NEUROLOGY

Degenerative Diseases

Alzheimers: cortical & hippocampal atrophy > memory loss, aphasia, apraxia. ↓ Ach (N.B. of Meynert), NE, dopamine, & serotonin. Chr 21 (Downs) (±14,19). Apolipoprotein E4/E4 ↑ # of plaques, early onset.

Path: *Neurofibrillary tangles*: τ protein. *Neuritic plaques*: βamyloid protein. *Both:* cytoplasmic, silver stained, paired helical filaments. *Granulovacular degeneration*: dark cytoplasmic granules w/clear halo in neurons. *No gliosis*.

Tx: donepezil, tacrine (acetylcholinesterase inhibitors, slow progression). Vitamin E & selegiline (MAOI, delay NH placement, not cognitive decline).

CJD: prion infects oligodendroglia. Spongiform encephalopathy. Path: loss of cerebellar granule & purkinje cells, atrophy. Gliosis (none in Alzheimers). *No inflammation*. CSF WNL (14-3-3 proteinase inhibitor protein specific). Dementia, myoclonus, spasticity, cerebellar & visual/oculomotor problems. 100% fatal. Normal protein PrPc on Chr 20, converted from α helix to β pleated sheet by prion. 10% familial (have mutant PrP in neurons & lymphocytes). EEG 1-2 Hz spikes, triphasic waves. MRI: ↑T2 signal in BG. Dx: Bx. Tx: 1) autoclave at 250°F (132°C) at 20PSI for 1hr, 2) bleach, 3)NaOH x 1hr . Transmitted from cadaver GH injections.

Huntingtons: chorea, demetia, family Hx. Personality change 1st, increased blinking, abnormal eye mvmt. Caudate/putamen atrophy > boxcar ventricles. AD, CAG repeat in huntingtin, chr 4. ↑ dopamine, NE, somatostatin (vs AlzDz); ↓ GABA, Ach. L-dopa worsens.

Westphal variant: <20yo, more aggressive, seizures, parkinsonism.

Subcortical dementia: No aphasia, apraxia, or amnesia (memory OK). Seen w/Parkinsons & Huntingtons

Picks: *frontal/ temporal, balloon ("Picks") cells* (neurons, tau+), neuron loss in cerebral cortex, gliosis, cortical spongiosis. Younger. Arithmetic preserved. Rare familial form, Chr17.

Tauopathies: tau is a MAP, Chr 17. Picks, CBD, PSP, Alzheimers,

Ubiquitin: binds abnormal proteins for transfer to lysosomes. Stains in Parkinsons (Lewy bodies), Huntingtons, Alzheimers, & others

αSynuclein: structural protein, forms Lewy bodies (Parkinsons)

Retts syndrome: Girls only. Normal until 2yo then rapid regression. X-linked. Stereotyped hand movements (wringing, tapping), hyperventilation, szs. No Tx.

Binswangers dz: HTN and dementia

Transient global amnesia: not seizures, probably 2° to transient ischemia of mesial temporal lobe.

Movement Disorders

Tremors: physiologic: 8-13Hz, awake and asleep. Pathologic 4-7Hz, awake only. Parkinsons: rest. Intention: cerebellar.

Essential: action, some familial, improves w/alcohol, propanalol.

Dystonia: Twisting/writhing movements, stopped by touching affected area. Idiopathic or secondary. Tx: L-dopa, anticholinergics. Thalamotomy.

Focal: Torticollis, blepharospasm, writers cramp. Tx: botox

Tardive dyskinesia: Stereotyped orolingual movement or dystonia. Caused by phenothiazines ↓ dopamine. Prevent/Tx: Reserpine, anticholinergics (trihexyphenydil/Artane, benadryl.) Phenothiazines (& Reglan) may also cause parkinsonism, acute dystonic reaction.

Hemiballismus: thalamoperforators, contralateral STN

Palatal myoclonus: central tegmental tract or Mollaret's triangle (red nucleus >< inferior olive >< dentate nucleus), persists during sleep

Parkinsons: Etiology unknown. ↓ neurons in SNpc, DMN vagus & locus ceruleus. Lewy bodies (eosinophilic intracytoplasmic inclusions w/ halo). Rest tremor, bradykineasia, cogwheel rigidity (micrographia, ↓ blink, masked facies, festinating gain, pain in 50%, GI problems, dysautonomia, weight loss, asymmetric). 20% have dementia. Dx: clinical.

Tx: Surgical: lesion contralateral VL or Gpi (best for tremor/ rigidity/ dyskinesias); Vim = tremor, unilateral only (dysarthria), STN = bradykinesia. 80% improve. DBS can be done bilaterally.

Fetal mesencephalic transplantation into SN caused dyskinesias, some improvement <60yo. Adrenal medullary transplant abandoned.

Medical*:*

benztropin (Cogentin)/ Artane: anticholinergics. *Amantadine:* releases dopamine, loses effect. *Sinemet:* dopa + carbidopa, dopa decarboxylase inhibitor, 2nd tier. SE: N/V, orthostatis, arrythmias, on-off periods, dyskinesias (Tx B6). CI: MAOI. B*romocriptine/ pergolide:* stimulates D2, vasoconstriction, fibrosis (bromocriptine is used for prolactinoma, pergolide isn't). *Selegiline/ Eldypryl:* MAOI, slows progression; *deprenyl:* MAOBI.

Parkinsonism: 80% Parkinsons disease, 10% Parkinsons-Plus (MSA, PSP, CBGD, diffuse lewy body dz), 10% secondary. (drugs: neuroleptics, reserpine, Ca-channel blockers, lithium)

PSP: downgaze palsy, pseudobulbar, gait palsy, eyelid freezing, no tremor, symmetric. MR: atrophy of midbrain & tectum. 70yos. No Tx.

Multiple system atrophy = Parkinsons-Plus, poor response to DA, lack Lewy bodies. Dx: Glial (esp. oligodendroglial) cytoplasmic inclusion bodies. Includes:

Striatonigral degeneration: syncope, stridor. Putamen atrophy

Olivopontocerebellar atrophy: AD, Chr 6, 15yo, LE ataxia, atrophy middle cerebral peduncle

Shy-Drager: autonomic probs, impotence, no lewy bodies(?); loss in putamen, SN, & interomediolateral horn cells

Corticalbasal Degeneration (CBD): Parkinsonism, cortical signs (apraxia, myoclonus) and *alien limb.* No Tx, etiology unknown.

Chorea gravidarium: resolves post-pregnancy

Meige's syndrome: facial dystonia (blinking, tongue thrust, etc) idiopathic (not phenothiazines) Women, 60yo, Tx: Botox.

Restless Legs: in uremia, DM etc. Occurs at night. Tx: Klonopin, Neurontin, L-dopa. Neuroleptics, caffeine, Ca-channel blockers worsen.

Wilsons disease: Parkinsonism/ bulbar signs/ dystonia/ ataxia/ psych probs. Wing-beating" tremor. ↓ ceruloplasmin, ↓ serum copper; ↑ urine copper; AR, chr 13; liver biopsy best; Kayser-Fleischer rings; hepatolenticular degeneration; Liver fibrosis, Renal tubular acidosis (metabolic acidosis). Decreased blink, arm swing (like parkinsons) Alzheimer II & Opalski cells in GP. Hypodense BG; Tx: penicillamine (w/B6 to prevent anemia), ↓ dietary copper

Hallervorden-Spatz: cysteine dioxygenase deficency. ↑ cysteine, chelates iron > free radicals. Iron in basal ganglia; no serum test; ↓ T2 "eye of the tiger" pallidum & substantia nigra; No Tx

Tourettes: AD. <21yo. >1yr sxs. Normal IQ. Dopamine reuptake defect (VTA to anterior cingulate pathway). Tx: Haldol.

Hereditary ataxias:
Friedrichs ataxia: Chr 9 (protein frataxin, GAA repeat), AR, <10yo, degeneration spinocerebellar tracts/cerebellum, post columns, *corticospinal*; spares MNs; ataxia, pes cavus/scoliosis, *arreflexia* (due to neuropathy 2° to dorsal root ganglia dz), *dysarthria*, *cardiomyopathy*; *10% diabetes mellitus*, optic atrophy/retinitis pigmentosa, no dementia. CSF normal; MRI: normal cerebellum, small spinal cord; Tx: serotonin? Diff Dx: Vit E def. Mental status normal.
Abetalipoproteinemia: peripheral neuropathy, retinitis pigmentosa, ataxia, dysarthria, acanthosis (abnormal RBCs), ↓↓ cholesterol, triglycerides; spinocerebellar/post columns (resembles Friedrichs); children; Vit E slows progression
Ataxia-Telangiectasia: Chr 14, AR, decreased IgA,G & E. Begins 2yo, ataxia, premature aging, gaze paresis, red eyes, OKN lost. ↑ AFP. Severe degeneration of cerebellar cortex, anterior horn, demyelination in post coluns, spinocerebellar, peripheral nerves. T-cell Leukemia/ lymphoma common.
Hartnup's Disease: AR, Defect in renal transport of neutral amino acids (tryptophan). Gait ataxia (triggered by sunlight & sulfa), emotional lability, delusions, tremor, rash on face (like pellagra). Tx: nicotinamide – like pellagra (not tryptophan)
Spinocerebellar ataxia (SCAs): All AD, 14 types, Trinucleotide repeats.

Muscle Disease

EMG: denervation/ reinnervation = increased duration, polyphasic. Myopathy = decreased duration. Both = decreased amplitude
Muscle Biopsy:
Denervation: cause atrophy, angular fibers (reduced to nuclei only). ALS, SMA, peripheral neuropathy
Muscular Dystrophies: sarcomlemma breaks, large, eosinophilic fibers (myonecrosis)> phagocytosis > fat & fibrous tissue.
Myotonic dystrophy: multiple central nuclei & ring fibers
Polymyositis: perifasicular inflammation
Dermatomyositis: perivascular inflammation > ischemia > perifasicular atrophy
Muscular dystrophy
Duchennes**:** X-linked (30% not familial), males (famales w/Turners), onset 3-6yo, mild MR, CK higher, heart affected, dystrophin *absent* (membranous, interacts with actin), fiber necrosis, face spared, CHF, woman carriers ↑ CK. Tx: Prednisone (slows progression)
Becker**:** X-linked, onset 12yo, no MR, dystrophin *abnormal*, no necrosis
Becker & Duchenne: calf pseudohypertrophy
Facioscapularhumeral: Chr 4., AD, congenital absence of a muscle (pectoralis, brachialis, biceps), has inflammatory cells (only 1); CK WNL, no necrosis, MR, CHF; hearing loss
Emery-Dreifuss: early contractures elbow flexors & neck extensors & calf; X-linked, benign
Myotonic: hand/muscle atrophy; myotonia (preceeds weakness), frontal balding (men & women), MR, cataracts, testicular atrophy, cardiomyopathy. Chr 19, CTG repeats on "myotonin", AD, congenital form always from mother (resolves), face/larynx etc. affected then distal extremities, most common adult form; EMG: dive-bomber (reptitive discarges w/minor stimulation)
Myasthenia Gravis: Women < 40yo, Men >50yo w/thymoma. 10% have thymoma (60% of thymoma have MG), 66% thymic hyperplasia. 10% have no AchR-antibodies. Pupil response OK. Tx: anticholinesterase (pyridostigmine) > Thymectomy (16-60yo best, 1/3 work without thymoma due to hyperplasia) > steroids > azathioprine > plasma exchange. Cholinergic (worsens) vs myasthenic (improves) crisis: give edrophonium. Aminoglycosides worsen. D-penicillamine can cause autoimmune myasthenia.
Neonatal MG: due to mothers with Mg, resolves over weeks.
Eaton-Lambert: 60% have small-cell lung CA (1/3 no tumor). Antibodies to presynaptic Ca channels & synaptotagmin at NMJ, prevents Ach release. *Proximal trunk/ LE* weakness, *Ocular mm spared*, Autonomic problems. EMG: Low amplitude to single stimulus (MG normal), Incremental response to >50/s stimuli. *No fasiculations (seen in neuropathy)*. Tx: guanidine & 3,4-diaminopyridine (DAP – K channel blocker, ↑ APs, also used in MS, can cause szs) (both ↑ Ach release), plasmapheresis, steroids. No response to anticholinesterase meds. Muscle relaxants lethal.
Periodic Paralysis: All AD.
Na channel (Chr 17): Hyperkalemic: precip by fasting, exercise, no hypertrophy, Tx: glucose. Normokalemic: not precip by fasting, hypertrophy, invovles cranial mm, no ↑ serum K, Tx: Na. Paramyotonia Congenita exercise & cold worsens
Ca channel (Chr 1): Hypokalemic: hypertrophy, Tx: daily KCl.
Polymyositis: painless, nontender. No skin lesions. Dysphagia, dysphonia. Ocular mm. not affected. ↑ CK. Adults. Muscle necrosis (T-cells)
Dermatomyositis: Butterfly (heliotrope) periorbital rash & rash over knuckles (Gottrons papules). Children & adults. Moderate CK. B-cell perivascular inflammation (humoral – immune complexes in walls of veins & arterioles), *perifasicular* atrophy – no necrosis. Antibodies/C3 increased. **Both**: Tx: steroids, females, 10% have cancer, UE/neck > LE, proximal.
Inclusion Body myositis: chronic myopathy, >50yo. Quads/hand & feet flexors. CK mild. Bx: ubiquitin+ inclusion bodies, denervation.
Congenital myopathies: central-core (related to malignant hyperthermia), nemaline
Issac's syndrome: myokymia (w/myotonia, hyperhydrosis), K+ channel Abs > presynaptic hyperexcitability. 20-30s, M=F. Tx: Dilantin, Tegretol, IVIG, pheresis.
Stiff-man syndrome: anti-GAD antibodies (forms GABA). IDDM assoc. Tx: BZDs. Vs tenanus: EMG silent-period preserved, disappears during sleep, no trismus.
Thyrotoxic myopathy: proximal mm weakness, diplopia, hypokalemia, males

Spinal/Nerve

Amyotrophic Lateral Sclerosis: Atrophy and hyperreflexia. Tongue fasiculations (worse prognosis). Anterior horn, Betz cell, and corticospinal tract degeneration. No sensory loss, no pain. CSF normal. EMG: denervation in multiple limbs & CN. Bunina bodies (MNs). Poss. Mechanism: glutamate excitotoxicity. 10% familial - Chr 21, AD, mutation in superoxide dismutase (SOD1), free radical scavenger. Tx: Riluzole (↓ glutamate release). DDx (anterior horn): polio, ALS, CJD, Werdnig-Hoffmann
Spinal Muscular Atrophies (SMAs)
All on Chr5, AR. Resembles childhood ALS clinically – due to anterior horn cell loss & CN motor neurons.
Werdnig-Hoffman (SMAI): congenital - limp infant, *no MR*, fasiculations only in tongue, ocular mm. spared. Possibly due to mutations in motor neuron trophic factors SMN1 or NAIP.

Kugelberg-Welander (SMAIII): older children, less lethal
Also adult types.
Viral myelopathy: Polio & West Nile attack anterior horn cells.
Guillain-Barre: motor/autonomic > sensory. Autoimmune against Schwann cells (or axons). All ages. Symmetric. Mortality 3%. Peaks 10-14d. 20-30% preceeding *Campylobacter* infection (diarrhea), also CMV. May occur *postoperatively*. EKG*: t-wave Δs* common. CSF: Normal except *high protein (peaks 4-6wks).* Path: *Perivascular* & endoneurial inflammation, segmental/ perivenular demyelination, particuluarly in roots & plexuses. Plasmapheresis, IVIG (not steroids). GM1 ganglioside in campylobacter wall > anti-GM1 Abs (GM2 in CMV)
Miller-Fisher variant: opthalmoplegia, ataxia, hyporeflexia, descending. Anti-GQ1b IgG. Good prognosis.
Also Acute Motor & Motor-Sensory Axonal Neuropathy variants.
Tick paralysis: Dermacentor tick toxin. Resembles Guillain Barre - ascending paralysis, but more rapid, CSF WNL. Tick removal – rapid improvement.
CIDP: polyradiculopathy, proximal weakness, sensory loss/paresthesias, CSF: ↑ protein, no cells. Demyelinating. EMG: ↓ nerve conduction. Tx: steroids
Transverse myelitis: all ages, MRI normal in 50%, prognosis variable. 40% idiopathic – rest MS, vasculitis, etc.
Myelopathy: ALS: corticospinal + anterior horn; Polio: anterior horn; HIV: vacuolar (similar to B12); HTLV-1; Friedrich's ataxia: posterior columns, spinocerebellar, corticospinal; B12: Posterior columns & corticospinal; Tabes dorsalis: posterior columns
Tropical spastic paraparesis: Japan/ tropics; corticospinal ± post columns; due to HTLV-1; chronic
Ischemic myelopathy: due to aortic aneurysm/dissection. Back/groin pain + myelopathy + claudication (2° to ischemia), from A. of adamkewicz. Aortic bypass may worsen.
Radiation myelopathy: Painless paresthesia, sensory before motor, early transient (3-6mo, paresthesias) or delayed progressive (12-15mo, coagulation necrosis of white matter, hyalinized vessels – resembles infarct). Tx: steroids.
Neuropathies: DM, leprosy, amyloid, polyarteritis nodosa, acute intermittent porphyria, uremia, metachromatic leukodystrophy, Fabrys, Krabbes
Onion Bulb: *Dejerine-Sotas* (AR, children, enlarged nontender ulnar, median, radial & peroneal n.), *Roussy-Levy* (ataxia, tremor, pes cavus), *Charcot-Marie-Tooth* (AD, can affect UE, steroids no effect, no autonomic effects, peroneal muscle *atrophy*, segmental demyelination), *Refsums*
Have mutation in peripheral myelin proteins (PMP22 in CMT)
Demyelinating: diptheria, lead, GBS, DM, hexacholophene
Sensory: amyloid,DM,ETOH
Autonomic: Fabrys, amyloid, porphyria, GBS, DM, vincristine, botulism
Motor: GBS, diptheria, porphyria, uremia, lead
Drugs: isoniazid (sensory), nitrous oxide
Cranial neuropathies: III: DM, syphillis; V: arsenic, sjorgen; VII: Bell's, Ramsay-Hunt, sarcoid, lyme, porphyria, PAN;VIII: wegeners, refsums; IX: diptheria. General: GBS, amyloid.
Porphyria: Acute intermittent: AD, abdominal pain/ gastroparesis/ constipation, *hyper*tension/ tachycardia (2° to autonomic neuropathy), psychosis, neuropathy (axonal motor/ autonomic), Skin is normal. Seizures, SIADH. Porphrobilinogen deaminase deficiency:↑ porphobilinogen, δ-aminolevulinic acid. May be provoked by porphyrigenic drugs: barbs, PTN, sulfa, estrogens. Tx: IV hematin.
All others have skin manifestations: Varigate, hereditary corproporphyria, Porphyria cutanea tarda (all above hepatic porphyrias), also erythopoetic porphyria
Diabetic neuropathy: Opthalmoplegia, acute mononeuropathy, mononeuritis multiplex have vascular origin, distal sensorimotor polyneuropathy due to direct neurotoxicity
Mononeuritis multiplex: painful, asymmetric, LE > UE, painful, prox > distal, evolves minutes to days, resolves in weeks Occurs w/DM, PAN
Amyloidosis: Familial or secondary. Neuropathy (from Ig light chains in endoneurium of blood vessels, axonal degeneration, small unmyelinated pain/temp & autonomic fiber loss). CTS. Angiopathy. Polypeptide amyloids β-pleated sheets. Herditary = prealbumin, transthyretin.
Brachial plexus lesions:
Upper trunk (Erbs): abnormal deltoids, biceps; waiters tip
Middle trunk:abnormal median sensory (index & middle finger), hand motor normal
Lower trunk: abnormal ulnar sensory (little finger), EIP (extensor indicis proprius) and APL abnormal
Medial cord: ulnar sensory abnormal; EIP normal
Lateral cord: abnormal median sensory, abnormal biceps and FCR, normal APB
Posterior cord (Klumpkes): wrist drop, IM shoulder injections
Brachial Neuritis = Parsonage-Turner; pain then proximal arm weakness (3-10d later, > sensory, distal); no WBC, ESR, fever. Can be AD.
Rheumation arthritis: PIP (Bouchard) only; Degenerative = PIP + DIP (Heberdens)
Hyperhydrosis – T2/3 ganglionectomy (leave T1 to prevent Horners)
Scleroderma: entrapment neuropathy (CTS), anti-Scl-70 or 86. Tx d-penicillamine
Sjorgens: xerostomia, conjunctivitis (Schirmers test). Anti-Ro (SS-A) & La (SS-B). Vasculitis, neuropathy

Demyelinating Disease

ADEM: postviral/postvaccination. ↑ESR. CSF ↑ pressure, WBCs, RBCs, protein. Perivenular demyelination. Involves deep grey matter (vs MS) Tx: Steroids. 25-50% mortality.
Multiple Sclerosis: CSF: IgG index >1.7 (>15%), protein not >100, ↑ MBP, oligoclonal bands, mild pleocytosis. Tx: ACTH, steroids (↓ duration, not with optic neuritis), βinterferon (↓ relapse, no ↑ infections). VERs usually abnormal. Path: *Perivenular* demyelination w/axonal sparing; *perivascular lymphocytes*, *macrophages*, reactive astrocytes. No PNS involvement. Risk equal to habitat when <15yo. Northern = worse. Optic neuritis causes ↑ blind spot, no VF defect. Lesions abut dorsal surface in spine.
Marburg=fulminant, Devic=optic n. and spinal cord; Schilders=kids, fatal
Experimental allergic encephalomyelitis = model, T-cells to MBP
Other Demyelinating Dz: PML, SSPE, rubella, HIV, Binswangers, CO, leukodystrophies, EtOH, cyclosporin, ampotericin, hexachlorophene, triethytin, radiation, MTX, lead, mercury
Oligoclonal bands: MS, SSPE, syphillis, NOT TB

Toxic/Metabolic

Vitamins: Thiamine: rice eaters, alcoholics. Wernickes, beriberi (heart dz); painful sensory *neuropathy* (distal LE dysesthesias/hyperpathia), orthostasis (2° to neuropathy), Strachan's syndrome (sensory ataxia, optic n. atrophy, deafness).
Niacin: pellagra (rash, post column/CNS

probs), due to tryptophan def, corn eaters. B12 (Cobalmin): subacute combined degeneration, megaloblastic anemia, neuropathy, centrocecal scotoma. Folate: megaloblastic anemia, neuropathy, due to methotrexate (dihydrofolate reductase inhibitor) Pyridoxine (B6): due to isoniazid (INH). Neuropathy. Vitamin A: increase causes pseudotumor. Vitamin E: spinocerebellar degeneration/ ataxia, polyneuropathy. Kids, hepatic dz. Chromium: diabetes. Zinc: dermatitis.

Methionine metabolism:

Methionine > homocysteine.
Homocysteine > methionine (methionine synthetase - requires B12 & folate (methyl- THF)) *or*
Homocysteine > cysteine (by cystethionine βsynthetase – requires B6).
B12 def (SCD): ↑ homocysteine & methylmalonic acid (Methylmalonic-CoA > Succinyl-CoA also requires B12 in amino acid metabolism).
B6/ CβS def: Marfans, homocystinuria, hyperhomocysteinemia: ↑ homocysteine & methionine.
Folate/ MTHFR def: ↑ homocysteine
Folate: folate > DHF > THF (by MTHFR) > methyl-THF > accepts methyl group from homocysteine in above reaction > THF
Cyanocobalmin (B12): metabolized to cyanide

Subactue combined Degeneration: Post. Columns (first) then corticospinal – esp. *cervicothoracic* (may occur in medulla). Demyelination & axonal degeneration, *spongiosis* (not seen in Friedrichs ataxia), vacuoles in myelin. May have visual probs – centrocecal scotoma. CSF WNL.
Vitamin B12 (cobalmin). Absorbed in ileum. Methionine synthetase requires B12 >*Elevated serum methylmalonic acid and homocysteine* (best indicator of intracellular B12 levels. Microbiological assay best method for Serum B12 but is less reliable). DNA synthesis failure. Nitric oxide also inactivates methionine synthetase.
Pernicious anemia: lack intrinsic factor to transport B12 in ileum. Schilling test: B12 then B12 + IF. B12 IM qD. Tx: IM B12 qmonth - Oral B12 will not correct.
Intrinsic SCD: Idiopathic, not B12, motor then post columns.

Toxicology

Arsenic: insecticides. encephalopathy, neuropathy (axonal), abdominal pain, palm/soles pigment, Mees lines (fingernails). BAL. Detect in hair
Lead: enephalopathy (resembles AIP), diffuse brain swelling (kids), MR, wrist drop (painless motor neuropathy), black gingiva, RBC basophilic stippling (anemia), ↑ urinary corproporphyrin and δ-aminolevulinic acid. Tx: BAL & EDTA.
Manganese: miners, Parkinsons, affects striatum, Tx: l-dopa
Mercury: fish, hat dyes/felts, paper/pulp plants. cerebellar signs/ataxia, tremor, mood change, visual loss, renal tubular necrosis. Path: calcarine cortex & cerebellar granular layer. Inhibits protein translation. Tx: penicillamine (not BAL)
Thallium: cardiac, GI probs, *alopecia*, arthropathy, neuropathy
Aluminum: dialysis pts, osteomalacia, encephalopathy
Copper: OCPs, Wilsons Dz
Carbon Monoxide: GPm necrosis; parkinsonism 1-3wks after event (suicide, fire)
Iron: desferoxamine
Gold: BAL, penacillamine
Organophosphates: insecticides, rat poison. anticholinesterases (sweating, cramps, n/v, ↑ salivation – not dry mouth). Tx: atropine + pralidoxime (2-PAM)
TOCP: triorthocresyl phosphate, causes rapid UMN & LMN paralysis
Ergot: rye grains/bread. Posterior colums/dorsal roots, neuropathy, skin ulcers. vasoconstrictor
Tylenol: N-acetylcysteine
Cyclosporin: encephalopathy; occipital lobe white matter changes resembling hypertensive encephalopathy – cortical blindness. Demyelinating. Transplant pts
Isoniazid: anti-TB. Neuropathy due to pyridoxine deficiency. Give with pyridoxine.
Nitrous Oxide (N2O): abuse (dentists, health care). Peripheral neuropathy, megaloblastic anemia. Numbness, paresthesias, ataxia, spasticity (resembles B12)
Methanol: moonshine, hemorrhagic putamen/claustrum necrosis, blindness/acute central scotoma Tx: EtOH
Ciguatoxin: food poisioning, tropics/South. Fish (snapper, grouper). ↑ permeability sodium channels – excitability. N/V (6hrs) > paresthesias, HA, ataxia. *Temperature reversal*. Resolves 1-2d.
Lathyrism: spastic paraparesis from eating only chick-peas (toxin causes glutamate toxicity)
Paraquat: insecticide, kills dopaminergic cells, causes parkinsonism.

EtOH: withdrawl 72hr (vs benzos 7-10d). Prevention: chlordiazepoxide. Superior vermis (Purkinje cell, molecular layer) atrophy.
Fetal alchohol syndrome: impaired neuronal migration., MR, microcephaly
Wernicke's: gait ataxia, nystagmus (most common) opthalmoplegia (bilateral lateral rectus 2nd), confusion. Also), hypothermia. Thiamine def. Ocular problems recover 1st. Mamillary body, PAG, PVG lesions (enhance on MR). ↑ serum pyruvate, TTP, ↓ transketolase
Korsakoff's: short-term retrograde memory deficits (immediate memory/ attention OK). DM thalamus. Only 20% improve w/Thiamine.
Central pontine myelinolysis: correction of hyponatremia. never extends into medulla, demyelination, affects oligos, preserved neurons, no inflammation
Marchiafava-Bignami: demyelination of corpus callosum and ant comissure
Cocaine: causes noncaseating granulomas of basal areas/ meningitis
Diffuse Brain Swelling: in kids: lead, tetracycline, vitamin A
CRF: peripheral neuropathy most common (legs, mixed). Tx: transplant (not dialysis)
Hepatic encephalopathy: Ammonia ↑ GABA synthesis. Asterixis. Alzheimer type II astrocytes, hyperplasia of protoplasmic astrocytes in deep cortical layers & deep nuclei. T1 hyperintense BGs. Involves cortex, spares hippocampus, GP, deep folia of cerebellar cortex. EEG: triphasic waves (can occur w/others) Tx: lactulose.
Reye syndrome: Virus + ASA. Hepatitis, encephalopathy, hypoglycemia, cerebral edema. Tx: supportive
High-altitude sickness: cerebral hypoxia. Tx: steroids, diamox, O2.

