Lectures
General medicine
Stomatology
Special pathophysiology
1995 -2025

6 NEUROPATHO-PHYSIOLOGY

Neurodegenerative disorders

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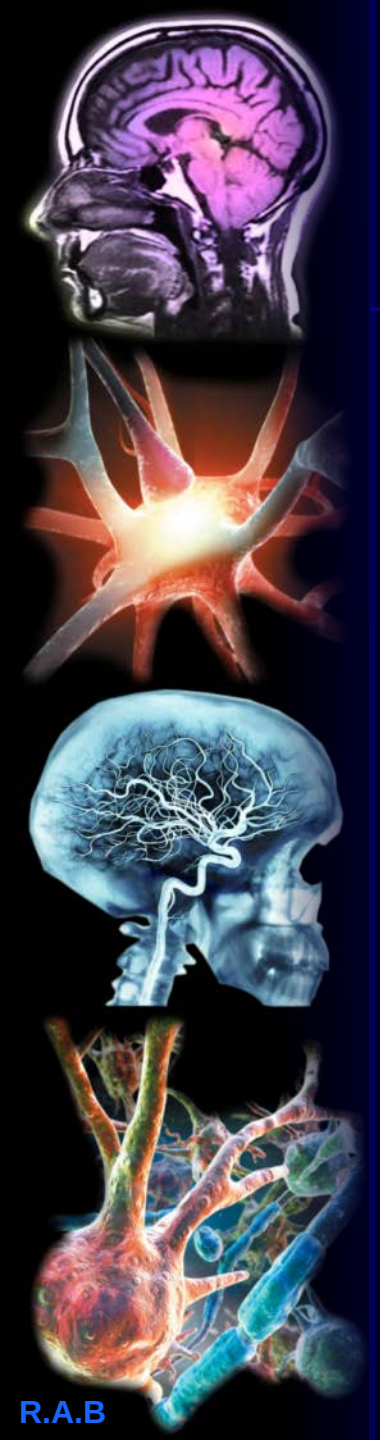

Characteristics

- Def: Neurodegenerative disorders = group of chronic, **progressive uncaurrable** CNS disases discovered obviously later in life and characterized by varios **pathoanatomic** findings inlcuding massive death of neurons (nerve cells) = gray matter.+ axons = pathways (white matter).
- Manifestations widely differ and depend on particular CNS area affected
- Symptoms that worsen over time and typically appear.
- Causes: combination of genetic, environmental, and age-related factors, and they share features like selective vulnerability of specific neuron populations.
- The causes are multiple - **hereditary, acquired**
- Macroscopic manifestations are different - **visible** (ACH) <-> **less obvious**
- Molecular mechanisms - known to many, unknown elsewhere → protein accumulations identified in deposits;
- Symptomatology may be heterogeneous
- Different categorization, **100-unit units; diversification continues**

R.A.B

Neurodegenerative disorders

- Path.: Miscroscopic findings
- progressive neurodegeneration,, not uniform but targets specific neuron types and brain regions.
- Neuronal loss and atrophy: Shrinkage and death of neurons.
  - grey matter <-> grey and white matter
  - focal <-> mutifocal <-> diffuse (global)
  - specific areas <-> no specificity
  - only brain <-> brain and spinal cord <-> CNS and PNS
- Reactive gliosis: Proliferation of astrocytes and microglia as a response to injury, contributing to inflammation.
- Synaptic and network dysfunction: Early loss of synapses and disrupted neural circuits before widespread cell death.
- Protein aggregates/inclusions: Misfolded proteins that accumulate intracellularly or extracellularly (detailed below).Other common features:
- Cytoskeletal abnormalities, altered energy metabolism, DNA/RNA defects, and chronic inflammation

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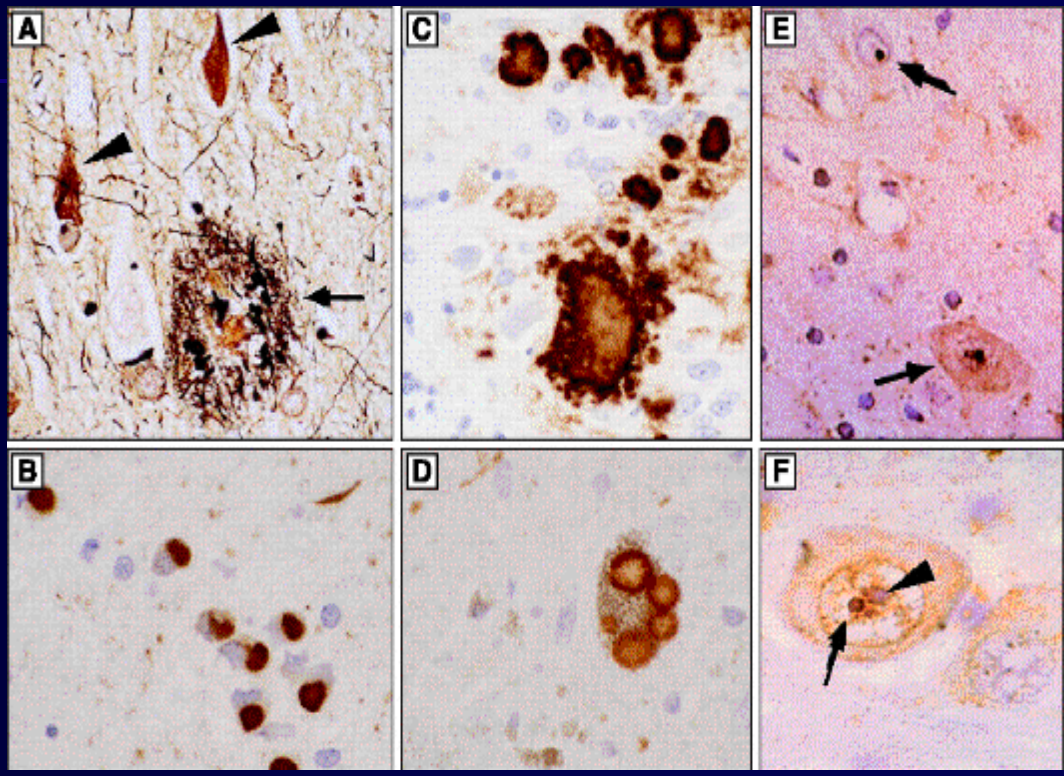
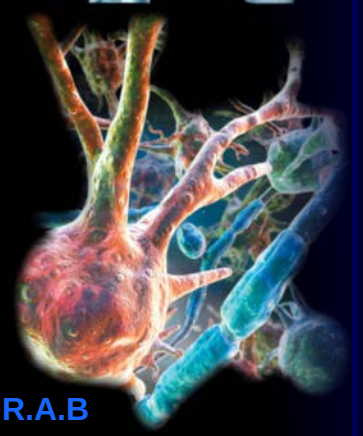
Intra& extracelullar inclusions

- Senile plaques-outside the cell
- Amyloid plaques-outside the cell
- Neurofibrillary targets - in the cytoplasm
- Levy bodies - in the cytoplasm
- Spheroids - in the cytoplasm
- Glial cytoplasmic inclusions – in the cytoplasm
- Inclusions – at the core
- Lafora bodies - in the cytoplasm





(A) **Alzheimer's disease.** neurofibrillary tangles + extracellular amyloid plaque(arr)
(B) **Pick's disease** - Fibrillar tau inclusions
(C) **Prion disease** PrPSc amyloid deposition in
(D) **Parkinson's disease** - multiple Lewy bodies in a nigral neuron
(E) **Machado-Joseph's disease** - neuronal intranuclear inclusions **ataxin-3** in.
(F) Mutant **ataxin-3**, demonstrating that it is distinct from the nucleolus.

