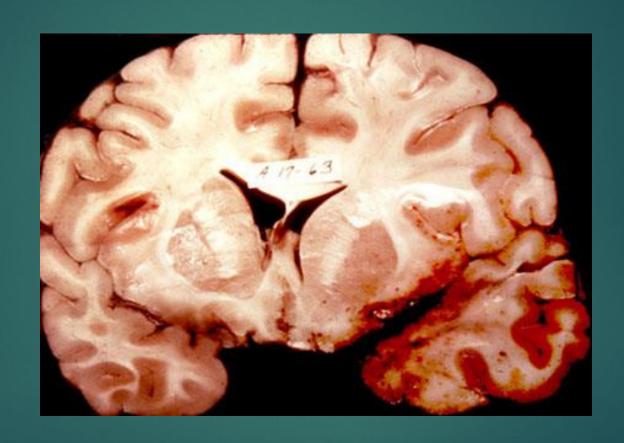
Herpes encephalitis



Herpes Simplex



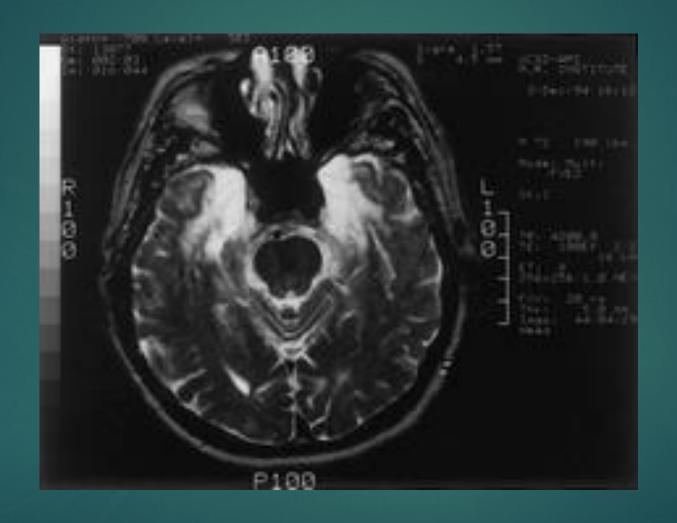
Herpes Encephalitis



Herpes Encephalitis

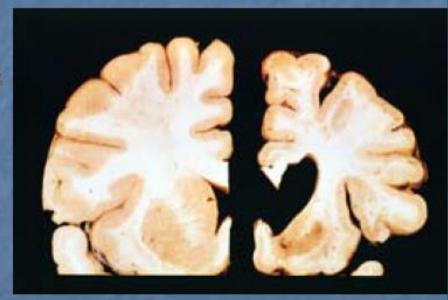


Hippocampal Damage

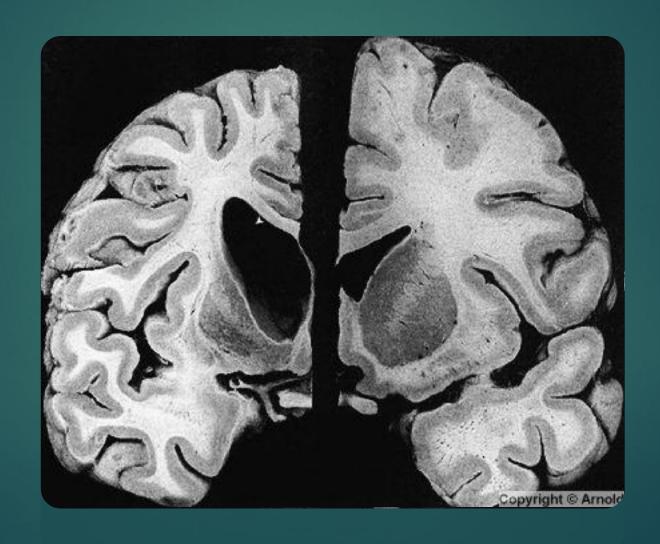


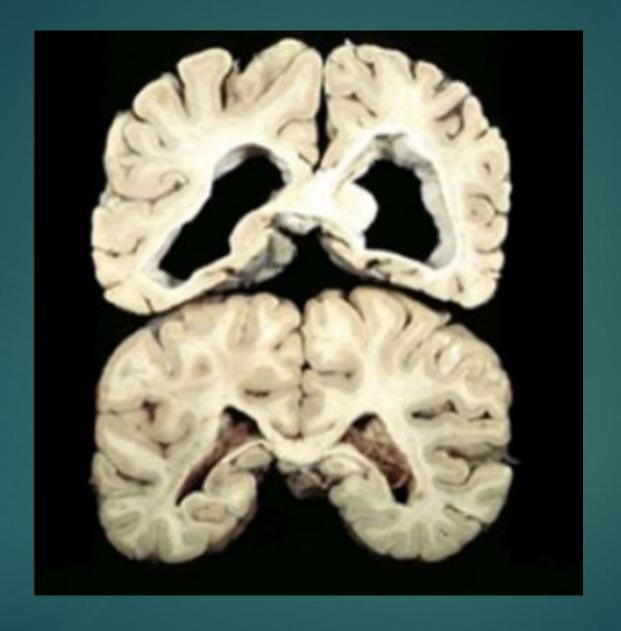
Huntignton Disease

- Hereditary
- Progressive
- Extrapyramidal motor
- Choreaform movements
- Huntington gene
 - Trinucleotide repeats
 - CAG
 - Normal 6-34 copies
 - HD has 50-70 repeats
- Caudate nucleus atrophy
- Suicide and infections



Huntington's chorea: autosomal dominant disease with onset in middle life. Note atrophy of caudate nucleus

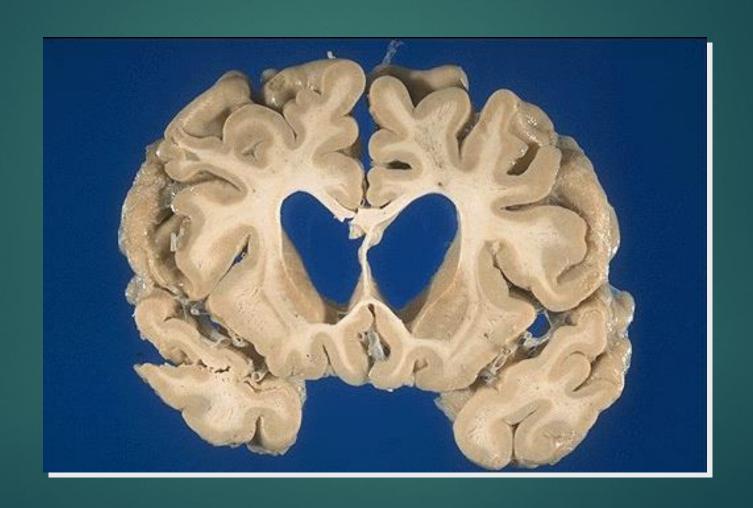




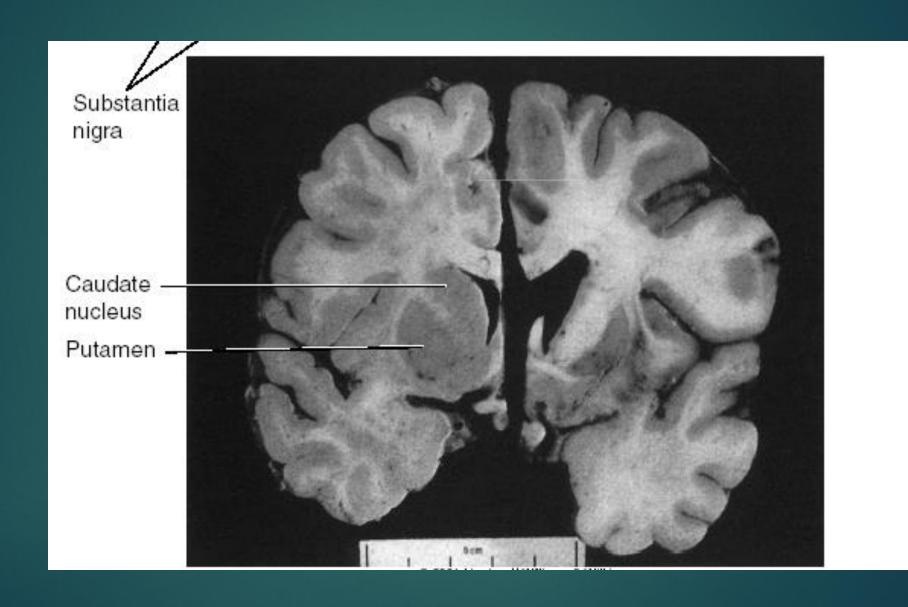
Huntington's

Normal

Huntington's Disease: Atrophy of Caudate Nucleus



Huntington's Neuropathology

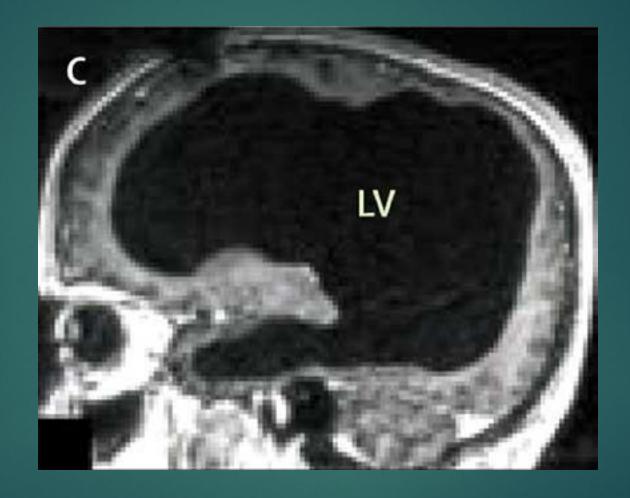


What will you see on CT?

- A 44-year-old man presented with a 2-week history of mild left leg weakness.
- ► At the <u>age of 6 months</u>, he had undergone a ventriculoatrial shunt, because of <u>postnatal hydrocephalus</u> of unknown cause. When he was <u>14 years old</u>, he developed ataxia and paresis of the left leg, which resolved entirely after shunt revision.
- ► His neurological development and medical history were otherwise normal. He was a married father of two children, and worked as a civil servant, a tax collector.
- On neuropsychological testing, he proved to have an IQ of 75: his verbal IQ was 84, and his performance IQ 70.

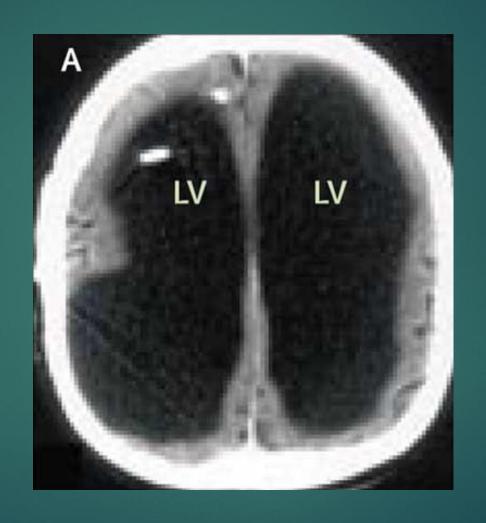
Lancet 2007; 370: 262

French Tax Man, 2007



Hydrocephalus at 6m; shunted until 14; leg weakness led to MRI

French Tax Man 2

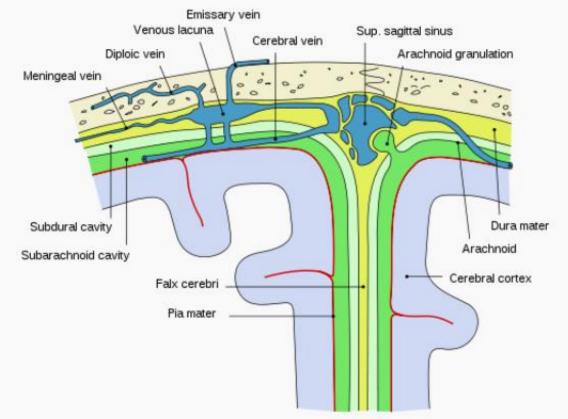


Taxman 3

- ► CT showed <u>severe dilatation of the lateral ventricles; MRI revealed massive</u> enlargement of the lateral, third, and fourth ventricles, a very thin cortical mantle and a posterior fossa cyst.
- ► We diagnosed a <u>non-communicating hydrocephalus</u> (flow of CSF is blocked along one or more of the narrow passages connecting the ventricles), with probable stenosis of Magendie's foramen
- The leg weakness improved partly after neuroendoscopic ventriculocisternostomy, but soon recurred;
- ► After a <u>ventriculoperitoneal shunt</u> was inserted, the findings on neurological examination became normal within a few weeks. The findings on <u>neuropsychological testing and CT did not change</u>.

- ► Arachnoid granulations are small protrusions of the arachnoid through the dura mater.
- ➤ They protrude into the venous sinuses of the brain, and allow cerebrospinal fluid (CSF) to exit the subarachnoid space and enter the blood stream.

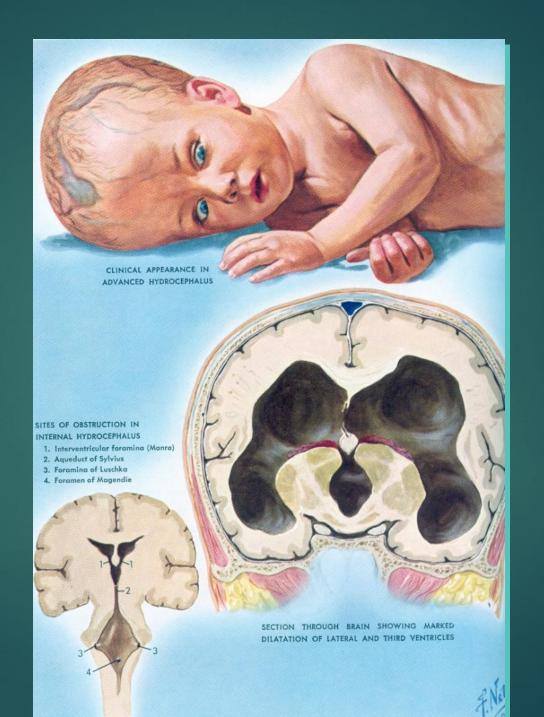
Arachnoid granulation

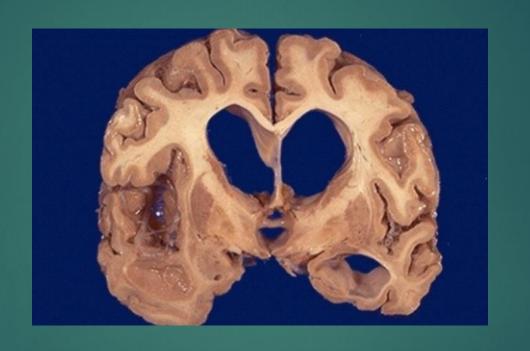


- Noncommunicating: Can't get out of ventricles
- Communicating: CSF can't get to arachnoid granulations