Infectious Disease

Meningitis: H flu=alcholics, diabetics, kids, CSF leaks. Type B. Causes subdural effusions. 3rd gen cephalosporin. Steroids decrease deafness. Prophylaxis for all contacts <18yo.
S. pneumo= elderly, skull fx/ CSF leaks (recurrent), TBI, alcoholics, sickle-cell. Vanc + 3rd gen ceph, PCN.
N. Meningiditis=rash, rapid, meningeal fibrosis. Waterhouse-Friedrichsen (shock, adrenals) Gram (-) diplococcus. PCN, Cephalosporin. Rifampin prophylaxis for all contacts. Vaccine for epidemics, military recruits
Listeria: Gram+ Rod (intracellular). Neonates, renal transplant, CRF, immunosuppressed, steroids. Glucose, G/S may be normal. Amp/Gent

GNR: Ceph/gent.
Neonatal meningitis: GNR > group B strep > listeria.
Tuberculous: ↓↓ glucose. INH/Rif/PZA x 12mo ± steroids
Skull fx: closed = pneumococcus > H flu. Open = GNR
Malignant otitis/ petrositis: facial palsy, otorrhea, elderly DM. Pseudomonas.
Steroids: infant H. flu; severe TB; neurocystercercosis w/↑ ICP.

Brain abscess: aerobic/microaerophillic Strep. Sinus infxn most common cause. Infants Tetralogy of Fallot #1 (also transposition great vessels). Also pulmonary AVMs (Rendu Osler Weber) Neonates: Citrobacter, Bacteroides, Proteus. SBE usually causes strokes, mycotic aneurysm – not abscess.

Bacterial Encephalitis:
Bacterial: Legionella (CSF -), Mycoplasma, Listeria (immunosuppresed, CSF +), Brucella.
.

Subdural empyema: Streptococcus
Epidural abscess: Staph aureus (pseudomonas in addicts)
Tuberculosis: CSF: ground glass, low Cl, protein very high. Basilar exudate, basilar & cortical "popcorn" calcifications, parenchymal granulomas (ring-enhancing). Caseating (cheesy - yellowish) necrosis, Langhan's giant cells. Noctural wakefulness. Potts dz : affects disk space 1st.
Fungal: Immunocompetent: Histo, Blasto, Coccidio. Immunodeficient: Candidiasis, Aspergillosis, Cryptococcus, Mucor.
Yeast: crypto, coccidio, histo, blasto
Hyphae: aspergillosis, mucor
Both: candida (pseudohyphae)
Tx for all: Ampho B.
Aspergillosis: Invades blood vessels > infarcts. Dichotomous (45° Y-shaped) Branching *septate* hyphae (silver stain on all fungus). Immunocompromised. Most common fungal abscess.
Mucormycosis: Nasal infxn, diabetics, immunosuppression. Angioinvasive. *Nonseptate* right-angle branching hyphae.
Cryptococcus: India ink/ mucicarmine (stains capsule red). Bird feces. Single bud w/halo. Meningitis. Gelatinous perivascular "pseudocysts" in BG, path: perivascular macrophages & yeast. ("Swiss-Cheese" brain)
Candida: Most common CNS fungus. ICU/immunosuppressed, causes retinitis.
Histoplasmosis: usu pulmonary, very small, inside macrophages, Mississippi valley
Coccidiomycosis: So. Cal. Large yeast – "sporangia". Usu. Pulmonary.

Parasites
Cystercercosis: Taenia solium. Pork tapeworm – but obtained thru fecal contamination (vs taeniasis and trichinosis – from eating undercooked pork). Ingest eggs > penetrate gut > oncospeheres > larvae encyst in CNS. Tx: Praziquantel.
Echinococcus: Taenia echinoccocus. Hydatid disease. Dog tapeworm/easting infected sheep. Larvae in cysts = hydatid sand (Small cysts in larger cyst)
Schistosomiasis: fluke. Deposits ova in Batsons veins > spinal cord granulomas >myelitis. Puerto Rico. Praziquantel
Toxo: Obligate intracelluar protozoa. Cats/congenital. *Cysts contain tachyzoites* visible on H&E. Seurm IgG almost always (+), CSF usually mornal. Tx: pyrimethamine/ sulfadiazine (w/ Leucovorin rescue)
Amoebic meningitis: Naegleria & others. Freshwater ponds, basilar meningitis. Enter cribiform plate. Tx: metronidazole.
Malaria: Plasmodium falciparum. Encephalopathy. Infected RBCs > stroke.
Trypanozones: T. Brucei = African sleeping sickness (Tsetse fly). T. gambiense = chronic meningitis. T cruzi = Chagas dz (reduviid bug)

Viral meningitis/ encephalitis:
Enterovirus #1. Encephalitis: Arbovirus = #1 epidemic, HSV = #1 sporadic. Herpes & rabies enter nerves, use fast retrograde transport to enter CNS. Most cause microglial nodules & perivascular lymphocyte cuffing.
Arboviruses: Arthropod: Eastern (summer, rare, 75% mortality, children); Western (summer, more common, infants, 5% mortality); Venezuelan (epidemics, mortality <1%, adults, south); St Louis (adults); LaCrosse (common, kids, mortality <1%)
Herpes encephalitis: Limbic lobe: Bitemporal, cingulate, subfrontal, insula. SF RBCs, mononuclear cells. EEG: temporal PLEDs, slow waves. Dx: PCR on CSF or Bx & Cx. (HSV2 = neonates, diffuse). Path: Cowdry type A (intranuclear eosinophilic inclusion) in neurons, astrocytes, & oligos, found early. Tx: acyclovir.
Rabies: Travels peripheral nerves to CNS. Glycoprotein G on envelope attaches to nicotinic Ach receptor or NCAM. Path: Negri bodies (eosinophilic cytoplasmic) in Purkinje cells of cerebellum & pyramidal cells of hippocampus, limbic neurons. Tx: Ig. Transmitted by saliva (not from mice/rats, rabbits, reptiles).
SSPE: caused by measles @ 5-15yo from infection <2yo. EEG: 2-3/s spikes, burst suppression pattern (bursts of high-voltage slow waves w/ low-voltage stretches). Dementia, seizures, myoclonus, ataxia.↑ measle serum & CSF titers; ↑ CSF IgG & oligoclonal bands (resembles MS). Eosinophlic Nuclear & cytoplasmic inclusions in glia & neurons. Grey & white matter. Gross demyelination, atroophy.
PML: JC papovavirus. Demyelinating. *Oligodendroglia* in periphery of lesion altered to large, dark, *ground-glass* nuclei w/ *owls eye inclusion.* Giant astrocytes (Alzheimer type I). No enhancement. No inflmmation (vs MS-has macrophages). Spares cortex. Dx: CSF PCR. Occurs w/HIV, lymphoma/ leukemia, sarcoid.
HIV: dementia complex #1 (subcortical dementia, motor deficits). Glycoprotein 160 (precursor > Gp120 & Gp41) attaches to CD4 receptor (T-helpers) and galactoceramide (oligos, neurons) – disrupts Ca/long term potentiation > ↑ intracellular Ca > neurotoxicity. Vacuolar myelopathy: posterior & lateral columns, low thoracic. Myelitis: CMV causes *pial enhancement*. Encephalitis: unique *multinucleated giant cells* (syncytial macrophages). Both HIV (perivascular) & CMV (subpial/ ependymal) (& toxo) produce microglial nodules.
Tx: zidovudine (AZT - myopathy), 3TC (neuropathy) (CMV = Ganciclovir)
CMV: large eosinophilc nuclear inclusions (Cowdry A) with halos. Causes neonatal encephalitis (see TORCH), HIV encephalitis, myelitis.
Sarcoid: favors CN7. Mononeuritis multiplex, (& other neuropathies, myopathy). Serum ACE up. Steroids. Neurologic in 5%. Noncaseating granulomas, basal/hypothalamus. Dx: Bx of non CNS tissue. Steroids. Note sarcoid may resemble MS but MS does not cause neuropathy.
VonEconomo's encephalitis: (encephalitis lethargica). After influenza, develop parkinsonism
Syndenham's chorea: after rheumatic fever (group A strep, carditis + arthritis). No Tx necessary. May recur years later. Preadolescent females
Whipples dz: *Tropheryma whippleii.* Jejunal Bx: PAS+ cells. Ataxia, ophthalmoparesis, dementia (myoclonus, szs). Resembles Wernickes. Oculomasticatory myorhythmia (penudular convergance of eyes with rhythmic "smiling") pathognomonic. Tx: antibiotics

Syphillis: Meningovascular = Huebners arteritis. General paresis of the insane (chronic meningoencephalitis). Tabes dorsalis (Thoracic, lumbar, post columns, dorsal roots, bladder/bowel incontinence, absent DTRs, argyll-robinson pupils, charcot joints). Congenital (Hutchinsons triad: notched teeth, deafness, keratitis) Nontreponeal tests: RPR, VDRL – false (+). Treponemal: MHA-TP, FTA-ABS, confirmation. If serum (+), check CSF.
Cat-scratch fever: *Bartonella*. Epitrochlear lymphadenopathy (due to scratch on arms). MRI: Pulvinar hyperintensity. Meningitis or enchpalitis (immunosuppressed).
Neonatal/TORCH: CMV (#1): migration abnormalities, HCP, periventricular calcifications, microcephaly, chorioretinitis (Tx gangcyclovir)/optic atrophy, MR, deafness; Toxo: <26wks, no migration probs, chorioretinitis, hydrocephalus, scattered *cerebral* calcifications (not periventricular); Rubella: BG/cortical calcification, small brain, cataracts, deafness, cardiac probs, aqueductal stenosis. HSV: 2-4wks postpartum, diffuse encephalomalacia (not just temporal).
Lyme Dz: Borrelia burgdorferi. Tickborn spirochaete. erythema chronicum migrans = slowly spreading ring of erythema, aseptic meningitis. Radiculopathies (sciatica), neuropathies, Dieterle stain. CN7 commonly affected (weeks after rash). Dx: ELISA. Ceftriaxone > Tetracycline, erythromycin.
Ramsay-Hunt: herpes infection of CN7; vesicles on EAM
Bell's Palsy: +- hyperacuisis, taste changes; peaks 2-5d; ?HSV; Tx: steroids x 1 wk
Botulism: Rapid onset bulbar paralysis. Pupils unreactive (large, fixed, vs MG - reactive) (also ptosis, opthalmoplegia, diplopia, dysphagia, dysarthria). EMG: (looks like Eaton-Lambert) decremental response at low frequency (2-5Hz), incremental response at high-frequency (20-50Hz). Canned vegtables containing exotoxin (raw honey in infants – organism injested & produces exotoxin in gut). 3 types of exotoxin : A (used in botox injections), B, & E. Symptoms appear 12-36hrs. CSF WNL.
Presynaptic ↓ Ach release due to ↓ vesicle release (Zinc-dependent protease, cleaves synaptobrevin, SNAP25 & syntaxin) Descending. Tx: Antitoxin, guanidine. DDx: Guillain Barre (abnormal NCV, sensory affected, CSF abnl), tick paralysis
Tetanus: Exotoxin transmitted by retrograde axonal transport, inhibits Renshaw cells (↓ glycine vesicle release by cleaving synaptobrevin – Zinc dependent protease) – tetany. May be local, generalized, or cephalic. 50% mortality. Incubation days to weeks. Usually in soil. May also occur in neonate by contaminated umbilical cord, contaminated heroin. EMG: continuous discharges of normal motor units, loss of normal "silent period" (due to renshaw cells) Tx: Antitoxin (Ig), PCN, debridement.
Diptheria: ascending paralysis, ophthalmoplegia, demyelinating sensorimotor neuropathy at DRG & roots without inflammation. Exotoxin inhibits myelin synthesis. Antiserum.
Black Widow: depletes Ach into NMJ
Leprosy: Neuropathy – due to bacillus growth in peripheral axons & Schwann cells (lepromatous) or due to perineural granulomas (tuberculoid)

Ophthalmology

Adie pupil: degeneration of cilliary ganglion (parasympathetics), large pupil – no response to light (responds to near, same as argyll-robertson); very sensitive to miotics due to denervation hypersensitivity (0.1% pilocarpine – normal pupils don't respond); young women; may have absent DTRs, benign
Argyll-Robertson: small pupils, react to accomodation, not light. no response to mydriatics. Lesion unknown (pretectal area?)
Marcus-Gunn pupil = afferent pupillary defect (APD)
Colliers sign: Bilateral lid retraction – *Diencephalic syndrome* (wasting, ↑ food intake, euphoric)
Nyctalopia: night blindness, retinal degeneration (retinitis pigmentosa) or Vit A deficiency.
Macular damage: severe visual loss
Scintillating scotomas: migraine aura
Hypertensive retinopathy: segmental narrowing of arterioles (copper wire)
Diabetes: *Pupil sparing* CN3 palsy, painful, abrupt, resolves w/in 6mo (Most deadly complication of diabetes = heart disease)
Diabetic retinopathy: microaneurysms, vascular proliferation
Most common cause acute diplopia: CN6 (>3>4). CN4 most common injury in facial trauma. CN4 most commonly affected w/herpes zoster opthalmica (V1). Pupil affected 1st by CN3 compression (peripheral fibers)
Bielschowskys sign – CN4 injury, head tilted to *opposite* side; eye up & in
Gradenigos Syndrome: osteomyelitis of petrous apex. CN6 (&3) palsy & retroorbital pain, from otitis (cholesterol granuloma can also occur at petrous apex)
Horners: no response to 2% cocaine. + hydroxyamphetamine: no effect = 3rd order (postganglionic), dilation = 1st or 2nd order (epinephrine opposite). Sympathetics: hypothalamus > interomediolateral column > T1 root > Sup cervical ganglion > ICA (pupil) & ECA (sweat). ICA Dz (dissection) doesn't produce anhydrosis.
Tunnel vision: retinitis pigmentosa, glaucoma, papilledema
Retinitis pigmentosa: Degeneration of all layers of retina. Tunnel vision, Nyctalopia. Occurs w/ mitochondiral dz, Laurence-Moon-Biedl, Friedrichs ataxia, Cockaynes, abetalipoproteinemia, Refsums, or alone (AR, Chr 3).
Nystagmus:, downbeat = cervicomedullary, ocular bobbing = pons, oscillopsia = vestibular, impaired opticokinetic reflex = parietal or vestibular (elicit by rotating drum away from lesion), see-saw = parasellar; convergence & nystagmus retractorius = pineal/ tectal (Parinauds), ocular dysmetria (overshoot) = vermis, spasmus mutans = infants only, congenital (nystagmus on gaze then fixation on object)
INO: Ipsilateral MLF: Impaired adduction ipsilateral eye, nystagmus in contralateral eye. Bilateral MLF: impaired adduction bilaterally. Pathognomonic for MS. Both have preserved convergence.
1-1/2: MLF + PPRF/CN6. Complete opthalmoplegia isilaterally, only abduction contralateral. Convergence OK.
Optic neuropathy: Ischemic: painless, abrupt, *inferior* altitudinal defect. HTN/diabetes – posterior ciliary a. Exclude temporal arteritis. Optic disc papillitis > pallor. Embolic: Central retinal a. Cloudy retina, grey narrow arterioles w/ segmented columns of blood, cherry-red fovea. Toxic/nutritional: bilat central scotoma
Optic neuritis: painful, visual loss/APD (complete blindness resolves to enlarged blind spot/ centrocecal scotoma), 75% develop MS, recovers. Steroids (IV then po – po alone worsens)
Papilledema: no visual acuity loss, enlarged blind spot, venous pulsations absent in 15% of normals (not reliable), engorged capillaries from short ciliary arteries

Drusen: hyaline in optic n., resembles papilledema
Cavernous sinus thrombosis: pain, proptosis, visual loss
Diptheria polyneuropathy: opthalmoplegia
Tolosa-Hunt: eye pain + opthalmoplegia + V1 sensory loss. Pupil spared. Lesion in cavernous sinus/SOF (III, IV, V1, VI)
Thyroid: afffects inferior & medial rectii (upgaze affected more than lateral)
Optic nerve thickening: Graves dz, orbital pseudotumor, optic neuritis, papilledema, cav-mal, glioma, meningioma, lymphoma, met
Orbital pseudotumor: enhancing mass, enlarges muscles or optic n., resembles lymphoma
Schirmers test: measures tear production (Sjorgens)
Leber's optic atrophy: centrocecal scotoma, young men, mitochondrial DNA mutation
Neonates: no red reflex = congenital cataracts; white reflex = retinoblastoma
Heterochromia iridis: due to congenital Horners, injuries to sympathetic n. to pupil during birth. Causes different color eyes (blue/brown) & anisocoria. Sympathetic innervation required to eyes to change from blue to brown. May be AD.
Myopia corrected by concave lens; astigmatism by cylindrical lens; hyperopia by convex lens.
Coloboma: Gap in the eye due to failure of embryonic fusion of choroid fissure, usually in iris.
Amblyopia: "Lazy eye", can be do to anything that causes unilateral ↓ vision – usually cross-eye. Patch good eye. Best 2-4yo, 7-9yo latest.
Ocular albinism: defect in tyrosinase gene, ↓ melanin in retina > misrouting of fibers to LGB results in disordered layering in LGB > lack of binocular vision & diplopia
Junctional scotoma: lesion at junction of optic n. & chiasm. Ipsilateral scotoma + contralateral superior quadrantopsia (Meyers Loop)
Meyers loop (optic chiasm) vs von Willebrands knee (temporal): Both give pie-in-the-sky (superior quadrantopsia). Willebrands = homonymous. Meyers = ipsilateral scotoma.
Retinal emboli: Cholesterol (Hollenhorst plaque) = ICA. Calcific = cardiac valves. Platelet-fibrin = large vessel mural thrombi. Fat = long bone fracture.

Ear stuff
Hearing loss: conductive = low-pitch, neural = high-pitch
Weber = forehead, Rinne = mastoid
Menieres Dz: vertigo, low-pitched tinnitus, *low-pitch* deafness (high pitch late), fullness in ear, nystagmus. Endolymphatic duct ruptures into scala media dumping K into perilymph. Hair cell degeneration. Tx: salt restriction, diuretics
Vestibular neuronitis: Vertigo without tinnitus, deafness. Viral, self-limited (also caused by ASA, EtOH, quinine, aminoglycosides. ASA also causes tinnitus.)
Benign positional vertigo: middle-age, elderly. Turning head to affected side causes vertigo & rotatory nystagmus. Calcified otolith in posterior semicircular canal. Tx: exercises.
Presbycusis: neuronal degeneration, high-pitch loss
Pulsatile Tinnitus: dural AVM, glomus tympanicum, aberrant ICA

Seizures
Seizure foci: high glycine, extracellular K; low GABA, taurine. Decreased binding and removing Ach. Surrounding = high GABA. Diencephalon inhibits – goes from tonic to clonic. Caused by cortical pyramidal cells (glu)
AEDs: *Neonatal* = phenobarb. *Complex partial* = tegretol > dilantin. *Absence* = ethosuximide > depakote. *Myoclonic & atonic* = depakote (ACTH in infants). *Lennox-Gastaut* = depakote. *Preeclampsia* = MgSO4. *Absence status* = IV BZDs. *Complex partial status* same as GTC.
Pregnancy: Recommened to continue during. Risk of anomlies ↑ from 2% to 4% (equal w/all AEDS). PTN ↑ bleeding – give vitamin K, depakote ↑ neural tube defects.
Mechanisms: Na channel blockers: PTN, Tegretol, Lamotrigine, Neurontin, topiramate (& other new drugs); Barbs & benzos (& topiramate) ↑ GABA; Felbamate NMDA block; Topiramate AMPA block; Tigabine blocks GABA reuptake; ethosuximide & zonisamide ↓ Ca current.
Interactions: All ↑d by INH; PTN & CBZ ↑ by chloramphenicol (also PB), cimetidine, diltiazem, demerol (also PB), Omeprazole; CBZ & VPA ↑ by erythromycin; ASA ↓s all; PTN ↓d by antacids, cipro, rifampin, warfarin?, & others, ↑ by sulfa, uremia. Dialysis affects CBZ & PB, not PTN. PTN ↑s coumadin levels, PB & CMZ ↓ them.
CBZ ↓ all other AEDs except PB. PB ↓ all. PTN ↓ all. VPA ↑ all (displaces PTN from plasma proteins)
Phenobarbital SE: Dupuytren's contractures. T1/2 = 96hrs.
Dilantin: *Atrophy of Purkinje and granular layers of cerebellum.* Neuropathy, gingival hyperplasia, hirsutism arrythmias/ hypotension IV; interferes w/vitamin K – bleeding & ↑s coumadin. T1/2 = 24hrs.
Tegretol: leukopenia/pancytopenia. ↑ by erythromycin. T1/2 = 12hrs.
Valproate/Depakote: GABA agonist. SE: thrombocytopenia, alopecia, pancreatitis, neural tube defects. T1/2 = 8hrs.
Felbamate: aplastic anemia/ hepatotoxicity (not used).
Absence: 3/s spike-wave. Last 10-15sec, (+) automatisms, no aura, no postictum.
Partial-Complex: Last 90sec, automatisms, aura, postictum.
Geschwind syndrome: hyperreligious, philisophical – from ↑ hippocampal activity/ kindling (attach emotional significance to all stimuli).
Mesial temporal sclerosis: neuronal loss in Ca1,3,4 & dentate gyrus. (Spares Ca2, subiculum – unlike hypoxia). ↓ somatostatin & neuropeptide Y neurons. Axonal sprouting in dentate (mossy fibers). Seen in 65-70% of temporal lobe epilepsy. MRI 80-90% sensitivity. Possible related to febrile seizures.
Lennox-Gastaut: 2-6yo. Partial complex, Drop attacks, GTC. Cognitive decline. 2/s spike/wave. TS may develop. Tx: Depakote.
Rasmussens: Intractable focal epilepsy w/ progressive hemiparesis, 3-15yo, 50% epilepsia partialis continua. Meningitis/ encepahlitis, perivascular cuffing, ?Abs to glutamate receptors. Tx: steroids
Infantile spasms: "salaam spasms", myoclonic head jerks. Tx: ACTH. Can occur in Tuberous sclerosis, PKU, Sturge-Weber or Wests syndrome
Wests syndrome: infantile spasms, EEG: hypsarrythmia (large slow waves), MR. Several hundred szs per day. Begins 3-8mo, disappears by 5yo, Can lead to Lennox-Gaustaut.
Hyperexplexia: startle, glycine receptor defect, Tx: clonazepam
Benign juvenile myoclonic epilepsy: common cause of myoclonus in adolescents. Initally occur after waking. 4-6Hz spike-wave. Depakote. Does not resolve w/age.

Benign childhood epilepsy w/ centrotemporal spikes: nocturnal, focal face, drooling, resolves by 16yo.
Breatholding spells: after startle, for of syncope, can include myoclonus, resolves by 6yo, no ↑ risk of epilepsy
Febrile szs: GTC, <15min, nonfocal, single, 6mo-5yr. No ↑ risk later szs (others say ↑ to 1%). <1yo requires LP to r/o meningitis.
Myoclonic Szs: Lafora body Dz, Unverrict-Lundborg (8-13yo, no dementia, cystatin B cysteine protease mutation), ceroid lipofuscinosis, sialidosis, MERRF.
Lafora disease: AR, Lafora bodies: PAS+ basophilic intracytoplasmic polyglycosan inclusions in brain, skin, liver (Bx). Begins 11-18yo, myoclonic szs, dementia, die by 25yo; Labs WNL. Tx: Depakote, methsuximide
Temporal lobectomy: most often causes superior quadrantopsia
EEG: Activity comes from pyramidal cell synaptic potentials – synapses from thalamic (downward deflection) and cortical (upward) axons on pyramidal dendrites (not nonpyramidal cells or action potentials)
GTC: high frequency, high amplitude waves. Focal sz: low frequency (2-4Hz), rectangular wave. 40% have interictal activity (60% w/multiple EEG). Vertex transients: normal, at skull vertex, may be confused with spike. Stage 2. Other normal variants: Lamba(awake) & POSTS (asleep, both triangular), K-complex (arousal during stage 2 sleep), .14 & 6 rhythm (kids, drowsiness)
PET: foci ↓ interictal, ↑ during sz.
Posttraumatic: open (bullet/ shrapnel) = 50%, Closed = 5%.