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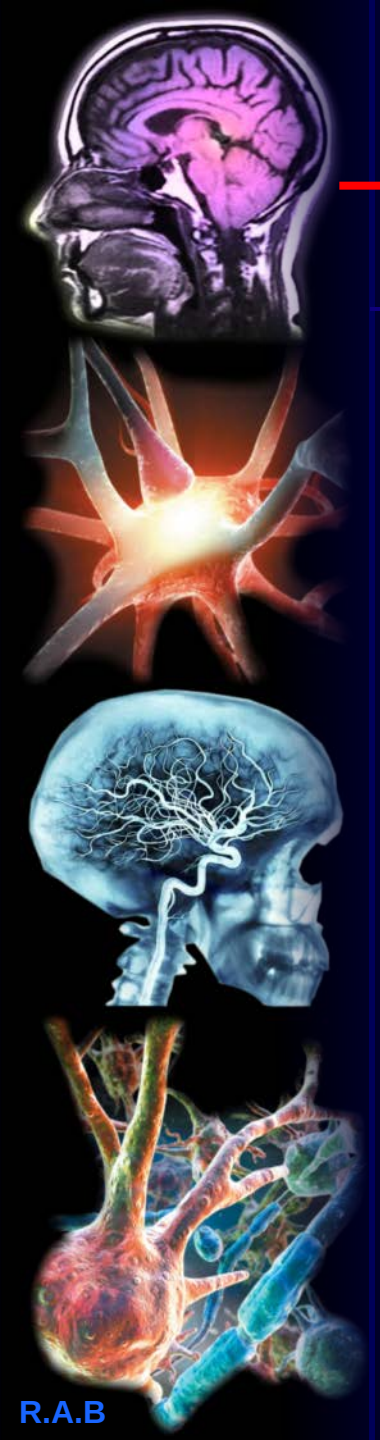

Aggregates of proteins

- Amyloid-beta protein
- Alpha-synuclein protein
- Hyperphosphorylated tau protein
- Prion protein
- Superoxide dismutase
- Huntingtin
- Atrophin
- Ataxin
- Laforin
- Glial fibrillary acidic protein
- Proteolipid protein
- Polyglucosan
- Neuroserpin

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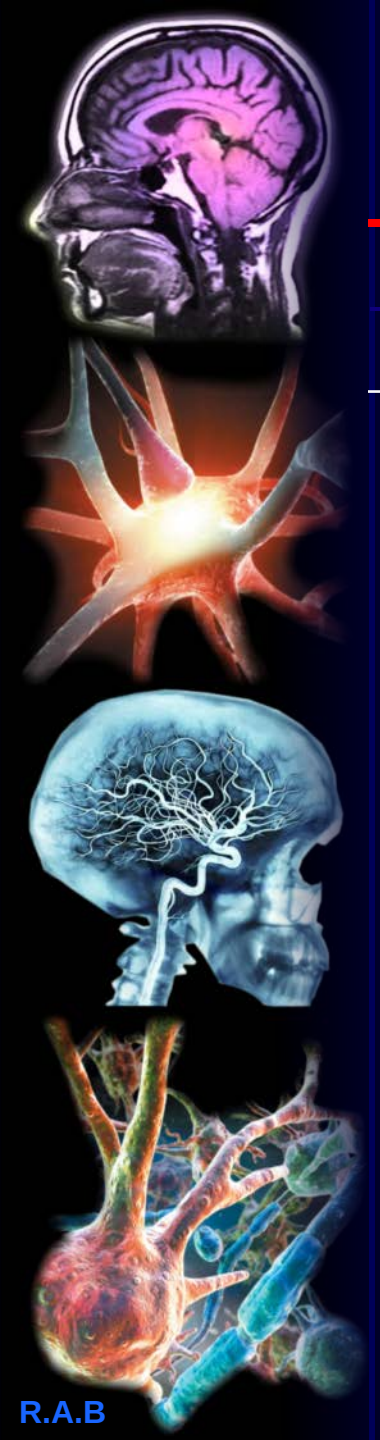

Accumulation disorders

Principal Protein	Disease
Amyloid-beta protein Amyloidoses	Alzheimer's disease Down's syndrome Dementia with Lewy bodies
Alpha-synuclein protein Synucleinopathies	Parkinson's disease Dementia with Lewy bodies Cortical Lewy body disease Multiple system atrophy Neurodegeneration with brain iron accumulation
Prion protein Prionoses	Creutzfeldt-Jakob disease, Kuru Fatal familial insomnia Gerstmann-Straussler-Scheinker disease

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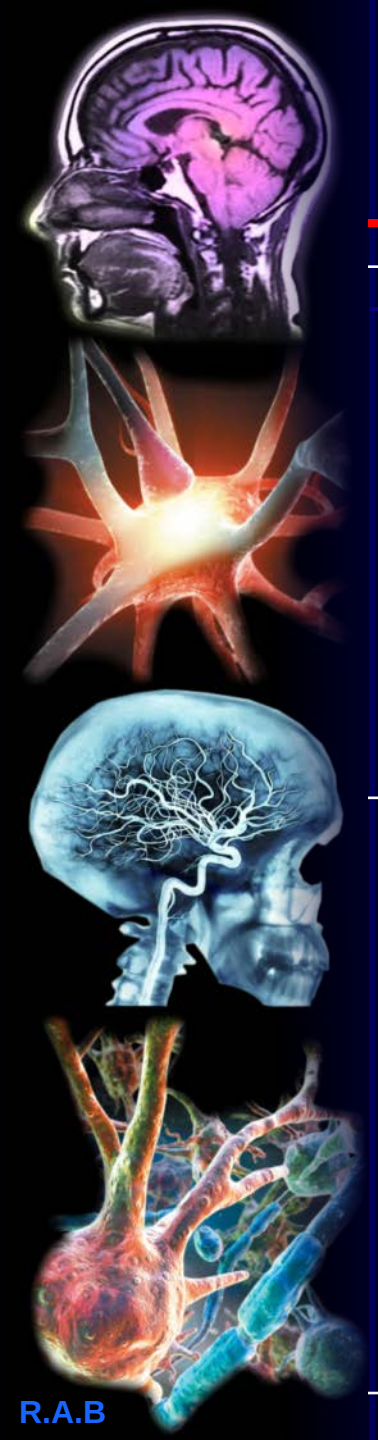

Accumulation disorders

Taopaties Hyperfosphorylated tau	Alzheimer's disease Down syndrome Frontotemporal degeneration (M. Pick) Progressive supranuclear palsy Sy.Guam (parkinson-dementia complex) Corticobasal degeneration Palidopontonigral degeneration Niemann-Pick disease Type C
Ataxinopatie Ataxín 1 6p22.3 Ataxín 2 12q24.12 Ataxín 3 14q32.12 Ataxín 7 3p14.1 Ataxín 8 AD 13q21	Spinocerebellar ataxia type 1 (SCA1) AD 6p22. 3 Spinocerebellar ataxia type 2 (SCA2) AD 12q24. 12 Congenital predisposition to ALS (amyotrophic lateral sclerosis). sclerosis, AD) Disposition for Parkinson's disease (AD) Machad-Joseph disease AD 14Q32. 1 Spinocerebellar ataxia type 7 AD 3p14. 1 Spinocerebellar ataxia type 8 AD 13q21 Spinocerebellar ataxia type 10 AD 22q13. 31

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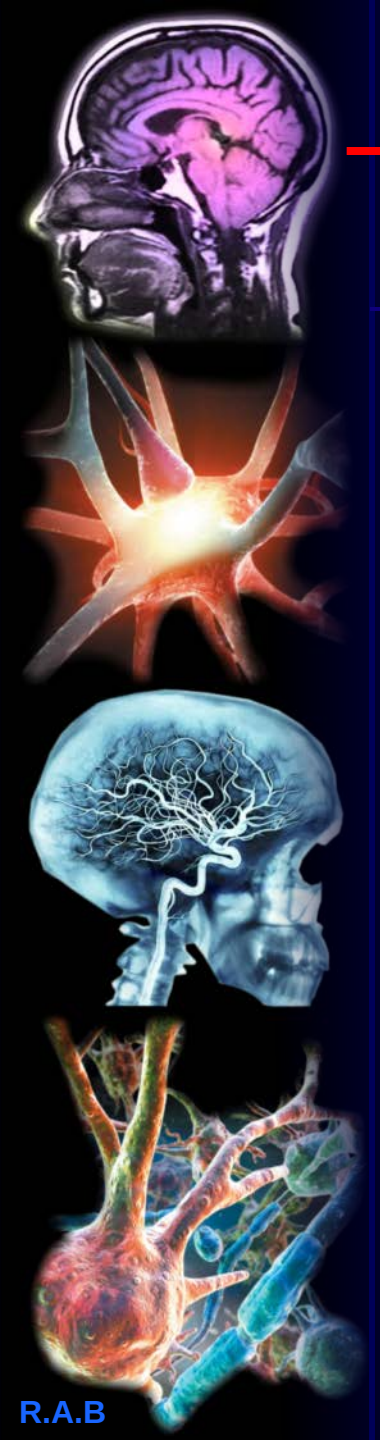

Accumulation disorders

Principal Protein	Disease
Superoxide dismutase	Familial amyotrophic lateral sclerosis
Huntingtin	Huntington's disease
Atrophin 1 (ATB1)	Dentatorubral-pallidoluysian atrophy (DRPLA),
Laforin	Lafora's progressive myoclonus epilepsy
Glial fibrillary acidic protein (GFAP)	Adult Alexander disease Alzheimer's disease (AD)
Proteolipid protein	Pelizaeus-Merzbacher disease
Polyglucosan	Polyglucosan body disease
Neuroserpin	Familial encephalopathy with neuroserpin inclusion bodies (FENIB
Frataxin	Friedreich's Ataxia (FRDA)