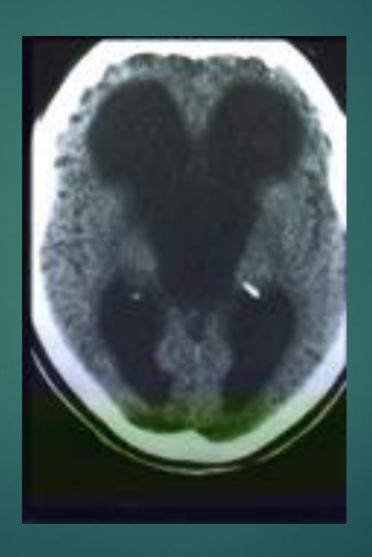






Hydrocephalus

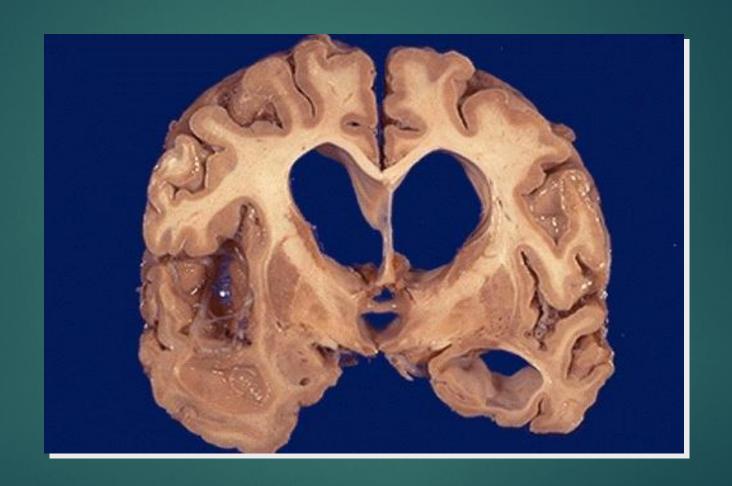
Hydrocephalus MRI

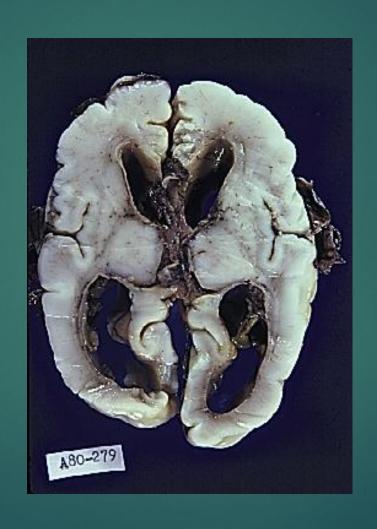


Hydrocephalus: Outside

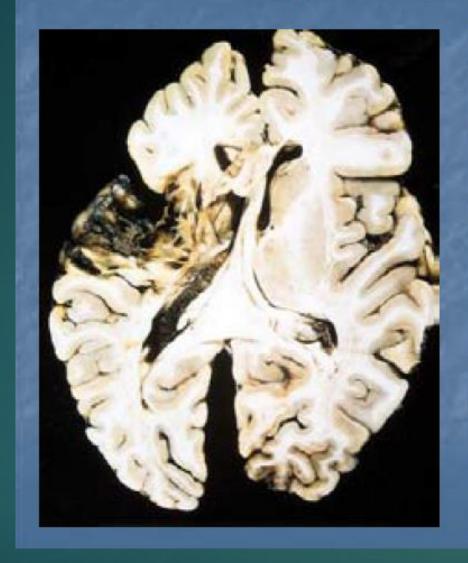


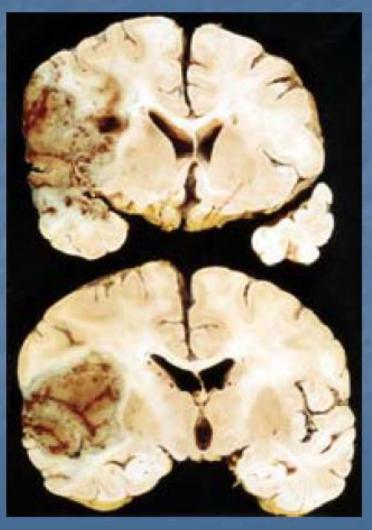






Ischemic Infarcts





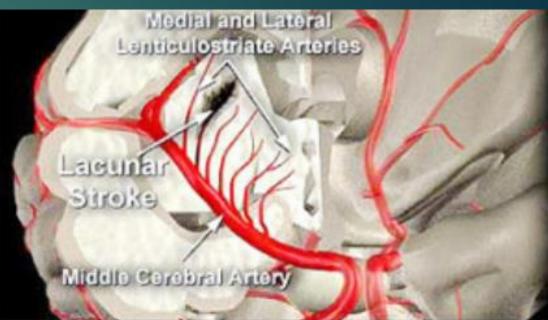
Blockage: oxygen deprivation beyond the blockage

Occlusive (ischemic) CVA



Lacunar Infarcts

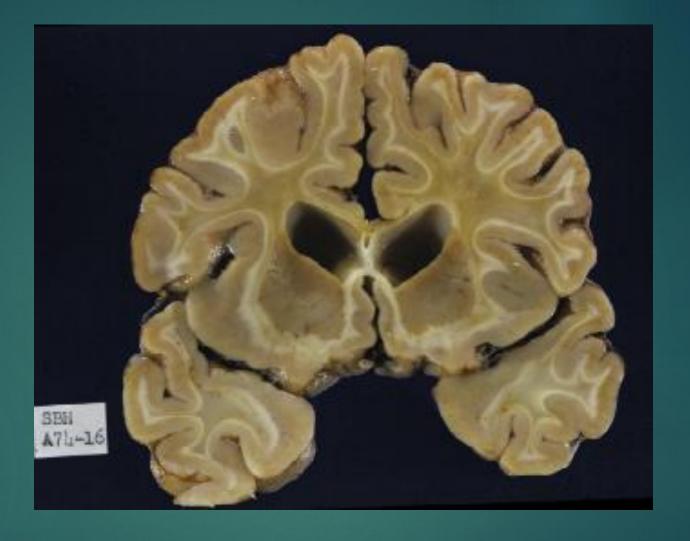




Stroke that results from occlusion of one of the penetrating arteries that provides blood to the brain's deep structures.

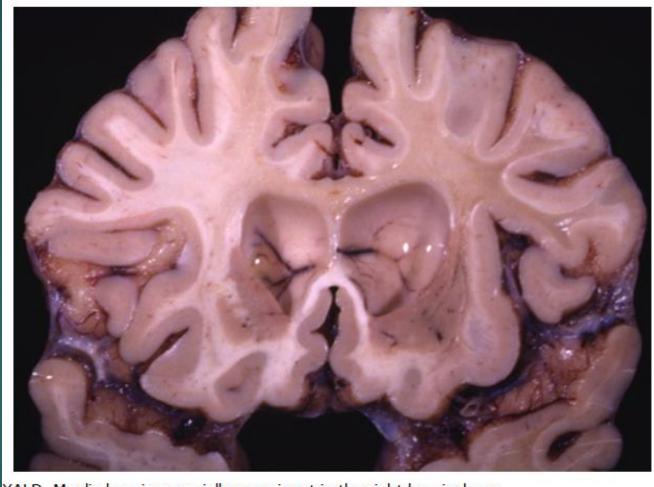
Leukodystrophy

Where is White Matter?



Progressive loss may appear in body tone, movements, gait, speech, ability to eat, vision, hearing, and behavior. There is often a slowdown in mental and physical development.

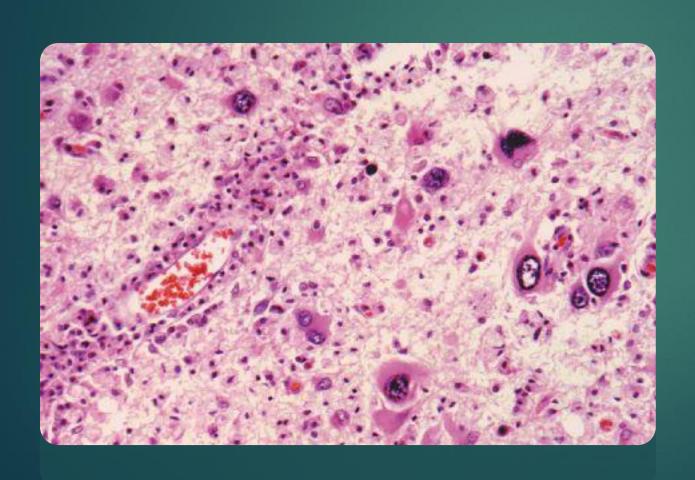
Adrenoleukodystrophy: Myelin loss

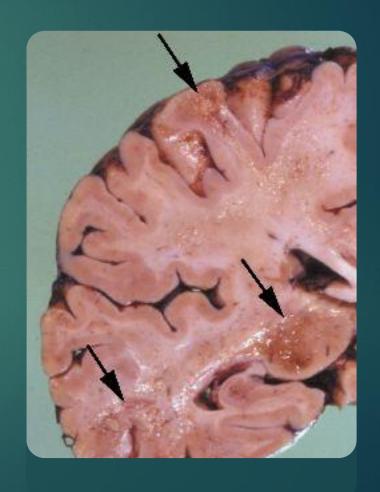


XALD. Myelin loss is especially prominent in the right hemisphere.

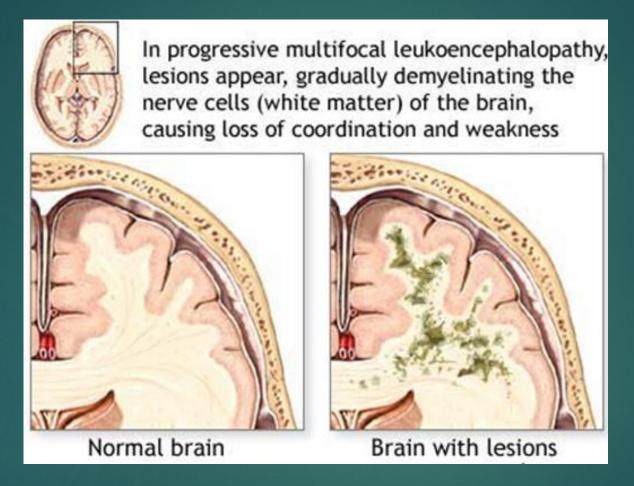
The initial abnormalities are <u>apathy and behavioral change</u>. <u>Visual loss, spasticity, and ataxia follow, and patients usually die a few years later.</u>

Progressive multifocal encephalopathy (PML): JC virus with immunosuppressed state = white matter disease



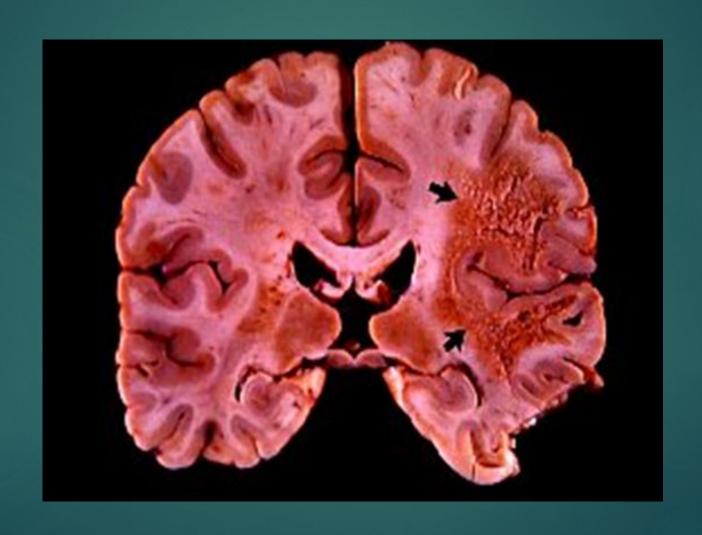


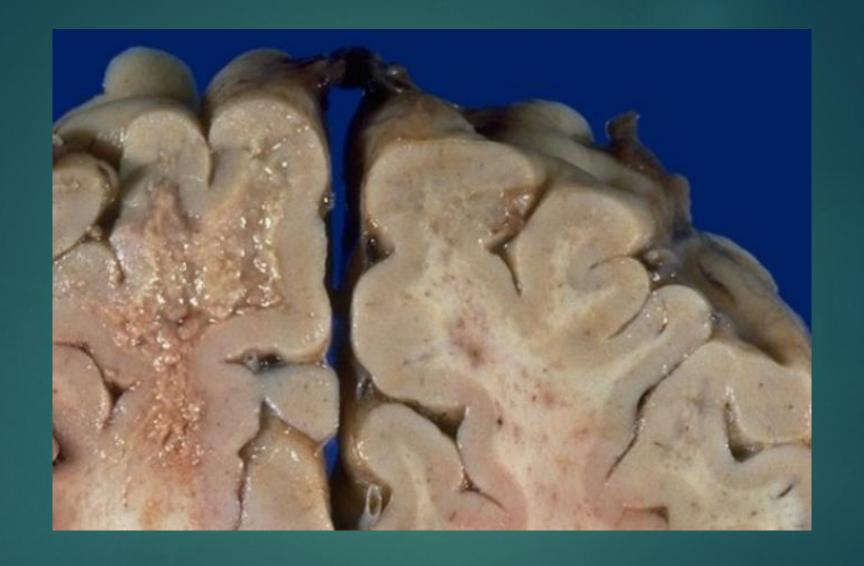
Multifocal leukoencephalopathy: JC virus



Progressive multifocal leukoencephalopathy (PML) is a viral encephalitis caused by the JC polyomavirus; because the virus preferentially infects oligodendrocytes, demyelination is its principal pathologic effect.

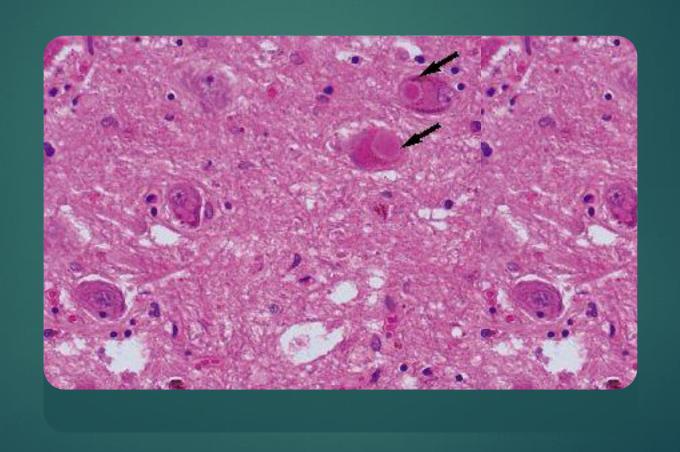
Multifocal leukoencephalopathy





Progressive Multifocal Leukoencephalopathy

Lewy bodies: seen in Parkinson's disease (substantia nigra and locus ceruleus) and in Lewy body dementia (cerebral cortex)



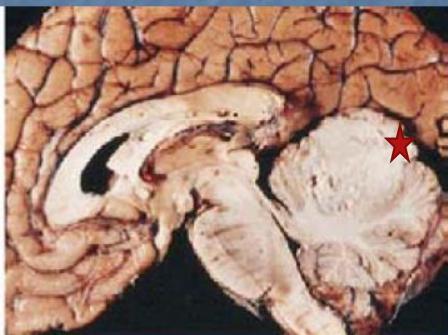
Lissencephaly: Gyral Flattening



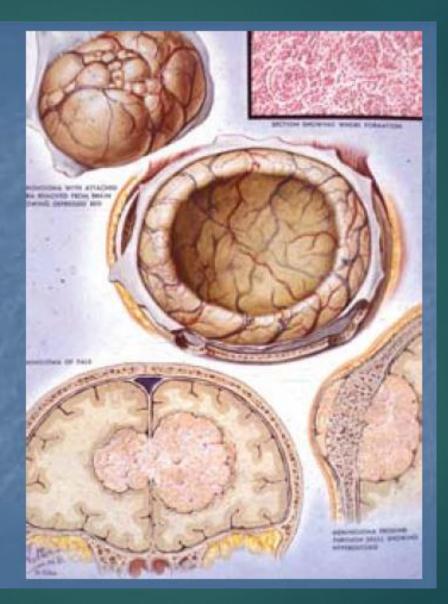
Meduloblastoma

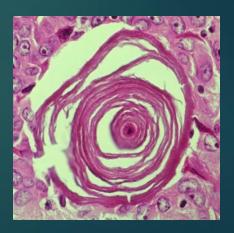
- Children
- Midline cerebellum
- Subarachnoid spread



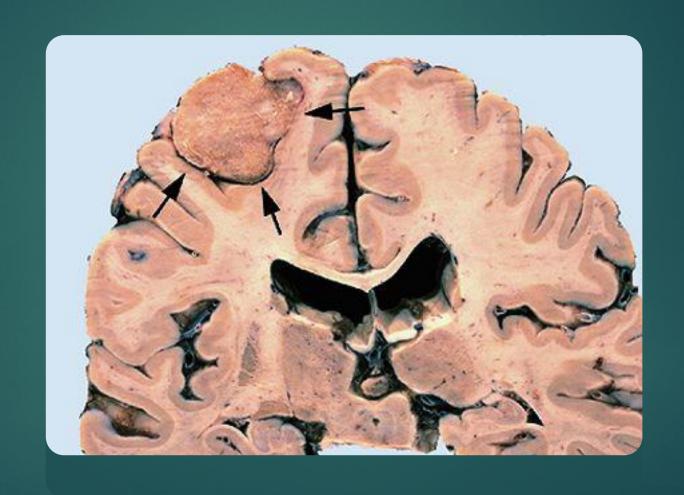


- Arise from meninges
- Benign in a biological sense
- Consider where it is
- Fibroblast looking
- Cells in whirls and clusters
- Psammoma bodies