Developmental/Genetic

Reflexes: Disappear: rooting 3mo; moro & grasp 6mo; Babinski 6-12mo (abnormal >2yo). Parachute appears 9mos.
Achondroplasia: Chr 4, spinal stenosis, hydrocephalus
Neural Tube Defects
Anencephaly: most common congenital malformation. Area cerebrovascula contains vessels, nerve tissue. Decreased maternal folate, zinc or copper.
Neuronal Migration Disorders
Mouse models: mutant reelin gene
Lissencephaly: Chr 17 deletion assoc. Type I: 4 layer cortex w/ thin overlying white matter. Type II: no layers, glioneuronal heterotopias.
Miller-Diecker: lissencphaly, pachygyria, microcephaly, abnormal facies, multiple organ dysfunction, polydactyly AR, Chr 17, LIS1 gene
Norman-Roberts
Walker-Warburg: lissencephaly, *congenital myotonic dystrophy*, hydrocephalus, agyria, retinal dysplasia/ micropthalmia, ± encephalocoele. AR. Type II.
X-linked lissencephaly – subcortical band heterotopia: Doublecortin (DCX), a MAP
Pachygria: cortex has 4 layers (not 6). 12-16wks.
Heterotpoias: Nodular/ periventricular: *normal IQ*, szs. Familial: X-linked (lethal in males), Filamin-1. Subcortical Band: *MR*, szs
Polymicrogyria: 4 layer cortex, MR, szs
Cortical dysplasia: focal areas of abnormal cortical cytoarchitecture
Schizencephaly: familial: defect in EMX2 homeobox gene
Colpocephaly: Seen in agenesis of corpus callosum, periventricular leukomalacia. Damage to white matter 2-6mos gestation.
Aperts: Syndactyly, cleft palate, ± frontal encephalocoele, severe MR, prognathism (anterior open bite). Coronal only (turribrachycephaly); GI/GU/cardiac anomalies
Crouzons: Malformed ears, agenesis of the corpus callosum, malaligned upper teeth, variable sutures. Increased HCP, Less severe MR (64% IQ >90) **Both**: AD, hypertelorism, blindness, deafness, exorbitism.
Carpenter syndrome: all sutures fused
Holoprosencephaly: Alobar: Severe facial abnormalities, monoventricle, no septum, falx, fused thalami/ BG. Maternal diabetes, trisomy. Semilobar: partial falx & interhemispheric fissure. Lobar: no facial abnormalities, grey matter over corpus callosum, anterioinferior fusion of cortex, squared frontal horns, thalami/BG separated. Azygous ACA common. Septum absent in all.
Septo-optic Dysplasia: Absent septum & optic nerve hypoplasia. 50% schizencephaly. 50% pituitary dysfunction, ectopic pituitary
Arrhinencephaly:: no olfactory tracts, grey matter in place of corpus callosum. Kallmans syndrome: anosmia, hypogonadism (GnRH neurons in hypothalamus missing – derived from olfactory placode like olfactory receptor neurons), MR.
Agenesis of corpus callosum: Partial = splenium, rostrum. Probsts bundles (white matter periventricular bundles), 50% associated abnormalities (chiari, Dandy-Walker). High riding 3rd ventricle opens into interhemispheric fissure, parallel lateral ventricles. May have MR. "Bat-wing" deformity.
Aicardi's syndrome: agenesis, infantile spasms, MR, chorioretinitis
Joubert syndrome: AR, dysgenetic split vermis, MR, agenesis, polydactyly, oculomotor probs, cystic kidneys.
Rhombencephalosynapsis: fused cerebellum
Phakomatoses: All AD except Sturge-Weber
NF1: Chr 17, 50% sporadic.
Neurofibromin: tumor suppressor, inhibits ras oncogene by ↑ Ras-GTPase (also ? EGFR, p53)
Skin: >6 café au lait, axillary freckling,
Eye: Lisch nodules (iris), buphthalmos (cow-eye, due to lid neurofibroma), retinal phakomas
Spine Xray: enlarged foramen, scoliosis, vertebral scalloping, dural ectasia, lateral thoracic meningocoele.
CNS lesions:
1. meningoangiomatosis (collars of meningothelial cells around vessels)
2. sphenoid dysplasia (empty orbit)
3. moya-moya, aneurysms, ectasia
4. white matter nonneoplastic "hamartomtous" lesions: dysplastic glia, diminish w/age, ↑ T2, can enhance – obtain serial MR
5. BG lesions: ↑ T2, nonenhancing

CNS tumors: optic gliomas, spinal astrocytoma, neurofibromas
Other tumors: plexiform neuromas common in V1, visceral, endocrine tumors
NF2: Chr 22, Protein: Merlin (aka Neurofibromin2, schwannomin). Links membrane to actin cytoskeleton. Tumor suppressor. (Also in regular schwannomas & meningiomas)
No lisch nodules or cerebrovascular abnormalities (Café-au-lait, cutaneous or plexiform neurofibromas rare).
Skin plaques (rough, raised, hairy areas), juvenile cataracts, calcified choroid plexus, meningiomatosis
Tumors: Bilateral acoustic schawnnomas (or 1 w/family history), other CN schwannomas, spinal ependymoma, meningiomas (multiple, kids), astrocytomas,
Tuberous sclerosis: Bournvilles, , usu sporadic, Chr 9/11/16, variable penetrance; Genes: TSC1 (chr9, hamartin), TSC2 (chr16, tuberin). Tumor suppressors, functions unknown
Triad: adenoma sebaceum, 65% MR, seizures (infantile spasms). Seen in <50%;
CNS lesions:

1. Cortical tubers: <5% enhance, no transformation, thick gyri
2. Subependymal nodules: candle gutterings, 1/3 enhance, calcify (can see on Xray), no transformation
3. Subependymal giant cell astrocytoma
4. Hamartomatous white matter lesions
5. Aneurysms, stenoses

Skin: ash leaf spots, subungal fibromas, shagreen patch;
Tumors: cardiac rhabdomyomas, retinal phakomas/angiomyolipoma, visceral cysts, pancreatic & liver adenoma (malignant > benign) tumors

Sturge-Weber: nonhereditary, port wine stain in *V1*, focal seizures, hemiparesis, hemianesthesia, tramtrack calcification of cortex (not cortical vessels), large enhancing choroid ipsilateral, leptomeningial angioma (enhances), hemispheric atrophy, *glaucoma* in kids

VonHipel-Lindau: Chr3, AD, variable penetrance; hemangioblastoma (CNS + retinal), renal cell, pheochromocytoma, viceral tumors/cysts, erythrocytosis; 25% hemangioblastomas have VhL. No skin lesions.

Klippel-Trenaunay-Weber: spinal cord hemangioma & enlarged limb

Rendu-Osler-Weber: AD, AVMs (lung, liver, brain) and skin telangetasias, epistaxis, aneurysms, pulmonary AVF

Wyburn-Mason: unilateral facial nevi w/ optic pathway/midbrain AVMs

Cowden Disease: AD, germline PTEN mutation. Cobble-stone fibromas of oral mucosa, multiple hamartomas: skin, thyroid, breast, adnexal. *Lhermitte-Duclos* (also neuromas, neurofibromas, meningiomas).

Li-Fraumeni: AD, p53 germline mutations, various brain tumors (mostly glioma), sarcomas, etc

Turcot syndrome: AD, colon polyps/ CA & medullos, GBM. APC germline mutation in some.

Basal cell nevus syndrome (Gorlin's): AD. PTCH mutation (Chr9q): Patched, Sonic-hedgehog receptor (Shh > binds Ptch > releases inhibition of Smoothened > TGFβ, Gli, Wnts). Basal cell CA (esp around eyes & nose, at puberty), jaw cysts, skeletal abnormalities (synostosis, hypertelorism, frontal bossing, prognathism, Sprengels), *calcified falx*, plantar/ palmar pits. Pitted teeth, cleft lip/ palate, ocular defects, cataracts. Hydrocephalus, seizures, MR, deafness. *Medulloblastoma*, meningiomas.

Gardner's syndrome: osteomas, colonic polyposis, soft-tissue tumors

Trisomy: Pataus (13) = hypotelorism, cleft lip, polydactyly, dextrocardia, holoprosencephaly, microcephaly/ opthalmia, hypertonia, cataracts, severe MR. Edwards (18) = hypertelorism, dolichocephaly, microgyria, cortical dysplasias, callosal agenesis, Chiari II, syndactyly, VSD; Downs (21) = hypotelorism, brachycephaly, heart dz, Alzheimers, cataracts, small abnormal brain, BG calcification, moyamoya, os odontoidium, spinal stenosis. Most common cause of MR. Fragile X = most common hereditary MR, 1/3 female, large ears, arched palate, hypotelorism, vermian hypoplasia, large testes, hyperextensible, prominent thumbs (carrier women: arched palate, hypotelorism). Trinucleotide repeats.

Cri-du-chat: 5q deletion, severe MR, microcephaly, hypertelorism

Praeder-Willi: 15p deletion, obesity, hypogonadism, mod MR

Klinefelter: XXY, male hypogonadism, MR

Turners: XO, no MR, CNS probs

Lesch-Nyan: X-linked. HPRT deficency. ↑ uric acid, gout, coreoathetosis, self-mutilation. Tx allopurinol

Lawrence-Moon-Biedl: GnRH deficency (like Prader-Willi). Hypogonadism, retinitis pigmentosa, polydactyly, MR

Sphingolipidoses: all AR except Fabrys. Cherry-red spot from greying of nerve axons which ↑s prominence of fovea (no axons). Most have accumulation in neurons with distension & glassy appearance.
Hepatosplenomegaly in Niemann-Pick & Gauchers?, Sandhoffs.

Fabrys: α-galactosidase (lysosomal), ↑ ceramide trihexosides, pain episodes, X-linked. Childhood strokes (brainstem), neuropathy (autonomic, lipid in epineurium & endoneurium – not Schwann cells)

Gauchers: glucocerebrosidase, Jews, nonneural. ↑ AFP. ↑ Glucocererbrosides.

Niemann-Pick: sphingomyelinase, supranuclear vertical gaze paresis, Jews, normal HC, hepatosplenomegaly

Sandhoff: Hexosaminidase A & B, non-Jews, hepatosplenomegaly

Tay-Sachs: Hexosaminidase A, rectal Bx, Jews, macrocephaly (no visceromegaly), Zebra bodies on EM. Carriers: 50% ↓ Hex-A in blood (also DNA testing)
Both of above: ↑ GM2 gangliosides accumulate, cherry-red macula (& Niemann-Pick, Pseudo-Hurlers)

Pseudo-Hurlers: βgalactosidase, ↑ GM1 gangliosides, cherry-red spots

Mucopolysaccharidoses:
All AR except Hunters, ↑ glycosaminoglycans

Hurlers: α-L-iduronidase, ↑ dermatan & heparan sulfate, gargoyle face, MR, corneal opacity, thick meninges

Scheies: milder, no MR

Hunters: X-linked, iduronate sulfatase, skin pebbling, *normal corneas*, ↑ dermatan & heparan sulfate, no MR

Sanfillipos: heparan sulfate in urine, cortical atrophy

Morquios: skeletal deformities, ligamentous laxity, ↑ keratan SO4

Sly: odontoid hypoplasia

Morquios & Scheies & Maroteaux-Lamy: normal IQ

Farber: ceramidase def., ↑ chondroitin SO4. Hoarse cry, arthropathy, skin granulomas, MR

Leukodystrophy:
AR except ALD & P-M.

Adrenoleukodystrophy: peroxisome def., X-linked, male children, long chain fatty acid accumulation (peroxisomal defect), perivascular lymphocytes (others – no inflammation), *begins occipital*, bronze skin, ↓ cortisol (adrenal)

Alexanders: *rosenthal fibers*, sporadic, *frontal, megalencephaly/ macrocephaly* (above 2 enhance). Etiology unknown. No serum test – requires Bx.

Canavans: *spongiform, complete* demyelination, aspartoacylase, ↑ N-acetylaspartic acid. Infants. *Affects U-fibers* (subcortical arcuate fibers - all others spare), *Internal capsule spared, macrocephaly*

Krabbes: galactocerebrosidase, *psychosine* kills oligodendrocytes, *globoid cells* (large multinucleated, nuclei at periphery), *BG density*, ↑ startle, spasticity w/ ↓ DTRs, normocephalic. Neuropathy (endoneurial fibrosis).

Metachromatic leukodystrophy: AR, most common, arylsulfatase A, ↑ sulfatides (urine). <2yo, juvenile, or adult. Dx: nerve Bx (PAS+), MR, ataxia, myelopathy, infants. Neuropathy: sulfatides in peripheral nerve Bx (macrophages & Schwann cells): eosinophilic, metachromasia w/ cresyl violet, toluidine blue, or pseudo isocyanin stains (affinity for iron, all blue).

Pelizaeus-Merzbacher: Complete absence of myelin. No dysmorphia, X-linked, proteolipid protein (myelin) deficiency, *"tigroid"* pattern (myelin spared around vessels), 100% pendular nystagmus, become symptomatic as infants, may survive to adulthood, sudanophilic (sudan stain)

Cockaynes: AR, dysmorphic facies, microcephaly, premature aging, deafness, photosensitivity, defective DNA repair, striatocerebellar calcification, retinitis pigmentosa
Canavans & Alexanders: macrocephaly
Cockaynes & P-M: 100% nystagmus
Aminoacidurias also cause leukodystrophy
Zellweger syndrome: AR, *polymicrogyria*, hypomyelination, peroxisomal defect, cerebrohepataorenal
Refsums: AR, phytanic acid, ichthyosis, deafness
DNA Repair defects: Cockaynes, Ataxia-Telangiectasia, Xeroderma Pigmentosa (cerebral, cerebellar atroophy, ataxia, MR), Fanconis anemia, Blooms
Lysosomal disorders: MLD, Krabbe, Niemann-Pick, Fabry, GM1 & 2 gangliosidoses (Tay-Sachs etc), Canavan, all mucopolysaccaridoses, ceroid lipofuscinoses
Peroxisomal disorders: Zellweger, ALD
Glycogen Storage Diseases:
All AR, glycogen accumulation, myopathies.
Pompes (Type II): acid maltase, Chr 17, # forms: 2 childhood & 1 adult, accumulates in DRG, ant horn & throughout body; PAS+ vacuolar myopathy
McArdles (Type V): myophosphorylase, cramps during exercise, myoglobinuria, (+) ischemic exercise test (lactate doesn't rise), glycogen in muscle only
Tauris: phosphofructokinase def. Excerise cramps (as above) + hemolytic anemia (↑ retics).
Aminoacidurias
AR except Lowes. Cause leukoencephalopathy, demyelination.
Phenylketonuria (PKU): AR, phenylalanine hydroxylase deficiency, ↑ phenylalanine, phyenylpuruvic acid, ↓ tyrosine; MR, seizures, musty odor; blond, blue-eyed.
Biopterin deficency: PKU Variant. ↑ phenylalanine, normal hepatic phenylalanine hydroxylase, Stiff-baby.
Homocysteinuria: AR. cystathionine βsynthetase deficiency. ↑ methionine, & homocysteine > collagen formation disorder. 50% MR, osteoporosis, cataracts, infarcts/ thromboses. Arachnodactyly & lens ectopia (like Marfans, Marfans has no MR) Tx: Vit B6.
Methylmalonic acidemia: AR. Mitochondrial. Methylmalonic-CoA > Succinyl-CoA by methylmalonyl-CoA mutase (deficient – requires B12). Neonatal encephalopathy, seizures, stroke. ↑ ammonia, glycine, propionic acid (ketoacidosis), lactic acidosis. *Bilateral "Punched out" (hypointense) GP* - ?2° to ischemia. Tx: Limit protein, some respond to B12.
Lowes Syndrome: Oculocerebral Renal. X-linked. Defective AA transport. MR, Fanconi's, rickets. Small CSF-like spheres in white matter.
Glutaric acidemia: dilated sylvian fissures, migration abnormalities
Mitochondrial: *MELAS, MERFF, Leigh* (AR, ↑ pyruvate & lactate, BG/ PVG/ PAG spongiform necrosis, ↑ T2), *Kearns-Sayre* (AD, ↑ pyruvate, retinitis pigmentosa), *Lebers hereditary optic atrophy, Menkes.*
Maternal inheritance. Most cause encephalopathy & myopathy, ↑ lactate.
Ragged red fibers: abnormal mitochondria (on Gomori stain)
Trinucleotide repeats: found in Fragile X, myotonic distrophy, huntingtons, spinocerebellar atrophies, friedrich's ataxia. Cause anticipation (worse/ earlier in successive generations)
Neuronal ceroid lipofuscinosis: Accumulation of lipid pigments ceroid & lipofuscin. Kids (Batten's) or adults. Dementia (kids), szs, blindness, myoclonus. Kids die, adults variable course. Cortical atrophy (grey matter dz, not white).
Channelopathies:
K+: ataxia-myokymia, long QT, benign familial neonatal convulsions (KCNQ2/3), Issacs syndrome
Ca+: Eaton-Lambert, Hypokalemic periodic paralysis (skeletal muscle dihydropyridine-sensitive Ca channel), Malignant hyperthermia (mutation in RYR1 gene for muscle SR ryanodine-channel), familial hemiplegic migraine, episodic ataxia type 2
Menke's kinky hair: X-linked, defective GI copper absorption, seizures, MR, tortuous intracranial vessels
Familial dysautonomia (Riley-Day): AR, Jewish children, small fiber neuropathy – loss pain/temp, autonomic dysfxn (loss of tears on crying, corneal ulceration, nonreactive pupils, temperature dysregulation, sweating, hypotension, dysphagia, vomiting, ileus, poor feeding), hyporeflexia. No tongue papillae. No tx.
Hirschprungs: defect of neural crest migration, Chr 10.
Orofacial Digital Syndrome: Only females. Psudoclefts of mandible, tongue, palate. Hypertrophied buccal frenuli. Tongue hematomas. Alopecia. MR.
X-linked: Fabrys, Hunters, ALD, Pelezius-Merzbacher, Menkes, Lowes, Lesch-Nyan. AD: Huntingtons
Adult: MLD, Krabbe, Sanfillipos, Glycogen stroage Dz, Wilsons, Leigh, Niemann-Pick, Gaucher, ceroid lipofucinoses, MELAS/ MERRF
Laurence-Moon-Biedl: AR. MR, retinitis pigmentosa, hypogonadism, spastic paraplegia, obesity, polydactyly, cataracts, renal anomalies,

Pain/Functional
Cluster headaches: increased intraocular pressure & skin temp (vs migraine). Tx 100% O2, ergotamine. (Methysergide causes retropleural/peritoneal fibrosis). CCBs, steroids, Lithium may be prophylactic.
Migraine: Classic = visual aura; common = no aura; basilar = more severe (blindness, hemiplegia, coma). Tx: Abortive: Sumatriptan (CI: CAD) > Ergotamine (N/V), Midrin. Prophylactic: verapamil (CCBs), amitriptyline (TCAs), propanolol, Depakote prevent.
Postcoital HAs may mimic SAH.
Narcolepsy: REM occurs at onset (stages reversed). 70% have cataplexy (consciousness preserved); sleep paralysis, hypnagogic hallucinations (not somnambulism). Tx: Ritalin, TCAs. Total number hours sleep per day is normal
Cataplexy: consciousness preserved
Raynauds: mast cell dysfunction, sympathectomy not helpful
Dejerine-Roussy: from VPM/VPL thalamus
Vascular
Stroke: 12-24h = neuronal necrosis starts, 1-2d = PMN infiltrate; 5-7d = lipid-laden macrophages (gitter cells), 10-20d = gemistocytic astrocytes; >3m fibrillary astrocytes
Lacunar: lipohyalinosis (HTN)
Atherosclerosis: fatty streak > foam cells. 2% tandem lesions
Vasculitis: Wegeners: Glomerulonephritis, lung/sinus granulomas, neuropathies Antineutrophil cytoplasmic antibodies (ANCA). Necrotizing. Small arteries. Tx: Cyclophosphamide.. Takayasu: pulseless disease (aorta), vision loss & loss of peripheral pulses. Kawasaki: lymph nodes, aneurysms; Buergers: tobacco; Behcet: Japan/Mediterranean, oral/genital ulcers, uveitis, colitis, rash, brainstem encephalitis. Steroids.
Also: amphetamines, ergot, cocaine.
Temporal arteritis: All > 60yo. ECA only (except ophthalmic). Giant cells. Skip

lesions (need large segment for Bx). Incr ESR Tx: steroids

Polyarteritis nodosa: Fibrinoid necrosis of epineurium vaso nervorum (vs amyloid – endoneurium) > mononeuropathy multiplex, nephritis, skin purpura, microaneurysms. Asymmetric. Males. Immune complex deposition.

Cogan syndrome: Vasculitis limited to CNS. Deafness, keratitis.

Amyloid angiopathy: lobar hemorrhage, amyloid β protein (Congo red > green birefringence under polarized light). Occurs in vessels of leptomeninges & superfical cortex (not deep structures), causes aneurysmal dilations, >70yo.

Mineralizing angiopathy: calcified vessels, seen w/ XRT + MTX in kids

Marfans: AD (30% sporadic). CHr 15, fibrillin (microfibrils abnormal). tall/ thin, arachnodactyly, lens ectopia, pectus excavatum, pes cavus (high arches), scoliosis, blue sclera, MVP/ aortic regurgitation, thromboses, ↑ risk of aneurysms, strokes(?), homocystinuria, *no MR*. No Tx.

(Homocystinuria has above but also has MR, strokes, & is AR. Lenses subluxed upward in Marfans, downward in homocystnuria)

Hyperhomocysteinemia: Occurs in 5% of population. Does not have stigmamta (MR etc) of homocysteinuria & levels are lower. Due to multiple enzymatic defects (cystethionine β synthetase most common), folate/ B6/ B12 def., or systemic dz. Asymptomatic til 30-40s then CAD/ atherosclerosis/ thromboses (endothelial damage due to ROS due to homocysteine oxidation in plasma). Tx: folate (B6 or B12 in certain cases).

Lupus/ SLE: Antinuclear Abs. Stroke: due to antiphospholipid Abs. Vasculitis: less common, immune complex deposition, segmental dilation & narrowing, aneurysms. Scattered ↑ T2.

Fibromuscular Displasia: ICA narrowing, beaded. Carotid dissection/ stenosis.

Moyamoya: Rete mirable "puff of smoke" due to proximal ACA/ MCA stenosis, transosseous/ transdural collaterals. <10yo present w/deficits, 20-30yo w/SAH. Associated w/Downs. Steroids for recurrent TIAs. ASA. EC-IC bypass or EDAS.

Sickle Cell Disease: strokes, moyamoya, aneurysms

Hemolytic-Uremic syndrome: Bilateral BG hypodensity 2° infarcts

Hypertensive encephalopathy/ Eclampsia: Occipital lobe hypodensity/ hemorrhage

Superficial Siderosis: Hypointense covering of brain on T2, due to repeated hemorrhages w/ hemosiderin in meninges. Causes sensorineural hearing loss & ataxia.

Misc

Paraneoplastic syndromes:
Stiff-man (anti-GAD), *Sensory neuropathy* (anti-Hu = antineuronal nuclear, small cell), *cerebellar degeneration* (anti-yo = anti-Purkinje cell, lung > ovarian > lymphoma), *opsoclonus* (anti-Ri, peds neuroblastoma, adults breast*), retinal degeneration* (anti-Ri also, adults, small cell), *limbic encephalitis* (small cell, medial temporal lobes)

Depression: ↓ NE & 5-HT. SSRIs: ↑ 5HT. TCAs & MAOIs ↑ 5HT & NE (TCAs block reuptake for both).

Schizophrenia: ↑ dopamine. Antipsychotics block dopamine and/or serotonin. ↑ activity of Nacc & temporal structures (amygdala), ↓ prefrontal cortex activity.

Anxiety: ↑ 5HT, NE. Tx: Buspar.

OCD: ↓ serotonin. Tx: SSRIs.

Enuresis: Tx: Impiramine

ANATOMY

Brainstem syndromes:
Wallenbergs (lateral medullary): CN5 (ipsilateral facial analgesia), 8 (vertigo), 9, 10 (hoarse,etc), sympathetics (ipsilateral Horners), solitary nuc. (taste), cuneate/gracile nuc. (ipsilateral numbness), spinothalamic tract (contralateral pain/ temp loss – only 1 contralateral); no weakness

Webers: ventral midbrain; CN3 w/crossed hemiplegia

Claude: dorsal midbrain; CN3 w/ataxia

Benedikts: CN3 w/ ataxia and hemiplegia

Parinauds: upgaze palsy, loss of accomodation (fixed pupils) – only 1, large pupils w/ light/ near dissociation, convergence nystagmus, nystagmus retractorius, lid retraction

Millard-Gubler: base of pons, CN6 & 7 and contralateral hemiplegia

Medial medullary: contralat hemiparesis (not face), contralat numbness, ipsi CN12

Lateral pontine (SCA): ipsi ataxia, contralat pain/temp, deafness, N/V

Locked-in: Bilateral basilar pons

Pseudobulbar palsy: lesion of *bilateral* UMN corticobulbar tracts above brainstem (eg IC); unable to move eyes, mouth but can yawn & cry (reflexive). Brisk jaw-jerk/reflexes. Also frontal signs, emotional lability may occur due to adjacent frontal fiber damage.

Bulbar palsy: LMN CN palsy (usu IX-XII)

Top-of-the-Basilar: sudden onset AMS, EOM/ pupil/ visual (homonymous hemianopsia) abnormalities, usu. Embolic.

Cranial nerves

Cortical fibers synapse directly on V, VII, NucAmb, XII (NOT on III,IV,VI,DMNX)

Corticobulbar fibers bilateral except to lower VII (contra) & XII.

I (Olfaction): SVA. 1° receptor cells (= bipolar cells) in mucosa, axons form olfactory nerve, through cribiform plate > 2°: mitral & tufted cells (= glomeruli) in bulb, (also has granule cells – no axons, inhibitory); > Olf. Tract >

1. Lateral olfactory stria: to anterior olfactory nuc. (aka olfactory tubercle, > medial forebrain bundle and stria medullaris), amygdala, and pyriform cortex (=primary, area 34, > entorhinal cortex (=secondary), DM thalamus, prefrontal cortex (conscious perception, input from pyriform and DM thalamus)), or
2. Medial olfactory stria > septal area, anterior commisure to contralateral areas

Olfactory tubercle neurons project to directly, not to olfactory tract/bulb

In mucosa: sustenacular cells support, basal cells are receptor precursors – olfactory neurons are only ones to continually regenerate.

There are >2000 different receptor cells for odorants. Use G-proteins > cAMP or IP3. 2 specific glomeruli in bulb for each odorant.

Accessory olfactory system: For detection of pheromones, rudimentary in humans. Vomeronasal organ > vomeronasal/ terminal n. ("13th cranial nerve, CN0") > accessory olfactory bulb > Vomeronasal nucleus in amygdala. Contain GnRH cells – related to GnRH cells in hypothalamus, mediates sexual dimorphism

CN0 has Schwann cells > schwannoma

II: CNS tract – has oligodendroglial, not Schwann cells. SSA. (rods/cones) > bipolar cells (1°) > ganglion cells (2°) > 3° centers:

1. LGB > visual cortex (conscious vision) **or**
2. Pretectal/EW nuclei (pupillary reflex, see below) **or**
3. Superior colliculi (> tectopontine (> cerebellum) & tectospinal tracts; pursuit, head/neck mvmt) **or**
4. suprachiasmatic nucleus of hypothalamus (circadian rhythms)

Retina: Part of CNS – has blood-retina barrier & Muller glia.
Receptor cells: rods/cones. rhodopsin (rods) > transducin (G-protein) > PDE > cGMP to GMP > ↓ Na & Ca current (hyperpolarizing) > ↓ glutamate release to bipolar cells (> "on-center" cells stimulated, "off-center" cells inhibited, "on-center" bipolar cells stimulate its ganglion cells and inhibit ganglion cells from "off-center" bipolar cells also); Rods = B/W, dim light. Cone = color, daylight. Both Use glutamate. Conduct by electric conduction, not action potentials.
Ganglion cells: Only cells in retina that can initiate action potential. Types: W = small, slow, tonic & phasic to SC & pretectum, dark; X (or P) = medium sized, tonic, to layers 3-6 LGB & pretectum, color; parvocellular stream;Y (or M) = rapid, phasic to layers 1&2 LGB & SC, B&W, magnocellular stream;
Horiztontal cells Synapses from & to depolarize rods/cones for lateral inhibition
Amacrine cells: Bipolar > Amacrine > Ganglion cells
Fovea (center of macula) contains only cones. Rod goes to amacrine cell before ganglion cell.
LGB**:** ipsilateral 2,3,5. contra 1,4,6. Layers 1&2 magnocellular, 3-6 parvocellular, 3&4 off-center, 5&6 on-center (1&2 mixed).
Ganglion cells and LGB cells have "on-center, off-surround" concentric fields.
Cortex: *Primary*: Area 17 (layer IVCα = magnocellular input, layers IVCβ & IVA = parvocellular input, layer IVB = cortical input, has stripe of Genarri), *Secondary*: Areas 18 (±19) (no stripe of Gennari). No concentric fields, cells repond to lines, borders. *Simple cells* = position & orientation of line, rectangular fields. *Complex cells* = orientation. movement (not position in field). *Hypercomplex cells* = length, shapes.
Ocular dominance columns in cortex alternate eye dominance, have orientation & location specificity. Together strips form *ocular dominance bands.* Absent in 2 areas of area 17: those representing blind spot of retina & monocular temporal crescent. *Orientation columns* also exist.
Hypercolumn: 2 adjacent columns w/same field from each eye.
Magnocellular stream: "where stream". Y-cells > Layer 1/2 LGB > area 17 (layer IVCα) > parietal cortex. Spatial, movement, orientation (visual neglect, apraxia).
Parvocellular stream: "what stream" X-cells > Layer 3-6 LGB > area 17 (layers IVCβ & IVA) > inferior temporal. Color, shape (faces, etc. visual agnosias, achromotopsias)
Critical period exists where inputs from both eyes need to form cortical connections. In amblyopia in kids patch dominant eye intermittently. NMDA receptors mediate connection forming.
Superior colliculi: lesion gives loss of pursuit (tracking) eye movement
Blindsight: nonconscious response to visual stiumli (ie threat) – from noncortical projections, superior colliculus

III:
GSE to extraocular mm: Superior rectus, inferior rectus, inferior oblique, medial rectus
Levator palpebrae (Mullers muscle = sympathetic, less severe ptosis);
Parasymathetics (GVE): EW to short ciliary nn. (sympathetic = long & short) to iris (constriction) and ciliary mm. (accomodation).
Accomodation: Ganglion cells(2°) to LGB to cortex to (directly and indirectly) EW & CN3 (motor) nuclei (not to pretectal nuclei) to Ciliary muscles (meridional and circular fibers) causes eyeball to narrow, lens to relax and become more spherical for accomodation
Pupillary light reflex: no LGB. (1°) bipolar cells in retina to (2°) ganglion cells to (3°) pretectal nuclei to (4°) EW nuclei (via posterior commisure) to (5°) ciliary ganglion to short ciliary nerves to iris
Sympathetics to pupil: 1° hypothalamus > via hypothalamospinal tract > 2° C8-T3 lateral horn (Ciliospinal center of Budge) > 3° superior cervical gangion > around ICA > short & long ciliary n. > iris & Mullers muscle

IV: GSE. Superior Oblique > eye down & In; only crossed n.; Lesion: worst = downgaze to opposite side. Bielschowskys sign – head tilted to opposite side; eye up & in. Difficulty walking down stairs.