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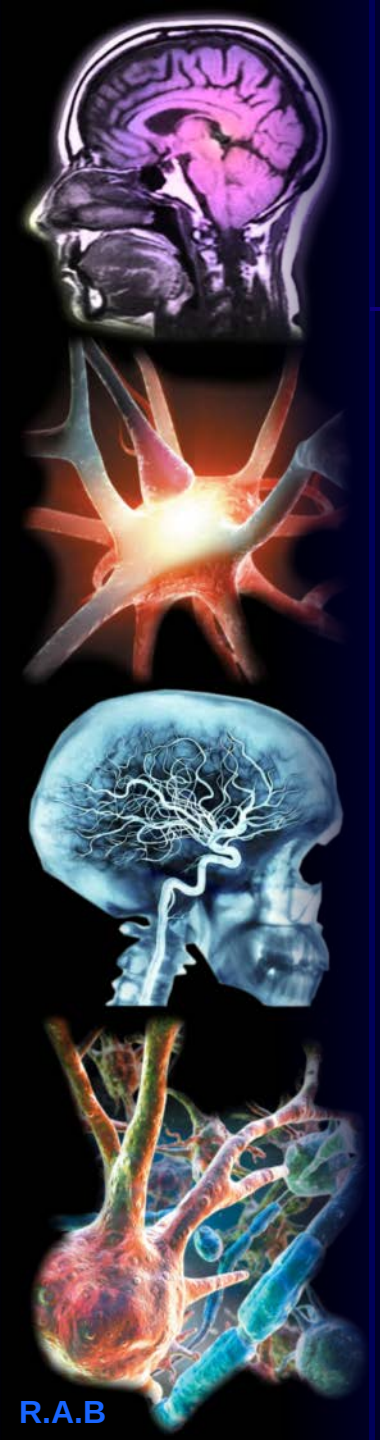

Plausible mechanims

Endoplasmic reticulum stress

Incorrectly conformed proteins studied in more detail in connection with prionoses + taopathioes

- Primary protein disorder (mutation) allowing the formation of bonds (pairs) between neighboring proteins of the same type
- The protein is all right, the transport system with the maintenance of conformation is defective – chaperones, chaperonins
- Why do proteins form insoluble clusters, why can not they be degraded

Trinucleotide repeate mutations

- 14 known, first described in Fragile X chromosome
  - Why do they exist ? A small number is normal and necessary
  - Diseases are all Neurological + to a greater or lesser extent mental degradation or dementia is present

Role of ncRNA

- miR-7/miR-153 in regulation of α-synuklein (SNCA)

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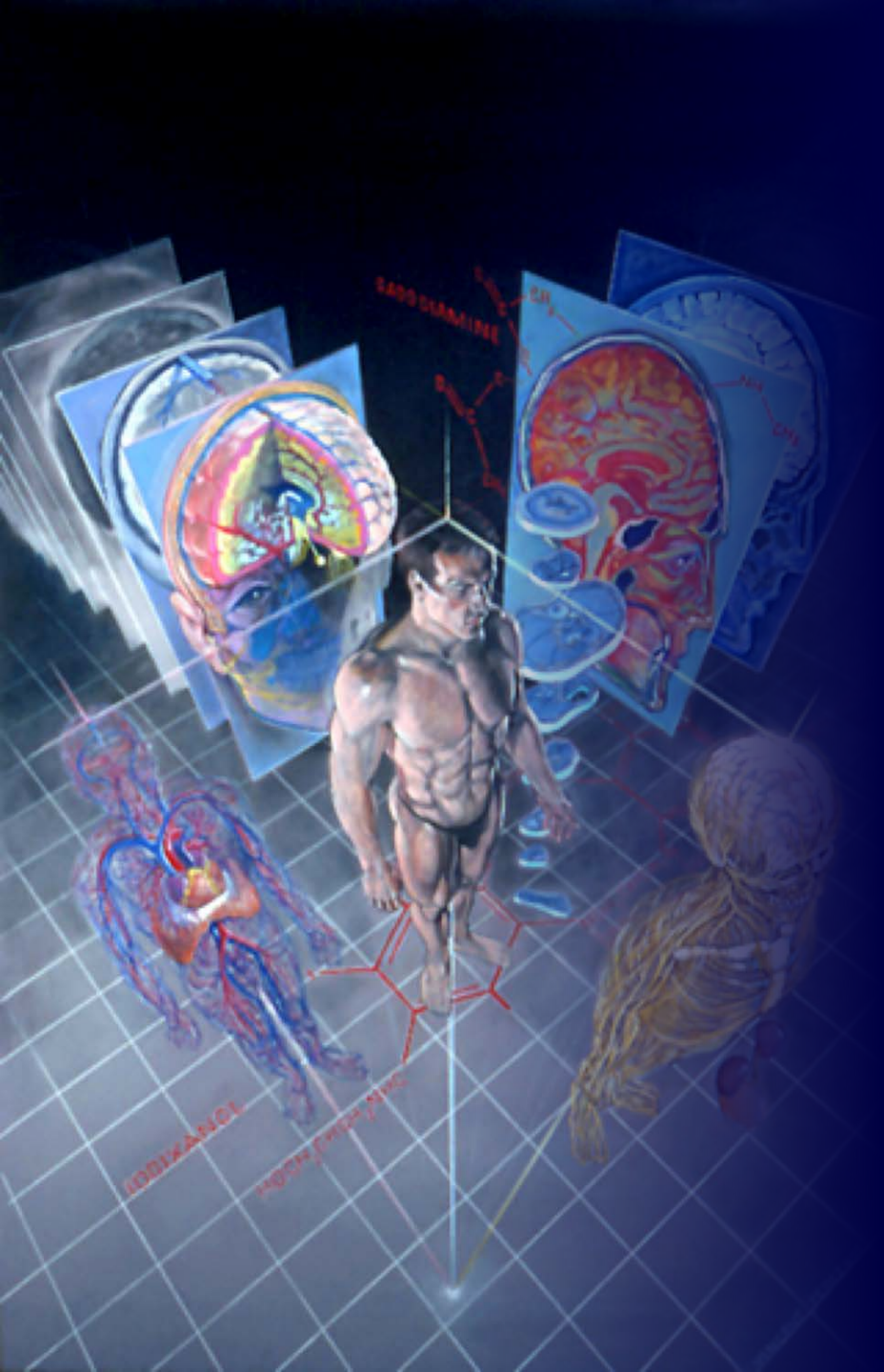
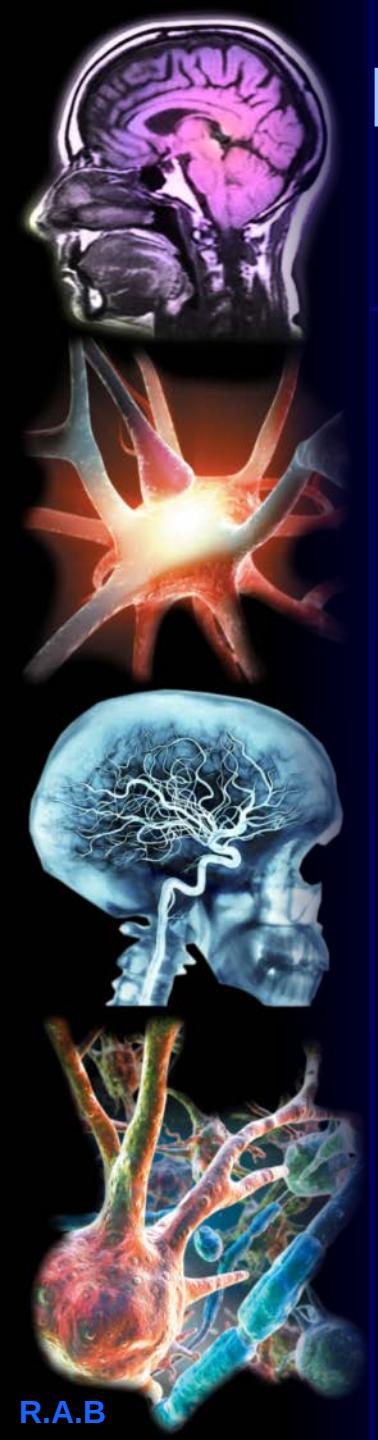