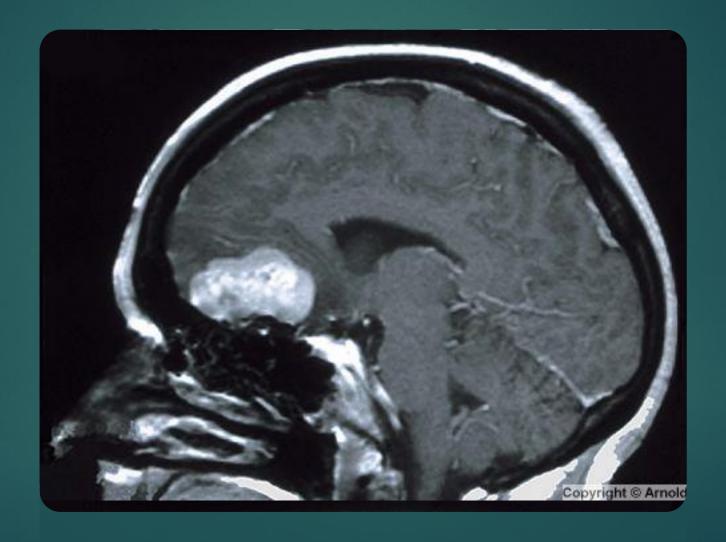




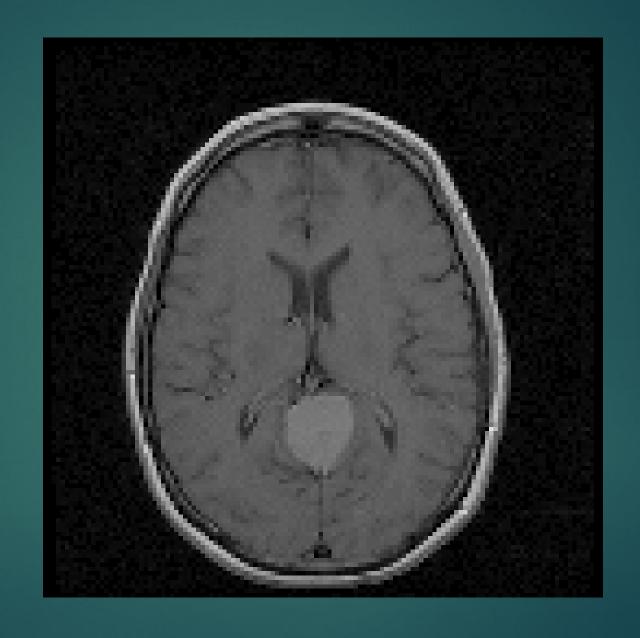
A meningioma in a common location, over the frontal convexity



Menigioma in subfrontal (olfactory) area







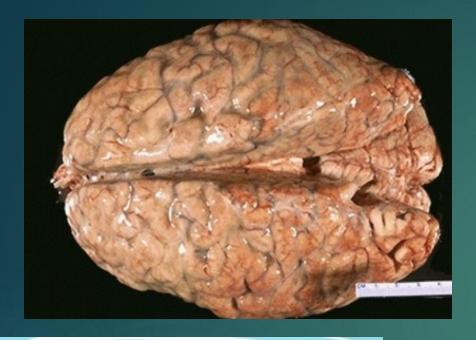


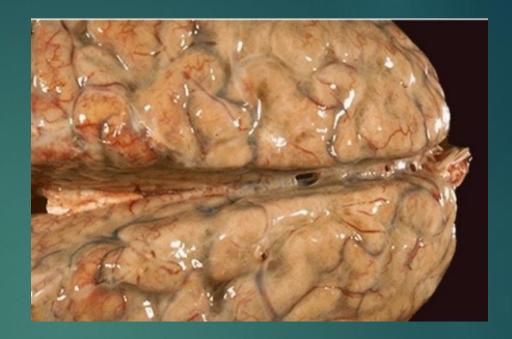
Meningioma 3



Meningioma 4: Supraorbital

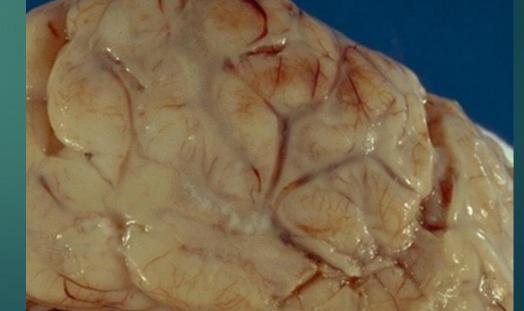






Infectious causes of chronic meningitis

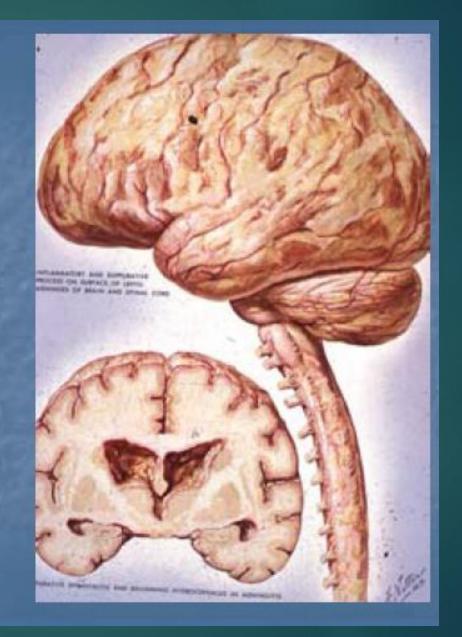
- Tuberculosis
- Cryptococcosis
- Coccidioidomycosis
- Histoplasmosis
- Candidiasis
- Blastomycosis
- Syphilis
- Brucellosis
- Toxoplasmosis
- Nocardiosis
- Lyme disease
- Actinomycosis



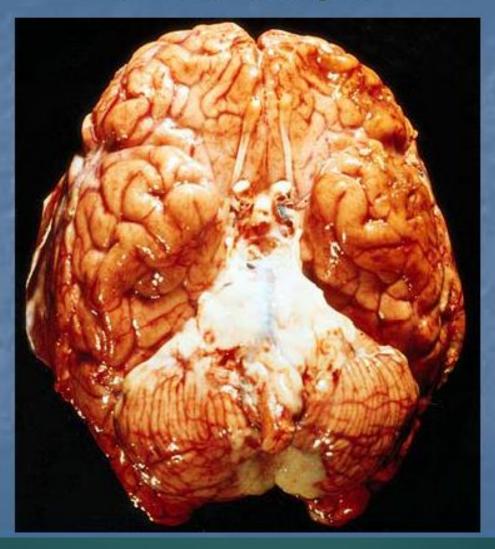
Acute Meningitis

Bacterial Meningitis

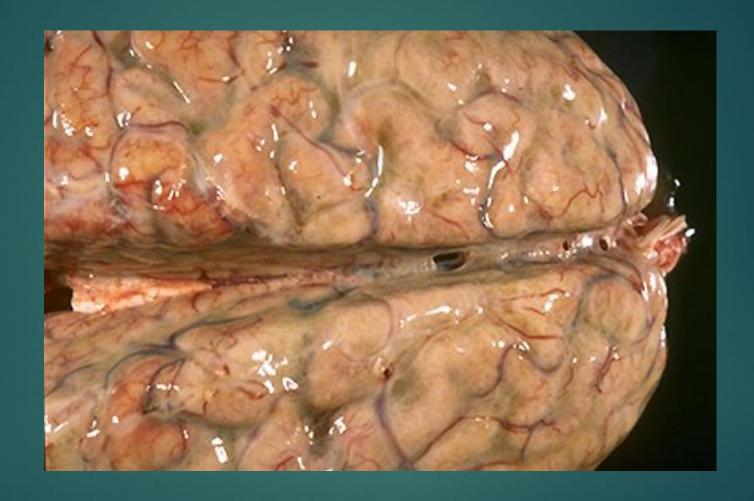
- Exudate over cerebral hemispheres
- Bacteria grow in CSF
- CSF
 - Cell count
 - Glucose
 - Protein
- Age of patient
- Complications
 - Scarring
 - Epilepsy
 - Abscess



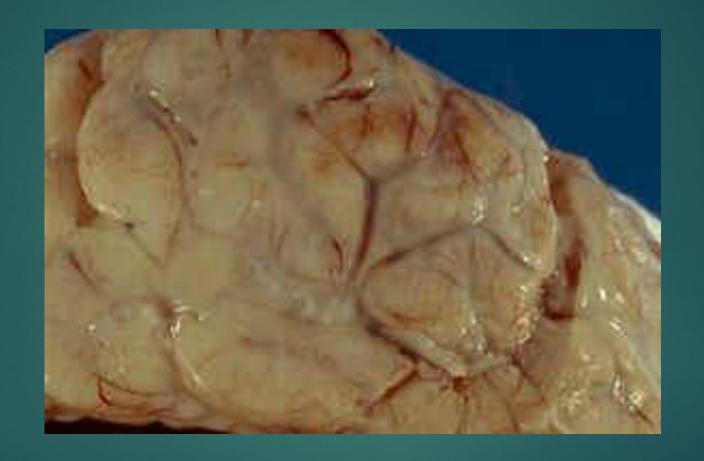
Bacterial Meningitis



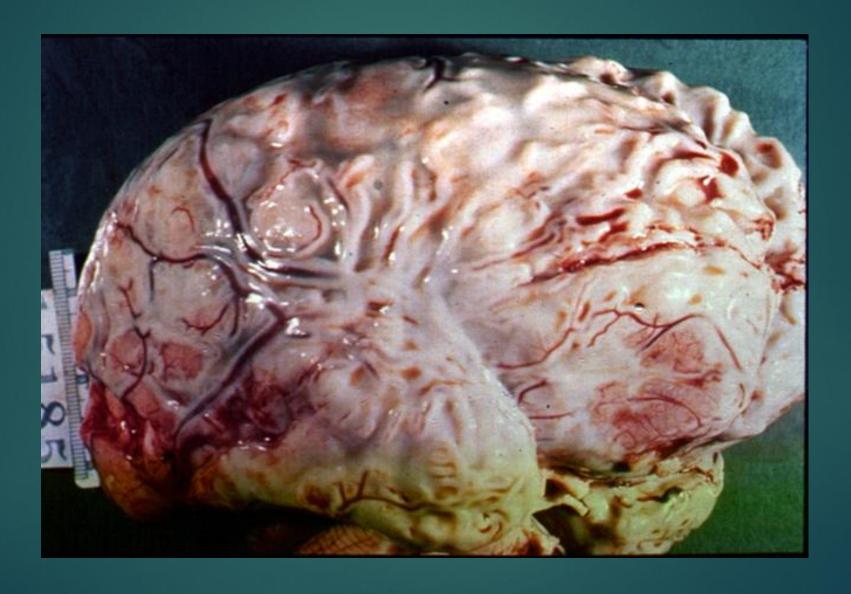
Meningitis



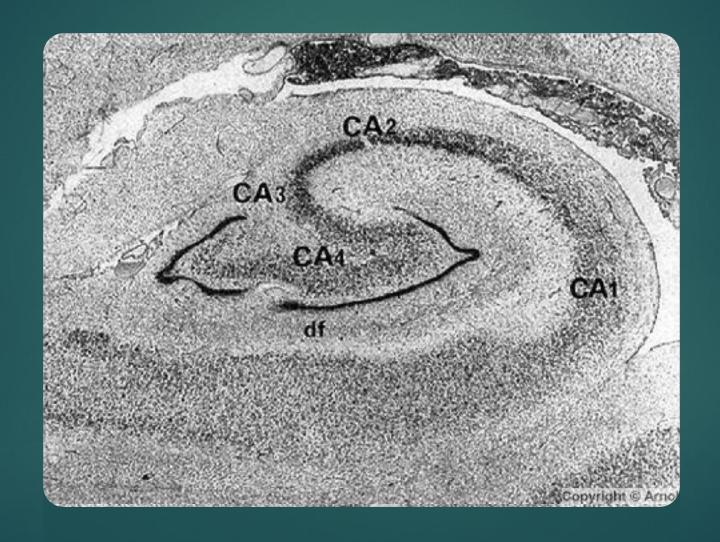
Meningitis 2



Meningitis



Normal hippocampus



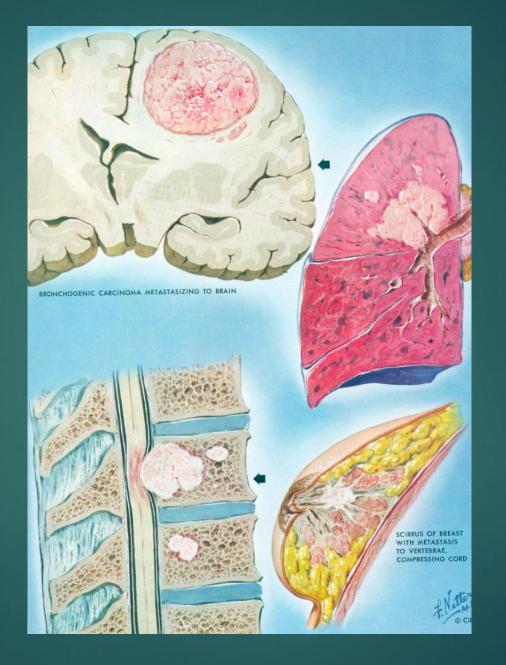
Hippocampal sclerosis: severe neuronal loss in chronic temporal lobe epilepsy



Mesial temporal lobe epilepsy: hippocampal atrophy (mesial temporal sclerosis=MTS)



Metastatic Lesions



Metastasis



Metastasis: Lung



Metastatic lung carcinoma in left frontal lobe



Cerebral edema and brain swelling around a metastatic small cell anaplastic lung carcinoma in the left frontal lobe.

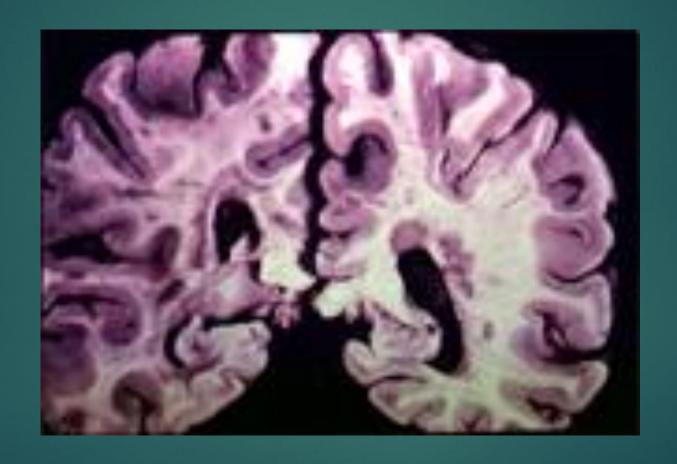


Multiple Sclerosis

- Lesions dispersed in space and time
- Come and goes
- Symptoms
 - Optic nerve
 - Urination
 - Heat makes worse
 - Weakness
- Degeneration of white matter
- Plaques



Multiple Sclerosis 1



Multiple Sclerosis 2: demyelinating white matter lesions





Multiple Sclerosis

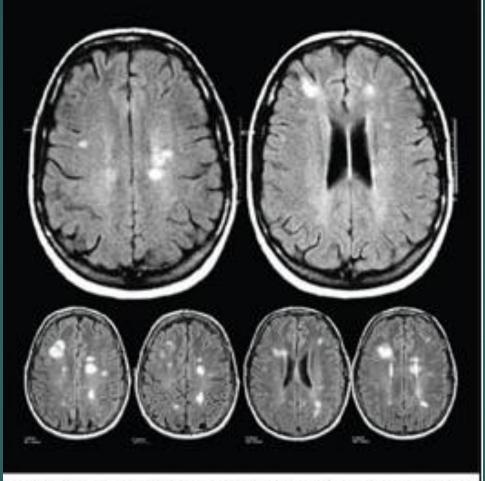
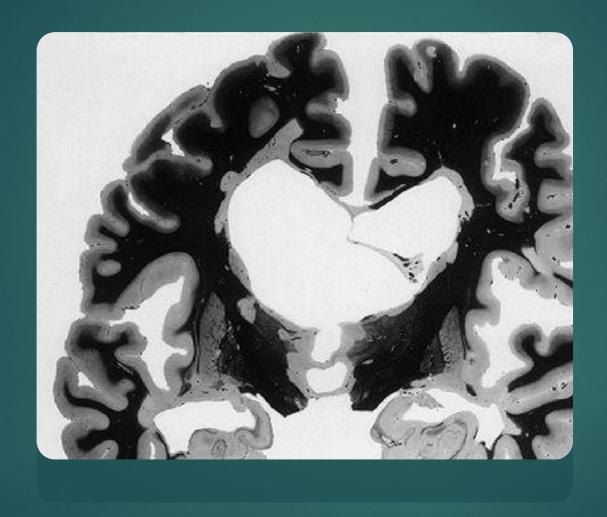


Figure 2. MRI showing brain lesions (white) in a patient with multiple sclerosis. Source: Courtesy of the Canadian Network of MS Clinics.