V: V1 = ophthalmic > SOF > nasociliary & lacrimal nn. V2 = maxillary > inferior orbital fissure or rotundum. V3 = mandibular, > ovale.
Motor (SVE): Motor nucleus of V > tensor palatini & tympani (hypoacusis), mastication (temporalis, masseter, pterygoids, anterior belly of digastric, mylohyoid). Weakness causes deviation of jaw away.
Sensation (GSA):
Trigeminal (aka Semilunar, Gasserian) ganglion (1°) projects via spinal tract of CNV to *principal sensory* (2°, touch, wide rang of pressure, large receptive fields) and *spinal nuclei of V* (2°, pain/temp).
Mesencephalic nuc. (proprioception, pressure, contains 1° neurons (only nucleus in CNS w/1° sensory neurons, from neural crest, analogous to sensory ganglia).
Tracts:
Ventral trigeminothalamic = pain, crossed (from principal sensory & spinal). *Dorsal* = touch, uncrossed (principal sensory only). Both to VPM.

VI: GSE. Lateral Rectus. Longest CN. *Nerve* lesion causes *unilateral* lateral gaze paralysis. *Nuclear* lesion causes deviation away *bilaterally* (i.e. of both eyes), gaze toward lesion is paralyzed (opposite of frontal eye fields) called "lateral gaze paralysis"
PPRF – horizontal gaze center adjacent to CN6 nucleus. Inputs from cortex (FEFs), cerebellum, SC, & vestibular nuc. Output to cerebellum, vestibular nuc., pretectal region, IN of Cajal & Nuc. of Darkshevich to integrate horizontal & vertical eye movement
Stimulation: rostral = vertical gaze; caudal = ipsilateral horizontal.

VII: Geniculate ganglion: sensory/ taste cell bodies only. *Nervus intermedius* carries sensory & parasympathetic fibers.
Parasympathetics (GVE): Input from hypothalamus & solitary nuc.
1. Superior salivatory nuc. (1°) > greater petrosal n. > pterygopalatine gang. (2°) > lacrimal gland
2. Superior salivatory nuc. (1°) >chorda tympani > submandibular gang. (2°) > submandibular, sublingual glands.
Lesion distal to geniculate ganglion has no decreased lacrimation, greater petrosal n. already off
Motor (SVE): Facial nucleus > staepedius (hyperacusis), stylohyoid, posterior belly of digastric (anterior from CN5), facialmm. (part of motor nucleus supplying lower face receive crossed input only from cortex)
Taste (SVA): Anterior 2/3 tongue. Chorda tympani > geniculate ganglion (1°) > rostral nucleus solitarius (2°) > central tegmental tract > VPM thalamus (± parabrachial nuc. of pons) > insular cortex (perception) (parabrachial > amygdala/ hypothalamus for emotional response)
Sweet (sucrose), bitter (alkaloids), & umami (glutamate) receptors are metabotropic, sour (H+) & salty (Na) are ionotropic. (Spicy-hot mediated by trigeminal nerve)

Receptors may respond to multiple tastes, but usually 1 preferentially.
Sensation: ear (GSA), soft palate (GVA) > spinal nuc of V
Mobius syndrome: congenital absence of both facial nuclei (± abducens nucleus)
VIII: SSA
BAER: I° cochlear n. > II° cochlear nuc > (via trapezoid body) > III° Superior olive > IV° lateral lemniscus/ nucleus > V° Inf. Colliculus > VI° MGB > VII° Cortex
Dorsal cochlear neurons bypass Sup olive & lateral lemniscus nuc, to Inf Coll (III°)
Lesions above trapezoid body cause partial deafness (contra > ipsilateral)
Commisure of Probst: in between lateral lemniscus nuclei. Also has Inferior Colliculi commissure.
Cochlea: Sound enters scala vestibuli, transmitted to scala media by Reissner's membrane. Hair cells in scala media (organ of Corti) sit on basilar membrane, touch tectorial membrane; sit in endolymph (high K, low Na). Vibrations at apex have lower frequency. Scala vestibuli & tympani contain perilymph, communicates w/CSF. Cochlear nerve (bodies in spiral ganglion) synapse on hair cells.
Cochlear nuclei: fibers group into 3 acoustic striae: ventral, dorsal (from respective nuclei) & intermediate (from both). Dorsal = high frequency, ventral = low. Ventral to superior olive, dorsal direct to inferior colliculus.
Superior olive: Attenuates loud sounds. Input is from contralateral cochlear n. via trapezoid body; Output is via olivocochlear bundle back to contralateral cochlea directly to hair cells to ↓ sensitvity to sounds and to tensor tympani (V3) and stapedius (7)
Medial Sup. Olive = time differences
Lateral Sup Olive = intensity difference
Trapezoid body is only commissure needed for sound localization
Cortex: AI = area 41, A2 = area 42. Area 22 = auditory association area. Wernickes = posterior area 22. Prosody = Right opercular (posterior temporal =- comprehension of prosody)
Vestibular system
Utricle > superior vest ganglion > Lateral vestibuluar nucleus
Saccule Posterior part > inferior vest ganglion > inferior vestibular nucleus. Anterior part > Superior vestiblar ganglion > lateral vestibular nucleus.
Detect linear movement: utricle in long axis of body, functions when upright; saccule in dorsoventral plane, fuctions when supine. When head is erect: utricle horizontal, saccule vertical. Sensation occurs in macula – contain otoliths & hair cells.
Semicircular canals: angular movement. Ampulla (dilation at 1 end) contains endolymph and crista ampullaris – sensory organ). Fluid remains still but hair cells move.
Hair cells > Horizontal SC & anterior SC (aka superior) to superior ganglion, posterior SC to inferior ganglion (1°) > Vestibular nerve > medial & superior vestibular nuclei or floculonodular lobe directly (2°)
Vestibular nuclei: Lateral: (Dieter's) from utricle (& anterior saccule?) to lateral vestibulospinal tr. – extensor tone/posture; inhibited by anterior lobe of cerebellum; has no connections w/other nuclei;
Inferior: from posterior saccule to cerebellum; integrates input from vestibular labyrinth & cerebellum;
Medial: largest, *crossed* to all extraocular nuclei & cerebellum, medial vestibulospinal tract to neck mm.;
Superior: *uncrossed* to CN3,4; Interstital: cells lie among fibers of vestibular root
MLF*: Ascending*: from medial & superior vestibular nuclei to CN 3,4,6 nuclei to control eye movement. *Descending:* medial vestibulospinal tract & medial reticulospinal tract to cervical cord motorneurons to influence head/trunk movements relating to eye & vestibular movement (from superior colliculus, PPRF, IN of Cajal, & medial vestibular nucleus).
Caloric nystagmus: COWS = fast phase, deviation is reverse
Postrotatory nystagmus: Slow phase in direction of rotation, fast phase opposite
IX:
Motor (SVE): Nuc. Ambiguus > stylopharyngeus
Parasympathetic (GVE): Inf salivatory nuc > tympanic n./plexus > lesser petrosal n. > otic gang. (2°) > parotid
Sensation (GSA): middle ear (tympanic n.), pharynx > Superior Gangion (1°) > Spinal Nuc of V
Carotid Sinus (GVA): Herrings n. > CN9 > Inferior Ganglion (1°) > nucleus solitarius (2°) > DMN of X (↑ BP decreases HR, TPR, force, BP, CO)
Carotid Bodies (SVA): Chemoreceptor (CO2) > Inf Ganglion > Reticular Formation > Reticulospinal fibers > inspiration.
Taste (SVA): nuc. Solitarius > VPM thalamus > postcentral gyrus
X:
Motor (SVE): nuc. Ambiguus > pharyneal br. (all mm except stylopharyngeus (IX) and tensor veli palatini (V)) > sup. Laryngeal n. > internal (sensory) & external laryngeal (cricothyroid)
Recurrent laryngeal=(off ganglion)all laryngeal except cricothyroid
Taste (SVA): > solitary nuc.
Aortic sinus (GVA) Inf ganglion > solitary nuc.
Aortic Bodies (SVA): > Inf Ganglion > Reticular Formation
Parasympathetic (GVE): dorsal motor nuc.
Sensory (GSA): ear > spinal tract 5.
XI: SVE. C1-6, to trapezius, SCM
XII: All tongue mm. except palatoglossus (X). Exits preolivary sulcus. GSE (not SVE – comes from somites not brachial arches). UMN crossed from contralateral cortex (UMN causes deviation away)
CN Nuclei:
Nuc. Ambiguus: motor (9,10,11)
Solitary nuc: rostral = taste (7,9,10), caudal = carotid sinus/body (9)
Superior salivatory: parasympathetic (7);
Inferior salivatory: parasympathetics (9) (both in reticular formation)
Dorsal motor nuc = parasymathetic (10)
Ganglia: Nodose = inferior vagal; Gasserian = CN5
Reflexes: Pupil = 2 & 3. Dolls = 3 & 8 (VestNuc > PPRF > CN3/6). Jaw-jerk = 5 only; Corneal = 5 & 7. Pupillary = 2 & 3. Gag = 9 & 10. Cough = 10 only. Oculocardiac: V1 to X.
Eye movement
Saccades = frontal eye fields (area 8) & parietal eye fields > contralateral PPRF (parietal synapse in Superior Colliculus 1st > PPRF). Right PPRF = Right gaze.
Smooth Pursuit = eye > LGB > area 17 > temprorooccipital eye fields (>< FEFs) > dorsolateral pontine nucleus (DLPN) > vermis/flocculus > med vestibular nuc > NPH/CN nuclei;
Lateral Gaze: PPRF, CNVI nuclei (post limb IC); Vertical Gaze: FEFs > ant limb IC > synapse in riMLF & interstitial nuc of Cajal 1st > PPRF.
Lesion of one CN6 nuc. impairs *both* eyes from moving to that side
FEFs go to riMLF/PPRF, not to CN nuclei directly.
Stimulation: rostral PPRF = vertical; caudal PPRF = ipsilateral horizontal; Superior colliculus & FEFs = contralateral horizontal.
Lesion: cortex/ putamen = toward; thalamic = persistent down gaze; pons/ cerebellar = away, pontine = pinpoint; midbrain = towards

Pons/cerebellum (ie contralateral paramedian br. of basilar, contralateral SCA) eyes deviate away; FEFs (contralateral MCA) eyes devate towards
Opticokinetic reflex: keeps eyes straight when head is moving (eg. on a train).
Direct opticokinetic path: Retina > nuc of optic tract & Nuc of accessory optic system > cerebellum/vestibular nuc.
Indirect path: Same as pursuit path (temporalocciptal cortex); lesion gives defect with target moving towards same side
Nucleus prepositus hypoglossi: provides info to CN6 nucleus about current head/eye position.
Cerebral peduncle: lat>med: POTpontine > corticospinal/bulbar (UE>LE>CN) > frontopontine
Cerebellum:
Stimulation elicits nothing.
Lobes: flocculonodular = vestibular (nystagmus, imbalance). Anterior = spinocerebellar, tone (sl. hyperreflexia). Posterior = pontine, coordination.
Zones: vermis (truncal ataxia, scanning speech), intermediate (appendicular ataxia, hypotonia), lateral (tremor, decomposition, dyscoordination, delay of initiation). (Note no hypertonia. Hypotonia from vermis or intermediate zones.).
Gait ataxia may be due to cerebellar or posterior colums disease (Romberg only + in latter)
Vermis & IZ have somatotopic organization, not lateral zone.
Layers: *Molecular* = basket, stellate. *Purkinje*. *Granular* = granule, Golgi II.
Cells: *Granule*=glutamate, all other GABA. Parallel fibers to Purkinje dendrites (spiny).
Climbing fibers: from inferior olive, crossed, to Purkinje dendrites (smooth)
Mossy fibers: all others. End in glomerulus (Both: glutamate)
Glomerulus: (granular layer) Mossy fibers & Golgi axons > Granule dendrites
Peduncles:
Inferior: Restiform: All afferent.dorsal spinocerebellar, cuneocerebellar, olivocerebellar (contralateral, largest # of fibers). *Juxtarestiform*: Afferent: vestibulocerebellar (> flocculonodular lobe). Efferent: Cerebellovestibular.
Middle: All afferent. Pontocerebellar (crossed)
Superior: Afferent: ventral spinocerebellar, Efferent = Cerebellothalamic.
Cerebellothalamic tract: dentate > decussates at inferior colliculus > contralateral VL (VA?/VPL) > motor cortex. VL: head medial, feet lateral, extremeties ventral, back dorsal.
Only interposed synapse in caudal red nucleus.
Some fibers descend to contralateral reticular nuclei and inferior olive then decussate back to ipsilateral cerebellar cortex.
Spinocerebellar tracts: Dorsal = LE, ICP, from dorsal nucleus of clarke (C8-L2); *Ventral* = LE, contralateral, SCP, L1-S2 cell bodies; *Cuneocerebellar* = UE, analogous to dorsal SCT. All go to anterior lobe.
Note: propioception from LE in dorsal spinocerebellar, UE in posterior column
Ganglia: medial to lateral:
Fastigial: to reticular formation & vestibular nuclei
Interposed: (emboliform & globose) to red nucleus to thalamus to motor cortex
Dentate: to VL (VA/VPL) thalamus to motor cortex
Inferior Olive: inputs from red nucleus, cortex, and spinal cord to contralateral ICP to cerebellum (ant & post lobes) via olivocerebellar tract
Red nucleus: inputs: 1) interposed nucleus of cerebellum to VL thalamus, 2) cortex. Output: rubrospinal tract, inferior olive (> contralateral cerebellum). Stimulation elicits contralateral flexion
Feedback circuits:
1. Frontal lobe > Pontine nuclei > Cerebellar cortex > Dentate nucleus > VL thalamus > Motor cortex (Area4)
2. Red nucleus > Inferior olive > Cerebellar cortex (ant & post) > Interposed nuclei > Red nucleus
3. Spinocerebellar tracts > Anterior lobe cerebellum > Fastigial Nucleus > Reticular formation/Vestibular Nuclei > Vestibulospinal & Reticulospinal tracts

Diencephalon: thalamus, hypothalamus, subthalamus, epithalamus (pineal, habenulum, stria medullaris) (metathalamus = geniculate bodies)
Habenulum: Input/Output: septal area/ hypothalamus (via stria medullaris); fasiculus retroflexus (>< VTA >< raphe nuc)
Stria medullaris thalami: anterior thalamus, preoptic, septal areas to habenular nucleus
Pineal: composed of glia (5%) & pinealocytes. Secretes serotonin (>melatonin). Antigonadotropic. Overactive delays puberty, hypofunction precocious puberty. Innervated by sympathetic n. – release NE to stimulate melatonin. Also has corpa arenacea or brain sand (calcifications).
Hypothalamus: anterior/medial = parasymp.; Posterior/lateral = symp. (ant/post = temp, lat/med = feeding)
Preoptic: GnRH (sexually dimorphic)
Suprachiasmatic: circadian rhythym
Supraoptic: ADH, uniform large cells (no distinct groups). Projects to pituitary only.
Paraventricular: oxytocin, distinct cell groups (magnocellular (oxytocin) & parvocellular). Projects to brain stem/spinal cord. Also TRH, CRH.
Arcuate: GHRH, dopamine.
Anterior: parasympathetic, heat loss
Ventromedial: staiety center
Dorsal: stimulation > feeding, savage behavior
Lateral: feeding center
Posterior: sympathetic, heat conservation, wakefulness
Median eminence: where axons from arcuate etc. release releasing hormones into venous plexus
Pituitary axis: Supraoptic & paraventricular nuclei contain magnocelluar neurons > synapse directly on posterior lobe of pitutary. (Both have input from subfornicial organ)
Arcuate etc. contain parvocellular neurons, synapse on venous plexus in median eminence > anterior pituitary.
Feeding: Neuropeptide Y ↑ feeding thru paraventricular nucleus. Neuropeptide Y containing neurons in the arcutae nuc. Inhibited by leptin from fat cells. VMH & LH centers oversimplified.
Input: MFB, fornix (hippocampus), stria terminalis (amygdala), DLF (midbrain central grey), retinohypothalamic, nucleus solitarius. Generally from limbic system/ amygdala/ hippocampus – not neoortex.
Output: MFB, stria terminalis, Dorsal Longitudinal Fasiculus (parallels MFB thru medial hypothalamus), mamillothalamic, mammillotegmental, hypophyseal, descending autonomic
Tuberoinfundibular tract:: hormones from arcuate nucleus (tuberal region) released in capillary plexus in median eminence to portal veins to capillaries in anterior pituitary
Supraopticohypophyseal tract: Magnocellular neurons from supraoptic & paraventricular nuclei (histologically identical, both nuclei in supraoptic region) to posterior pituitary
Pituitary: Anterior:
Pars distalis: hormone secretion. Basophils, acidophils, chormophobes.

Pars intermedia: basophils, chromophobes, & colloid cysts (remnants of Rathke's pouch). Produces MSH (melanotropin), stimulates melanocytes to produce melanin
Pars tuberalis: around stalk. Squamous cells, follicles of suboidal cells, hypophyseal plexus veins
Posterior: *Pars nervosa & infundibulum*. Has pituicytes (resemble astrocytes). Has Herrings bodies (storage of ADH & oxytocin) & glomeruli
Superior hypophyseal a. to infundibulum, median eminence, pars tuberalis. Inferior hypophyseal a. to pars nervosa. Anterior lobe has no direct supply.
Anterior lobe from ectoderm (Rathkes pouch), Posterior from neurectoderm (diencephalon)

Thalamus

Sensory: VPL (body), VPM (face)(both to 3/2/1), VPI (vestibular), LGB (to 17), MGB (from inf coll. To 41/42, tonotopic)
Non-specific: to parietotemporal association areas:
Pulvinar: Auditory/vision relay. Projects to sensory association corticies: occipital (18/19), parietal, & temporal (not frontal).
LP: Output to 5/7 (SIII)
Motor: VL (VLo: from GP to area 6/8, VLc from cerebellar/red nuclei to area4); VA (from GP, to area6 & nonspecifically to cortex (esp prefrontal) for recruiting), Centromedian: (from GP/area4, to putamen. Stimulation at 6-12 Hz produces activity (recruiting) of large areas of cortex)
All 3 receive input from GP via thalamic fasiculus.
Limbic/Behavioral:
Anterior /LD: from MB (mammillo-thalamic tract) and hippocampus (fornix), to cingulate.
DM: to/from prefrontal lobe (also input from limbic structures), affected in Korsakoffs, controls affective behavior/memory, smell (from olfactory areas)
Intralaminar: CM: To putamen (see above). Parafasicular nuc.: To caudate. Both receive ARAS/spinothalamic input & have diffuse cortical projections for arousal. Rostral intralaminar nuclei: thalamic pacemaker.
Thalamic reticular nucleus: thin sheet on lateral wall. No cortical projections, projects to other thalamic nuclei & reticular formation. Receives all affarents & efferents w/ collaterals. Mostly GABAeric?
Extremities ventral, back dorsal; head medial, caudal lateral

Basal Ganglia

Control intensity & timing of movement
1. Direct Loop: ↑ thalamocortical excitation. Cortex (glu) > Striatum (GABA) > GPi (GABA) > VA/VL/CM (glu) > cortex (VL>motor, VA>premotor)
2. Indirect Loop: ↓ thalamocortical excitation: : Cortex (glu) > Striatum (GABA) > GPe (GABA) > Subthalamus (glu) > GPi (GABA) > thalamus > cortex
3. Nigrostriatal loop: Facilitates direct loop by D1 receptors & inhibits indirect loop by D2 receptors. Cortex (glu) > Striatum (GABA) > SNpr > SNpc (dop) > Striatum > GP > Thalamus > Cortex.

D1 receptors on striatonigral neurons, D2 receptors on striatopallidal neurons.
Dopamine does not directly excite/inhibit striatal neurons, but changes K conduction to raise/lower RMP.
GP = diencephalon, Put/Caud (& GPe?)= telencephalon.
Output
Striatum:
1. to GP: GABA & to GPe = enkephalin (spiny type I), to GPi = substance P (spiny type II) (Aspiny neurons are intrinsic Putamen only)
2. to SNpr (GABA)

GPe: to STN
GPi:
1. Thalamus: Ansa lenticularis + Lenticular fasiculus (Forel's field H2) > Thalamic Fasiculus (Forel's field H1) > VA/VL/CM (Thalamic fasiculus also contains fibers from cerebellar dentate nucleus)
2. Pallidotegmental: to VTA

Thalamostriate fibers: from CM/ parafasicular nuc. to striatum
Damage: GP = athetosis, ST = hemiballismus, Striatum = chorea, SN = rigidity, tremor
Subthalamus: Subthalamic nuclei + Zona incerta (grey matter b/t thalamic & lenticular fasiculi). Use glutamate
Substantia Nigra: Neurons contain melanin granules. Fibers to putamen, caudate, sup colliculus, thalamus (*not GP*). Pars Reticulata: input. Pars compacta: output, dopamine (to spiny neurons in putamen).

Hippocampus

Function: integrating short-term memory, assigns salience to stimuli for emotion (modulates limbic system/ hypothalamus) & memory. No olfaction.
= Subiculum, hippocampus, dentate gyrus
All archicortex - 3 layers.
(Parahippocampal gyrus has 5 layers).
Hippocampus proper = Ammon's horn (Ammon = egyptian god with rams' head)
C-shaped: Parahippocampal gyrus (outside) > Subiculum (transition) > hippocampus (CA1>2>3) > Dentate gyrus (hilus = CA4) (curves back over subiculum).
CA1=parvocellular (vulnerable to anoxia. = Sommer's sector). CA3=magnocellular
Alveus: white matter b/t hippocampus & temporal horn composed of efferent fibers; most medial portion is *Fimbria* (> fornix)
Cellular Layers of Hippocampus (in to out): Polymorphic layer (axons,output) > pyramidal cell layer(soma) > molecular layer (input, dendrites). Dentate gyrus: pyramidal cell layer replaced by granule cell layer.
Input:
1. Entorhinal cortex, Via
   A. Perforant pathway >dentate (mossy fiber) >CA3 (Schaffer's collaterals) > CA1 >subiculum) or
   B. Alvear pathway (straight to hippocampus),
2. Fornix (septal nuclei, substantia innominata etc)
3. Cingulate cortex

Output: Fornix. Subiculum / pyramidal cells of hippocampus > alveus > fimbria > fornix. Subiculum > postcommisural (Main output, to MB, ant thalamus, hypothalamus). Hippocampus > precomissural (septal area > lateral hypothalamus).
Also direct output to entorhinal cortex & amygdala (small).
Hippocampal commisure: between fornices
Schaffer's collaterals: branches of pyramidal axons which synapse on other hippocampal cells (i.e. CA3 to CA1)
Dentate: efferent fibers only to hippocampus (mossy fibers).
Indusium griseum: remnants of hippocampus over corpus callosum.
Fornix: main efferent from hippocampus. Body (rostral to thalamus) > Columns (posterior to anterior commissure).
Forniceal commissure: aka psalterium. Is rostral to anterior commissure.
Papez circuit: Probably serves short-term memory (MB, Ant. Thalamus) more than emotion. Bidirectional. Subiculum > fornix > MB > MT tract > Ant. Thalamus > Cingulum > entorhinal cortex > subiculum

Amygdala

Function: Interface between cortex and hypothalamus/brain stem for emotional response & emotional memory.

Stimulation : Fear & Rage

Corticomedial group: olfaction, > hypothalamus/pituitary (high concentration of enkephalins, somatostatin, and dopamine)

Central nucleus: input/output to hypothalamus & autonomic brainstem

Basolateral group = cortical, sensory input (temporal), uses glutamate

Input: Olfactory (lateral olfactory stria), taste (Nucleus solitarius), and auditory (temporal cortex). Sensory, prefrontal & cingulate cortex.

Output:

1. Stria terminalis (CM > hypothalamus, septal area),
2. Ventral amygdalofugal tract (BL > hypothalamus, PAG)
3. Diagonal Band of Broca (septal area)
4. Direct: Cortical/ hippocampus/ DM thalamus/ striatum/ brainstem.

Only meager projections back from hippocampus, thalamus & hypothalamus.

Kluver-Bucy: Bilateral damage. Docility, Hyperorality, hypersexulaity, visual agnosia (psychic blindness), hyperphagia, exploring

Limbic system: amygdala, septal area, hypothalamus, anterior thalamus, anterior cingulate & orbitofrontal cortex, ± hippocampus. Controls emotion (self & species preservation, learning, emotional processing/ social behavior).

Output of limbic system to brainstem: DLF (hypothalamus), fasiculus retroflexus (habenulum), Mamillotegmental fasiculus, MFB (amygdala/ septal area/ hypothalamus).

General path: hypothalamus (endocrine) > Midbrain PAG > Autonomic & Motor CN nuclei

All tracts bidirectional.

Limbic system has analogous loops to basal ganglia:

1. Direct path: Limbic/Prefrontal cortex & intralaminar nuclei > NAcc (ventral striatum) > ventral pallidum > DM/Ant thalamus > cortex. ↑ responsiveness (memory/ emotion /learning) to stimuli.
2. Indirect Path: same as above but VP > STN > VP. Inhibitory
3. Mesolimbic: Nacc > VTA > Nacc. Excitatory. Analogous to SNpc. (both use dopamine).

LAMP = membrane glycoprotein marker for limbic system neurons

Septal area: Subcallosal and paraterminal gyrus & septal nuclei (NucAcc, Meynert). Relay for hippocampal afferents to hypothalamus. Input from *fornix (hippocampus)*, brainstem, hypothalamus (MFB), anygdala (diagonal band of Broca), medial olfactory stria.

Output: *MFB to hypothalamus*, stria medullaris to habenulum, diagonal band of Broca to amygdala, also hippocampus (fornix), cortex, thalamus, MB. (not basal ganglia)

Medial Forebrain Bundle: septal area to hypothalamus to brainstem (reticular formation & autonomic areas). Bidirectional.

Sunstantia innominata = Nucleus basalis of Meynert. Ach. Functions in sleep/wake, memory, emotion. Input: amygdala, olfactory cortex. Output: diffuse cortex (activating). ↓ in Alzheimers.

Mesocorticolimbic system: Midbrain *Ventral Tegmental Area* (VTA, aka interpeduncular nucleus) to limbic system (*NAcc*, amygdala, hypothalamus, cortex); Uses Dopamine; Acts similar to SN in BG system. ↑ excitation of Nacc to ↑ stimulation of DM thalamus & limbic cortex to ↑ responsiveness to stimuli. Role in positive reinforcement/Addiction

Nucleus accumbens: where putamen & caudate meet anteriorly; functions w/septal nuclei. Recives VTA input. Role in addiction/ gratification.

Reticular system: Functions in pain, autonomic control, posture, eye movements, arousal, sleep/wake.

ARAS: ascending reticular activating system. Pons & midbrain: locus ceruleus (NE), pedunculopontine nucleus (Ach), ventral tegmental area (Dop) and Raphe nuclei (serotonin) to

1. central tegmental tract to thalamus (intalaminar & reticular nuclei) and
2. medial forebrain bundle to septal nuclei/basal nucleus of Meynert

Raphe nucleus in low pons/medulla is inhibitory (serotonin)

Raphe nuclei & locus ceruleus also send descending fibers to spinal cord. To affect pain transmission (see analgesia)

Nucleus reticularis pontis oralis functions in wakefulness & REM sleep. Excited by hisaminergic neurons in posterior hypothalamus; inhibited by GABAergic neurons in anterior hypothalamus.