EXAMPLES OF DISEASES



Neurodegenerative disorders 1

1. Degenerative diseases with impaired cortex
   - M. Alzheimer (demencia presenilis, sy. Heidenheim)
   - M. Pick (demencia presenilis, atrophia Pick)
   - M. Mast (degeneratio corticis fronto-parietalis)
   - M. Mills (dgeneratio corticis frontosagitalis, hemiplegia ascendens)
   - Sy. Nevin (atrophia cerebralis spongioformis paesenilis)
   - M. Holmes (degeneratio corticis parieto-occipitalis)
2. Degenerative diseases with a predominant lesion of the cortex and subcortical structures (prosencephalodiencephalic)
   - M. Huntigton (chorea hereditaria progressiva)
   - M. Heidenheim (subakútna spongioformná encefalopatia)
   - M. Vogt (chorea congenita)
   - M. Creutzfeld-Jacob (degenatio cortico-striato-spinalis)
   - M. Biswanger (progresívna subkortikálna encefalopatia)
   - M. Marchiafava-Bignami (degeneratio corporis callosi)
   - M. Menkes (atrophia pallido-cerebellaris)
   - M. Minor (degeneratio corporis striati)
   - M. Hallerworden-Spatz (degeneratio globi pallidi progressiva)
   - M. kuru (sy. usmievajúcej sa smrti)
   - Sy. Alpers (deg. cortico-striato-celebellaris)
   - Sy. Lhermitte-McAlpin (degeneratio pallido-cerebello-pyramidalis)
   - M. Hammond (athetosis idiopathica, deg. cortico-striata)
   - M. Homen (degeneratio nuclei lentiformis)

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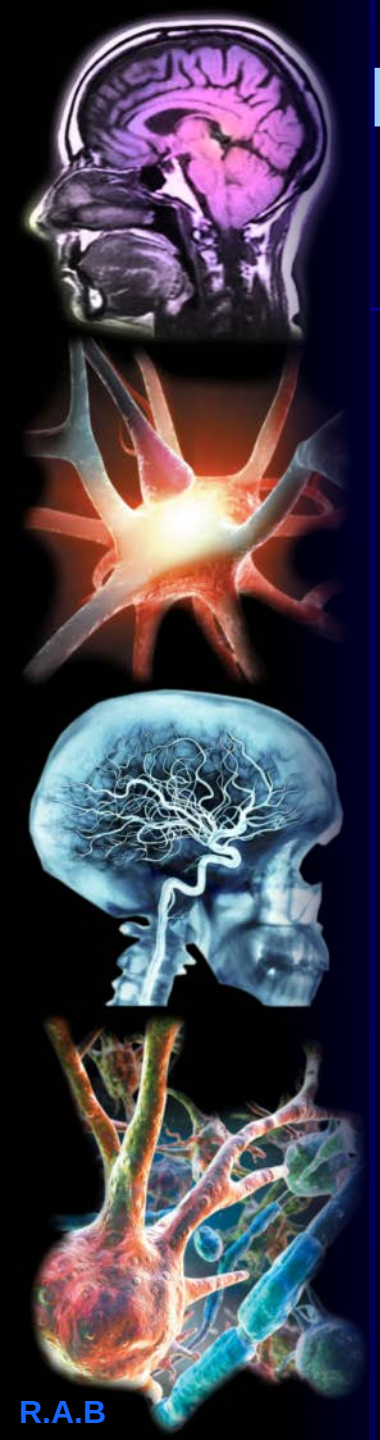

Neurodegenerative disorders 2

A) with extrapyramidal symptomatology

M. Parkinson (paralysis agitans)
Sy. Hunt (paralysis agitans juvenilis (degeratio globus pallidum)
Sy. Ziehen-Oppenheim (dystonia musculorum deformans)
M. Wilson (degeneratio hepatolenticularis)
Familiárna benígna chorea

B) with pyramidal or vegetative symptomatology

Sy. Ferguson-Critchey (hered. spast. paraplegia,extrapyramid. sy.)
Sy. Seligmüller (hereditárna dystonic paraplegia)
Sy. Barnard-Scholz (Kjellinov sy.) (hered. spast. paraplegia)
Sy. Sjögren-Larsson (kongenitálna ichtyosis with spasticity and oligophrenia)
Sy. Shy-Drager (primary orthostatic hypotension)
M.Poskanzer (sy. pf hemiatrophy and hemihypertrophy)

c) with progressive extensive ophthalmoplegia, PEO)

- Sy. Wood-Schaumberg (nigro-spino-dentátovovu degeneráciou)
-- Sy. Sanger -Brown (with spinocerebelárnou atrophy)
- Sy. Bassen-Kornzweig (abetalipoproteinemia)
- Sy. Refsum
- M. Refsum -Thiébaut (heredopathia atactica polynuriformis)
- Sy. Laurence-Moon-Biedl (degeneratio diencephaloretinalis)

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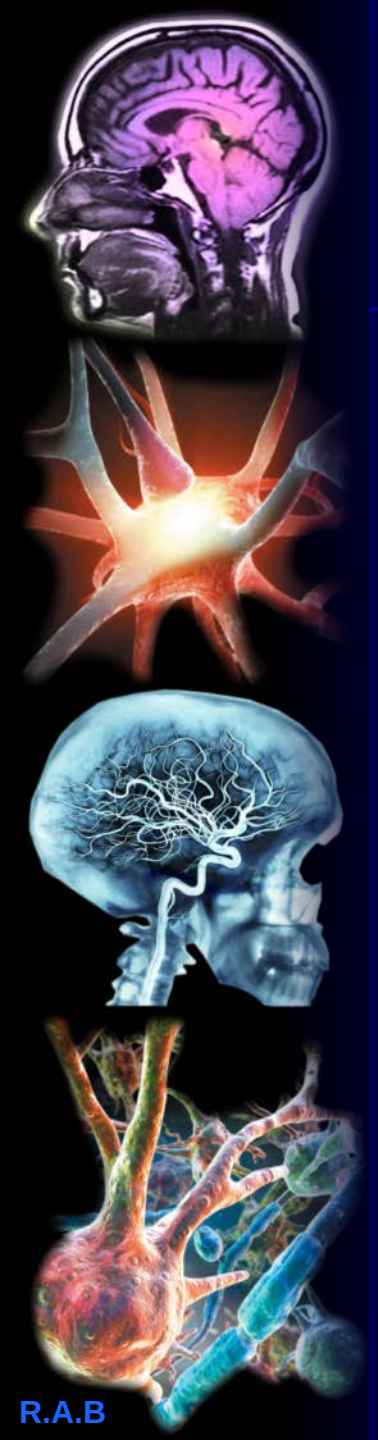


Neurodegenerative disorders 3

Spino-cerebellar degeneration

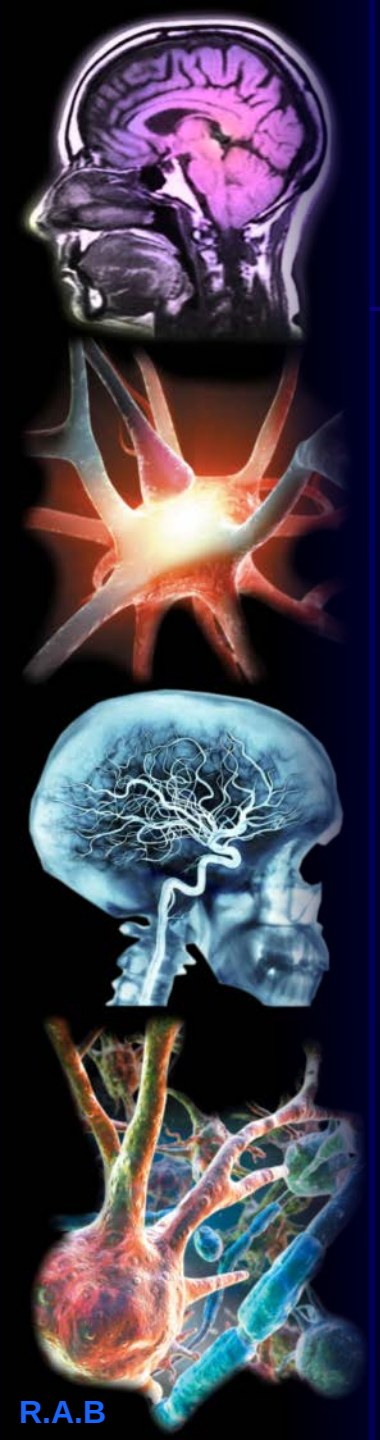
Familial spino-cerebellar degeneration in kids)

- ataxia telangiectasia (M. Lous-Barr-Henner)
- cerebellar ataxia with optic atrophy
- cerebellar ataxia with retinal degeneration
- congenital granulocellular hypoplasia
- cerebellum hyperplasia with congenital cataract (sy. Marrinesco-Sjögren)

Familial spino-cerebellar degeneration in adults

- hereditary spinocerebellar ataxia (M. Friedreich)
- hereditary areflectoric dystaxia (sy. Roussy-Lévy)
- hereditary spastic ataxia (sy. Pierre-Marie)
- hereditary spastic paraplegia
- olivo-ponto-cerebellar degeneration (M. Menzel)
- cortico-cerebellar degeneration (M. Holmes)
- dyssynergia cerebellaris myoclonica (M. Ramsay-Hunt)
- cerebrocerebellar degeneration
- acute intermittent cerebellar ataxia
- vestibulocerebellar ataxia
- Sy. van Bogaert (deg. spino-cerebelo-olive)
- Sy. Mr Déjerine-Thomas (deg. olivo-ponto-cerebellaris)
- Sy. Guillain (deg. olivo-ponto-cerebello-spinalis)
- Sy. Sanger-Brown (deg. dpino-celebellaris)