► MS: chronic periventricular lesions

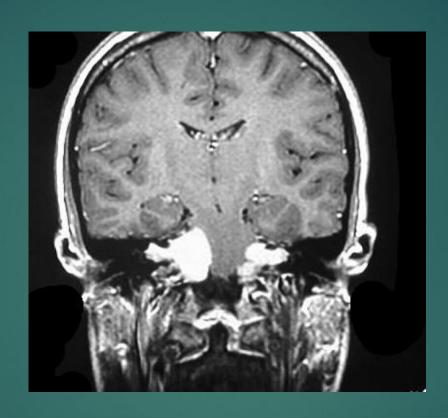


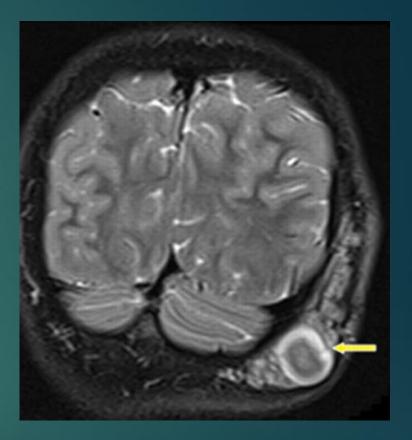


Multiple Sclerosis

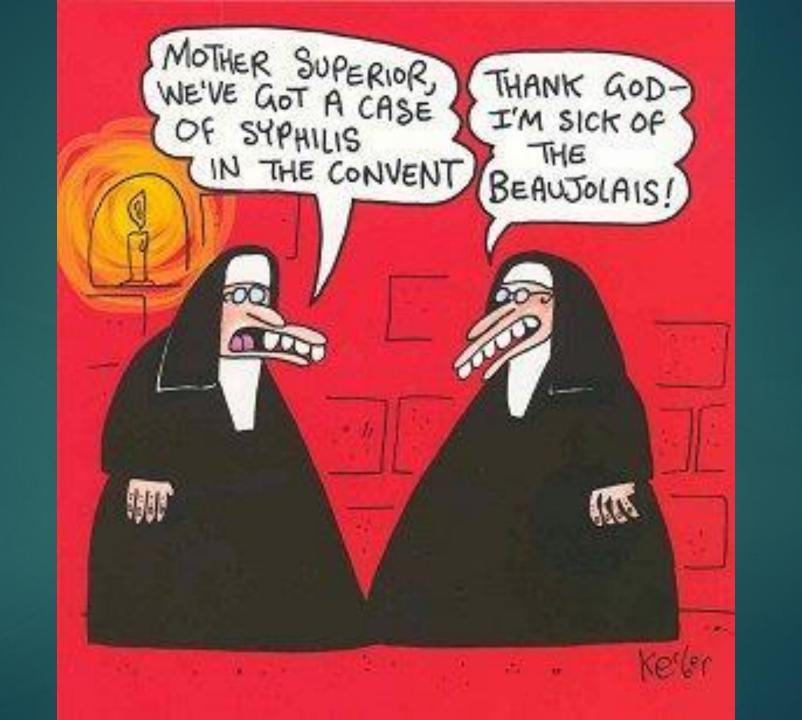
Neurofibromatosis







Genetic disorder that cause tumors to grow in the nervous system

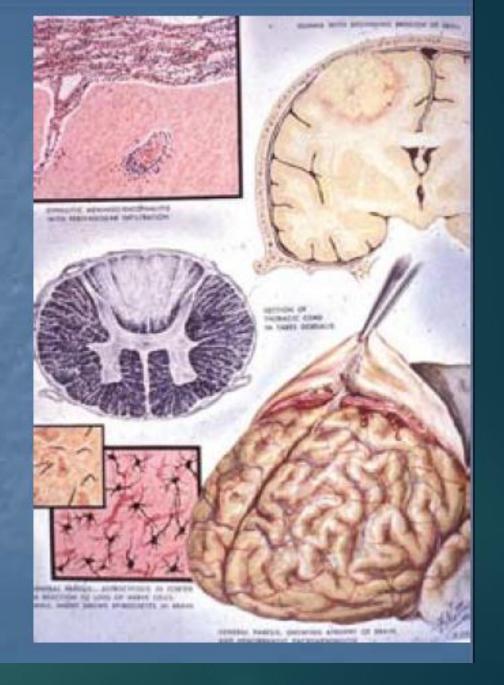


Arteritis = Inflammation
Of walls of arteries

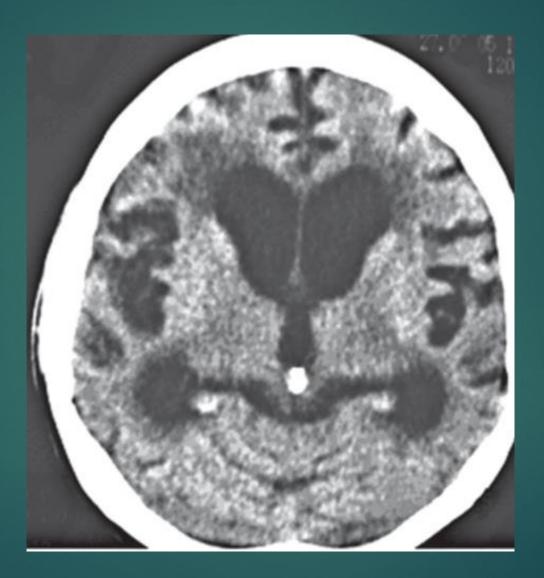
Tabes dorsalis =
Loss of coordination
Of movement;
syphilitic myelopathy,

Tertiary Syphilis

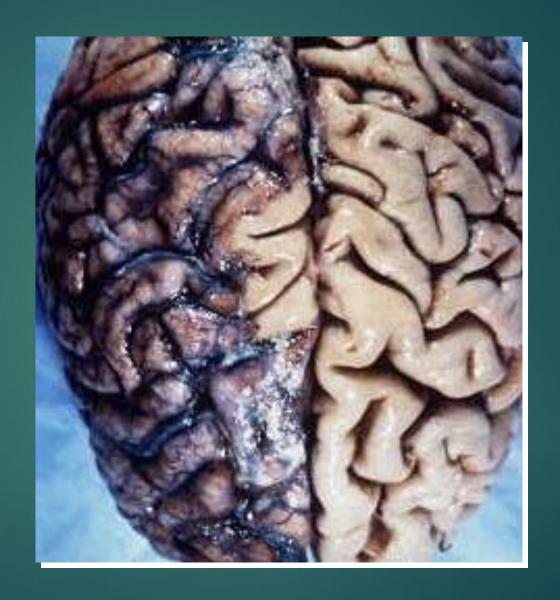
- Years after initial infection
- Obliterative end arteritis
- Meningitis
- Brain proper
- Tabes dorsalis



Neurosyphilis



Neurosyphilis 2



Obesity: F, AC, Hip, BG ↓↓

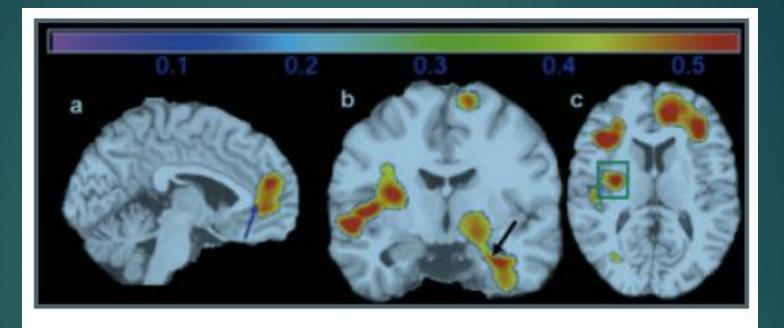


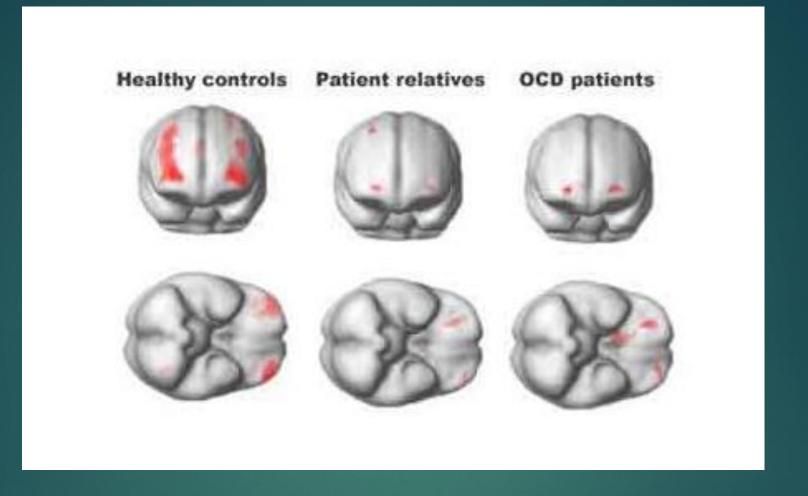
Figure 5.

Correlation map (r-value image) effect sizes for a comparison of 14 obese persons (BMI > 30) to 29 normal weight persons (18.5–25). Obese persons had lower GM and WM volumes in the frontal lobes, anterior cingulate gyrus (a, blue arrow), hippocampus (b, black arrow), and basal ganglia (c, green box). Cor-

Elderly persons with higher adiposity are at increased risk for brain atrophy and consequently dementia.

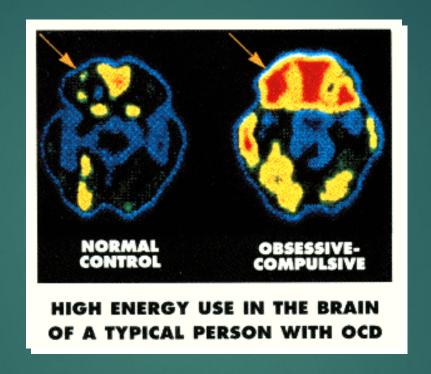
Paul Thompson, 2009

OCD



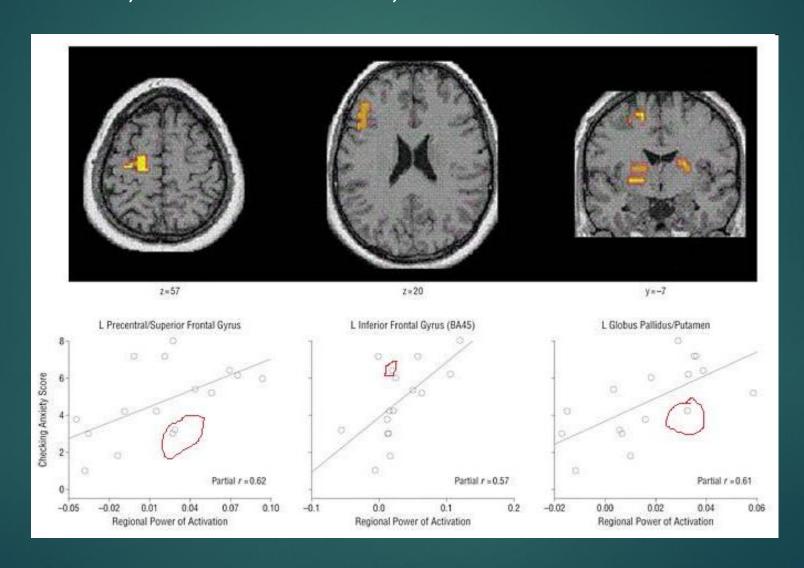
<u>Under-activation in the lateral orbitofrontal cortex</u> (decision making) in both the OCD patients and their family members.

Obsessive Compulsive Disorder: Caudate and Orbitofrontal



OCD patients and their close relatives fared worse on the computer task than the control group. This was associated with decreases of grey matter in brain regions important in suppressing responses and habits - the orbitofrontal and right inferior frontal regions. "Impaired brain function in the areas of the brain associated with stopping motor responses may contribute to the compulsive and repetitive behaviors that are characteristic of OCD.

OCD: Checking Behavior: Precentral Superior Frontal, Inferior Frontal, GP/Putamen



Hoarding

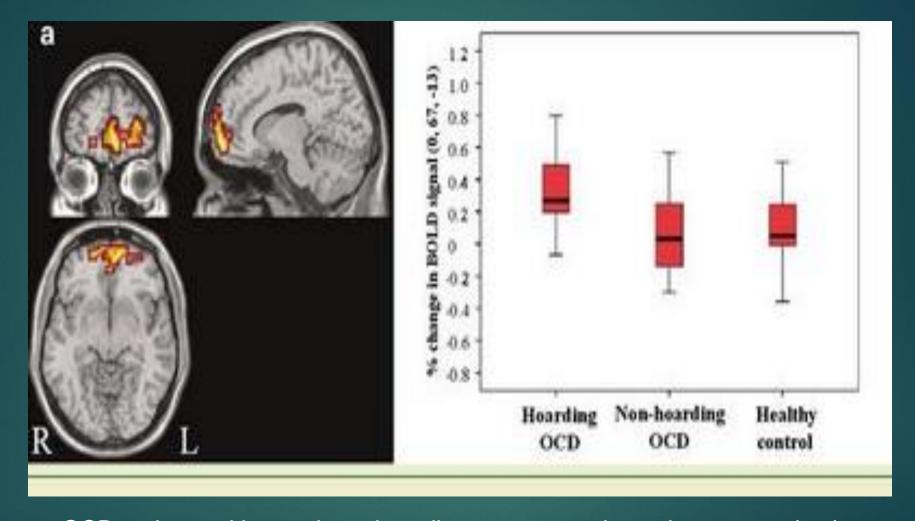
- ► Hoarding patients have <u>significantly lower activity in the dorsal anterior</u> <u>cingulate cortex</u> than non-hoarding OCD patients, and a different pattern of cognitive deficits was found, such as <u>more difficulty making decisions and impaired decision-making</u>.
- Compulsive hoarding syndrome appears to be a discrete entity, with a characteristic profile of core symptoms that are not strongly correlated with other OCD symptoms, distinct susceptibility genes, and unique neurobiological abnormalities that differ from those in non-hoarding OCD.
- ▶ 999 OCD patients in 219 families. Families with two or more hoarding relatives showed a unique pattern on chromosome 14, whereas the other families' OCD was linked to chromosome 3.

OCD: Traumatic Hoarding

- Compulsive hoarding can newly emerge as a result of brain injury.
- ► The greatest lesion overlap in hoarders is in the <u>right medial</u> <u>prefrontal cortex</u>, <u>orbitofrontal</u> <u>cortex</u>, <u>anterior cingulate cortex</u>, <u>and adjacent white matter</u>



OCD: Hoarding

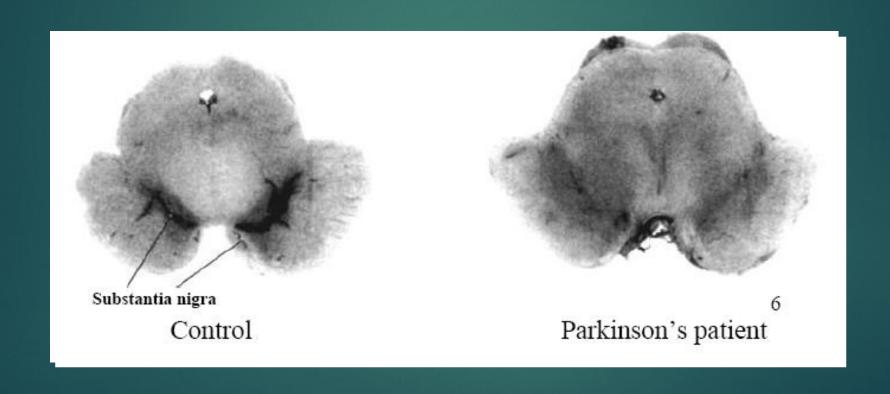


OCD patients with prominent hoarding symptoms showed <u>greater activation</u> in bilateral anterior ventromedial prefrontal cortex (VMPFC) than patients without hoarding symptoms and healthy controls.