Parvocellular Area: BP manitenance, respiration?

Cortex:

Neocortex: 6 layers. layers 2-3 corticocortical (2&3=association, 3=commisural), 4 = thalamocortical (input), 5=pyramidal (corticospinal), 6= corticothalamic (5&6=projection)

Homotypic cortex: has typical layers (association areas). Idiotypic/ heterotypic cortex has altered layers (primary motor/sensory areas)

Has columnar organiztion of 100-300 neurons w/same function.

Parallel networks for language, attention, learning/memory, face/object recognition, & comportment.

2 heteromodal association areas: temporoparietal (sensory integration), and prefrontal (integrates motivation with stimuli – punishment/reward).

Allocortex: 3 layers. Pyriform cortex (paleopallium, 3-5 layers), hippocampus and dentate gyrus (archipallium, 3 layers). Note entorhinal cortex = parahippocampus, pyriform cortex = uncus.

Mesocortex. 3-6 layers. Paralimbic areas: cingulate/ subcallosal/ paraterminal gyri, parahippocampal gyrus, temporal pole, insula, & caudal orbitofrontal cortex.

Band of Baillerger: in layer 4b. In area 17 is Stripe of Gennari (not in 18/19 – extrastriate cortex).

Temporal lobe: medial = PCA, superior/lateral = MCA. Superior gyrus = language, middle & inferior = visual discrimination. Deficits: Bilat middle & inf = psychic blindness, Bilat heschls = deafness, unilat = slight contra loss; vestibular cortex (post to Heschl) = decreased OKN; time perception (either side); dom = auditory leaning, nondom = visual learning

Parietal lobe: dom = math/language, nondom = spatial;

Parietal lesions: Dominant: Gerstmanns (finger agnosia, right-left confusion, acalculia, agraphia), also alexia, anomia, tactile agnosia, ideational & contsructional apraxia; Non-Dom: anosognosia (= neglect, denial of illness), dressing apraxia, topographic memory loss, constructional apraxia, asomatognosia (hemineglect)

Angular Gyrus: visual processing of words; damage causes alexia and agraphia - inability to read/ write with intact speech comprehension, Gerstmann's

Occipital lobe: Bilateral: cortical blindness; Anton's syndrome (aka Anton-Babinski, denial of blindness); Dominant: simultagnosia (identify parts of picture, not whole thing); prosoprognosia. Right occiptotemporal: color agnosia, left = color anomia; Balint synd: psychic gaze paralysis/peripheral inattention (bilateral posterior parietooccipital)

Primary motor (Area 4): lesion = hypotonia, paresis (no fine movement); BG lesion = hypertonia. Neurons innervate synergistic sets of muscles (not individual mm.) Cortical columns represent movements, not individual muscles. Chiefly functions is distal mm.
Premotor area (6): Planning/ timing. Lesion produces apraxia of complex, learned movements, unable to produced delayed response; has homonculus
SMA (medial area 6): LE anterior, face posterior. Functions in coordinating bilateral movements. Stimulation – gross bilateral movement w/urge to move (premotor – discreete movement, requires higher stim, no perception of urge to move). Movement on either side activates. Lesion –spasticity (vs area 4) and involuntary grasping, akinesia, poverty of speech (all resolve in 6 weeks). Unilateral lesions usually cause no permanent deficits.
Both SMA & premotor send fibers directly to spinal cord, have homunculi, and higher threshold than MI.
Frontal Eye Fields (area 8): area 8 > Superior colliculus, IN of Cajal, Darkschewitsch Nuc > PPRF > MLF > CN3,4,6 nuc. Fibers don't go to CN nuclei directly. For voluntary saccades.
Stimulation: bilateral deviation away
Lesion: cant target objects on command (eyes tonically to same side).
Occipital Eye Fields: aka posterior parietal, temporooccipital (widely dispersed). Subserve involuntary smooth pursuit. Stimulation: eye deviation away (like FEFs but higher threshold, longer latency). Lesion: eye deviation to same side (like FEFs) but can target w/ saccades And have problems following objects
Sensory Cortex: 3a = muscle spindles, 3b = skin (slow & rapid), 1=rapidly adapt skin, 2 = pressure/joint. Input: 3b > 2 > 1. Damage causes topagnosia (decreased localization), astereognosis (no pain/temp loss).
Each has separate homunculus.
Vestibular & gustatory cortex lie in operculum.
SII: on superior bank of lateral sulcus. Homunculus is inverted. Stimulation elicits *bilateral* sensations. Role in identifying objects by touch & storing memories (old view – pain perception)
Somatosensory association (areas 5&7)
Agnosias: cant identify object. Visual = bilateral occipitotemporal (ex Prosoprognosia - faces). Tactile = area 40 (supramarginal). Auditory = area 22.
Apraxia: Ideational = dominant parietal, failure to carry out sequences of acts, although can do parts. Have pt act as combing hair w/out comb. Ideomotor = Dominant Parietal (supramarginal gyrus/ arcuate fasiculus). Can perform acts spontaneously but not on command. Can conceive mvmt but not perform until cued; test by using utensils, dressing, etc. Note actions conceived in dominant parietal cortex, travels arcuate fasiculus to L frontal & corpus callosum to R frontal for performance.
Aphasia: conduction = impaired repetition (Wernickes (fluent paraphasic) with retained comprehension & awareness of deficit), transcortical motor/sensory = normal repetition, echolalia (sensory = temporoparietaloccipital jxn, motor = frontal lobe). Brocas & Wernickes = impaired repetition. Pure word deafness (can still read, echolalia) = area 22, anterior (bilateral > left).
Subcortical (Left BG) lesions may also cause aphasia.
Exner's area: superior to Brocas. Causes agraphia without aphasia.
Alexia without agraphia: Left occipital lobe (geniculocalcarine tract and corpus callosum). Usu has hemianopsia & color anomia. With agraphia = left angular gyrus (Gerstmans). Without hemianopsia = rare, deep white matter, corpus callosum (not geniculocalcarine)
Color anomia: left mesial occipitotemporal lobe; **Achromatopsia:** right inferior occipitotemporal (color blindness)
Prefrontal cortex: Orbitofrontal: social appropriateness (lesion – disinhibition), connects w/limbic system; Dorsolateral: motivation (lesion – apathy), connects to motor areas.
Fasiculi: Uncinate: antertior temporal to orbitofrontal; Arcuate: Superior & Middle frontal gyri to temporal (Wernicke to Broca); Cingulate: medial frontal & parietal to parahippocampal.
Corpus callosum: Does not have projections between areas 1,2,3 (S1),4 (M1), or 17 (V1).
Section: splenium = unable to read left field; ant. 1/3 = nothing; all = left hand apraxia
Tapetum: white matter lateral to temporal horn/ atrium (medial to optic radiations)
Calcar avis: medial to temporal horn/ atrium
Gyri: Precuneus: medal b/t paracentral lobule (S1) and cuneus (separated by parietooccipital sulcus); Lingual: posterior to parahippocampal gyrus (medial to collateral sulcus); Occipitotemporal: inferior, lateral to collateral sulcus. Inferior frontal: lateral: pars orbitalis > triangularis > opercularis. Medial: gyrus rectus > subcallosal area > paraterminal gyrus. (contiguous w/ cingulate) Supramarginal: end of Sylvian fissure. Angular: end of superior temoral fissure (more posterior) Both separated from superior parietal lobule by intraparietal sulcus. Cingulate: b/t cingulate sulcus (superior) & sulcus of corpus callosum
Corticobulbar fibers: Project to sensory relay nuclei (gracilis, cuneatus, trigeminal, solitary nuclei), reticular formation, & motor CN nuclei.
Fibers to gracilus & cuneatus nuclei leave pyramids & transverse reticular formation or medial lemniscus.
Fibers to trigeminal & solitary nuclei are from frontoparietal cortex.
Corticoreticular fibers from premotor, motor & sensory cortex to medulla (gigantocellular) & pons (oral pontine).
Motor fibers from 1° motor area; bilateral except CN 7 (lower) & 12. (However lesion to fibers to 12 is asymptomatic or mild)
Pseudobulbar palsy requires bilateral lesions.
Internal capsule: *Anterior limb*: frontopontine, anterior thalamic radiations. *Genu:* corticobulbar, corticoreticular. *Posterior limb:* Corticospinal, Parieto-occipital-temporal-pontine, superior thalamic radiations, corticofugal fibers
Sublenticular = auditory radiations,
Retrolenticular = visual radiations.
Skull Base
Floor of 4th ventricle: Rostral to stria medullares: median eminence > facial colliculus > sulcus limitans.> inferior cerebellar peduncle. Caudal (Rhomboid fossa): hypoglossal trigone > vagal trigone. Area postrema most caudal. Below 4th ventricle: dorsal median sulcus > gracile tuburcle > dorsal intermediate sulcus > tuberculum cinereum > dorsolateral sulcus. Ventral: pyramid > preolivary sulcus/ XII > olive > postolivary sulcus > IX, X, XI.
3rd ventricle:
Infundibular recess: ventral to mamillary bodies.
Circumventricular organs: *pineal*, *subforniceal* (at foramen of Monroe; detects serum osmolarity, controls ADH & oxytocin release, projects to supraoptic nucleus, angiotensin II receptors), *subcommisural* (below posterior commissure, has BBB), *organum vasculosum of lamina terminalis* (GnRH & somatostatin release), *median eminence of*

hypothalamus (contains plexus for pituitary releasing hormones), *neurohypophysis, area postrema* (emesis, paired, sensitive to apomorphine & digitalis, consists of astroblasts & some neurons)

Nasal septum: ethmoid (superior) & vomer (inferior). Cartilage anterior
Orbit: maxilla (inferior), lacrimal (medial anterior), ethmoid (medial posterior), frontal (superior), sphenoid (posterior superior), palatine (posterior inferior), zygomatic (lateral)
Inferior orbital fissure: occ V2
Anterior clinoids: Optic canal & ICA medial, SOF lateral
ICA dural rings: Proximal = oculomotor membrane b/t ICA & CN3, roof of cavernous sinus. Distal = dura.
Lillequist's membrane: Between CN3 medially, divides interpeduncular cistern from chiasmatic cistern. Seen b/t ICA & CN2.
Cavernous sinus: CN6 only 1 inside
Tendinous ring: CN2, 3, 6, nasocillary, & ophthalmic a. inside (Outside: frontal and lacrimal nn. off V1, CN4, ophthalmic v.)
Dura: supratentorial = V, infratentorial = X and C1-3 (no VII)
Falciform ligament: between anterior clinoids, over optic n.
Floor of 3rd ventricle: Ant to post: optic chiasm > infundibulum > tuber cinereum > MBs
Lateral ventricle: Medial to lateral: fornix/ septal v. > velum/ choroid > thalamus/thalamostriate/anterior caudate v
Transvelum interpositum approach: between choroid & thalamus (lateral)
Pterion: frontal, greater wing of sphenoid, parietal, squamous temporal
Asterion, Bregma, opisthion
Houghtons lines
Petrous bone: Geniculate ganglion: posterolateral to ICA, posteromedial to formen spinosum, anterior to superior semicircular canal, medial to cochlea; lateral to middle ear cavity. GSPN: runs over & parallel to ICA. Dorello's canal: contains CN6.
Petrous ICA: drill away Glasscocks triangle posteriormedial to foramen ovale (foramen spinosum to arcuate eminence to GSPN)
Cavum: septum pellucidum, vergae (posterior), velum interpositum (3rd vent)
Cisterns: *Ambient:* SCA, CN4, basal v. Rosenthal. *Interpeduncular:* CN3, basilar a. *Quadrigeminal:* Vein of Galen. *CPA:* CN5,7,8, AICA. *Prepontine:* Basilar a. *Lateral cerebellomedullary:* PICA, choroid plexus of 4th ventricle.

Spinal Cord

Descending Tracts

Lateral motor system = corticospinal + rubrospinal
Medial motor system = vestibulospinal + reticulospinal
Corticospinal tract: Lateral: 90%. Cross at decussation. Anterior/Ventral: 10%, remain ipsilateral, then cross at level of termination in SC, posture control. All synapse on interneurons 1st (2°) in ventral horn & use glutamate. When damaged rubrospinal takes over. Babinski from corticospinal (or cortical) damage.
Note no direct connection to CN 3, 4, 6, DMN vagus. From: Betz cells 3%; Area 4 = 30%, area 6 = 30%; area 1,2,3 = 40%. 40% of fibers are poorly myelinated.
Rubrospinal tract: (Fibers from cortex 4/6 & cerebellum >) red nucleus > crosses in ventral tegmental decussation > cervical/thoracic cord. Flexor tone.
Vestibulospinal tracts: Lateral: from lateral vestibular nuc, to all levels SC, extensor tone; Medial: from medial vestibular nuc., to cervical cord only, CNXI Nuc. (neck mm.), role in vestibular modulation of head position via neck, runs in MLF. Both remain ipsilateral.
Tectospinal: From superior colliculus, reflex movements for sight; cross at origin; to cervical levels only
Reticulospinal tracts: Pontine reticular nuc > medial reticulospinal tr ipsilateral > extensors. Medullary reticular nuc > lateral reticulospinal tr bilateral > flexors & autonomic info.

Ascending Tracts

Lateral spinothalamic: pain/temp; body in DRG (1°) > axons enter Lissauer's tract > synapse in Lamina II on soma (2°) > cross @ level of entry in ventral white commissure > (most fibers to reticular formation = **spinoreticular tract**) > VPL/ VPI & intralaminar nuclei (3°) > sensory cortex.
(some spinoreticular fibers remain ipsilateral)
Paleospinothalamic tract: C fibers to layer 2 to reticular formation, intralaminar nuclei, PAG; burning pain.
Neospinothalamic tract: Aδ fibers to layer 1 to VPL, sharp pain
Visceral pain: Aδ & C fibers in sympathetic nerves > lamina 7 > spinothalamic tract (parasymathetics carry nonpainful sensation)
Anterior spinothalamic = light touch; cross @ level of entry. To VPL.
Nucleus dorsalis of Clarke: thoracic to C8, layer 7, proprioception, forms dorsal spinocerebellar tract
Dorsal spinocerebellar tract: Muscle spindles & Golgi tendon organs of LE (1°) > synapse ND of Clarke (lamina 7, T1-L2) @ level of entry (2°) > DSCT > Inferior Cerebellar Peduncle > ipsilateral *anterior* lobe cerebellum. Uncrossed. Detects Individual muscles. At levels L3-S5 ascend in fasciculus gracilis to L1/2 then synapse in NDC (2°).
Ventral: LE, synapses ventral horn (2°) > crosses @ level of entry > VSCT > crosses in pons to contralateral Superior cerebellar peduncle > ant lobe. L1-S2 cell bodies, Golgi tendons organs only, detects muscle groups (whole limb);
Cuneocerebellar (& Rostral – cats only): UE, analogous to dorsal & ventral; enter @ C1-8 > ascend in fasiculus cuneatus > synapse in accessory cuneate nucleus in medulla (2°) > ant lobe cerebellum.
Dorsal Colums/Medial Lemniscus: Touch/Pressure. DRG (1°) > Gracilus (LE) / Cuneate (UE) Fasiculus > Gacilus/ Cuneate Nuc. (2°) > decussation > medial lemniscus > VPL thalamus (3°) > area 3/2/1 & SII (> motor cortex for feedback)
Note transmits proprioception only from UE, not LE.
Lateral cervical system: (aka spinocervical thalamic tract). Light touch. Enter C8-L4 > synapse in lamina 4 > ascend in SCTT > synapse in lateral cervical nucleus (C1-4) > medial lemiscus > VPL > area 3/2/1
Rexed's lamina: lamina I: fast pain. = lamina II: Substantiosa gelatinosa. Slow pain, ascend/descend several segments in *Lissauer's tract* (outside lamina I). Both have *substance P* & glutamate receptors for 1° nociceptive afferents. Layer 3& 4: nucleus proprius (touch/pressure/proprioception); Layer 7: zona intermedia (dorsal nucleus of Clark); Layer 9: motor neurons.
Dorsal roots: Ganglionic neurons use glutamate, substance P, somatostatin, CCK. Roots divide into medial (from encapsulated sensory organs, Golgi,muscle spindles, thick myelin) and lateral (from free nerve endings, thin myelin, pain/temp) bundles. In the spinal cord these divide into ascending & descending branches.
Ventral horn SC: flexors = dorsal, extensors = ventral (same as tracts); trunk = medial, hand = lateral
Somatotopic organization: Cortex, BG, Red nucleus, reticular formation, Vermis & intermediate zone of cerebellum
Anaglesia: PAG (midbrain) & PVG (hypothalamus) (both enkephalin) to

nucleus raphe magnus in medulla (*serotonin, NE*) to dorsal horn of spinal cord (enkephalin) to inhibit nociceptive 1° sensory neuron axons and projection neurons' dendrites. PAG stimulation elicits fear, diplopia, etc. PVG better tolerated.

Brainstem sections:

Medulla: Inferior Olive, accessory cuneate, dorsal nucleus X, nucleus ambiguus, solitary nucleus

Pons: Superior vestibular nucleus,

Spine/Peripheral Nerves:

Brachial Plexus: Roots (C5-T1) > Trunks (Upper/ middle/ lower) > Divisions (ant/ Post) > Cords (Lateral/ Medial/ Posterior)

Arise from roots before plexus:

Dorsal scapular: C5. rhomboids, levator scapulae (stabilize scapula).

Long thoracic: C5,6,7. serratus anterior (abduct scapula > winged scapula, cut during axillary node dissection).

Arise from upper trunk:

Suprascapular: supra (abduction) & infraspinatus (ext rot)

Arise from cords:

Lateral & medial pectoral: pectoralis major; (lateral & medial cords)

Musculocutaneous: (lateral) brachialis, coracobrachialis, biceps (elbow flexion)

Median: (lateral & medial cords). Travels w/ brachial a. in arm. Goes thru 2 heads of pronator teres in forearm. Gives off *anterior interosseous n.* (FPL, index FDP, pronator quadratus). *Palmar cutaneous branch:* arises 5cm proximal to wrist. *Recurrent motor br*. To thenar muscles arises distal end carpal tunnel.

Muscles: Hand = LOAF: Lumbricals 1&2, opponens, APB, FPB (superficial); all other flexors/ pronators in forearm, palmaris longus.

Autonomous zone = tip of index finger.

Ulnar: (medial cord). Runs behind medial epicondyle, thru Guyons canal. *Dorsal cutaneous branch* (sensation to dorsum of digits 4 & 5) leaves in forearm.

Muscles: Adductor pollicis, FPB (deep), hand intrinsics; FCU, FDP3/4

Autonomous zone = tip of little finger

Subscapular: (posterior) teres major (adducts humerus), subscapularis (med rot humerus)

Thoracodoral: (posterior) lattisimus dorsi (adducts shoulder)

Radial: (posterior). Around spiral groove of humerus. Divides below elbow into *posterior interosseous* (thru arcade of Frohse, all muscles in forearm & hand) and *superficial branch* (sensory)

Muscles: triceps, brachioradialis (musculocutaneous = brachialis), extensors/ supinator, APL (injury from crutches). If cut in forearm no motor loss, only sensory.

Autonomous zone = 1st web space dorsum

Axillary: (posterior) deltoid, teres minor (injured with anterior shoulder dislocation)

Thumb: Median = Abductor pollicis brevis (perpendicular to palm), FPB (superfical), opponens, FPL; Ulnar = adductor policis, FPB (deep); Radial = abductor pollicis longus (parallel to palm). Ad/Abduction is perpendicular to palm, flex/extension is in plane of palm.

Interosseous muscles: palmar = adduct fingers; dorsal = abducts 1&4, flexes

Lumbricals: extends IP joints, flexes MCP joints

Carpal tunnel: contains FPL, FCR, Median N., FDS, FDP

Guyons canal: ulnar a. & n.

Lumbar plexus

Superior gluteal: gluteus medius, min. (thru greater sciatic foramen, above pyriformis m.; inf. Gluteal & sciatic below pyriformis)

Inferior gluteal: gluteus maximus

Femoral: iliopsoas, quads

Obturator: adductors, gracilis

Sciatic: hamstrings (biceps), part of adductor magnus, semitendinous, semimenbranous. To:

- Tibial: gastroc, TP, FHL (all foot mm.)
- Common peroneal: to
  - Superficial peronal: peroneus longus & brevis
  - Deep Peroneal: Tib ant, extensors

Biceps fermoris only has innervation from peroneal component of sciatic n. > differentiate sciatic from peroneal n. injuries

Ilioinguinal n.: at risk in appendectomies (McBurneys incision)

Ulnar n. vs C8 root injury: ulnar n. splits 4th digit, C8 covers entire finger. *C8*: EMG ↓ ECU (radial), APB (median), paraspinous mm, NCV normal. *Plexus (Lower trunk/ medial cord)*: normal paraspinal, abnormal sensory median antebrachial cutaneous n.

Radial n. vs C7 root: *C7:* FCR (median). *Posterior cord*: deltoid.

Peroneal n. vs L4/5: *L4/5:* loss of foot invertors

Femoral n. vs L3: *L3*: loss adductors/ quads

C1: has no dorsal ramus

Odontoid: 2 primary ossification centers at base, 1 secondary at apex.

Canal diameter: Cervical =18mm, stenosis = 12mm; Lumbar = 20-22mm, stenosis <15mm

Cervical ligaments: posterior longitudinal ligament becomes tectorial membrane

Facets: Cervical: inferior facet is medial. Thoracic: coronally oriented. Lumbar: superior facet is medial.

Neck: Recurrent laryngeal n.: left around aorta, right around subclavian a.; both off vagus, posterior to inferior thyroid a. Superior laryngeal n.: travels w/superior thyroid a. in 15%. Phrenic n.: anterior to anterior scalene, behind IJ. Subclavian a. & v. run between anterior & middle scalene. Stellate Ganglion: inferior cervical + upper thoracic ganglia

Bladder: parasympathetics: pelvic n. (S2,3,4) to detrusor mm. Voluntary: Pudendal (S2,3,4) to external sphincter. Sympathetics: inferior splanchnic n. to inferior mesenteric ganglion to inferior hypogastric nn. to internal sphincter (α), & bladder wall relaxation by inhibiting parasympathetics in pelvic ganglion. (T10,11,12). UMN = spastic, propantheline or oxybutnin (Ditropan), imipramine (TCA, anticholinergic); LMN = atonic, bethanecol, methacholine.

Melanocytes located in cervicomedullary pia. Made by tyrosinase.

Vascular

Internal capsule: Ant limb = Heubner; Genu = ICA perfs/ Heubner; Post limb = ant. choroidal; Ant & post = lenticulostriate a (from M1). *No PCA*

Striatum: Lenticulostriate a, Heubner, Ant choroidal

Thalamus:: PCA: ant & post choroidals, thalamoperforators (basilar, PCOM, P1), thalamogeniculate (*MCA doesn't supply*)

Substantia Nigra: PCA/Pcom

Cortex: ACA = hemiparesis (LE), mild sensory; Achor = hemiplegia, hemianesthesia, homonymous hemianopia. PCA = cortical blindness, Balints, prosopagnosia

Ventricles: lateral = anterior and lateral posterior choroidals, 3rd = medial posterior

SSS drains to right transverse sinus

Aortic arch: R Innominate (> R CCA > R VA > R thyrocervical trunk > subclavian) > L CCA > L subclavian (> VA).

L VA off aortic arch in 5%.

Rarely can have nonbifurcating CCA w/ ECA branches.

Aberrant ICA: runs behind tympanum > pulsatile tinnitus. Do not biopsy.

Persistent stapedial a.: intratympanic, from petrous ICA to MMA

Intracranial ICA:

Petrous: > vidian a. > caroticotympanic a > middle ear

Cavernous: meningohypophyseal a. C4/5 (tentorial of Bernasconi & Cassanari, inf.

Hypophyseal, dorsal meningeal), inferolateral trunk C4, McConnel's capsular.
Supraclinoid: Sup. Hypophyseal.
Intradural: ophthalmic > pcom > ant choroidal.
Hypophyseal a.: inferior = post pituitary superior = anterior pituitary
Ophthalmic a.: 0.5% arise from middle meningeal. May also arise from cavernous genu (C3)
Fetal P-comm: unilateral in 20%, bilateral in 8%
Anterior Choroidal: Cisternal segment > Plexal point (enters choroidal fissure) > Plexal segment. Supplies: optic tract, *post limb* IC, BG, substantia nigra?, thalamus, amygdala, hippocampus (mostly from PCA), tail of caudate (*not hypothalamus*). Had been sacrificed as Tx for Parkinsons. Anterior temporal lobe masses displace it medially.
Injury: Hemiplegia, hemihypesthesia, homonymous hemianopsia (cognition unimpaired)
ACA: A1 to ACOM> A2 to pericallosal/ callosomarginal jxn> A3
A1: medial lenticulostriate aa. (8-10 perfs to optic n, chiam, hypothalamus, etc).
ACOM: perfs to chiasm
Heubner: (medial striate a.) from A2 > A1. anterior limb IC, BG
MCA: M1 (to bifurcation)> M2 (insula, to sylvian fissure edge) > M3 (cortical, opercular)
Sylvian point:most posterior branch of MCA leaving sylvian fissure
(Lateral) Lenticulostriate a.: from M1. BG, IC.
Anterior temporal a. from M1.
PCA: P1 (to PCOM)> P2 (in ambient cistern) >P3 (quadrigeminal) > parietooccipital, calcarine
Thalamoperforators: from basilar tip, pcom, P1
Medial post choroidals: from P1; midbrain tectum, thalamus, 3rd ventricle
Lateral post choroidal: from P2; thalamus, lateral ventricle choroid
Med & Lat thalamogeniculate a. : from P2, post thalamus, crus cerebri
P3: Post temporal a. (anast. W/MCA); Internal occipital> Parietooccipital (to MCA), Calcarine (to ACA)
Vertebral a: Left dominant in 50%, right 25%, neither 25%. 40% one hypoplastic. 1-25% terminates in PICA. Both off subclavian a.
PICA: vermis, medial cerebellum. Loops around tonsils
AICA: anterolateral cerebellum.
Labyrinthine a.: off AICA in 85%, basilar in 15%.
SCA: supplies deep nuclei
Superior Sagittal Sinus: to Right transverse sinus (inferior SS to Left)
Trolard: to SSS. Labbe to transverse sinus
Deep veins: Anterior caudate + terminal vv. > Thalamostriate + septal (anterior) + epithalamic + atrial/ choroidal vv. > Internal cerebral v. (at venous angle) + Basal v Rosenthal > VOG.
Basal Vein of Rosenthal: ambient cistern
Thalamostriate v. : injury results insomnolence, hemiparesis, & mutism (not seizures).
Posterior fossa Vv.: Ant-Post: *Precentral cerebellar v.*, *Superior vermian v.*, (both to vein of Galen, both sacrificed in infratentorial supracerebellar approach)
Inferior vermian (to straight sinus)
Adamkiewicz: Left T11 (T4-T8 most vulnerable to low flow)
Persistent fetal arteries: *Persistent trigeminal*: 0.1-0.5%, cavernous ICA to basilar, ↑ AVMs, aneurysms; *Persistent hypoglossal*: cervical ICA to basilar thru hypoglossal canal, basilar may be hypoplasic or absent below; *Persistent otic*: petrous ICA to basilar thru IAC; *Proatlantal intersegmental:* b/t arch C1 & occiput, ECA or ICA to vert.