R.A.B



Neurodegenerative disorders 2

Progressive bulbar paralysis (PBP)

- classic type (Duchenne paralysis, sy. Duchenne)
- infantile type (M. Fazio-Londe)
- PBP with dementia complex and extrapyr. sy. (sy. Guam)
- PBP with deafness and optic atrophy (M. Bown)
- PBP with corneal dystrophy, spastic paralysis

Amyotrofická laterálna skleróza (ALS)

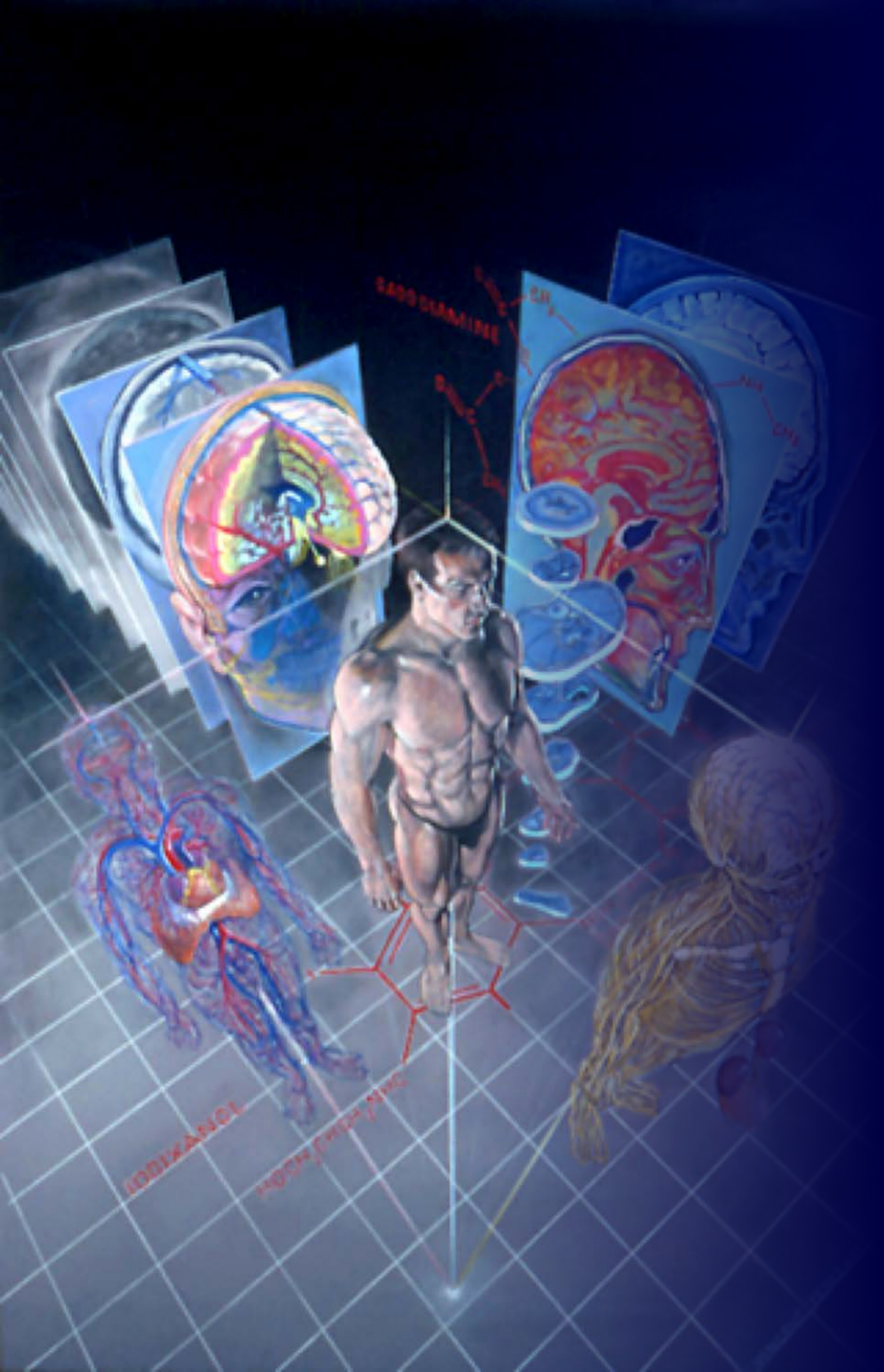
- ALS with dementia (and extrapyramidal sy.) (type Guam)
- ALS with posterior cord involvement

Progressive spinal muscular atrophy (PSMA)

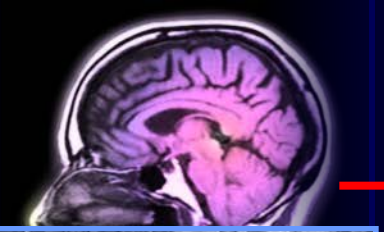
- atrophy spinalis progressiva infantilis (M. Werding-Hoffman)
- juvenile scapulohumeral atrophy (M. Kugelberg-Welander
- adult scapulohumeral atrophy (sy. Vulpian-Bernhard)
- distal muscle atrophy (M. Aran-Duchenne)

Spinal atrophy-sensory (ganglia)

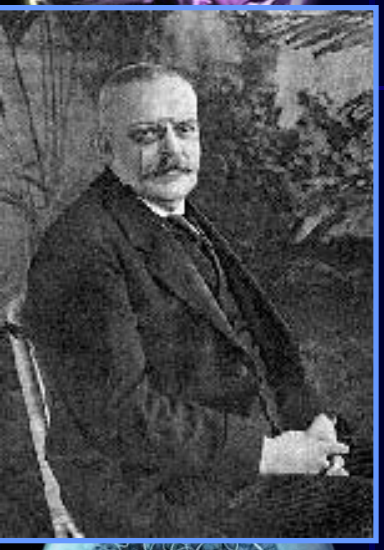
- Sy. Biemondov (ataxia of posterior cords)
- Sy.Peron-Droquet-Coulon (hereditárna sensoric neuropathy)
- Sy.Morvan (neuropatia senzoria radiculata hereditaria)
- M. Morvan (neuropatia sensoria progressiva infantum)