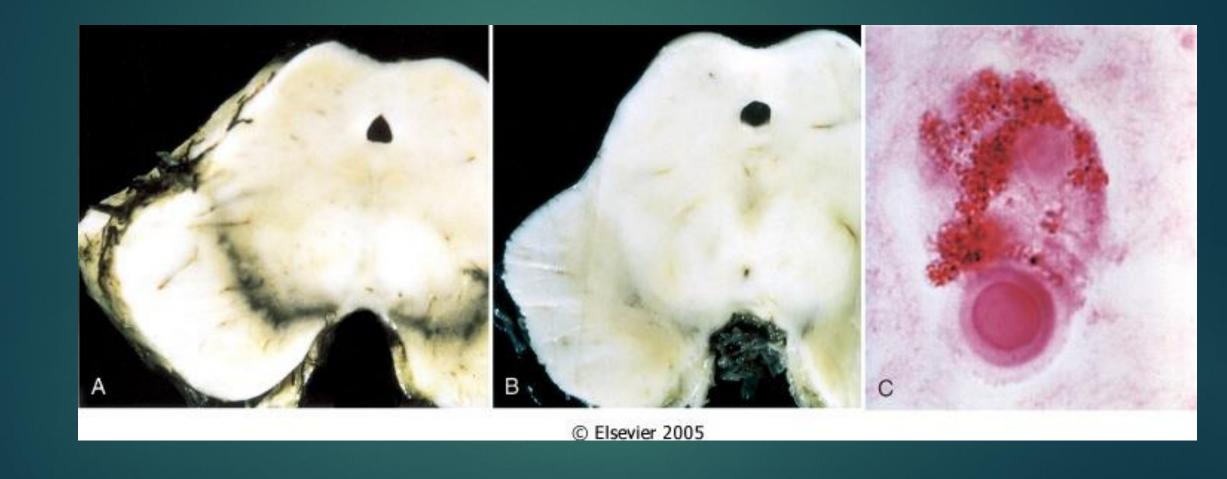
Parkinsonism

- This diagnosis is made in the absence of a toxic or other known underlying etiology
- ► Parkinsonism is a clinical syndrome:
 - diminished facial expression
 - stooped posture
 - slowness of voluntary movement
 - festinating gait (progressively shortened, accelerated steps)
 - rigidity
 - ▶ "pill-rolling" tremor.

Parkinsonism: Depigmentation in substantial Nigra



Parkinson's disease



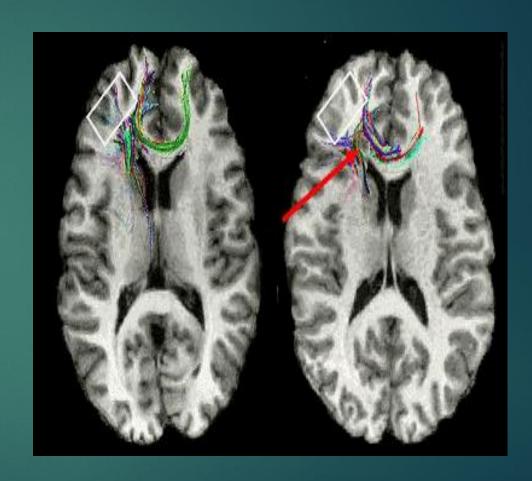
Pedophilia: FMRI Results

- ► Pedophiles had a significant <u>lack of white matter connecting six</u> different areas of the brain all known to play a role in sexual arousal.
- They team found activity in parts of pedophiles' brains were lower than in other volunteers when shown adult, erotic material.
- ► The condition has also been <u>linked to low IQ</u>, <u>suggesting a possible</u> <u>link to brain development</u>.
- ▶ Pedophiles are three times more likely to be left-handed.
- Theory is that the <u>lack of adequate wiring between the different</u> centers results in pedophiles not being able to differentiate between appropriate and inappropriate sexual objects.

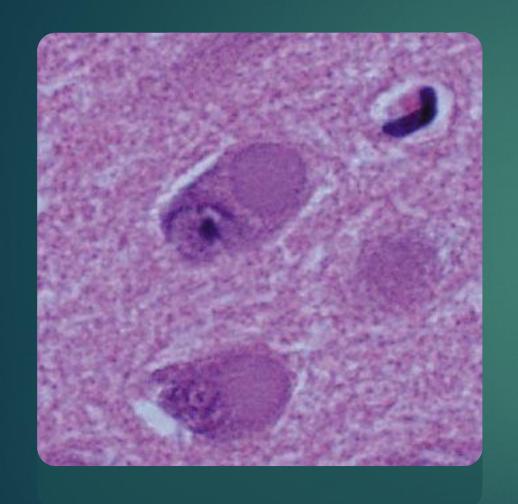
Periventricular nodular heterotopia: grey nodules in wrong place + dyslexia

Tracts appear in this image only if they are organized. In a normal brain (left), tracts run in an organized, uninterrupted fashion between points in the brain

(tracts in white box). In patients with periventricular nodular heterotopia (right), tracts are disrupted by nodules of gray matter (red arrow), leaving areas without organized fiber tracts (lack of tracts in white box), which might lead to poor connections between parts of the brain.



Pick bodies

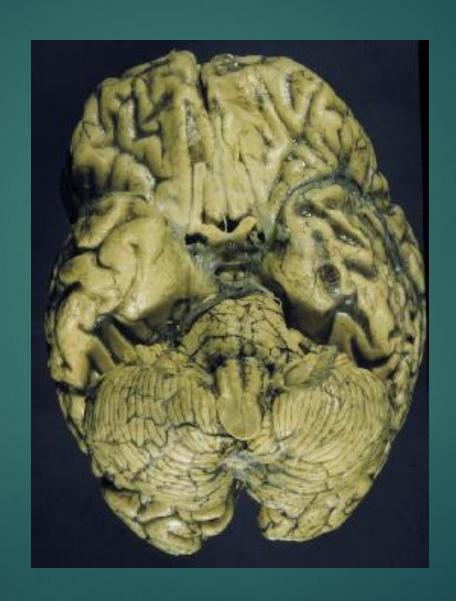




Pick's Disease: FTD



Pick's Disease 2



Pick's Disease 3



Be careful with Pig Brain Mist: Chronic inflammatory demyelinating polyneuropathy

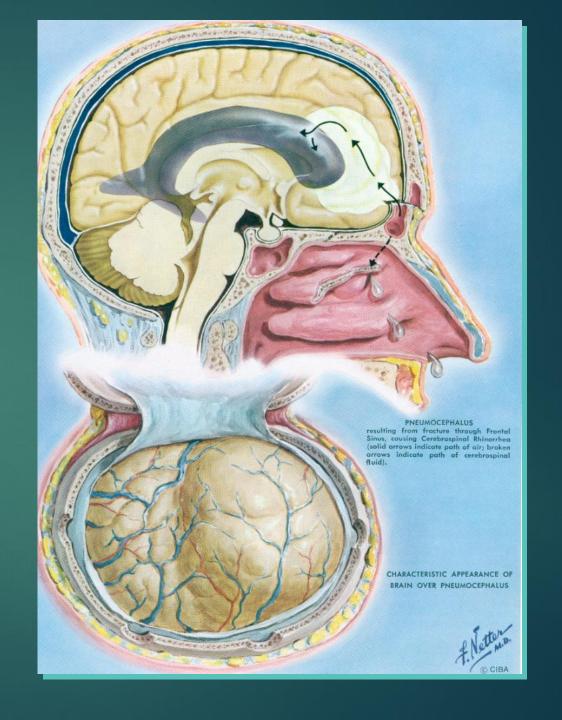
▶ Workers at <u>pork processing plants</u> who developed a rare neurological disorder 2 years ago [2007] after being exposed to [organic] mist while removing brains from pigs have improved but still display symptoms, according to a study by the Mayo Clinic in Rochester, Minnesota (MN).

The workers at "heads tables" at Quality Pork Processors in Austin, MN, and at another plant in Indiana had used compressed air to extract pig brains and developed chronic inflammatory demyelinating polyneuropathy, which attacks nerves and produces numbress, tingling and weakness in arms and legs.

Although the exact antigenic stimulus is not clear, the pathophysiology appears to be exposure to a neural antigen such as myelin via inhalation of the "pig brain mist".

Traumatic Pneumocephalus

Presence of air or gas within the cranial cavity. It is usually associated with disruption of the skull: after head and facial trauma, tumors of the skull base, after neurosurgery or otorhinolaryngology

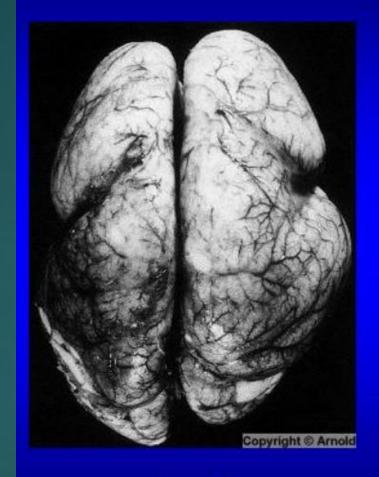


Polymicrogyria: What's wrong with this picture?



Polymicrogyria is characterized by a loss of the normal external contour of the cerebral convolutions, which appear small, unusually numerous and irregularly formed

FOREBRAIN ANOMALIES



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Agyria

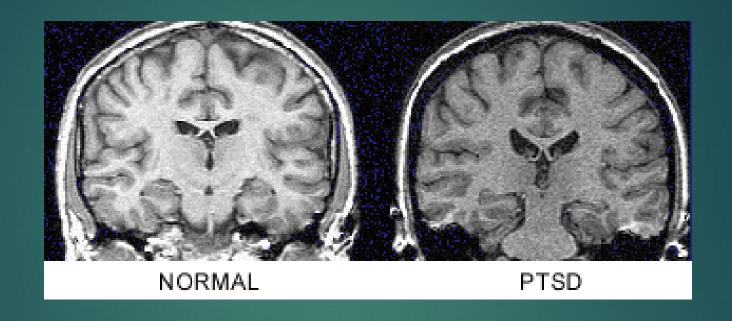
Polymicrogyria

Porenchephaly



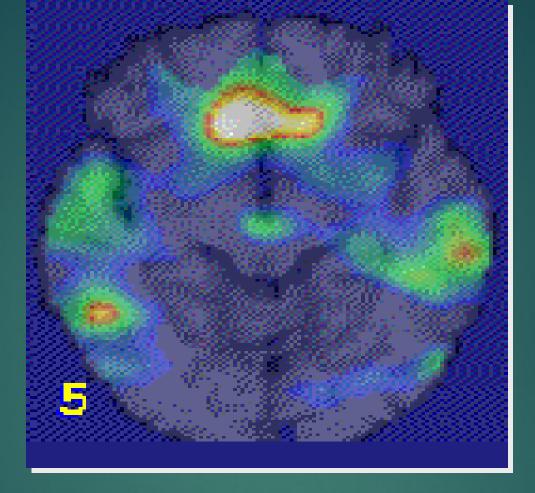
Porencephaly is an extremely rare cephalic disorder involving encephalomalacia. It is a neurological disorder of the central nervous system characterized with cysts or cavities within the cerebral hemisphere.

Post Traumatic Stress Disorder 1



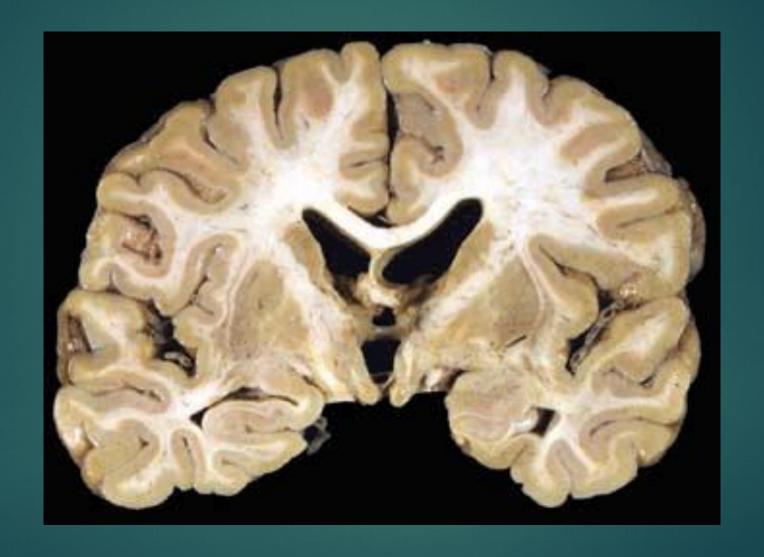
<u>Decreases in right hippocampal volume</u> in the PTSD patients were associated with deficits in short-term memory; in the combat veterans, level of abuse as quantitated with the Early Trauma Inventory and <u>a 12% reduction in left hippocampal volume.</u>

PTSD 2

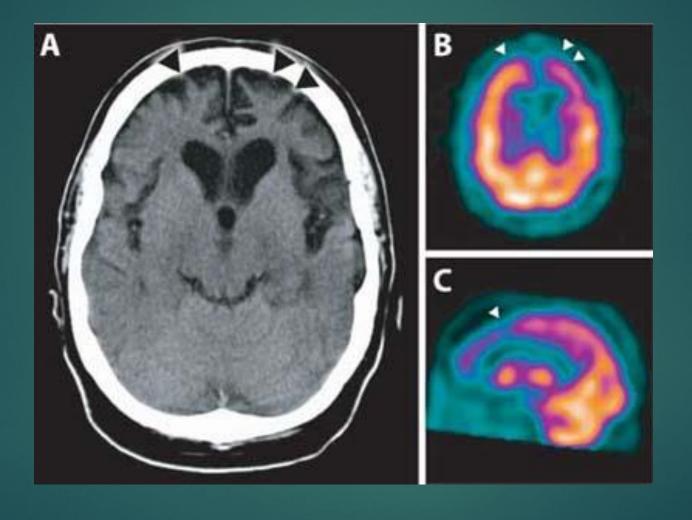


Women with childhood sexual abuse and PTSD, compared to sexually abused women without PTSD, exposed to personalized scripts of childhood sexual abuse, showed decreased blood flow in medial prefrontal cortex and failure of activation in anterior cingulate, with increased blood flow in posterior cingulate and motor cortex. PTSD women also had decreased blood flow in right hippocampus.

Progressive Supranuclear Palsy: loss of balance, motor function



Progressive Supranuclear Palsy



Frontal effects

Psychopathic Personality Disorder: Reduced Prefrontal Gray

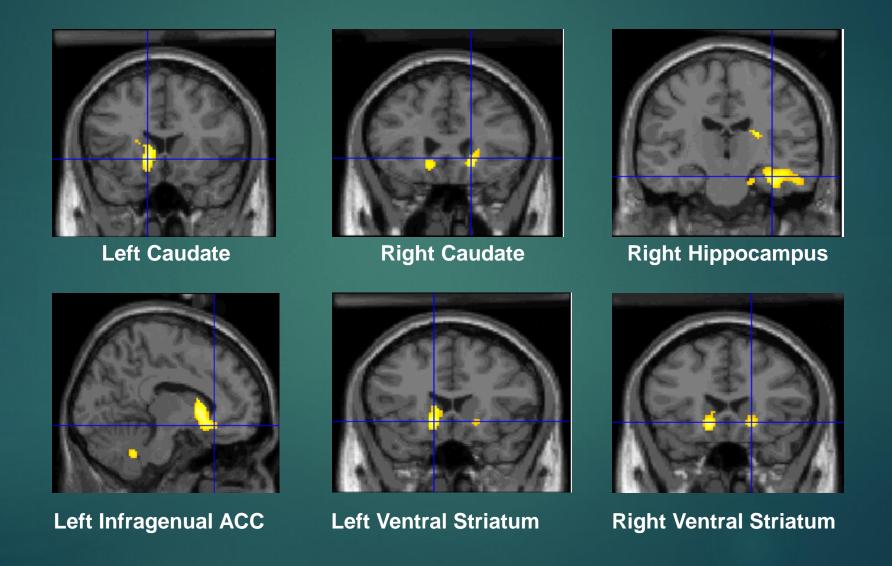




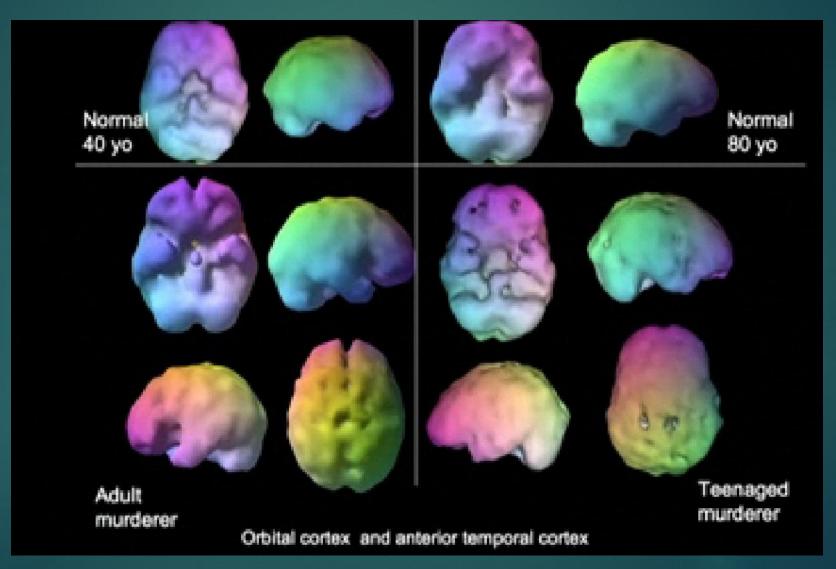
- ▶ Raine, 2000: 11.0% reduction in prefrontal gray matter volume
- Amygdala: 17% smaller
- ► May underlie the low arousal, poor fear conditioning, lack of conscience, and decision-making deficits that have been found to characterize antisocial, psychopathic behavior.