PATHOLOGY

Stains: Neuron: body = Nissl, processes = silver (Golgi, Bodian, Bielschowski), Luxol-fast blue = myelin. Gomori trichrome = muscle.India ink, mucicarmine = cryptococcus. Fat = Sudan, oil-red-O, Congo Red = β amyloid, PAS = glycogen, carbohydrate (fungi, parasites also), Gomori methamine (GMS) = fungi, AFB = mycobacteria
Hamartoma: disorganized cells in right location. Choristoma: Normal cells in wrong location
Markers: AFP = endodermal sinus; chromogranin = pituitary adenoma, paraganglioma; cytokeratin = cranio, chordoma, choroid plexus; desmin = teratoma; EMA, vimentin = meningioma; BHCG = choriocarcinoma; S100 = schwannoma, glioma, pnet, etc; PTAH = ependymoma. CD20, (CD45, CD3) = lymphoma (B-cells). CD1a = Langerhans cells. Melanoma: cytokeratin, HMB45, S100, (AE1/3-)
Rosenthal fibers: pilocytic, alexanders (large brain, cause unknown, sporadic)
Babes nodule: glial nodules, form in viral encephalitis
Schiller-Duval bodies: seen in endodernal sinus tumors
Alzheimer type II cells: Hyperplasic protoplasmic astrocytes with large irregular clear nuclei, prominent nucleolus, paired nuclei, no cytoplasm. Seen in hepatic encephalopathy and Wilsons disease (alzheimer type I more common – also has Opalski cells)
Perivascular lymphocyte cuffing: gangliogliomas, herpes encephalitis, AIDS
Basal ganglia calcification: Fahr disease (familial), hypo & hyperparathyroidism, anoxic, MELAS, Cockayne, NF, TS, Downs, carbon monoxide, lead
Basal ganglia necrosis: hypoxic, Toxic: methanol (putamen), carbon monoxide (GPm), cyanide, manganese. Leighs (↓ T1), Wilson, Alexanders, Canavans, MLD, Hallervorden-Spatz, metachromatic leukodystrophy, toxo, crypto, HUS, hepatic encephalopathy (↑T1), TPN (↑ T1)
Cerebellar atrophy: EtOH, chronic Dilantin, Friedrichs
Kernicterus: unconjugated bilirubin, GP, hiipocampus, STN
Seen in Rh incompatibility (hydrops fetalis), heridatary sperocytosis, hemolysis, Crigler-Najjar (glucuronyl transferase def.), Dubin-Johnson
Conjugated bilirubin doesn't cross BBB
Inclusions:
Cowdry type A: intranuclear, halo, large. HSV, CMV measles.
Cowdry B: small, no halo. polio
Ground glass: intranuclear. JC (PML)
Intracytoplasmic: rabies (Negri), Picks, Lewy (parkinsons), Lafora, Hirano (Alzheimers), Bunina (ALS), Marinesco (aging)
Astrocytes: corpora amylacea (normal aging, polyglucosan, often subpial, stain w/ fungal stains); Rosethal fibers
Microglia: elongated nuclei, scant cytoplasm.
Pituitary: Anterior = nests of epithelioid cells separated by fibrovascular septae. Posterior = loose spindle cells, has pituicytes (astrocytes).
Pencil bundles of Wilson: myelinated fibers in the caudate.
Fibrinoid necrosis: (of vessels) in post-XRT, PAN, temporal arteritis.
Calcospherites: prolactinoma, oligo, ganglioglioma, adult pilocytics
Segmental demyelination: PNS: diptheria, MLD, Charcot-Marie-Tooth
Rosettes:
Pseudorosettes: around blood vessel, ependymoma
True Rosettes: around fibrillary material, ependymoma

Homer-Wright: fibrillary material, medullos, neuroblastoma, pineocytoma, PNETs
Flexner-Wintersteiner: resembles cone photoreceptors, central lumen; pinealblastoma, Retinoblastoma
Eosinophilic Granular Bodies: intracytoplasmic. Seen in pilocytics, PXA, ganglioglioma
Immunohistochemistry:
Neurons: synaptophysin (axons & periphery of cell body), NSE (not neuron specific), NeuN (nucleus). EM: dense core granules.
Astrocytes: GFAP, S100 (nonspecific glial)
Oligodendroglia: NONE. (Myelin Basic Protein experimentally)
Ependyma: S100. (GFAP- except tanycytes - GFAP+). PTAH is a stain, not IHC marker.
Choroid plexus: Transthyretin, S100.
Microglia: HAM56, KP1
Leptomeninges: EMA
Melanocytes: HMB45, S100

RADIOLOGY

PET: Positron Emission Tomography. ^{18}F flouro-deoxyglucose (FDG) – measures glucose metabolism (also $H2^{15}0$ – blood flow). Requires cyclotron (for radioisotopes. Positron = same mass of electron but + charge.). Resolution 8mm.
Findings: GBM/ high grade tumor ↑, Low grade tumor ↓, radiation necrosis ↓, hetertopia normal or ↑, cortical dysplasia ↓, most seizure foci ↓ interictal, ↑ ictal, mesial temporal sclerosis ↓.
SPECT: Single Proton Emission Tomography. Measures blood flow. ^{99}Tc (technetium, HMPAO) or ^{133}Xe used. Resolution 10mm. Findings similar to PET.
Myelogram: "Feathering" = extradural; meniscus = intradural, extramedullary.
Diffusion-weighted MRI (DWI): ↓ diffusion (acute infarct) = bright, ↑ (cyst) = dark, Can detect infarct instantly (after 14d stroke becomes isointense).
Tumors: Tumor = dark, edema = bright. Necrosis = bright, abscess = dark.
Apparent Diffusion Coefficient (ADC map): Ischemia: hours = bright, days = dark.
Perfusion MRI: Contrast given during high-speed MRI to evaluate perfusion. If perfusion defect is larger than diffusion defect (mismatch) – represents penumbra.
Proton-density: high signal in demyelination (MS plaque)
MRSpect: Tumor: ↑ Choline & Choline:creatinine ratio, ↓ NAA. ↑ lactate in mitochondrial encephalopathies.
Magnetoencephalography (MEG): measures neuron firing (function), noninvasive, accuracy to 1mm. Uses SQIUD to pick up very low voltages. Use for epilepsy to map seizure foci, sensory/ visual/ auditory (> motor/ speech) areas.
Magnetic Source Imaging: MEG overlaid on high-res MRI.
Diffuse dural enhancement: meningitis, carniomatosis, postop, sarcoid, histiocytosis, intracranial hypotension, idiopathic hypertrophic pachymeningitis

PHYSIOLOGY

Cell cycle: M & G1 susceptible to radiation.
DNA syntyhesis: RNApol (3'-5') primer > DNApol (moves 3'-5'). Lagging strand – Okazaki frags, 5'-3'. UV – thymidine dimers. Transcription: RNApol 5'-3'. GTP energizes translation. Hydroxyurea blocks ribonucleoside diphosphate reductase & deoxynucleotide/DNA synthesis rate limitng step. UV light makes thymidine dimers.
Transcription: RNA polymerase binds to promoter – adds nucleotides 5' to 3'. Poly-A tail on 3' end. Terminated by rho. Amanita & rifampin (nonhuman) inhibit RNApol by binding to initiation sites. Elongation inhibited by actinomycin D.
Reverse transcription: RNAdep-DNApol makes DNA from RNA.
Translation: GTP energizes. Cytoplasmic ribosome 80S (60S+40S). Mitochondrial 70S (50S+30S).
cytosolic proteins: translated by free ribosomes, little modification;
secretory/organelle proteins: translated by ER, extensive modification (ex neuropeptides cleaved in ER/Golgi);
nuclear & mitochondial proteins targeted by posttranslational importation.
Inhibited by mercury, dipitheria toxin, erythromycin.
Organelles: *SER:* steroids, lipoprotein synthesis; *RER:* export protein translation, *Ribosomes:* cellular proteins translation (N-linked glycosylation), *Golgi complex*: export protein modification (fatty acid attachment, O-linked sugars, sugar phosphorylation, sulfation of tyrosine), *mitochondria:* matrix = Krebs cycle, membrane = electron transport chain
Extracellular matrix: composed of glycosaminoglycans & proteoglycans, collagen/elastin, and "adhesive" proteins: fibronectin (fibroblasts), laminin (epithelium), tenascin (glia). Integrins on cells bind to these (recognize RGQ seuence). Cell adhesion molecules (CAMs, ie N-CAM & Ng-CAM) bind cells to each other.
G-proteins: α unit binds GDP, βγ units anchor, inhibits activation by stabilizing binding of GDP and inhibiting GTP binding. Binding of ligand > GDP/GTP transfer > βγ units dissociates > protein activates > automatic GTPase > GDP > βγ reassociates. Activation of 1 G-protein inhibits activation of other G-proteins in the membrane. Pertussis & cholera ADP-ribosylate, prevent GTP hydrolysis & inactivate.
Second messengers: Phosphorylate/ dephosphorylate or directly open/close channels to alter activity.
1. Phospholipase C forms IP3 & DAG from PIP. IP3: releases Ca from ER. Ca binds calmodulin & protein kinase C.
DAG: activates PKC w/Ca. Used by α1 & muscarinic receptors
2. cAMP: Used by β-adrenergic, H2 & D1 receptors, ACTH & TSH. Closes K channels - ↑ excitability, activates PKA. Adenyl cyclase forms; Phosphodiesterase degrades.
3. cGMP: stimulated by NO.
4. Arachadonic acid: DAG > AA by phospholipase A2. Then forms prostaglandins, etc. Used by histamine.
Steroid hormones: have cytosolic receptors which binds to chromatin affecting mRNA transcription.
Neurons: no anaerobic glycolysis. Require O2 & glucose. Don't require insulin. Glucose crosses BBB by facilitated transport.
Dendrites have all organelles except Golgi; axons & hillock lack RER (Nissl), Golgi, ribosomes. Dendrites only have graded potentials, not APs.
Nissl substance = Rough ER.
Psuedounipolar = sensory (dorsal root) ganglia; Bipolar = CN8 ganglia, CN I&II.
Multipolar = all others
Golgi I: single long axon, projection.
Goligi II: short axon, cortical.
Intrinsic burst firing: due to low voltage activated (LVA) Ca channels
Cytoskeleton: Actin & spectrin link cytoskeleton to plasma membrane.
Microfilaments: actin. (βγ)
Neurofilaments: Neuron-specific intermediate filaments. Form neurofibrillary tangles (paired helical filaments assc w/tau MAP).Nonpolarized.
Microtubules: polymerize w/GTP. Polarized. Depolymerized by colchicine, stabilized by Taxol. Synthesis inhibited by vincristine.

MAPs: microtubule-associated proteins. Include tau, kinesins, dyneins.
Intermediate filaments: GFAPin astrocytes & Schwann cells
Nerve transport: anterograde (- to +) slow = 1mm/d, enzymes/proteins; fast = 100mm/d, organelles, kinesin; retrograde = fast, dynein. Fast = vesicles. Slow = microtubules, neurofilaments. Fast: actin, enzymes, organelles. Inhibited by colchicine. All use microtubles (not neurofilaments). Only fast is ATP dependent. Retrograde transport of herpes, rabies, polio, tetanus & cholera toxins.
Dynamin: GTPase, involved w/Clatharin in vesicle recycling.
Toxins: Diabetes = turnaround transport, vincrisitine, vinblastine = microtubules, dinitrophenol = oxidative phosphorylation.
Kindling: repeated stimulation results in synaptic reorganization into positive feedbackk circuit.. Afterdischarge: cell circuits continue to fire after stimulus is ended. Results in secondary generalization of seizures.
Autonomic: Sympathetic fibers to skin synapse in *paravertebral* ganglia thru rami, then to skin. Preganglionic = myelinated (white rami – T1-L3); postganglionic = unmyelinated (grey rami, all levels). Visceral symapthetic preganglionic fibers synapse directly on adrenal medulla or thru . Splanchnic nerves to *prevertebral* ganglia – coeliac, aortorenal, & mesenteric.
Parasymathetic preganglionic fibers synapse in ganglia in organ wall. Splanchnic n. also carry internal sensory info.
Small intensely flourescent cells (SIF): interneurons of sympathetic ganglia, use dopamine
VIP: used w/Ach in parasympathetic terminals
GI plexuses: Auerbachs = intramuscular, movement. Meissners = submucosal, secretion.
Sympathetic: viscous salivary secretion, bronchiole dilation, vasoconstriction (except coronary/ pulmonary & some skeletal muscle (Ach) – dilation), ↓ GI motility, ↑ sphicter tone, glycogenolysis/ lipolysis in liver, renin in kidney, sweat (Ach), pilomotor, ejaculation, adrenal medulla (80% epi, 20% NE)
Parasympathetic: watery salivary/ lacrimal secretion, lung mucous secretion, vasodilation only in head & pelvis, GI motility/ secretion, ↓ sphincter tone, glycogen synthesis in liver, erection (uses NO – Viagra), none to skin
Both to cardiac pacemaker cells & myocytes, & bladder
Neuron labeling: Horseradiash peroxidase (retrograde), 2-DG autoradiography (metabolic, labeling new AAs, anterograde), MRI, Gold (motor endings), Golgi staining, Axon degeneration (Fink-Heimer)
Astrocytes: Absorb extracellular GABA, K around neurons. Have K (only) channels & neurotransmitter receptors. Depolarize following ↑ extracellular K following APs in adjacent neurons (contribute to EEG). Do not conduct APs, (-)RMP. Have gap junctions b/t each other. Neurons & astrocytes have no contact, separated by 20nm. Store glycogen. Phagocytosis/ Gliosis. Processes form outer & inner limitimg glial membranes at pia & ependyma. Fibrous: white matter, GFAP(+). Protoplasmic: grey matter, GFAP(-).
Oligodendrocytes: Small body, no filaments. Myelinates >1 axon, doesn't have basement membrane (vs schwann cell). Nodes of Ranvier every 0.5-2mm. Myelin: composed of proteolipid protein & myelin basic protein. Contains Schmidt-Lanterman clefts – gaps in sheath to transmit nutrients.
Obersteiner-Redlich area: CNS/PNS junction.
Ependymocytes: cuboidal, have microvilli. Have cilia only in embryonic stages (blepharoplasts at base, stain w/PTAH). Gap junctions, not tight junctions. Tanycytes: line floor 3rd ventricle over median eminence & circumventricular organs, have end feet on capillaries of portal system (transport from CSF to portal system) & tight junctions. Choroidal cells: secrete CSF, have tight junctions, "plumper", have meningothelial (arachnoidal) rests.
Microglia: Resting have small oval nuclei, when activated (macrophages, Gitter cells) are large & spherical
Peripheral ganglia: Have neurons, satellite cells (analogous to Schwann cells) & fibrocytes.
Neurotransmitters: *Definition*: 1) in presynaptic terminals. 2) release w/AP, 3) exogenous NT has same effect, 4) concentration-response effect of drugs on exogenous NT same as on endogenous NT, 5) local mechanism for inactivation.
4 classes: Ach (from cholesteral, Monoamines (derived from amino acids; catecholamines from tyrosine, indolamines from tryptophan, histamine from histadine), Neuropeptides, and Amino Acids (Glutamate, GABA).
Neuropeptides made in soma, cleaved from prohormone, longer action. Small-molecule NTs (all others) made in cytosol of nerve terminals, actively transported into vesicles (some enzymes in vesicles – i.e. for NE). Amines & neuropeptides stored in dense-core vesicles.
Receptors: ionotropic = ion channels; metabotropic = G-protein coupled. Ach, GABA & glutamate use both, neuropeptides & amines only use metabotropic (except 5-HT3).
Locations: Ach*: Nucleus basalis of Meynert* (& Nuc diagonal band of broca, medial septum & lateral hypothalamus), *Pedunculopontine nucleus*, striatal interneurons, habenula, olivocochlear bundle, septohippocampal. NE: Locus ceruleus (midbrain, to CTT, MFB, & DLF), pontine & meullary reticular formations. Serotonin: Raphe nuclei (medulla), enteric. Dopamine: Substania nigra, Ventral Tegmental Area (both midbrain), Tuberoinfubdibular area (hypothalamus), zona incerta, area postrema. Epi: medullary reticular formation (dorsal tegmentum).
Glutamate: Cortical. GABA: BG
Non-neurotranmitter first messengers: Gases, work by diffusion. Incl. CO & NO.
NO (nitric oxide): aka EDRF, synthesized in neurons from *arginine* via nNOS (type I) (also in endothelium by eNOS (III) & inflammatory cells by iNOS (II)), type I & III stimulated by Ca/NMDA; ↑s cGMP, inhibits platelet aggregation, vasodilation, type II stimulated by cytokines, etc after injury & is proinfammatory > ↑ BBB permeability & vasodilation > edema;
Acetylcholine: Synth in nerve terminal by *choline acetyltransferase*. 1 quantum (vesicle) = 10K = 1 MEPP. Release blocked by botulism, tetanus, aminoglycosides, Eaton-Lambert.
Inactivation: acetylcholinesterase (not reuptake – choline then reuptaked)
Acetylcholinesterase inhibtors: neostigmine etc (reversible), organophosphates (irreversible).
Nicotinic: $\alpha^2\beta\gamma\delta$. α = binding sites` (2). In autonomic ganglia only have 2 subunits N- & C- terminals extracellular. 4 transmembrane segments (most conserved, M3-4 least conserved). 7 types – all inonotopic. All presynaptic, motor.
Blocked by:
Depolarizing: hexamethonium/ decamethonium & succinylcholine (↑ with ↓ temp, not reversed by anticholinesterases)
Nondepolarizing: curare & α-bungarotoxin, MG antibody

Reversible: neostigmine, etc.
Muscarinic: 5 types, all metabotropic. Blocked by atropine, pertussis; acts thru G-protein to open or close K, Ca or Cl channel. Parasympathetic postsynaptic & sympathetic to sweat glands, in brain. Can be inhibitory (cardiac) or excitatory (GI). Oxytremorine: selective muscarinic agonist.
Nicotinic: Fast EPSP (open Na & K);
Muscarinic: Slow EPSP (Open Na & Ca, close K), Slow IPSP (open K, Cl).
As membrane of motor neuron depolarize, EPSP ↓, IPSP ↑.
Dopamine: (phenylalanine >) tyrosine > (by *tyrosine hydroxylase*, rate-limiting, requires tetrahydropteridine, phosphorylation ↓ activity, NE inhibits, present only in nerve terminals) dopa > (dopa decarboxylase) dopamine > (dopamine βhydroxylase, requires ascorbic acid, in vesicles) NE > (PNMT, transcription ↑ by steroids) Epi.
Primary inactivation of all is by reuptake (Uptake I: presynaptic, high-affinity, TCAs inhibit; Uptake II: glia, low-affinity. Both energy-dependent. Uptake into vesicles by VMAT1,2 – inhibited by reserpine) Also metabolized by MAO (intracellular- mitochondrial memberane, A-form in neurons, B-form in astrocytes, X chromosome, forms HVA) & COMT (intracellular, forms DOPAC). MAOI-A = antidepressants, MAOI-B = anti-parkinsons. Lower dose of dopamine w/ MAOI.
Receptors: 5, all metabotropic. *D2* (&D3,D4) = parkinsons, pre- & postsynaptic, inhibitory ↓ cAMP, blocked by antipsychotics/ phenothiazes; *D1* (&D5)= postsynaptic, excitatory, ↑cAMP. Apomorphine: nonspecific agonist.
GABA: Inhibitory. Chloride channel. Brain & spinal cord. Glutamate > GABA by glutamic acid decarboxylase (GAD, cofactor B6 – deficiency causes szs, Abs in stiff-man syndrome). Inactivation by reuptake (metabolized to succinic aldehyde by GABA transaminase – Vigabatrin (anticonvulsant) inhibits)
Receptors: GABA-A: Ionotropic, rapid Cl- influx. Postsynaptic. αβ subunits – both bind GABA & barbs, Benzos bind α only (positive modulator, not direct agonist). Blocked by bicuculline, picrotoxin. Muscimol = agonist. GABA-B: Metabotropic, ↓ cAMP (↓ Ca pre, ↑ K post). Pre & postsynaptic, bind baclofen.
Glycine: inhibitory – spinal cord & brain stem only, Renshaw cells. Strychnine blocks receptor (causes rigidity). Opens Cl- Channels.
Serotonin: Raphe nucleus. From tryptophan (rate limiting enzyme tryptophan hydroxylase, cofactor tetrahydrobiopterin), to melatonin. Inactivation: Reuptake, MAO (forms 5-HIAA). Neurons destroyed by 5,7-DHT; p-chlorophenylalanine depletes brain levels.
Receptors: 20+ (5HT1 to 7 & subtypes). All metabotropic (↑ cAMP) except 5-HT3 (cation channels). 5-HT3 presynaptic on dopaminergic neurons –↑s dopamine release. Excitatory: 1D, 2, 3. Inhibitory: 1B, 4. Both: 1A.
SSRIs: eg fluoxetine (Prozac) antidepressants.
Atypical antipsychotics: combined serotinin (5HT2A)/ dopamine (weak D2) antagonists (fewer extrapyramidal Sxs). Include clozapine, risperidone, olanzipine (Zyprexa), ziprasidone.
Nefazadone (Serzone): nonspecific 5HT2 blocker, antidepressant
Migraines: 5-HT1B & 5-HT1D on trigeminal n. to cerebral blood vessels. Triptans (eg sumatriptan – Imitrex) 5HT1D antagonist.
Ondonsetron: 5-HT3 antagonist (antiemetic, ↓ dopamine).
Buspirone (Buspar): antianxiety, 5HT1A partial agonist
Fenfluramine: serotonin-releasing agent, causes panic disorder experimentally.
LSD: blocks 5HT receptors.
Melatonin: from serotonin
Glutamate: doesn't cross BBB, synthesized from glucose in Krebs cycle and from glutaminase in astrocytes. Involved in long-term potentiation/ memory.
Receptors: 3 ionotropic (NMDA, AMPA, kainate), 8 metabotropic.
NMDA: requires glycine coagonist, blocked by Mg (released by depolarization), Ca (also Na & K) channel. Ligand & voltage gated. Blocked by 2-amino-5-phosponovaleric acid. NMDA & AMPA receptors activated in seizures. Kainate (K-type): Na, K channel, binds AMPA, excitotoxicity.
AMPA (Quisqualate, Q-type): binds AMPA & glutamate. Na, K.
Both: ligand only, no Ca, don't require glycine, blocked by quinozalinediones (NBQX);
L-AP4: metabotropic receptor in retina, hyperpolarizing.
Riuzole blocks – stops excitotoxicity (used in ALS)
Aspartate: excitatory, climbing fibers
Neuropeptide transmitters: Made in soma on ribosomes from mRNA, packaged & modified in Golgi appparatus, usually cleaved from prohormone. Inactivated in synapse by peptidases.
Opioids: Include *enkephalins* (widespread, esp in midbrain, PAG, vagal nucleus (antiemetic), locus ceruleus & amygdala (euphoria), spinal cord; inhibitory), *dynorphin* (limbic/ hypothalamus), *β-endorphin* (arcuate nuc. only). Precursors: POMC, proenkephalin, and prodynorphin. All can produce enkephalins. Receptors are metabotropic: μ (morphine, endorphin agonist, naloxone antagonist), δ (enkephalins, ↑K - hyperpolarization), κ (dynorphin).
Gut-brain peptides: substance P (dorsal horn of SC - primary nociceptive afferents & widespread in CNS, excitatory), CCK, bradykinin, VIP, somatostatin, neurotensin.
Pituitary & Releasing Hormones: some project outside hypothalamus.
POMC: > ACTH (> αMSH & CLIP) & βlipotropin (> γlipotropin & βendorphin)
Histamine: found only in tuberomammillary nucleus of hypothalamus
Adrenergic: α1 = poststynaptic, α2 = presynaptic; β1 = heart, β2 = bronchi; β = ↑ cAMP; α = Ca/ IP3 & ↓cAMP
Neuropeptides in sympathetic ganglia function as modulators (not transmitters)
Adrenergic Drugs: , Prazosin α1 agonist, Clonidine central α2 agonist, Phenoxybenzamine (dibenzyine) noncompetitive α antagonist, Phentolamine competetive α antagonist,; Yohimbine: α2 antagonist; Isoproterenol: β agonist, Metoprolol: β1 antagonist., Sulpiride: D2 antagonist, Guanethidine: blocks release of NE.
Hexamethonium: ganglionic Ach blocker
Action Potential: RMP: resting membrane potential mostly from K. Axons –95, neurons –65. Na open > Na close (absolute refractory) > K open (relative refractory), *Cl unchanged*.
Na & Ca channels excitatory; K & Cl channels inhibitory.
Equilibrium potential: electrical force = chemical force, no *net* movement of ions across membrane.
Na/K pump: 3 Na out, 2 K in. Uses 1 ATP. 2subunits (αβ). Inhibited by ouabain. Hyperpolarizes membrane. Electrogenic. Contributes to RMP.
Tetrodotoxin: blocks Na channels; **TEA** block K channels
Membrane stabilizers: Hypercalcemia, hypokalemia, anesthetics, acidosis.

Destabilizers: alkalosis (induces szs), caffeine, strychnine

Synapse: Ca entry causes release of vesicles. Synaptic Delay 0.5sec. 20-50nm (NMJ) wide. Ca channels in presynaptic *active zone*.

Ca removed by: 1)active transport into SER, mitochondria, & out of cell 2)cytosolic binding proteins 3) diffusion (not reversal of flow thru Ca channels).

Release: Vesicles anchored to actin cytoskeleton by synapsin & rab3A – released by phosphorylation by Calcium-dependant kinase (CAMKII). NT released by fusion pore or exocytosis.

Fusion: SNAREs on vesicle (synaptobrevin) & plasma (syntaxin, Rab3 removes Sec1 blocking protein 1st) membranes fuse. Ca binds to synaptotagmin which releases it from SNARE complex, allowing binding & stabilization by SNAPs & NSF. Tetanus & botulinum toxins cleave these proteins.

Vesicle recovery: synaptotagmin/AP2/ AP3 causes formation of clatharin coat, Ca/calcineurin activates dynamin – intitiates endocytosis

Types: Axodendritic: excitatory, axosomatic: inhibitory, dendrodendritic: olfactory builb only, axoaxonic: inhibitory, ↓ NT release.

Gray type I: excitatory, wide, assymetric (large postsynaptic density), round vesicles. Gray II: inhibitory, narrow, symmetric, oval vesicles.

In PNS (not CNS) is surrounded by basal lamina.

Nerve types: IA = Aα,muscle spindle (1°, annulospiral); IB = Aα,golgi tendon; II = Aβ, Aγ,muscle spindle (2°, flower-spray); III = Aδ, temp/touch; IV = C, pain,itch

Motor: Aα = skeletal; Aγ = muscle spindle; C = sympathetic

Sensory receptors: Meissners: touch, rapidly adapt, encapsulated, superficial, low-frequency, fluttering; Merkel disc: pressure/touch, slow, superficial, finger tips, Braille; Ruffini: pressure, slow adapt, encapsulated, deep; Pacinian: vibration, rapid adapt, encapsulated, deep, high-frequency, humming.

Superficial in dermal papillae, small receptive fields; deep have large fields.

Golgi tendon organ: tension. Increases w/ active contraction and passive stretch; group I sensory fibers, disynaptic

Muscle spindle: rate of velocity/change of muscle stretch; increases firing w/ stretch, decreases w/contraction; group I & II sensory fibers, monosynaptic reflex; Gamma motor neurons innervate intrafusal fibers to account for change in length, regulate spasticity. Activity ↓ after lesions of spinocerebellum

Intrafusal fibers: nuclear bag = dynamic or static, 1° ending; nuclear chain = dynamic, 1° and 2°.

Endoneurium = axon. Perineurium = fasicle. Epineurium = nerve.

Nerve injury: Chromatolysis = PNS only, cell body, *increased protein synthesis*, Nissl substance disappears, nucleus at periphery, swelling; reversible.

Wallerian degeneration = distal axon (proximally to next node of Ranvier). Regenerates 1-2mm/d (80% original diameter, ↓ conduction velocity, remyelinated). Retraction bulbs form from proximal & distal ends of cut nerve. Mixed nerves have poorer recovery. Oil-Red-O shows fat macrophages in nerve, EM shows myelin degeneration.

Neuroma: tangles of axons & collagen

Terminal degeneration: synapse degeneration (immediate, before Wallerian).

Transneuronal degeneration: of upstream or downstream neurons (ie optic n. > LGN).