Alzheimer disease



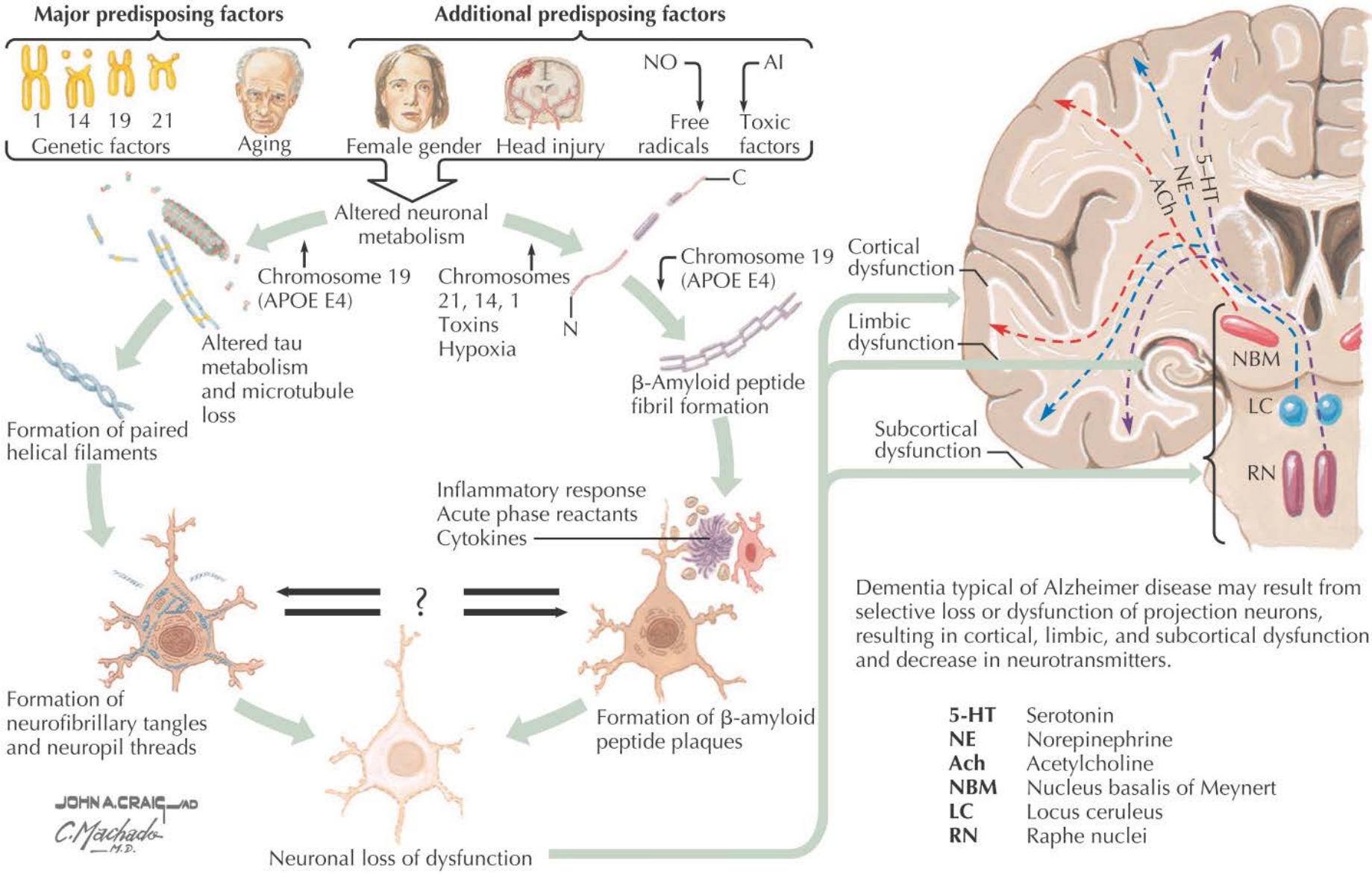
Alzheimer disease



- Definition: Progressive degenerative brain disease characterized by decline in cognitive functions sufficient to cause impairment in social and occupational performance
  - Increasing memory loss (declarative -> implicit)
  - Cognitive decline (reasoning)
  - Changes in behavior, personality, judgment
- Occ: most common cause of dementia among people > 65y; Typical late onset - 65+ yrs (< 10% of cases earlier, mostly caused by a specific gene mutation) approximately 50% aged 85 years Incidence: 5 millions in US; 1 millions in Germany; the risk doubles every 5 years, beginning at 65 years of age. increases exponentially with age; AD affects future AD prevalence show a 4x increase 2050; health care costs, morbidity, mortality, Of the 5 million cases, 3 mill are diagnosed and 1 mil receive treatment.
- Either sex affected - women 2-3 x often; when diagnosed they are in more progressive state (? longer life span) Women live longer with symptoms until diagnosis (they live alone lacking social and instrumental support triggering diagnosis)
- Prognosis: terminal illness with survival ~ 8 yrs post-diagnosis (women live longer) AD can't be diagnosed for certain until death
- Currently linked to several genes (transgenic mouse models)

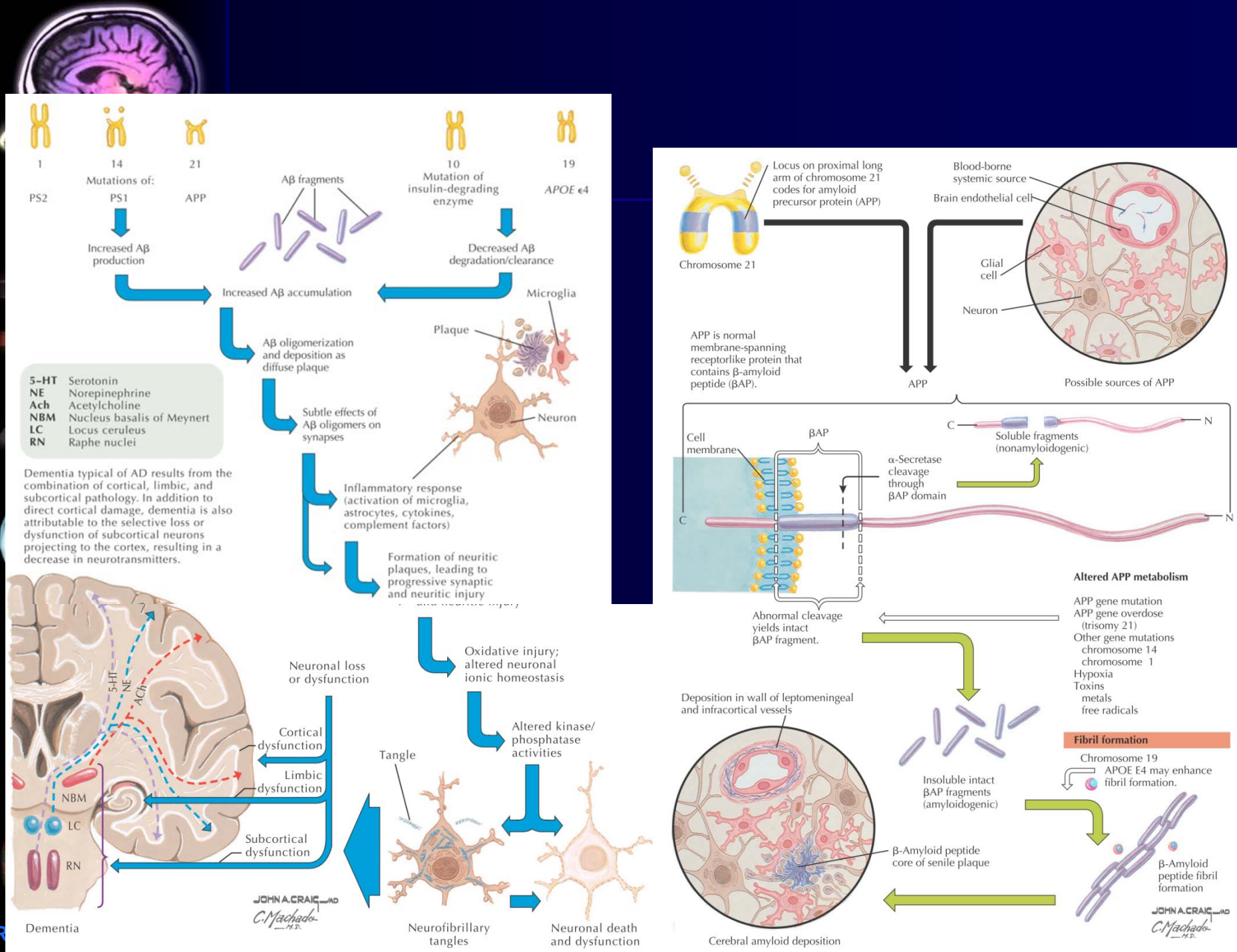
Auguste D, 51 years, 1906

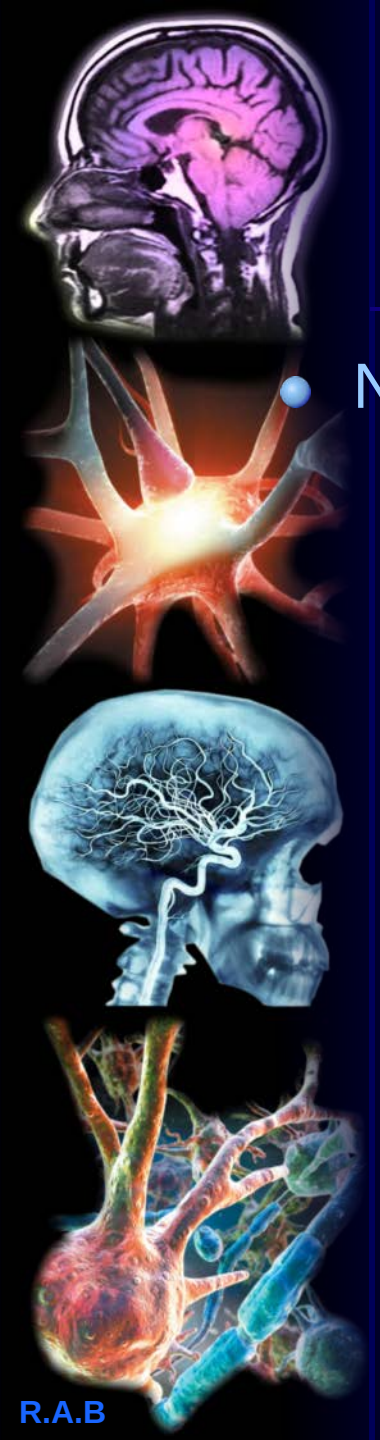
Combined pathology



Dementia typical of Alzheimer disease may result from selective loss or dysfunction of projection neurons, resulting in cortical, limbic, and subcortical dysfunction and decrease in neurotransmitters.