Psychopathy and Risky Decision Making:

Neural Activation Patterns for Psychopaths > Non-Psychopaths



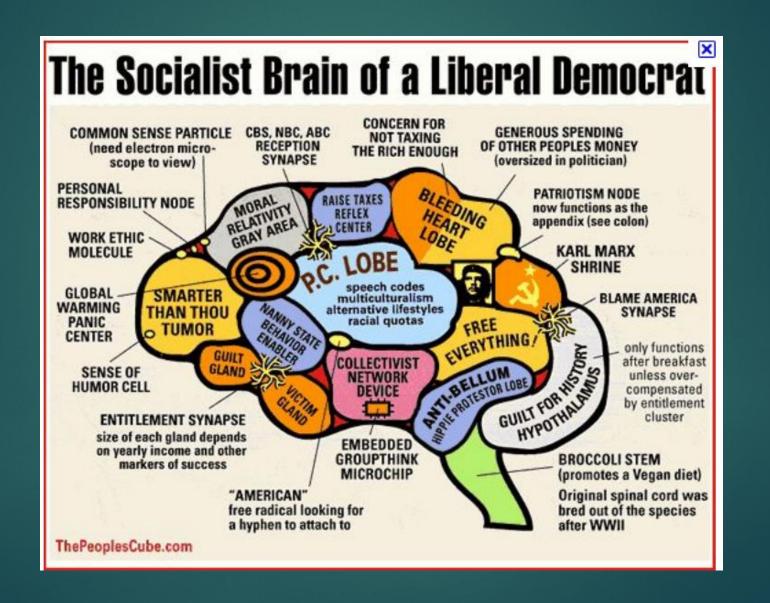
Psychopathy:
Orbital cortex and Anterior Temporal cortex
Low Activation



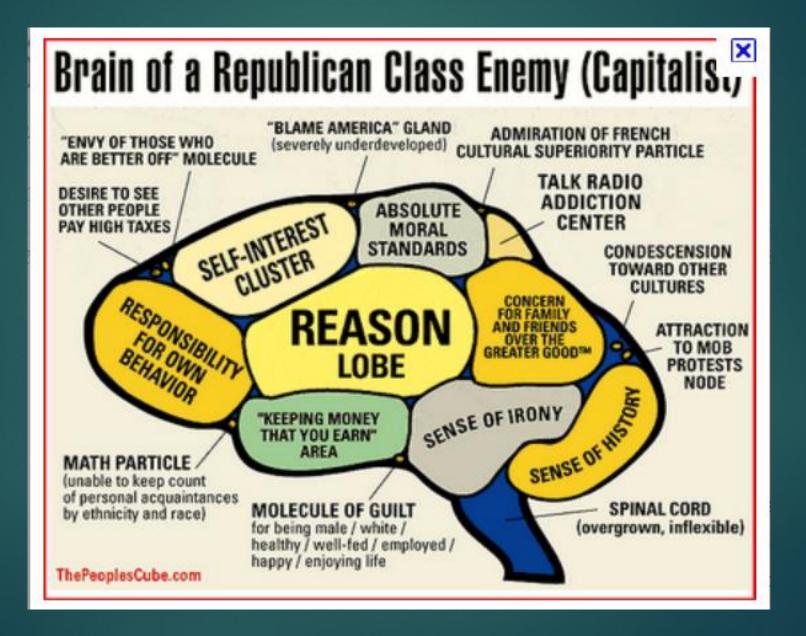
James Fallen on Psychopathy: Combination of Factors

- ▶ 1 Low Orbital Frontal activation pattern
- ▶ 2 MAO-A gene (monoamine oxidase A): high-aggression variant (low Serotonin), Warrior gene
- ➤ 3 Mother transmission to son (X chromosome), too little Serotonin: higher rates among males
- ▶ 4 History of childhood abuse or seeing lots of traumatic violence

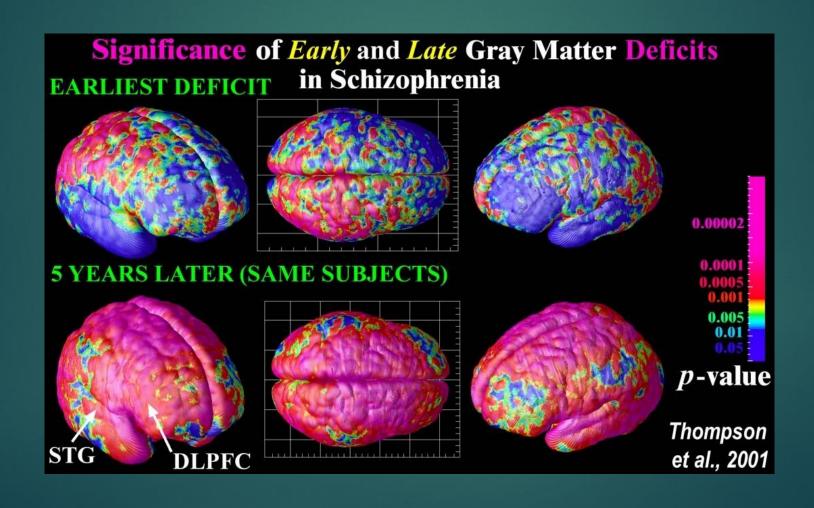
Democrat Brain



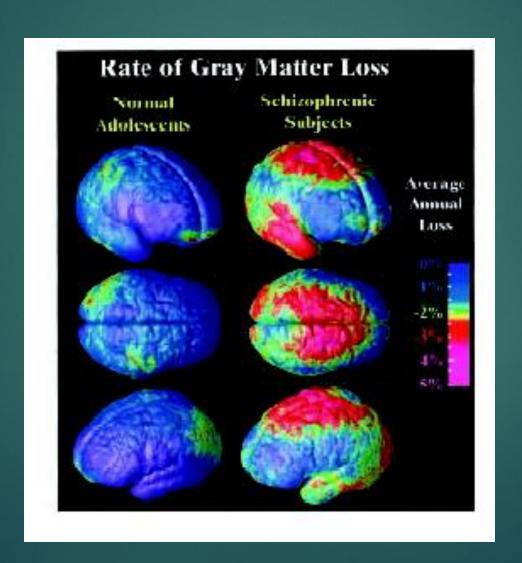
Republican Brain



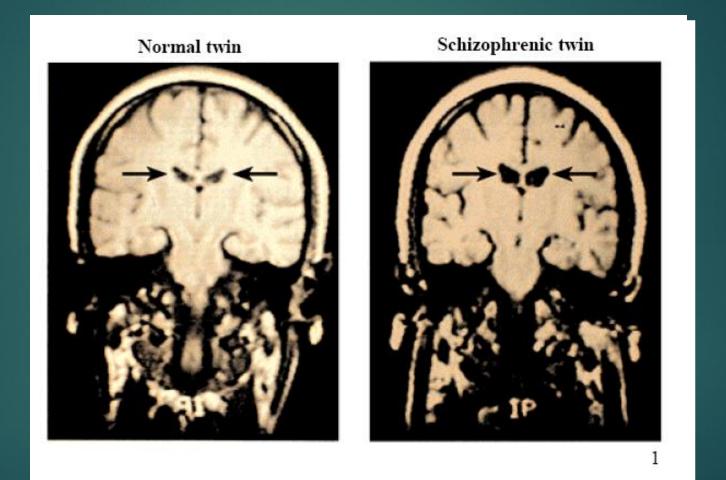
Schizophrenia: 4 x greater loss in Frontals, enlarged ventricles



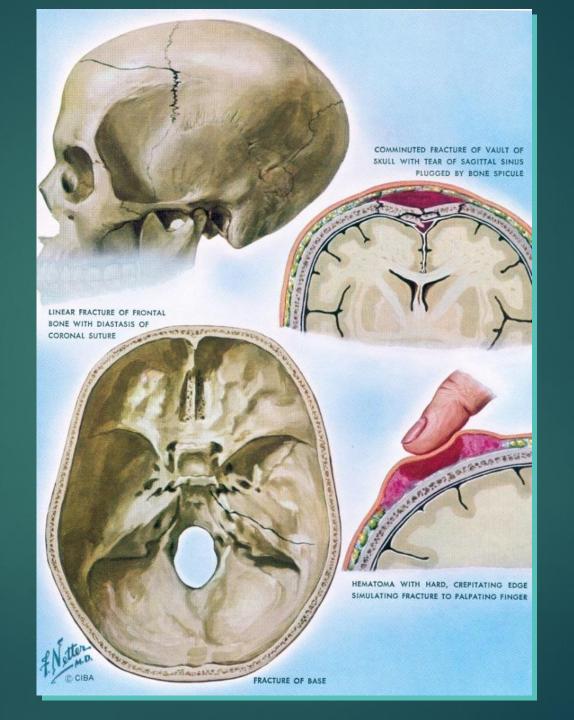
Rapid loss of brain volume during adolescence in schizophrenics



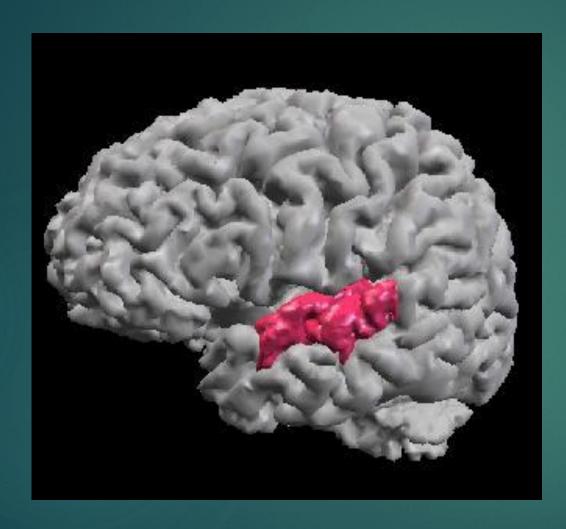
Schizophrenia 2



Skull Fracture



Schizotypal Personality Disorder 1



Reduction of left superior temporal gyrus

Brain Abnormalities similar to Schizophrenia, but normal medial temporal & ventricles

Dickey et al., 1999: Reduction of left STG gray matter volume in SPD subjects Dickey, 2002:

Schizotypal Personality Disorder 2



Fig. 1. Manual tracing of right (pink) and left (purple) fusiform gyrus on a coronal image of SPD subject.

Smaller Fusiform gyrus: Poorer facial recognition

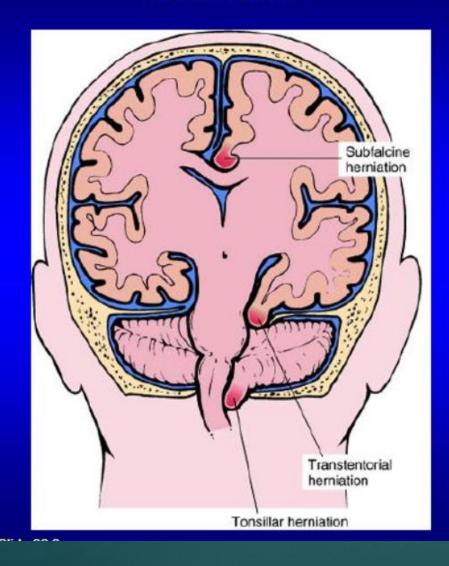
Dickey, 2003: Correlation of severity of illusions and magical thinking and smaller right fusiform gyrus volume

Space occupying Lesions

Contents of the Cranial Cavity

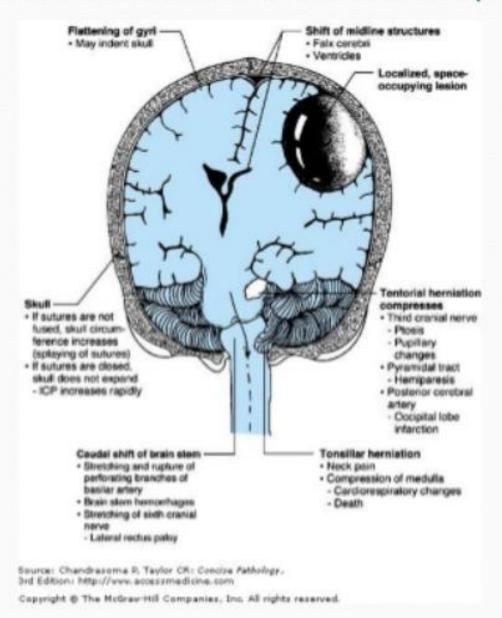
- 70 % brain tissue
- 12 % cerebrospinal fluid
- 15 % blood

HERNIATION



- •Brain surrounded by rigid skull
- •Rigid barriers divide the cranial cavity into <u>subcompartments</u> (falx cerebri, cerebellar tentorium)
- •Intracranial volume is fixed (brain parenchyma, CSF, blood)
- •Space occupying masses (tumor, hemorrhage, etc.), brain edema, increased CSF lead to increased intracranial pressure and may cause herniation
- •Herniation is displacement of expanding brain to adjacent subcompartments or through the foramen magnum

Results of Increased Intracranial Pressure (ICP)



Edema with Tentorial Herniation



Intracranial Pressure

death

977
ases,

-60 mm

Causes of space-occupying lesions

tubors

hemorrhages

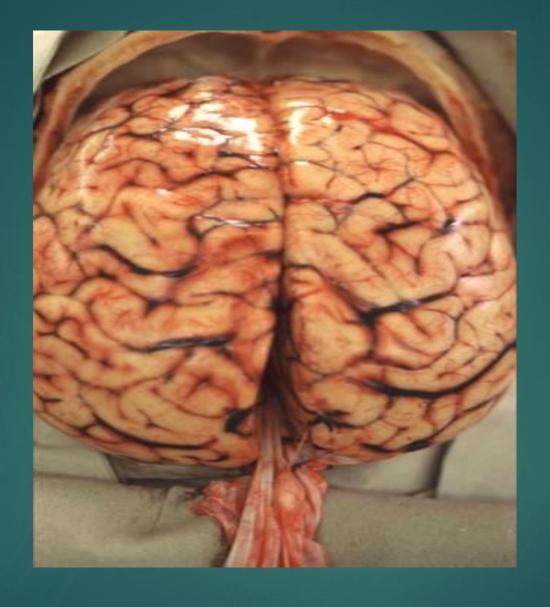
inflammatory processes

blockage of CSF (hydrocephalus)

brain edema

trauma

ischemia / anoxia



Edema

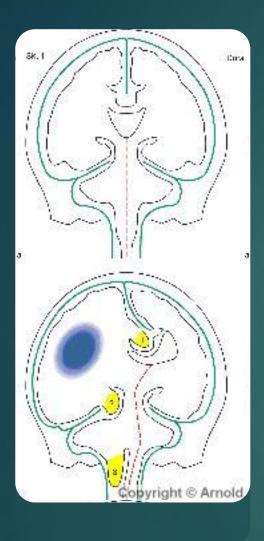
Herniations

Subfalcial herniation right and left supratentorial cavities

Uncus herniation supratentorial cavities infratentorial cavity

tonsillar herniation infratentorial cavity spinal canal

Retrograde: cerebellum infratentorial cavity supratentorial cavity



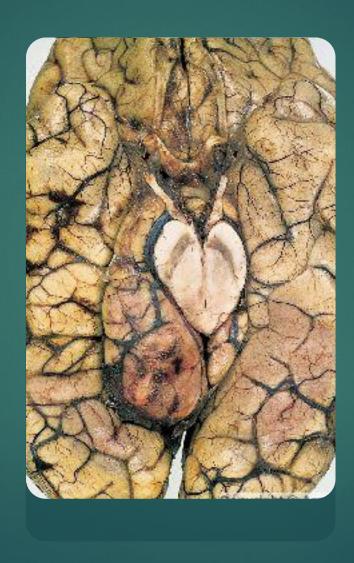
► Pathology of localized brain swelling:

subfalcine herniation of cingulate gyrus

transtentorial uncal herniation

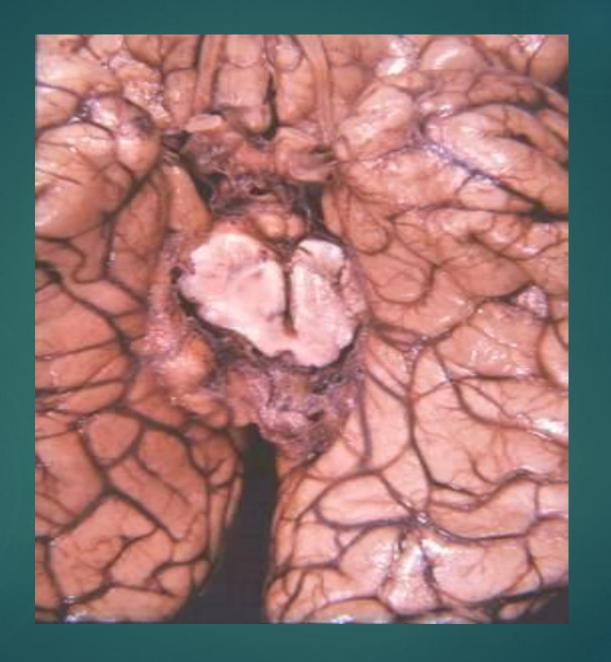
cerebellar tonsillar herniation into foramen magnum