Axon regeneration doesn't occur in CNS, axon sprouts form for 2 wks then die. Reasons: No endoneurial tubes, oligos don't form distal tubes like schwann cells, astrocyte scar, inhibitory factors – semaphorins, Nogo (from myelin), IN-1, astrocyte-associated proteo glycans: Condrotin SO4 (instead of heaprin SO4), tenasin (instead of laminin in immature CNS). Does occur in olfactory n. (has laminin, olfactory glia ensheath)

Neurotmesis: complete disruption of nerve Axonotmesis Perineurium and epineurium intact. Wallerian degeneration occurs.

Neuropraxia Lasts 6-8 weeks, motor > sensory; demyelination, conduction block on NCV

Neuronal death: Excitotoxicity: glutamate/ NMDA > ↑ intracellular Ca.

Apoptosis: chromatin condensation, DNA fragmentation, cell membrane blebbing, loss of nuclear membrane, fragmentation into phagocytosable apoptotic bodies (for macrophages – attracted by BDCF, recognize phosphatidylserine on bodies membrane). Occurs w/ radiation, steroids (lymphoma), cytotoxic T-lymphoctosis, growth factor withdrawl during development, cell cycle control. DNA cleaved into 180bp fragments by endonuclease, can be marked by insitu reaction – *TUNEL stain*.

Caspases (cysteine proteases) uniqely cleave on carboxy side of aspartate.. Synthesized as precursors, activated in cascade. 12 members, 3 (also 1 & 9) especially important in neurons. Cleave/ inactivate Rb & other cell-cycle proteins.

Bcl-2: inhibits apoptosis. bcl-x, NAIP (deficent in SMAs), & p35 also inhibit. Bax & Bad promote.

↓ trophic support > ↓ MAPK, IP3 > changes in mitochondria + Bax > cytochrome C release from mitochondria > apaf-1 > Caspase 9 > caspase 1 > Caspase 3

Necrosis: exogenous insults - ischemia, cell swelling/rupture

Myelination: myelin same composition CNS & PNS; myelin genes turned on by Schwann cells in PNS, astrocytes in CNS

NCV: Normal sensory = 50m/s (0.5-120m/s). *Axonal*: ↓ amplitude. *Demyalination*: ↑ latency, ↓ velocity. Sensory = SNAP, motor = MAP (normal 40-60m/s – slightly slower than SNAP).

Conduction block = focal myelin problem, usu reversible (neuropraxia).

NCV Increases with increased transmembrane resistance, decreased internal resistance, decreased capacitance; myelin increases transmembrane resistance and decreases capacitance

H-reflex: submaximal stimulation, reflex arc (sensory>motor. Monosynaptic = Achilles). Can detect S1 radiculopathy (also affected by neuropathy – ie sciatic) in 1-2d after onset. F-response: supramaximal stimulation, antidromic (motor>motor).Used for median, ulnar, peroneal, tibial n. M-response: direct motor response from stimulating mixed motor-sensory nerve.

Renshaw cells: use glycine. Recurrent negative feedback on αmotorneurons, other Renshaw cells & *IA inhibitory neurons* (inhibit antagonist muscles in stretch reflex) – releasing antagonist inhibition. Also receive input from descending tracts.

Reflexes:

Stretch (Knee-jerk): muscle spindles – IA afferent (excitatory) > αMN, monosynaptic. Golgi tendon organs > IB *inhibitory* interneuron > αMN (inhibits reflex). Tonic & phasic components.

Flexor-withdrawl: disynaptic/polysynaptic (has excitatory interneuron).

Babinksi sign: abnormal plantar flexion reflex (polysynaptic), L5-S2.

Muscle: I-band = actin (thin); H-zone = myosin (thick); A band = both. Z-line = actin. Thin (actin) filaments have troponin, tropomyosin attached.

Sarcoplamic reticulum releases Ca, binds troponin, releases tropomyosin from actin,

binds to myosin. Requires ATP for binding (cocks head – movement > ADP) & release.
Type I: Red. lost in MD, Werdnig, ↑ oxidative enzymes, ↓ glycolytic enzymes, more mitochondria & myoglobin, fire tonically, slower, less fatigueable ; Type Type II: White, lost in MG.
Smooth muscle: no troponin, Ca binds calmodulin to activate myosin kinase & phosphorolate myosin. Stimulated by local factors, not APs. Ca comes from extracellular, not SR..
Cardiac: gap junctions. AP last longer due to slow CA channels, slower velocity. Ca from SR & extracellular.
Cardiovascular: Parasymp.: heart only, Sympathetic: heart & all vessels except capillaries. Vasomotor center in medullary reticular formation (C1). Baroreceptors: carotid sinus > Herrings nerve (IX) > solitary tract > C1 inhibition. Aortic reprtors > vagus. Chemoreceptors: Carotid & aortic bodies . same path as above.
EMG: Myopathy = ↓ Voltage, ↓ duration, no ↓ motor units or recruitment;
Denervation/Reinnervation = ↑ duration, polyphasic, early ↓ voltage, late ↑ voltage, fibrillation, ↓ motor units & recruitment (begins 1-2wks; earlier in axonal than myelin dz); Myotonic discharges = slight movement of needle causes repetitive discharges (dive bomber)
Myokymia: undulating contractions, usually facial, 2-10 Aps at 1s intervals (5-60 Hz), usu due to brainstem dz
Jolly test: evoked potential testing muscles (APs)
Fasiculations: 3-5 phases, 5-15ms, 200uv Visible, motor unit, indicate irritability
Fibrillations: 2-3phase, 1-5ms, >300uv, single fiber, invisible, takes 10-25 days. Positive sharp waves. Denervation.
UMN injury: normal EMG, no fasiculations. LMN: fasiculations, EMG w/fibrillation, atrophy
SSEP: Erbs (N9) > N11 cervical > N13/P13 medulla > N19/P22 thalamocortical. Variables: age, sex, limb length, temp
ICP waves (Lundberg): A=>50mmHg for 5-20 min. B=shorter.
CSF: 0.33cc/min (450cc/d). 70% from choroid. Active process – Na/K pump. Decreased by NE, acetazolamide, furosemide, bumetanide; incr by CO2, volatile anesthetics. Check B-transferrin for leak.
Compared to blood: Osm & Na same, Cl, Mg higher, K, Ca, UA, Glu (45-80), protein lower. Protein < 45. Prealbumin in CSF, not plasma (on electrophoresis)
Froin's syndrome = loculated CSF in lumbar cistern with very high protein
Xanthochromia takes 1-2d to appear.
Cerebral Blood Flow: normal 50-55ml/100g/min. 8-23 = penumbra, <8 = infarction. Nerves (sympathetic) little effect. 1° controlled by local metabolism (glutamate, NO, adenosine, etc), ↑ CO2 (thru NO) & hypoxia. Autoregulated b/t CPP of 60-140. Primarily by large arteries/ arterioles.
Endothelial factors (NO, prostaglandins). NO also stimulated by Ach, substance P, ADH, oxytocin, trypsin, etc.
K channels in vascular muscle open (by NO/ cGMP, cAMP, AA, ↓O2, ↑ CO2) > hyperpolarize muscle cell > Ca channels close > ↓ Ca > dilation. Closure of K channels > contriction.
Vasospasm: may be due to ↑ endothelin (blocked by endothelin A antagonists). Hgb & thrombin induce endothelin. NO/ cGMP also impaired.
BBB: Transport mediated by *diffusion* (barbs), *active transport* (K, organic acids), *carrier mediated. Not vesicular transport.*
Carrier-mediated: glucose/hexoses (not galactose), AAs (3 types Na-dep. transporters: basic, acidic & neutral), lactate, purines (adenosine, not pyrimidines), choline, vitamins.
Capillary endothelial tight junctions (Blood-CSF in choroid = cuboid epithelial tight junction). Ependyma has no barrier.
Serum Osmolarity: controlled by subforniceal organ & organum vasculosum of lamina terminalis
Respiration: *Dorsal respiratory group (dorsal medulla)* = inspiration, main center. *Ventral group* = ventral medulla, nucleus retroambigualis, inspiration (rostral) & expiration (caudal), not active normally. *Botcinger complex* = retrofacial nucleus. Inhibitory, expiration. Active in normal breathing. *pre-Botcinger complex* = has intrinsic pacemaker for respiration. *Pneumotaxic center* = pons, controls rate & pattern. Hering-Breuer inflation reflex (mechanoreceptors): TV > 1.5l. Bronchi > vagus > inhibit dorsal group.
Chemoreceptors: in ventral medulla, sense increase in H+ (less with CO2, pH), excites resp center. Indirect: O2 via carotid bodies, etc (glomus cells have O2 sensitive K channels). CO2 required for breathing stimulation.
Cheyne-Stokes (speed up/ slow down) =hemispheric, central hyperventilation =midbrain/pons, apneustic (3sec pause after inspiration) =pons; Cluster = pons/medulla; Biot (ataxic, irregular) =medulla
Pituitary hormones:
Prolactin: milk production. ↑ by TSH, ↓ by dopamine. Cortisol ↑ prolactin receptors (permissive)
Oxytocin: milk ejection, uterine contraction in labor (direct stimulation of cervix, nipple; higher centers).
LH: Leydig cell > testosterone production. > ↓ GnRH & LH.
FSH: spermatogenesis. Sertoi cells > inhibin > ↓ FSH.
In middle of menstrual cycle estrogen ↑ FSH & LH.
GH: Stimulates IGF-1 (aka somatomedin C) which directly ↓ GH. Anti-insulin, ↑ glucose (directly & thru IGF-1). Highest 1st hour of sleep.
TSH: inhibited by T3 & T4 (TRH isn't). Also ↓ by dopamine, cortisol.
ACTH: peak in am, nadir at night.
ADH: stimulated by hyperosmolarity (osmoreceptors in carotid/ aortic bodies) ↓BP (baroreceptors in carotid/ aortic sinus); also by nausea, pain, skin warmth etc. Inhibited by alcohol. Causes H20 reabsorption in distal tubules of kidney
Releasing Hormones
TRH: from paraventricular, ↑ TSH, prolactin?
CRH: paraventricular, ACTH
GnRH: preoptic, LH/ FSH. Pulsatile release every 90min. ↑ be NE, ↓ by dopamine, endorphins
GHRH: arcuate, GH
Dopamine: arcuate, ↓ prolactin
Somatostatin: periventricular area, ↓ GH
Menstrual cycle: 1st half risning estrogen (low progestoerone) ↑ FSH/LH by pulsatile GnRH release. Ovulation GnRH surge (nonpulsatile) - ↑↑ LH > ovulation. After ovulation: Corpus lutem ↑ estrogen, ↑ progesterone, and inhibin - ↓ FSH/LH
Sleep: Stage 2: spindles, K-complex, 3: delta, 4: night terrors, somnambulism, REM: dreams (REM & non-REM) (nightmares), desynchronization of EEG. Glucose metabolism ↑ in REM & ↓ in non-REM compared to waking.
Alpha: 8-12/s, occipital lobes, closed eyes. *Beta* : 12-25/s, frontal. *Theta*: 4-7/s, temporal in elderly, children. *Delta*: 1-3/s, dleep, brain disease.
Active inhibition of ARAS (by raphe nucleus, serotonin). Muramyl peptides accumulate during wakefulness.
Awake: ↑ NE/5HT ↓ Ach; REM ↑ Ach ↓ 5HT/NE. Pedunculopontine nuc. has Ach & NE

Hypoxia/Ischemia: cortex layers 3, 5, 6; striatum, cerebellar Purkinje cells, CA1 (pyramidal). Penumbra 8-23cc/100g (normal 55). Neurons use glucose only (no glycogen). Man-in-the barrel. Venous = white matter. Resistant = U-fibers, claustrum.

Decerebrate rigidity: transection below red nucleus but above vestibular nuclei (or between the colliculi), lose cortical and rubrospinal stimulation of medullary reticular nuc > extension. Spasiticity abolished by sectioning dorsal roots to cut off γ loop. Anterior cerebellar lobe damage removes Purkinje inhibition of lateral vestibular nuc > ↑extensors (makes it worse)

Decorticate: above red nuclei.

Spasticity has hyperreflexia, rigidity doesn't

Memory: *Working:* few seconds (telephone #). *Long-term*: *Explicit/ declarative* = facts. Subdivided into: *Episodic* (autobiographical) and *semantic* (worldly knowledge). *Implicit/ nondeclarative/ procedural* = motor skills.

Explicit: Long term potentiation at perforant pathway/dentate and CA3/1 synapses. Theories: *Synaptic(Long Term potentiation)*: Glutmate > NMDA/AMPA receptors > 1) Ca influx initiates downstream changes (PKC required) to modify synapse (↑ NMDA/AMPA receptors etc) & 2) NO released, to presynaptic terminal to ↑ glutamate release. *Neurochemical:* Any neurotransmitter > G-protein > Ca release from ER (ryanodine-sensitive Ca channels) > ↑ ryanodine receptors, ↓ postsynaptic K channels.

Implicit: stored in motor systems.

Lesions: Bilateral DM thalamus, hippocamus (role in consolidation, short-term > long-term). Also perirhinal/perihippocampal cortex, septal nuclei & Meynert (Ach necessary). NOT fornices, mamillary body, amygdala. Hippocampal lesion causes anterograde (> retrograde) amnesia. Thalamic lesion causes only retrograde amnesia.

Aging: ↓ Ach, norepi, epi, dop, NOT serotonin. Gliosis in locus ceruleus & SN, loss dendrites layers 3 & 5, neuronal lipofuscin (cytoplasmic remnants of lysosomes) granules, Marinesco bodies (eosinophilic intranuclear) & iron (inf olive, thalamus, BG). Astrocytes: corpora amylacea (laminated basophilic bodies @ foot processes, subpial). Memory & learning are not routinely impaired. ↓ diastolic fxn (not systolic), ↓ renal fxn (Cr stable), WBC stable, ↓ FVC/FEV1.

Apolipoprotein E4/E4: Cholesterol transport protein. 4 alleles (E1-4). E4/E4 genotype: worse prognosis in TBI, ↑ plaques in Alzheimers)

Development/Embryology

Primitive streak d13, notochord d17, neural tube d22, anterior neuropore d24 (> lamina terminalis, failure = anencephaly), posterior neuropore d26.

Gastrulation: Formation of 3 germ layers in gastrula.

Induction: Sonic hedgehog (Shh) from Notochord (mesoderm, Spemann's organizer – follistatin, chordin, noggin) induces neural plate/ neurectoderm. Also Hensen's node secretes TGFβ to induce neurectoderm.

Regionalization: Foot plate produces Shh for ventral determination, FGF8 & BMP dorsal. Homeobox genes – axial.

Primary neurulation: 3-4wks, anencephaly, myelomeningocoele, Chiari I/II, cranioraschisis, cephalocoele

Neural plate > neural groove > neural tube

Disjunction:

Secondary neurulation**:** 4-5wks, vertebrae, dura, skull form. sacral, > occult dysraphism: diastematomyelia, meningocoele, lipoma, dermal sinus, tethered cord, neurenteric cyst, caudal regression syndrome

Ventral induction: 5-10wks, holoprosencephaly, SOD, Dandy-Walker.

Placodes: *Olfactory*: forms olfactory receptor neurons/ nerve, induces olfactory bulb. *Otic*: forms CN8, organ of Corti, cristae ampullares, maculae of utricle & saccule, vestibular & spiral ganglion

Vesicles: Pros- to tel & di; Mes; Rhomb to met (pons/ cerebellum) and myel.

Flexures: cephalic & cervical. Pontine then forms b/t met & myel & persists.

Telencephalon: cortex, striatum, nucleus accumbens, claustrum, amygdala, hippocampus, olfactory bulbs.

Diencephalon: GP, optic cups (> retina, optic n.), posterior pituitary, thalamus, hypothalamus, subthalamus, epithalamus (pineal/ habenulum).

Cerebellum: forms from rhombic lips. Granule Neurons: VZ to external granular layer to internal granular layer. Other cells VZ to cortex.

Stem cells: self-renewing (divide to produce progenitor cell & another stem cell). *Progenitors divide* only to produce downstream progenitors. Adults stem cells present in olfactory bulb, dentate gyrus of hippocampus, SVZ. Bone-marrow cells can be induced to produce neurons.

Neuronal proliferation**:** Neurogenesis**.** 2-4mo. In VZ cells migrate during cell cycle – M-phase at ependymyal surface and S-phase at marginal zone. SVZ occurs later, no variation during cell cycle. Occurs ventral-dorsal gradient in spinal cord, lateral to medial in thalamus. Projection neurons before interneurons. SVZ progenitors remain in adults.

Disorders: Phakomakoses, microcephaly, megaencephaly, arachnoid cyst, AVMs

Neuronal migration: 2-5mo. Occurs 1st in midbrain/ pons. (astrotactin = receptor; Slit proteins – diffusible factors)

VZ > preplate (transient) > marginal zone (becomes layer 1). Preplate split into Cajal-Retzius neuron layer & Subplate. Axons form intermediate zone (>white matter). Layers 6 > 5 > 4 > 3 > 2 form. Reelin mutation reverses this.

Neuronal differentiation: Isl-1 = spinal cord motorneurons.

Growth cones: composed of lamellipodia (feet) & filopodia (toes). Integrins bind to laminin & fibronectin in ECM and cadherins on target cells. Also cell adhesion molecules (CAMs) – Nerve-CAM (N-CAM) & Nerve-glial CAM (Ng-CAM). Neurotrophins (NGF – sympathetic & DRG, BDNF, CNTF, GDNF, CT-1, NT3) produced by target cells guide axons (bind to TrkA, B & C respectively, as well as p75). *Agrin*: released by motor neurons, causes Ach receptor aggregation.

Synaptogenesis: Coincides with wave of apoptosis – nonsynapsed neurons die due to lack of NGF.

Gliogenesis: from progenitors in VZ & SVZ. Radial glial produced during neurogenesis. ↑ EGFR expressions on progenitors > gliogenesis.

Myelination: PNS/SC=4th mo, brain = 5th mo; caudal to cephalad, dorsal to ventral. Corticospinal tracts finished at 2yo.

Neural Crest: craniospinal ganglia (dorsal root, sympathetic), APUD (enteric) neurons, schwann cells (& satellite cells in ganglia), melanocytes, pigmented layers of the retina, odontoblasts, leptomeninges, cartilage of brachial arches, , adrenal medulla, aorticopulmonary septum of heart, thyroid parafollicular cells (C-cells, produce calcitonin) .

Dura from mesoderm, pia/arachnoid from neural crest (others say arachnoid from mesoderm)

Corpus callosum forms anterior to posterior except rostrum

Adult neurogenesis: occurs only in olfactory bulb, dentate gyrus of the hippocampus, and SVZ.

Notochord: forms nucleus propulsus

Toxins

Curare, αBungarotoxin, muscle blockers, aminoglycosides, quinine, procainamide, MG: blocks/ inactivates AchR
Botulinum, Tetanus, Eaton-Lambert, sea snake toxin, tick paralysis: prevents Ach vesicle release.
Organophosphates: Achase blockers
Cholera, Pertussis: ADP-ribosylates G-proteins, prevents GTP hydrolysis.
Diptheria: inactivates tRNA transferase
Cocaine: Blocks reuptake of dopamine, NE
Amphetamines: block NE/dopamine reuptake, ↑ release.
Dihydropyridone: Ca channel blocker
TEA: block K channels
Tetrodotoxin: blocks Na channels
Cyanide: block Na/K pump
Strychnine: block glycine CL channels (Renshaw)
Picrotoxin, bicuculline: blocks GABA-A receptors
Latrotoxin (black widow): ↑ Ach release
Reserpine: dumps NE/dopamine from vesicles, prevents reuptake by VMAT 1,2. Produces long-lasting depletion
Atropine: muscarinic blocker. ↓ peristalsis, ↓*sweating*, ↑ pulse, dry mouth, blurred vision

CRITICAL CARE

Anethesia:
↑ metabolism (CMRO2): ketamine, N2O.
↑ CBF: halothane > ketamine > enflurane > isoflurane > N2O (not thiopental, fentanyl, etomidate).
Ketamine: ↑ ICP, dissociative (PCP analog).
Inhalational: all ↓ BP. *Enflurane:* seizures. *Halothane:* hepatitis, hypotension, ↓ CO, most ↑ ICP. *Isoflurane* best for CNS (not for induction, irritating). Etomidate: adrenal suppression when infused, seizures.
Thiopental: cardiovascular depression.
Methohexital (Brevital): ultra-short acting barb, lasts 5-10 min. *Seizures*, myoclonus
N2O: CI in PTX, SBO (expands).
Diprivan: has 1kcal/ml as fat. Midazolam: amnestic, premedication (not analgesic).
Succinylcholine: depolarizing, ↑K. CI in hyperkalemia, hemiparesis/muscular weakness, burns, eye trauma (↑ ICP & IOP). Duration 6 mins. Metabolized by pseudocholinesterase (plasma).
Nondepolarizing: Vercuronium/ pancuroinium. Reverse with anticholinesterase (neostigmine etc - pretreat with atropine to prevent bradycardia). Mivacurium metabolized by pseudocholinesterase.
Lidocaine: doesn't work in abscess/ acidic environment. IV > seizures, arrythmias (esp bupivicaine)
Glycopyrrolate: anticholinergic, ↓ secretions, reverse MR.
Spinal (subarachnoid) vs Epidural: quicker onset, more hypotension, ↓ dose > ↓ systemic toxicity, LP headache. Both use local ± opioid.
RSI: Preoxygenate > Sedative (Propofol, etomidate – less BP change, thiopental) > Cricoid pressure/muscle relaxant (sux).
Pseudocholinesterase deficency: of plasma cholinesterase, metabolizes Sux > proloned muscle relaxation. Inherited.
Analgesics: *Opioids*: Morphine constricts sphincter of Oddi (Demerol doesn't). Renal excretion (↓ in CRF), histamine release. Demerol: normeperidine accumulates > seizures. CI w/ MAOIs. OD Tx: naloxone. *Benzos:* OD Tx: flumenazil.
Malignant hyperthermia: occurs w/ halothane + succinylcholine. Rhabdomyolysis., acidosis. ↑ ETCO2 Familial mutation in RYR1 gene for muscle SR ryanodine- Ca channel. Tx: dantrolene, HCO3. AD.
Trauma: Cricoidthyroidotomy b/t thyroid & cricoid (<12yo do needle crico).
Tension PTX: hypotension, ↓ BS, trachea deviates away. Emergent (no CXR) needle thoracostomy midclavicular 2nd intercostal space. Chest tube 4th intercostal space. Do not place CT w/ acute abdomen & hemothorax. PTX <3cm can observe.
Pulses: radial = 80, femoral/carotid = 60.
Foley CI: pelvic fx in men, blood @ urethral meatus, high-riding prostate, perineal injury (get retrograde urethrogram 1st). Facial fx: place OGT (not NGT). Thoracic: Only 10% thoracic aortograms (+) w/aortic injury. Pelvic fx: do DPL above umbilicus. Can lose 3l. Agram for embolization – do not explore unless major vessel injury DPL: >10cc aspiration > lap. Neck zones: III = above angle of mandible, II = mandible to cricoid (must be explored), I = below cricoid. I & III = agram. Fluids: Give 3l crystalloid for 1 liter blood loss. Avoid subclavian CVL. Hct may be normal w/blood loss. Infants can lose blood in head to cause shock. If only 1 vial of blood send T&M. CHI: causes 50% of deaths.
Metabolic response to trauma: hyperglycemia, ↑ lipolysis, ↑ Na reabsorption, ↑ H2O reabsorption, metabolic alkalosis
Pseudodiabetes: ↑ACTH > gluconeogenesis
Air embolism: precordial doppler (most sensitive), ↓ EtCO2 (earliest), ↑ FEN2, ↓ CO, ↑ PAP, ↑ pulmonary vascular resistance, ventilation-perfusion mismatch
Neurogenic pulmonary edema: from caudal hypothalamus (also nucleus tractus solitarius & reticularis gigantocellularis & parvocellularis in medulla) w/systemic hypertension, may be blocked with sympathetic blockade.
Oxygen: O2 mostly bound to Hgb; Hgb & SaO2 (percentage of hemoglobin bound to O2, may be falsely↑ in anemia) important. Plasma O2 small role. O2 toxicity: >60% for >48hrs.
O2 Curve: shifted right (decreased affinity) with H+, CO2, ↑ temp, 2,3-DPG; left by banked blood, hypothermia.
Shunt Fraction is 10%, (Cc-Ca)/(Cc-Cv). ↑ Fi02 has no effect if >50%. (Shunt ↓ O2, dead space ↑ CO2)
ARDS: CXR bilateral infiltrates, PCWP < 20 (noncardiac), PaO2:FiO2 < 200. Acute lung injury (ARDS Precursor) PaO2:FiO2 <300.
Neonatal RDS: Lecithin: sphyingomyelin <1.5, ↓ surfactant, ground glass CXR
Ventilator: TV: 10cc/kg. PEEP: ↓ work of breathing, CPP; ↑ dead space, compliance. Barotrauma. Extubate: PO2 >70, CO2 <50, NIF > -20, TV > 5cc/kg, MV > 10L/m.
Keep plateau pressure < 35-40 to reduce barotrauma.
Assist-control: vent delivers TV when pt initiates (Pt says rate).
Brochospasm: Nebulized β-agonist (> racemic epi)
N-acetylcysteine (Mucomyst) cross-allergic w/sulfa.
NT intubation CI in apnea, facial fxs, coagulopathy, ↑ ICP.
PFTs: *Vital capacity* = max. inspiration to max expiration. *Tidal volume* = normal inspiration to expiration. *Functional residual capacity* = left after normal expiration. *Residual volume* = left after max. expiration. *COPD* = ↓ VC, FEV1, ↑ MV; *Restrictive* = normal FEV1, ↓ VC, ↓ RV.
Tracheostomy: Tracheoinnominate fistula: finger pressure thru stoma or ↑ cuff pressure.
CXR: Diaphragm can hide 500cc pleural fluid. Mediastinum >8cm = aortic injury. Pleural edema: Kerley B lines.
Acid-Base: Most common problem in mild-mod injuries = *resp or met acidosis*.