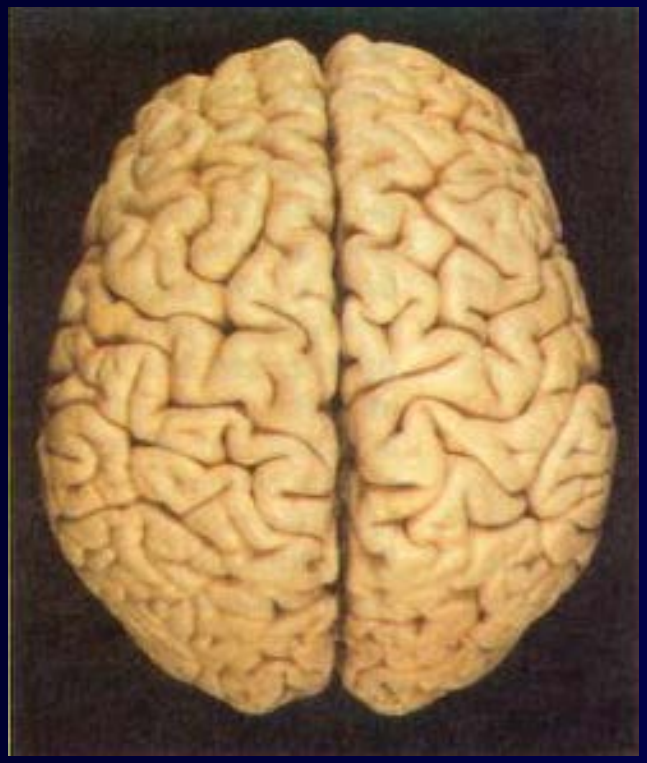
5-HT	Serotonin
NE	Norepinephrine
Ach	Acetylcholine
NBM	Nucleus basalis of Meynert
LC	Locus ceruleus
RN	Raphe nuclei


1
14
21
10
19
Mutations of:
PS2
PS1
APP
Mutation of insulin-degrading enzyme
APOE ε4
Aβ fragments
Increased Aβ production
Decreased Aβ degradation/clearance
Increased Aβ accumulation
Microglia
Plaque
Neuron
Aβ oligomerization and deposition as diffuse plaque
Subtle effects of Aβ oligomers on synapses
Inflammatory response (activation of microglia, astrocytes, cytokines, complement factors)
Formation of neuritic plaques, leading to progressive synaptic and neuritic injury
Oxidative injury; altered neuronal ionic homeostasis
Altered kinase/ phosphatase activities
Tangle
Neurofibrillary tangles
Neuronal death and dysfunction
Neuronal loss or dysfunction
Cortical dysfunction
Limbic dysfunction
Subcortical dysfunction
Dementia
5-HT Serotonin
NE Norepinephrine
Ach Acetylcholine
NBM Nucleus basalis of Meynert
LC Locus ceruleus
RN Raphe nuclei
Dementia typical of AD results from the combination of cortical, limbic, and subcortical pathology. In addition to direct cortical damage, dementia is also attributable to the selective loss or dysfunction of subcortical neurons projecting to the cortex, resulting in a decrease in neurotransmitters.
JOHN A. CRAIG, M.D.
C. Machado, M.D.
Chromosome 21
Locus on proximal long arm of chromosome 21 codes for amyloid precursor protein (APP)
Blood-borne systemic source
Brain endothelial cell
Glial cell
Neuron
Possible sources of APP
APP is normal membrane-spanning receptorlike protein that contains β-amyloid peptide (βAP).
APP
Cell membrane
βAP
α-Secretase cleavage through βAP domain
Soluble fragments (nonamyloidogenic)
C
N
Abnormal cleavage yields intact βAP fragment.
Altered APP metabolism
APP gene mutation
APP gene overdose (trisomy 21)
Other gene mutations
chromosome 14
chromosome 1
Hypoxia
Toxins
metals
free radicals
Deposition in wall of leptomeningeal and infracortical vessels
Insoluble intact βAP fragments (amyloidogenic)
Fibril formation
Chromosome 19
APOE E4 may enhance fibril formation.
β-Amyloid peptide core of senile plaque
β-Amyloid peptide fibril formation
Cerebral amyloid deposition
JOHN A. CRAIG, M.D.
C. Machado, M.D.

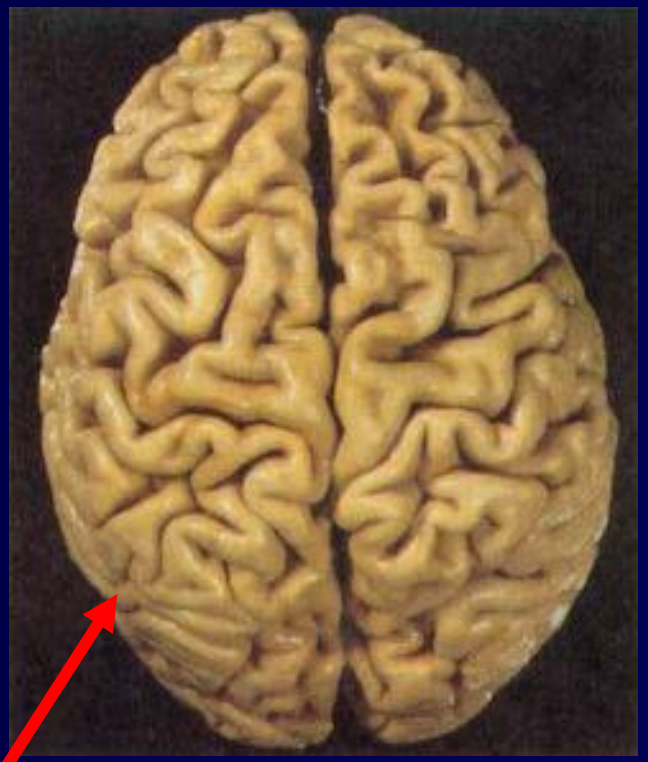


Macroscopic view

- Normal brain



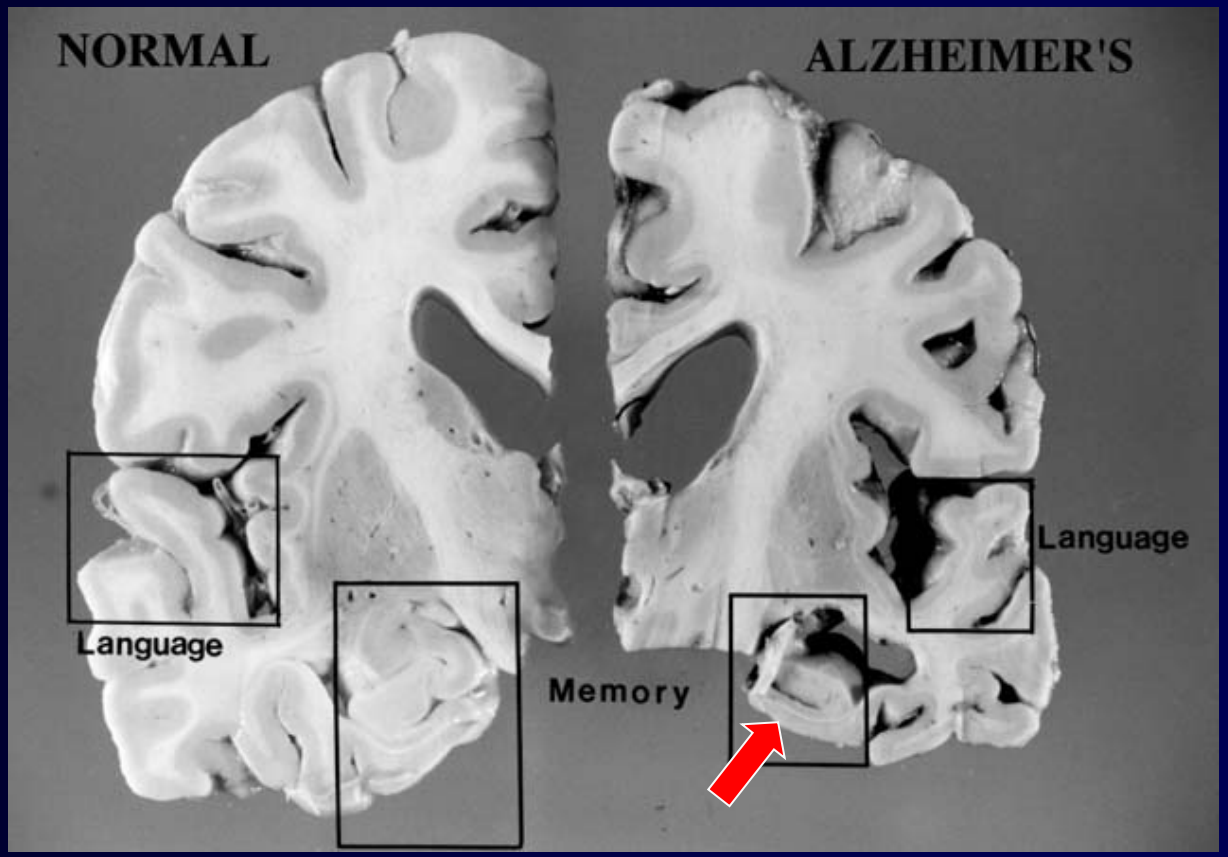
- Brain in AD patient



Shrinking of the brain gyruses, Decrease of brain weight, Enlargement of ventricles, narrowing of gray matter