Transtentorial herniation of medial temporal lobe



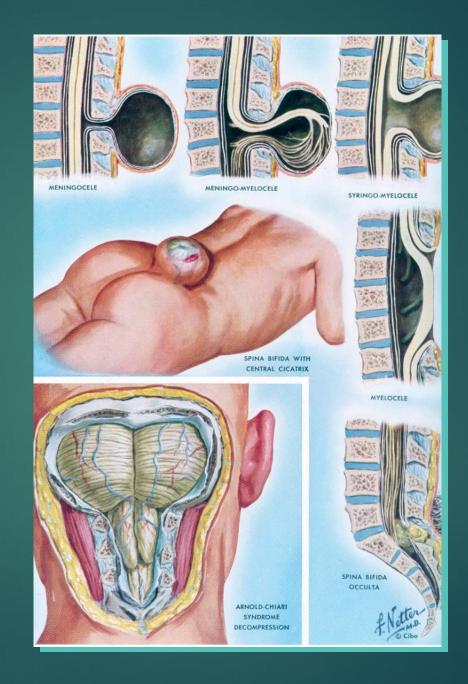
Uncal Herniation





Herniation

Spina Bifida

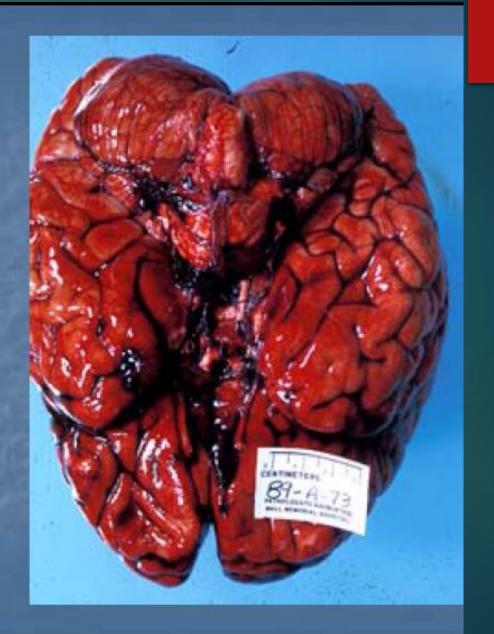


Spinocerebellar Degeneration



Subarachnoid Hemorrhage

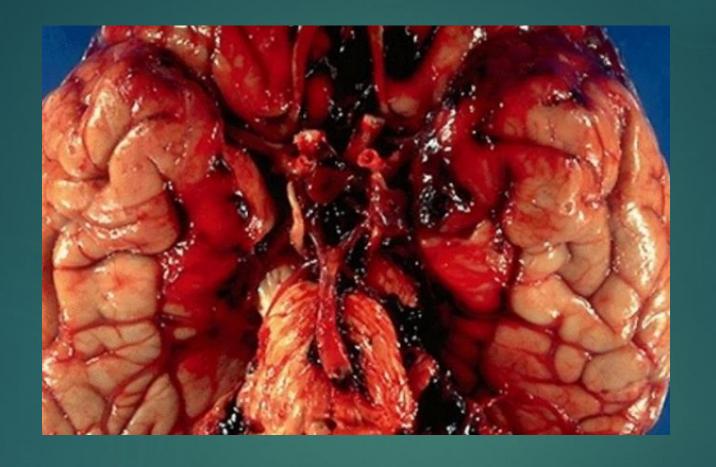
- Not as commonly due to trauma, but maybe.
- Arterial bleeding
- Typically from Circle of Willis
- Blood in subarachnoid space



Subdural Hemorrhage

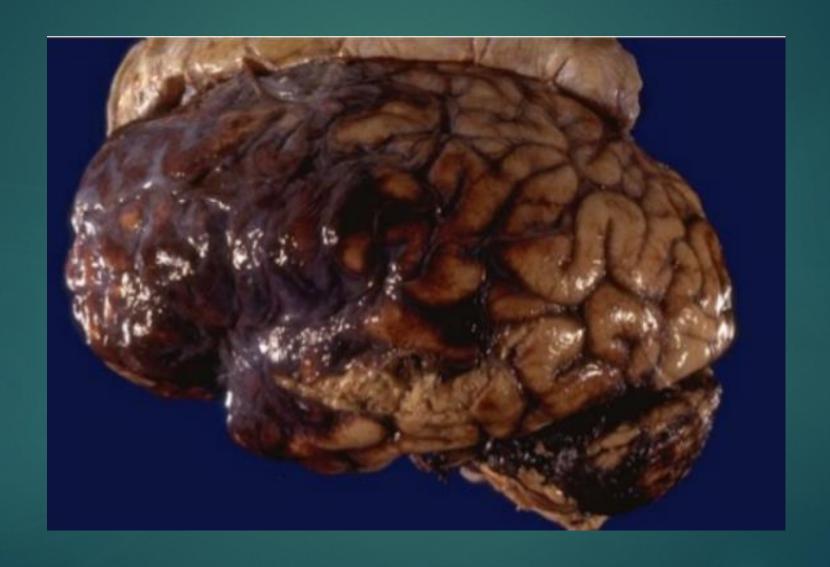
- Rotational injury tears little veins
- Slow venous bleeding



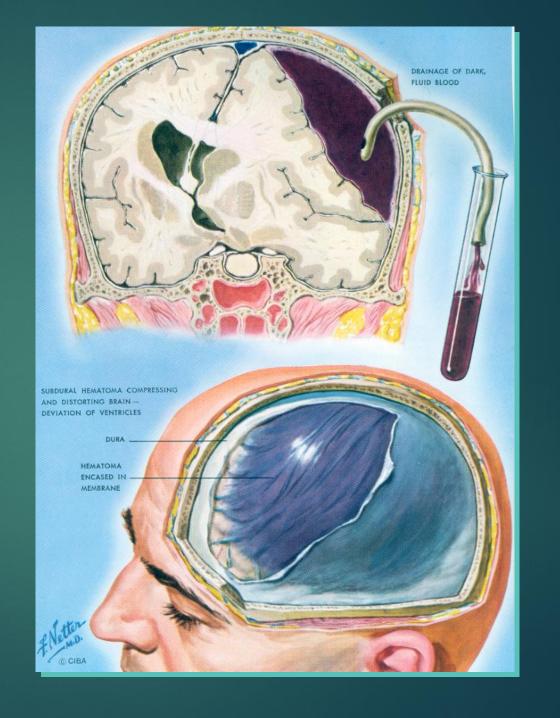


Subarachnoid Hemorrhage

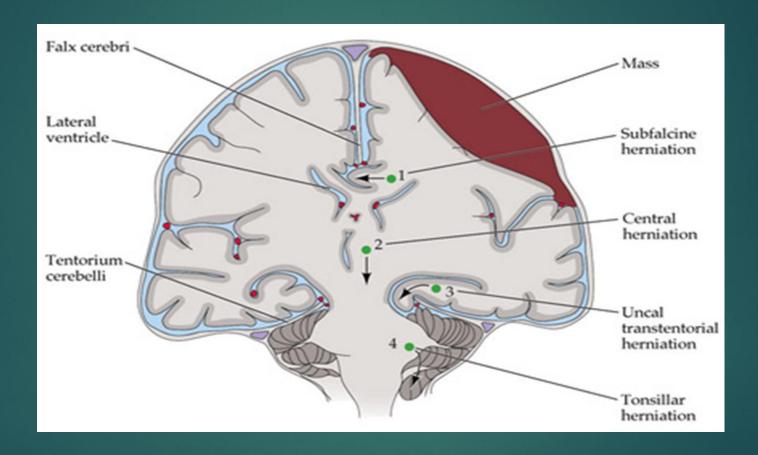
Subarachnoid Hemorrhage



Subdural Hematoma

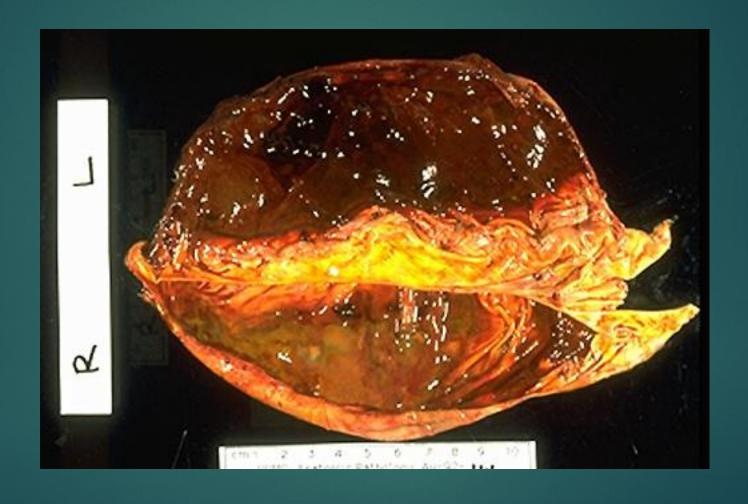


Hematoma and herniation



Herniation can be caused by a number of factors that cause a mass effect and increase intracranial pressure (ICP): these include traumatic brain injury, stroke, or brain tumor.

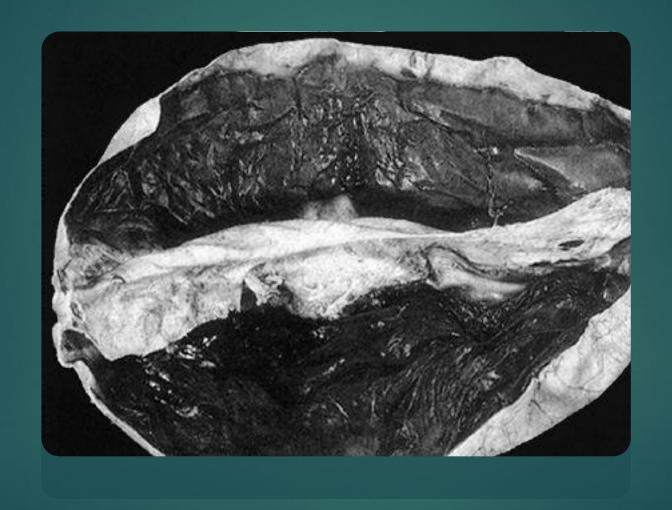
Subdural Hematoma



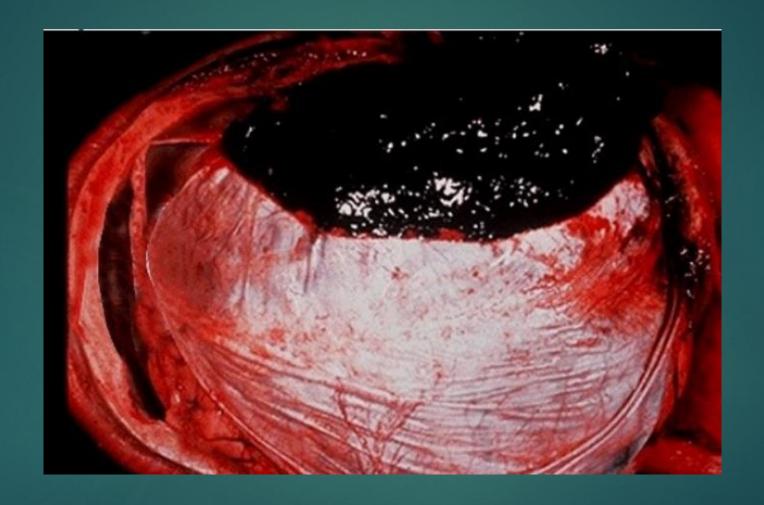
Chronic subdural hematoma



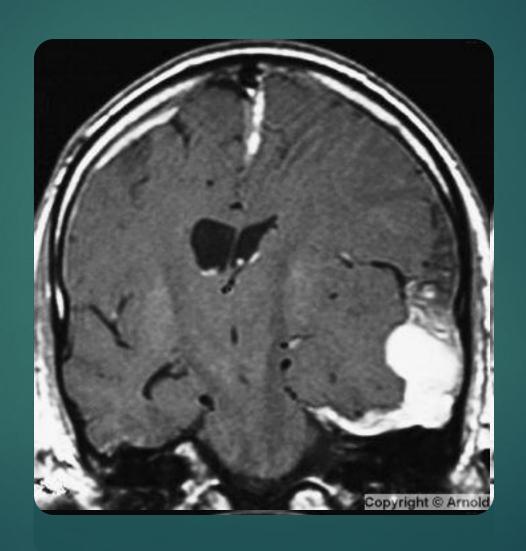
Bilateral chronic subdural hematomas



Subdural Hematoma



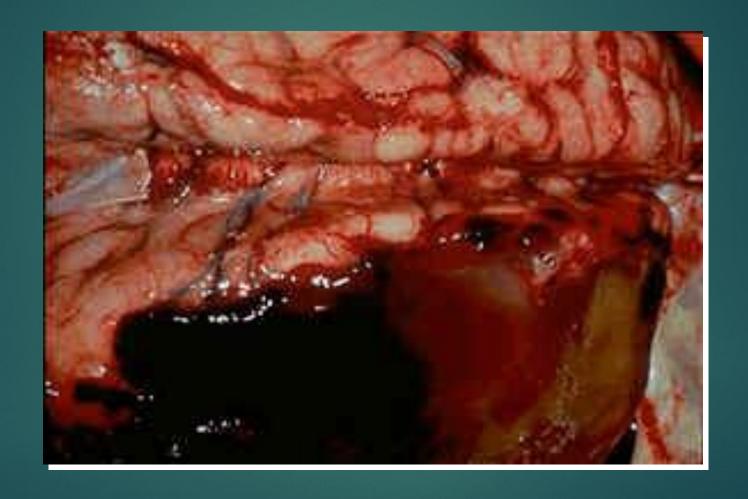
Acute subdural hematoma overlying temporal lobe (MRI)



Frontal and temporal contusions underlying subdural hematoma (removed)



Hematoma: Subdural



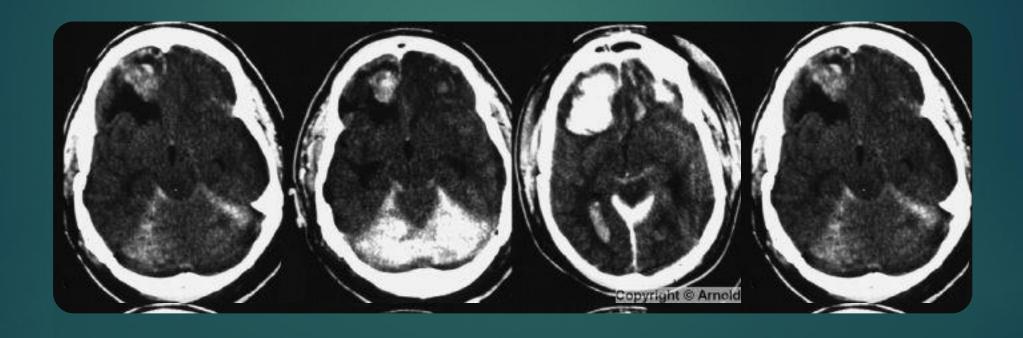
Toxins

- ► A classical example is Alcohol:
 - ▶ Direct toxic effect
 - ► Secondary nutritional deficits
 - Wernicke-Korsakoff syndrome
 - Cerebellar dysfunction occurs in about 1% of chronic alcoholics
 - ► The fetal alcohol syndrome