Metabolic alkalosis: caused by diuretics, hypokalemia, Cushings dz, primary aldosteronism, hypovolemia (tx NaCl). M*etabolic acidosis:* Addisons (nomal AG). *Salicylates*: resp alk > met acid. Ketoacidosis: Tx: volume, insulin, not HCO3.
NG suction/emesis = hypokalemic hypochloremic metabolic acidosis, paradoxic alkalotic aciduria (H+ loss for Na+ retention).
For ↑ CO2 by 10, pH ↓ by 0.08.
Coagulation: Intrinsic(PTT): 12>11>9> Extrinsic(PT): Thromboplastin>7 Both: 10/5>2(prothrombin)>1(fibrinogen)>fibrin (req. 13)
Vit K dependent: 2,7,9,10,C,S. *Shortest half-life = 7.*
12 activated by kallikrein. Fibrinogen binds platelets to each other, vWF binds to endothelium by glycoprotein 1b. Plasmin causes fibrinolysis. tPA activates plasmin from plasminogen. EACA inhibits plasminogen > plamin. (Aprotonin ↓ fibrinolysis by inhibiting plasmin & kallikrein).
Brain thromboplastin causes coagulopathy in TBI.
von Willebrands Dz: vWF & VIII:C (complete VIII); AD; abnormal PTT & BT (Tx: cryo or VIII).
Hemophilia A = procoagulant portion of VIII (Tx: cryo - not just VIII, more common,), B (Christmas Dz) = IX (FFP). Both ↑ PTT, X-linked recessive.
Malnutrition and VII def. : abnormal PT.
XIII def.: normal.
Dysfibrogenemia: ↑ PT, PTT & BT
Hypercoaguability: Antiphospholipid Abs (Lupus anticoagulant & anticardiolipin), Protein C (inhibits V & VIII, treat w/ FFP – contains C & heparin) & Protein S (promotes C) deficiency, antithrombin III (bnds thrombin & X), Factor V Leyden. Also nephrotic syndrome - ↓ protein C & S.
Heparin: ↑ ATIII. T1/2 = 90min. ↑ PTT, can ↑ PT at high dose. In OR can check ACT (activated clotting time, abnormal >120 secs). SE: thrombocytopenia (below, not with SubQ), osetoporosis (chronic). Tx: protamine (anaphylxaxis w/IDDM).
Coumadin: Inhibits vitK factors. T1/2 = 40hrs. SE: teratogenic, dermatitis. Tx; VitK, FFP. Metabolized by cytochrome p-450 in liver. Decreased by: barbs, tegretol, rifampin, cholestyramine, nafcillin, sulcrafate. Increased by most others. CI in pregnancy (crosses placenta).
DIC: ↑ PT, PTT & BT. ↓ fibrogen best correlation (↑ d-dimer). best treated with FFP, ± Heparin (thrombotic) (cryo if fibrinogen low, platelets if low)
Platelets: Aggregation ↑ by thromboxane, ADP, serotonin. 1 pack platelets raises by 6K. Glycoprotein Ib – vWF bind to endothelium (absent in Bernard-Soulier); Glycoproteins IIb-IIIa bind other platelets. (absent in Glanzmann's Dz).
Thrombocytopenia: 20K = spontaneous bleeding. Prophylactic transfusion <10K. Platelets "live" 7-10 days. (RBC life 120d)
Heparin induced: causes thrombosis, not hemorrhage. Occurs 4-15d after starting. 10% of patients develop Abs. TTP: Nonimmune (angiopathic). Adults. Fever, delerium, anemia, ARF. Treat w/antiplatelet agents and plasmapheresis (not platelets)
ITP: immune. Steroids/ splenectomy. Children & adults. Others: H2-blockers, thiazides, folate/ B12.
Impaired platelets: uremia, vWF dz, bypass, ASA, PCN. Tx: DDAVP (releases vWF & VII), cryo.
Prostaglandins: Arachadonic acid > thromboxane, prostacyclin, prostaglandins (PGEs), and leukotrienes by COX.
Thromboxane (TXA2): from platelets,vasoconstrictor, promotes platelet aggregation, responsible for ASAs platelet effects. Prostacyclin (PGI2): from endothelium, vasodilator, inhibits platelet aggregation thru ↑ cAMP. PGE2: ↓ IL-1, ↓ platelet aggregation, ↓ tumor cell proliferation, vasodilates depending on receptor, ASAs GI effects. PGE1 keeps PDA open (indomethacin closes). NSAIDs ↓ PGEs – renal vasoconstriction.
Leukotrienes: ↑IL1.
Other endothelium-derived factors:
Endothelin: produced by ECE. Vasoconstricts thru vascular muscle receptors (A & B) by ↑ Ca/ PKC or dilates thru endothelial receptors by ↑ cAMP. May play role in vasospasm.
Antiplatelet agents: Aspirin: COX inhibitor > ↓ TXA2 > ↓ GpIIb/IIIa /fibrinogen binding. Bleeding increased w/Tegretol, PB, cephalosporins, sulfa, PCN, EtOH. Clopridrogel (Plavix): ADP receptor blocker on plts. SE: TTP (less than ticlid). Ticlopidine (Ticlid): ADP receptor blocker; neutropenia, TTP.
Dipyramidole (Persantine, Agrrenox): inhibits platelet phosphodiesterase.
GPIIb/IIIa inhibitors: amaxicab (Reopro), eptifibatide (Integrillin), tirofibran (Aggrastat).
Anemia: Fe-def: microcytic, hypochromic, ↓ MCV, ↑ TIBC. Folate/B12 : macrocytic.
Hereditary spherocytosis: splenectomy corrects anemia (not RBC defect), perform >4yo, may relapse
Transfusion:
Use washed PRBCs: allergic rxn or IgA deficiency. γ irradiation prevents graft-vs-host disease.
Does cause immunosuppression, Causes hypothermia, immunosuppression, ↑K, ↓Ca, ↓Mg; doesn't improve wound healing. Citrate binds Ca > hypocalcemia (infuse Ca after 10 units PRBCs). O- = universal donor. Don't infuse w/ LR (Ca – coagulation).
Autotransfusion: Cell-saver. Can cause coagulopathy. CI: infection, enteric contamination, malignancy, sickle-cell
Infection: HIV risk: 1/300K to 1 million. HCV risk 1/30K. Also: CMV, EMV, malaria, yersinia, trypanosoma cruzi (Chagas).
HBV: Vaccine = anti-HBs Ab. Infection = anti-Hbe & HBs Abs. Exposure: IG + vaccine. HCV: lower transmission by needle stick, no prophylaxis on exposure. PRBCs have no clotting factors.
Febrile nonhemolytic: begins 1-6hrs. antibodies to donor WBCs – don't stop transfusion. Tylenol. Use *leukocyte-poor* RBCs. Allergic (anaphylaxis): Abs to plasma proteins, IgA deficency. No need to stop transfusion if no fever. Tx: Benadryl, Epi, IVF, *washed* PBRCs. Acute pulmonary injury: begins 1-2hr. *Donor* Abs to WBS > aggregation. Stop transfusion, resolves. Acute hemolytic reaction: ABO incompatibility. Occurs within *minutes* – fever, CP, LBP. Stop transfusion for early fever, Lasix, HCO3 (alkalinize urine). Check plasma & urine for Hgb, Coombs test.
Cryoprecipitate: has fibrinogen, vWF, factor VIII, ATIII. Tx: factor 7,8 deficiency, uremia, hemophilia A (8), vonWillebrands, cardiac bypass; (contains fibrinogen, factor8, vWF, fibronectin, antithrombin III)

FFP=hemophilia B (9), liver dz, coumadin.
DVT/PE: more common left iliac v. (aorta crosses). Homan's sign. (only 33% symptomatic). CXR: westermarks (wedge hyperdensity due to ↓ vasculature). S1Q3T3. U/S no compressibility most sensitive. Tx: 100% O2, Heparin (10K unit bolus > 1K/hr) > Coumadin x 3mos. V/Q: high prob – treat. Intermediate/ Low – agram.
Parameters: CVP <5, PCWP <12 (= LAP or LVEDP, preload, on vent best measured at end expiration, not accurate in ARDS, pulmonary HTN, valve dz), CO 4-8L/m; CI 2.5-3.5 L/m/M^2. PVR = 100. MAP = DBP + 1/3 (SBP-DBP). Lactate, SvO2 & pH assses O2 delivery.
Swan-Ganz: RA mean 8; RV 15-30/0; PA 15-30/8; PCWP 15 mean.
Shock: PCWP, CO, SVR: cardiogenic (↑↓↑), septic/anaphylactic (↓↑↓, use Norepi for septic, epi for anaphylactic), hypovolemic (↓↓↑, IVF ± dobutamine). Spinal: hypotension & bradycardia. Oxygen uptake >110, *arterial* lactate <4
% blood loss: 15-30% = tachycardia (not in spinal shock), ↓ pulse pressure (DBP ↑ due to vasoconstriction), 20% = orthostatic hypotension, 30% = ↓ systolic BP, oliguria, confusion >40% = anuria, lethargy. Dextrans ↑ coagulopathy, hetastarch does at > 1.5l. NO proven advantage crystalloid vs colloid in shock. BCxs (-) in 50% sepsis.
EKG: hyperkalemia: peaked T, hypokalemia: u-wave, hypocalcemia & quinidine:↑ QT; MI: subendocardial = ST depression, transmural = ST elevation. Pulmonary emboli: nonspecific ST change (Right side strain, tachycardia). Hypothermia: j-point elevation. Hyperthyroidism: afib. Pulsus paradoxus: ↓ of SBP of >10 on inspiration, cardiac tamponade.
Cardiac tamponade: Becks triad: hypotension, muffled heart sounds, ↑ JVD. Also pulsus paradoxus,↓ QRS. CT & tenion ptx both ↑ JVD & ↓ pulse pressure, ptx doesn't have pulsus paradoxus. Tx: subxiphoid pericardiocentesis @ left costal margin
Cardiac Drugs: Nitroglycerine: venodilator. causes methemoglobinemia (cyanosis w/normal ABG); CI include increased ICP, glaucoma. Nipride: venodilation = arteriodilation. cyanide (converted to *thiocyanate* in liver, excreted in *urine*, half life 4 days – causes ARF, psychosis. Tx w/hydroxocobalmin). Amrinone not α or β, Dopamine: D (renal dose) > β1 > α1 (with ↑ dose).
Dobutamine: β1. ↓ SVR. Epi α = β.
Norepi: α, mild β1. Neosynephrine pure α agonist. Isoproterenol: β1 & 2 (SBP no Δ, ↓ DBP, ↓ PVR, relaxes smooth muscle).
Digitalis:
Digoxin: inhibits Na-K ATPase, ↑ intracellular Ca – inotrope. Quinidine, amiodarone, verapamil, erythromycin, atropine ↑ levels. Long PR, short QT. Toxicity: visual changes, AV block, mesenteric ischemia – Tx w/ Dig Ab.
Dopamine vs dobutamine: affects β1
Frank-Starling curve: ↑ preload (EDV) > ↑ CO to a point then ↓.
Antihypertensives: ACEI: CI in renal artery stenosis. β-blockers: CI in asthma, w/ Ca-channel blockers.
MI: periop risk ↑ for 6mos post-MI. Tx: nitrates, ASA O2, Morphine, β-blocker, heparin (postop), tPA (BeMOAN); occur postop day 2-5 (often silent). Aortic dissection: Tearing pain. Nipride or labetalol for SBP <110.
Arrythmias
Afib/Aflutter: Verapamil, Diltiazem. (also digoxin for flutter) If unstable cardiovert 100J.
Other SVT: Vagal maneuver, Adenosine, verapamil, diltiazem (procainamide). If unstable cardiovert 100J.
Vtach, Vfib: Pulseless: Epi; Other: Lidocaine > procainamide > bretylium. VT most common in CAD, ↓K. Torsades de pointes w/quinidine, procainamide.
Asystole: Epi, atropine
Bradycardia: atropineif HR<60 & symptomatic
Preop risk: MI w/in 6mos, age >70, S3 gallop, JVD, >5 PVCs, aortic stenosis, emergency. Spinal = general for CAD. Quitting smoking 2wks before surgery ↓ risk in chronic smokers. Most important tests: EKG > Hgb > ABG > Cr.
Periop infections:
Wound: Postop day 5-7. Staph aureus most common (fever in 1st 24hrs = Strep, clostridium). ↑ with steroids, age > 70, malnutrition, remote infection, uncontrolled DM (not controlled).
Necrotizing fasciitis = strep, debrediment, Tdt.
Gas gangrene: Clostridum. Tx: PCN, fasciotomy, debridement (+- hyperbaric O2, no antitoxin (give tet-toxoid, Tet-Ig))
Rates: clean <1.5%, clean-contaminated 3%, contaminated 5%, dirty 33%. Uremia ↑s.
C. diff: Occurs w/ all abx. *Watery diarrhea*, cramps. Tx: *oral Flagyl* > *vanc*
CVL: Staph epi. Change CVL if Cx >15CFU. Propofol – lipid content ↑ infection (change line qd)
Pneumonia: ICU = GNR.
Pleural empyema: Staph aureus > Hflu
Tetanus prophylaxis: 0 or 1 immunizations = give toxoid + Ig, 2 = toxoid only, 3 in <5yrs = none.
Antibiotics: Aminoglycosides/Gent: inhibit 30s ribosome; poor CSF penetration, bactericidal, worsen myasthenic crisis, nephrotoxic (ATN), vestibular probs, ototoxic. Gram (-)no strep. PCN: inhibits bacterial cell wall synthesis. NO staph (extended PCNS do), GNR coverage. hemolytic anemia.
Aztreonam: GNR, no GPC, no cross-rxn w/PCN. AmphoB: nephrotoxic (RTA).
Fluconazole/Diflucan: no nephrotoxicity.
Vanc: Red man's, ototoxic, nephrotoxic.
Metronidazole (Flagyl): disulfiram reaction w/alcohol, neuropathy.
Ciprofloxacin: Gram (-), Pseudomonas. cannot give to children/pregnant women (interferes w/growth plate).
Cephalosporins: 8% cross-allergy w/PCN. No enterococcus coverage. Cefoxitin: 2nd gen. Better GNR/Anaerobes/Bacteroides (better for surgical prophylaxis). .
Ceftriaxone: cholestasis. Ceftazidime: 3rd gen. Psuedomonas, GPC (↓ GNR). Clinda: Inhibits 50s ribosome. Anaerobes.
Quinolones: inhibit DNA gyrase.
Imipenem: inhibits cell walls. Cilastatin ↓ renal excretion. SE: seizures.
Staph: vanc, Strep: PCN, enterococcus: amp or vanc/gent, Clostridium: spore-forming GPR. HIV: Abs dectectable 6-8wks > ELISA, Western
Probenecid: Inhibits organic acid transport by epithelial cells (choroid), keeps PCN elevated in brain (also 5-HIAA)
Alkalize urine: ↑ exretion of phenobarb, TCAs, ASA (weak acids) (not amphetamines - basic)
Chemotherapy: Vincristine: neuropathy, microtubule inhibitor (mitosis). MTX: folate antagonist (dihydrofolate reductase, FH2 > FH4, ↓ purines, glycine, thymidylates), necrotizing leukencephalopathy, myelosuppression; ↑ by PTN, sulfa, ASA. Leukovorin rescue: folinic acid, normal cells take up, tumor doesn't. Cisplatin: alkylating agent; nephrotoxicity, *ototoxicity*, neuropathy, TTP. XRT sensitizer. Procarbazine: mood changes, G6PD deficency problems; BCNU (Carmustine): alkylating agent. *Myelosuppression (dose-limiting*), nephrotoxicity.

Above cross BBB except MTX, also etoposide, 5-FU, hydroxyurea do. IL/interferon: parkinsonism. Tamoxifen: retinopathy. 5-FU: cerebellar ataxia.
Tumor biology: N-myc = oncogene, neuroblastoma.
Wound healing: 12h epithelial migration; 5d wound contraction (myofibroblasts, actin), collagen synthesis); 42d (6wk) max amount collagen; 2y max tensile strength (80% in 30d).
Also Inflammation (24hrs, PMNs & macrophages) > epithelialzation 48h > proliferative/ scar (fibroblasts secrete collagen 1-12d) > contraction
Collagen: Contain unique AAs hydroxyproline & hydroxylysine (require *Vitamin C & Zinc* for hydroxylation), also ↑ proline. Glycine every 3rd residue. Triple helix.
Type III appears 1st (24-48h) frame work; *I* = 72hrs, fibroblasts, most common in skin, *IV* = basement membrane, *II* = cartilage.
Collagenase: secreted by T-lymphocytes (by IL-1) and migrating epithelial cells
Macrophages (> fibroblasts) secrete GFs, steroids inhibit, most important cell in 1st 4 days.
Growth factors: TGFβ - stimulates collagen synthesis; bFGF & PDGF – make fibroblasts competent; IGF & EGF cause fibroblast replication;
Angiogenesis: bFGF begins angiogenic cascade; VEGF stimulated by hypoxia, chemotactic & mitogenic for endothelium TGFα endothelial proliferation; TNFα stimulates capillary tubule formation
Iron def: only transient effect ↓ tensile strength – unknown mechanism. Diabetes: affects all phases (collagen glycosylation, etc). XRT: prevents hypoxia-induced angiogensis. Nicotine: ↑ platelet adhesion & vasoconstriction. Steroids: stabilizes lysosomal membranes (Vitamin A destabilizes).
Glycosaminoglycans: in skin = hyaluronic acid, chondroitin SO4, dermatan SO4, heparin; not heparin SO4 or keratan SO4
Anion gap: Na – (Cl + HCO3), 12 normal High with ↑ acids (ARF, ketones, ASA, lactate, etc). Normal w/ ↓ HCO3 (Cl- increases; diarrhea, RTA). ↓ albumin causes ↓ AG.
Free H2O def=(Na-140) x kg x 0.6
Osmolarity = 2(Na+K) + Glu/18 + BUN/2.8. Free H2O deficit = .6 x kg x (Na/140 – 1).
Body H2O: Intracellular 66%, interstitial/ extracellular 20%, vascular/cavity 10%. Vol = 70ml/kg (females 60). Avg 5l.
Fluid status: best assessed by UOP (CVP if CRF or CHF). LR = low K+ (OK for bolus), also lactate, Ca; may precipitate panic attacks. 20-30% of NS remains intravascular after 3 hrs.
Kidney: Renin/angiotensin: juxtaglomerular apparatus produces renin > angiotensinogen to angiotensin I > ACE > angiotensin II > vasoconstriction, ↑ aldosterone. System stimulated by ↑K, ↓ Na. Aldosterone: from adrenal cortex, stimulated by AgII, ↓Na, carotid/aortic baroreceptors. ↑ Na reabsorption K & H secretion from distal tubules. ADH: stimulated by ↑*osmolarity*, ADH, carotid/aortic baroreceptors. ↑ H2O reabsorbption in distal tubules.
Loop of Henle: Reabsorption of Na passively follows active transport of Cl
Distal renal tubules: Na in, K, H out.
Renal disease: ATN: due to sepis, toxins, drugs, etc. Epithelial (granular) casts.
Acute interstitial nephritis: immunologic, due to PCN, NSAIDS, Lasix. Fever, rash, arthralgias. WBC casts, urine eosinophilia. Acute glomerular nephritis: RBC casts. Prerenal: Hyaline casts.
Pyelonephritis: WBC casts.
Nephrotoxic drugs: Aminoglycosides, ampho B, PCN, NSAID, ACEI.
ARF *Renal:* BUN/Cr <20, U.S.G. <1.020, FeNa > 1, UNa > 40, Una < 350. *Prerenal* is opposite. FeNa = (Una x Pcr/ Ucr x Pna) x 100 (U Need Pee). May be oliguric (<500cc/d) or nonoliguric. D/C Mg/antacids, ↓ digoxin, Nipride, procainamide. 10% > CRF. Dialyze for AEIOU (acidosis, electrolytes/K, inflammatoin/pericarditis, fluid overload, uremic encephalopathy)
Tx: CVVHD (continuous > intermittent dialysis. Dopamine, Lasix no benefit.)
Urinary retention: Tx: bethanecol.
RTA: I=nephrocalcinosis, urine pH >5.5; II= ↓ HCO3 reabsorption. Both: non-anion gap acidosis, hypokalemia
Myoglobinuria: Alkalinize urine (HCO3 IV), mannitol, IVF.
Fanconi's syndrome: Proximal renal tubular defects. Lowes, Wilsons dz. Lose glucose, Aas, PO4 etc in urine. Rickets
Diuretics: Lasix: inhibits Na/K reabsorption in ascending limb; ↓ Ca & K. Lasts 6 hours. In ARF double dose (20-40-80) until result. Thiazides: inhibits Na/CL transport in distal tubule. ↑ Ca. CI: diabetes, hyperuricemia, hyperaldosteronism. Mannitol: Osmotic diuresis in proximal tubule. SE: cardiac, renal, H/A, N/V.
MEN: All AD. I (Wermers) = pancreatic islet cell tumors, parathyroid adenomas, pituitary adenomas. IIA (Sipples) = pheo, parathyroid, thyroid (medullary CA). IIB = Pheo, thyroid, mucosal neuromas/ marfanoid habitus.
Zollinger-Ellison: duodenal or pancreatic gastrinoma, duodenal ulcers, increased serum gastrin (increases w/IV secretin). Occurs in MENI.
Carcinoids: most common in appendix
Hemachromatosis: ↑ Fe in blood. Genetic (HFE) or 2°. ↑ serum Fe, ferritin. Tx: phlebotomy. Carried by transferrin – minimal brain depsotion
Nelsons disease: adrenalectomy causes rapid pituitary adenoma growth
Hyperaldosteronism: hypokalemia, ↑DBP, metabolic alkalosis, polyuria, *no edema*
Acromegaly: = adults. Cretinism = kids (hydrocephalus)
Hypothyroidism: Primary (Hasimoto's): ↓ T4, ↑ TSH. Secondary/ pituitary: ↓ TSH, FT4. T4 coverted to T3 (more potent). Critically ill pts (sick euthyroid state) have ↓ T3 & T4, normal free T4 & TSH. Replacement doesn't benefit.
Thyroid measurements: If TBG ↑ (pregnancy, liver dz), total T4 ↑ but free T4 normal. T3RU ↑ in hyperthyroidism, ↓ in hypothroidism. Free T4 index = T3RU/norm x total T4. Should agree w/ T3RU.
Hyperthyroidism: ↓ TSH. Opthalmoplegia (IR & MR), proximal girdle weakness/ myopathy. Tx: PTU (anti-thyroid, β-blockers)
Hypocortisolism: Addisons. Hypotension, hyponatremia, *hyper*kalemia,, hyperpigmentation (in 1°, not 2° - low ACTH/MSH). Dx: Cortrosyn test – if no ↑ in cortisol then 1°. Addison's crisis: tachycardia/ hypotension *refractory to IVP/ pressors*. Tx: hydrocortisone IV + fludrocortisone PO (mineralocorticoid). Chronic steroid users at risk for up to 1 year after stopping steroids.
Hypercortisolism: Cushings Dz > adrenal tumor > ectopic. Hyperglycemia, hypertension, hypokalemia etc. Low-dose DST = 0.5mg QID x2d. High dose = 2mg QID (suppresion with Cushings, not others). Metyrapone test: increased 17-hydroxycorticosteroids (with Cushings, not with ectopic ACTH)
Steroid potency: cortisol = hydrocortisone = 1; prednisone = prednisolone = 4; methylprednisolone = 5 (less mineralocorticoids); dexamethasone = 30.

Steroid Side-effects: ulcers, hypokalemia, hyperglycemia/DM, HTN, osteopenia, obestity, cataracts/glaucoma, myopathy, infections, avascular necrosis of hip. (Vitamin A counters wound healing effects)
Parathyroid hyperplasia: hypercalcemia, MENI & II. ↑ Ca, ↑ PO4, ↑ AlkPhos, fractures
Stevens-Johnson syndrome: Dilantin and Tegretol (also PCN, sulfa, barbs, Mycoplasma, HSV, strep) Tx: steroids.
Dilantin hypersensitivity: S-J + Hepatitis, fever, eosinophilia,lymphadenopathy. Absence of epoxide hydroxylase > arene oxides
Haldol: lowers seizure threshold, neuroleptic malignant syndrome – treat w/dantrolene
Droperidol: antiemetic, antipsychotic, butyrephone, causes arrythmias (↑QT, torsades de point)
Ethambutol: anti-TB. Causes optic neuritis, color blindness
Hypomagnesemia: Ca Carbonate, ethacrynic acid, amphotericin, aminoglycosides. Same Sxs as ↓ Ca
Hypocalcemia: seizures, psych, dysrhythmias, tetany (Chvostek, Trousseau); adjust for hypoalbuminemia. Ionized Ca best measure. Causes: pancreatitis, ↓ Mg, CRF. EKG: Prolonged QT. Tx: 10% Ca gluconate – must correct hypomagnesemia 1st. (Calcium choride 3X more ioized Ca than gluconate. IV infiltration causes necrosis.)
Hypercalcemia: Sarcoid, hyperparathyroidism. Sxs: hypotension, stones, AMS, ulcers, pancreatitis. Short QT. Tx: Volume, Lasix, calcitonin (mithramycin, etidronate).
Hyperkalemia: weakness, arreflexia. Peaked Ts. Tx: CaGluconate (for cardiac), kayexalate, lasix, insulin/D5, HCO3, dialysis
Hypokalemia: EKG: flat Ts, U-waves. (10meq/hr IV, 20/hr CVL max.) Exacerbates digoxin toxicity. UrineK <30 = diarrhea. > 30 then if serum HCO3 < 24 = RTA. If >24 then If Ucl < 10 = emesis, NG, >10 = diuretics, steroids. Causes tetany, ileus. Pseudohyponatremia = due to hyperglycemia, hyperlipidemia. Must correct hypomagnesemia 1st.
Hyponatremia: caused by Addisons, hypothyroidism, renal failure, SIADH (euvolemic). Correct at 2.5meq/hr or 20meq/d max to avoid CPM.
Hypernatremia: correct at 1meq/hr.
Hyperphosphatemia: treat w/aluminum hydroxide.
Hypophosphatemia: weakness (respiratory)
Diabetes: #1 cause of death is cardiovascular. Nonketotic hyperglycemic coma: Glu >900 (<600 in DKA), NIDDM. ↓ fatty acid concentration than DKA. Mortality >50%.
DKA: ↑K (watch for hypokalemia w/correction). Tx: Insulin, NS, HCO3 for shock, pH < 7.1.
SIADH: Causes: Oat cell, Dilantin, Tegretol, thiazides, COPD. Tx: demeclocycline.
DI: Tx: DDAVP, pitressin, chlorpropamide.
Fat embolism: 12-48h later, always w/dyspnea, petechiae over shoulders/ chest, tachycardia, tachypnea. ↑ serum lipase in 50%. Look for fat in blood, urine. CNS dz does not occur without lung disease unless PFO/ ASD.
Nutrition: Req: Protein 1g/kg/d, Calories 35/kg/d (25 in paraplegics). TBI ↑ 1.7x BMR. (Burns ↑ 2-3x) Fat 9kcal/g, Pro 4, Carbs 4. Measure status w/prealbumin (T1/2 = 2d – shorter than albumin, transferrin; ↑ in CRF, steroids, ↓ in liver dz).Respiratory Quotient = VCO2/V02, <0.8 = fats 1° nutrient, >0.8 = carbs. Tube feeds: hepatic = branched chain Aas (aromatic Aas cause encephalopathy); renal = essential AAs, pulmonary = ↓ carbs, ↑ fats (25-50% of cals). TPN: most common complication = hepatic steatosis. (benign, resolves, ↑ LFTs). Glutamine important after injury/ stress. Essential fatty acids: linoleic (& linolenic?) acid, Deficency: alopecia, dermatitis from TPN, ↓ arachadonic acid ↑ eicosatrienoic acid. Zinc: impaired wound healing. Tube feeding diarrhea tx: check Cdiff 1st,change formula, ↓ feeds, add fiber (psillium),
GI meds: Sucralfate: needs H+ to activate – do not use w/H2 blockers. Omeprazole (Prilosec) = K+/H+ - ATPase inhibitor. Metoclopromide (Reglan) = dopamine antagonist, worsens Parkinsons. Phenergan: dystonia (tx w/benadryl).
Pancreatitis: Causes: hypercalcemia, (DIC, ARDS?)
ARDS: use PEEP, not diuretics, steroids
Respiratory stimulants: Doxapram – stimulates central centers
Vasovagal syncope: Tx anticholinergics (propantheline)
Immunology:
Humoral: Viral Ag > B cells > antibodies + complement.
Cellular: T-cells, T-helper (CD4) & T-suppressor/cytotoxic (CD8). Infected cells > viral Ag on MHC I or II > T-cell destruction.
MHC: Glycoproteins (ABO = glycolipids) *Class I:* HLA-A,B,C. On all cells, for Tc cells. *Class II:* HLA-DP,DQ,DR. On macrophages, B-cells, for Th cells. HLA-A,B & DR important for transplantation. Glia express low MHC I. Neurons express no MHC I or II.
Cytokines: Inflammatory: IL-1. Anti-inflammatory: IL-4,10,13.
Hemostasis: Surgicel = cellulose; Fibrin glue = fibrinogen + thrombin
EtOH withdrawl: 12hrs hallucinations, 12-24hrs seizures, 3-4d DTs.
Statistics: Sensitivity = TP/TP+FN. Specificty = TN/TN+FP. Positive Predictive Value = TP/TP+FP. NPV = TN/TN+FN. Prevalence = TP+FP/all. Study results: Type I error = false positive conclusion of hypothesis. Type II = false negative. P-value is chance of type I error (<0.05, 5%). Power = chance of not having type II error. (>80%). Mann-Whitney test: compare 2 groups where variable is not normally distributed (wide variation). T-test: compare 2 groups with normally distributed variable. Chi-square test: compare frequency values b/t 2 groups. ANOVA: examines differences of >2 groups. Validity: test measures what it intends to. Reliability: gives consistent results.
800-237-4558 - 247