Traumatic Brain Injury



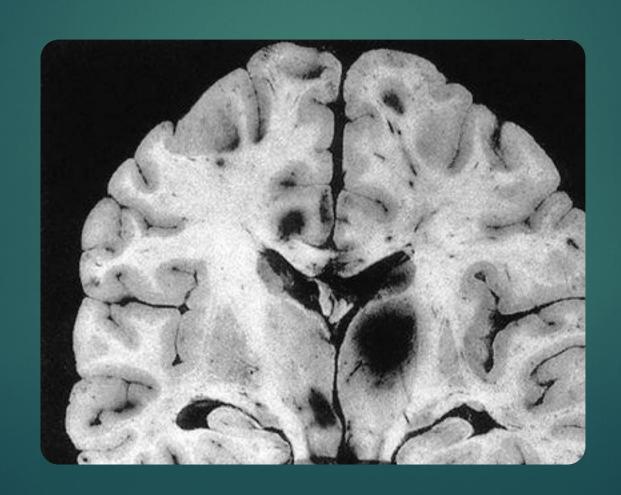
TBI: Contusions



"plaques jaunes": old orbitofrontal contusions



Due to shearing forces, traumatic hemorrhages may occur in the basal ganglia, midbrain, corpus callosum and cingulate



► Traumatic diffuse axonal injury



Traumatic Brain Injury: White Matter Laceration

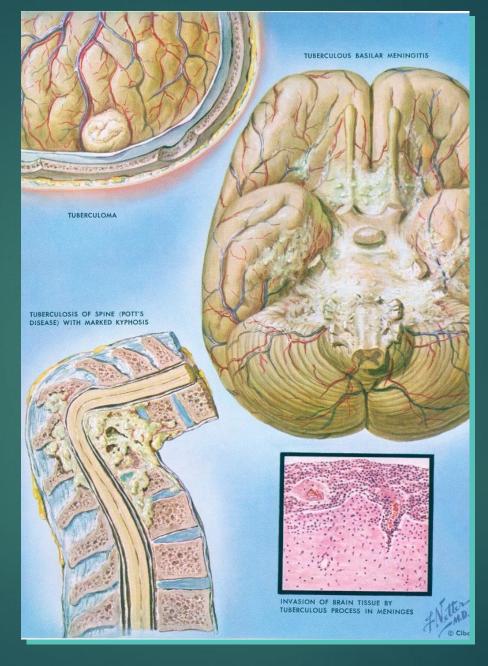


Thrill Seeking

- ► Increased insula activation (cravings)
- Decreased frontal inhibition



Tuberculosis



Infectious disease caused by various strains of mycobacteria



► Tuberous sclerosis: autosomal dominant neurocutaneous disorder with brain anomalies including cortical tubers (above) and tumors. Seizures and mental delay common.

Vascular Dementia

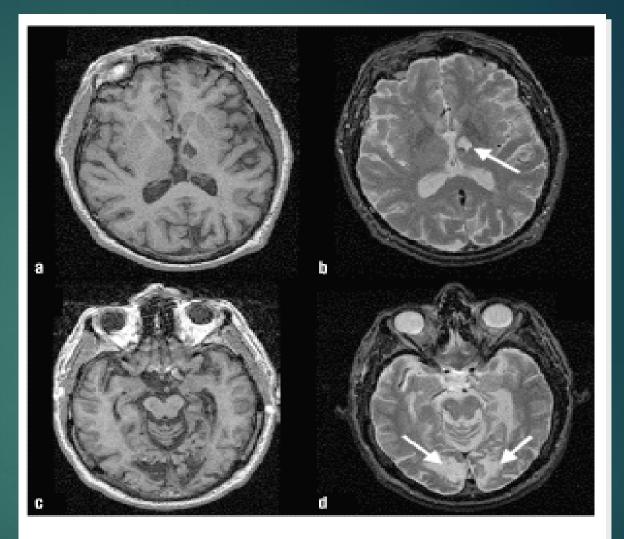
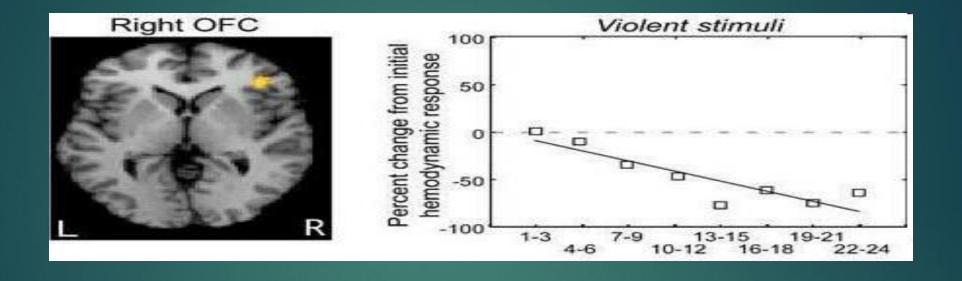


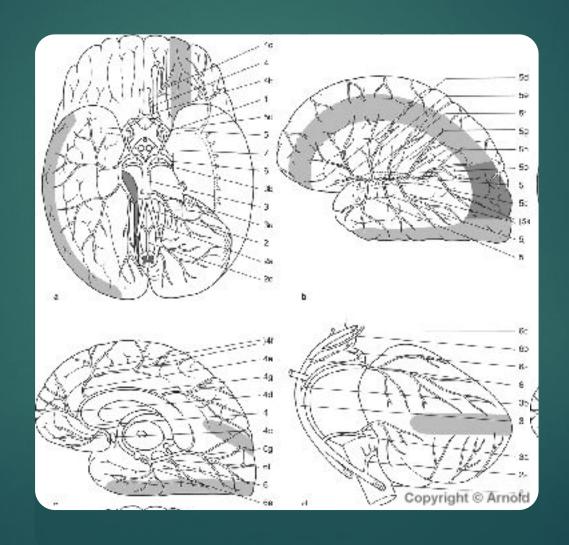
Figure 1. Strategic infarcts. Left thalamic infarct (arrow) that caused sudden-onset dementia with problems in memory and executive function, seen on T1-weighted (a) and T2-weighted (b) axial magnetic resonance imaging (MRI). Bilateral occipital (arrows) and left hippocampal infarcts in posterior circulation, seen on T1-weighted (c) and T2-weighted (d) axial MRI.

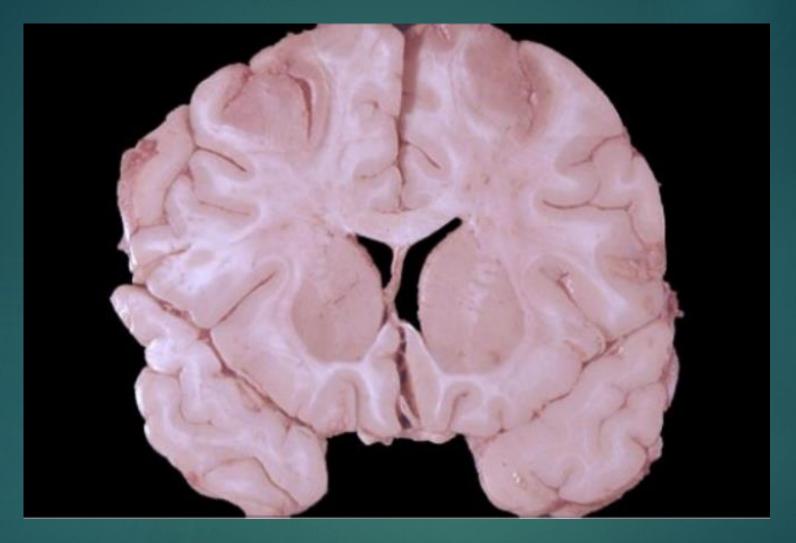
Watching Violence: Diminished RLOF



The yellow area of the brain is the <u>right lateral orbitofrontal cortex</u>, which has been previously associated with <u>decreased control over a variety of behaviors</u>, including reactive aggression. The graph illustrates that <u>as the number of violent movies watched increased the right IOFC activity diminished</u>.

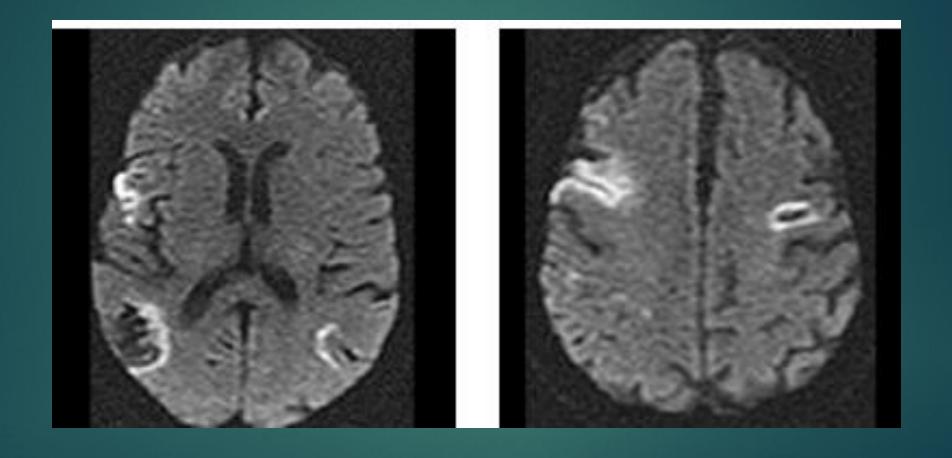
Arterial blood supply of the brain. Shaded areas are "watershed" boundary zones between adjacent arterial territories.





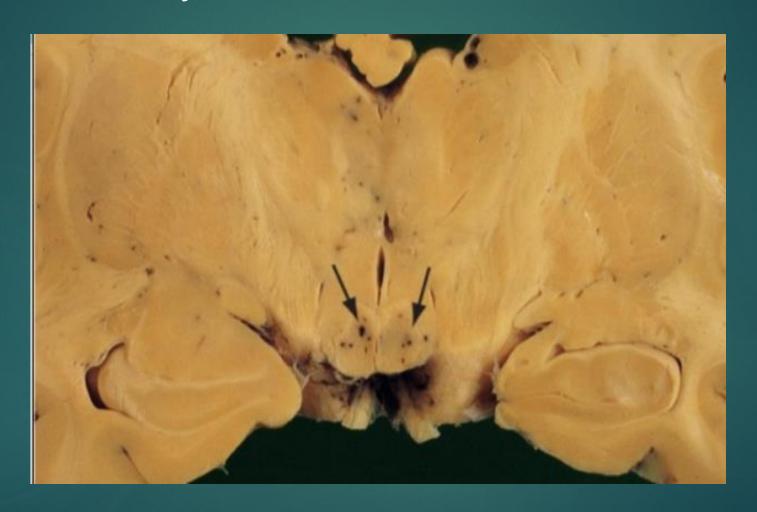
Watershed Infarcts

Watershed CVA: Hypoperfusion

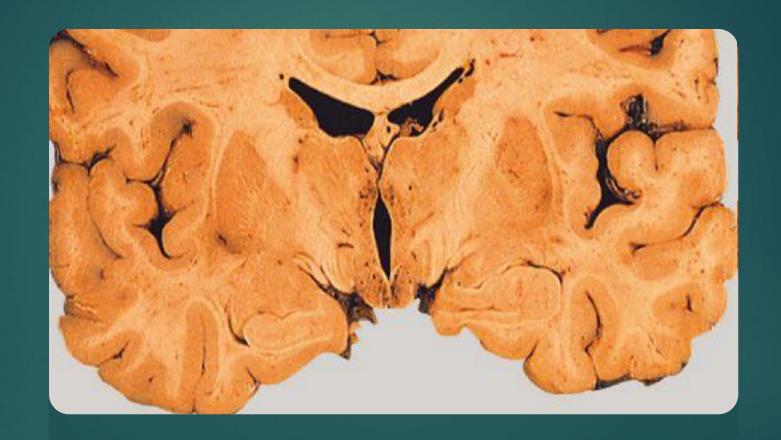


A stroke affecting areas of the brain farthest from direct perfusion with blood supply by the major cerebral arteries

Wernicke's: petechial hemorrhages caused by thiamine deficiency



Wernicke's Encephalopathy



Alcohol +/- malnutrition and thiamine deficiency.

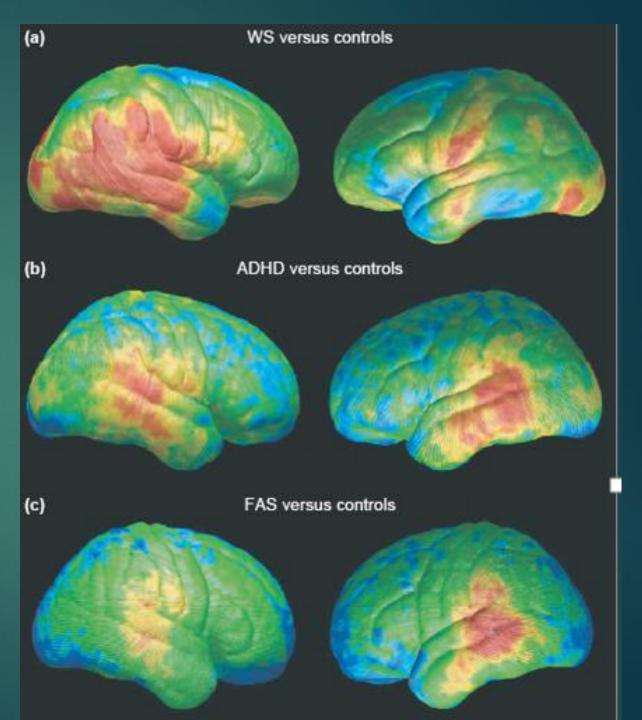
Lesions may occur in the vicinity of the 3rd and 4th ventricles

Wernicke's Encephalopathy



William's Syndrome, ADHD, FAS:

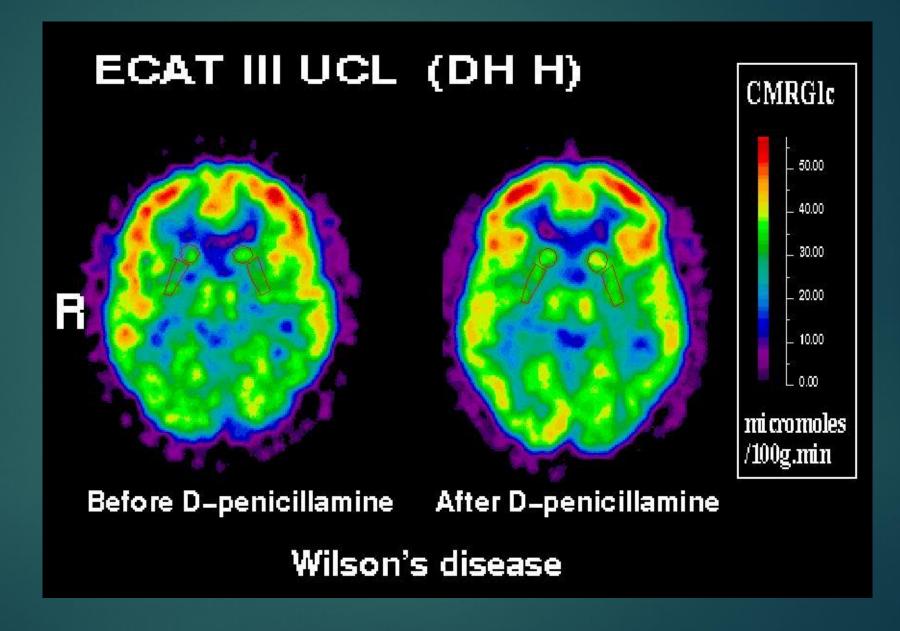
red > difference from control



Wilson's Disease: Kayser-Fleischer Ring



Wilson's Disease 2



Chelating drug

Websites

http://neuropathology-web.org/

My Website

www.charlesjvellaphd.com

► Tests: Logon: Vella

Password: Vella

► Seminar: Logon: Kaiser

Password: Kaiser