R.A.B

Macromorphological view

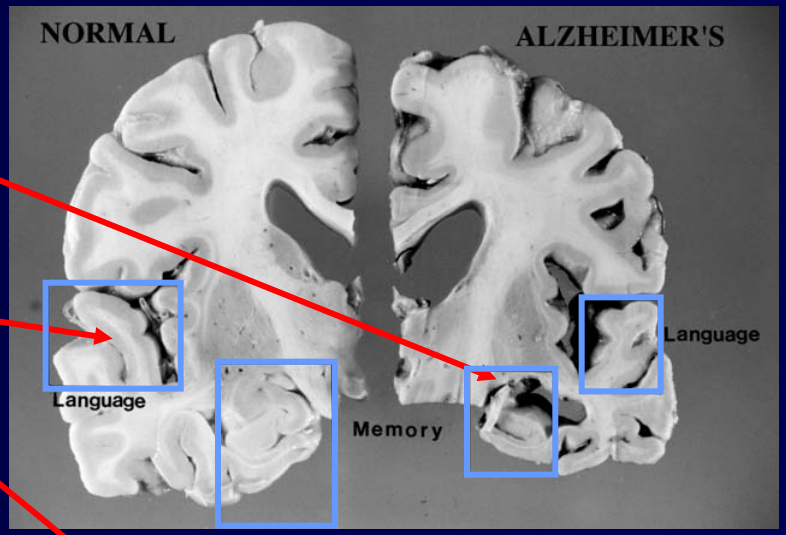


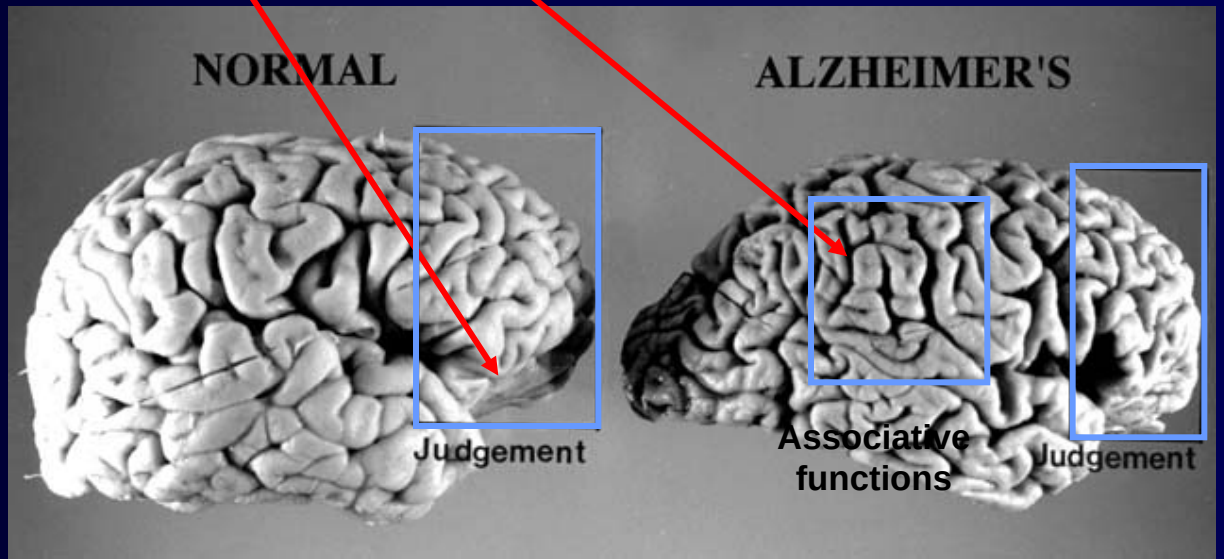
- Pathologic substrate for dementia may differ for men and women
- Women likely have greater losses of hippocampal pyramidal neurons

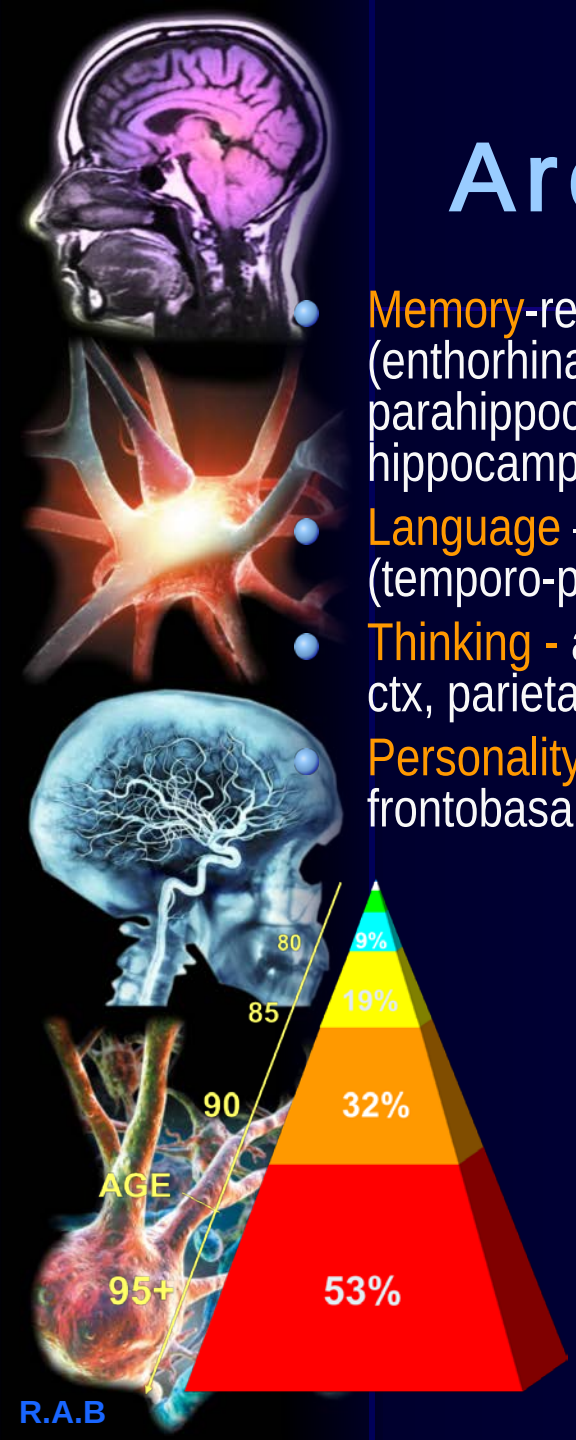
R.A.B

Areas with accumulations

- Memory-related areas (enthorhinal/perienthorinal parahippocampal ctx, hippocampus)
- Language – related areas (temporo-parietal ctx)
- Thinking - associative func. (frontal ctx, parietal ctx)
- Personality (frontopolar, frontobasal ctx)





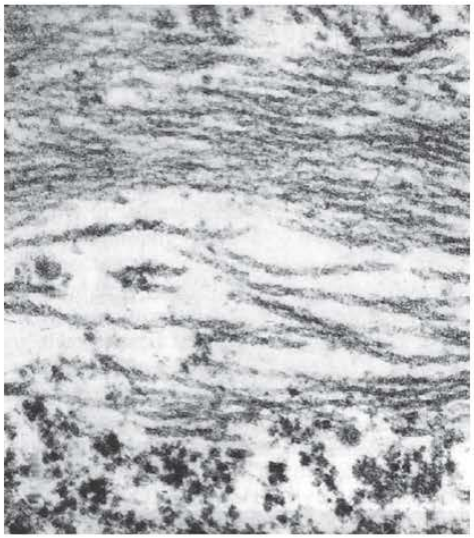


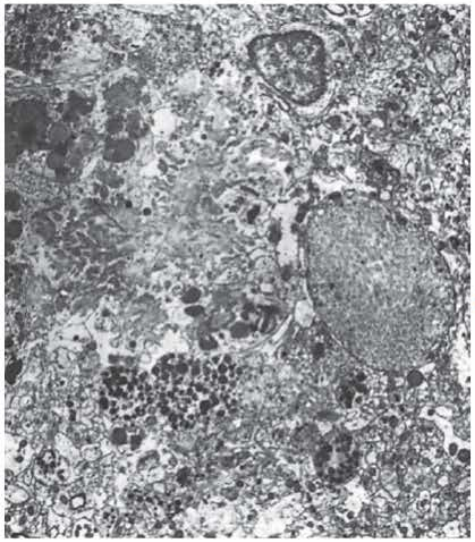
R.A.B

Microscopic pathology

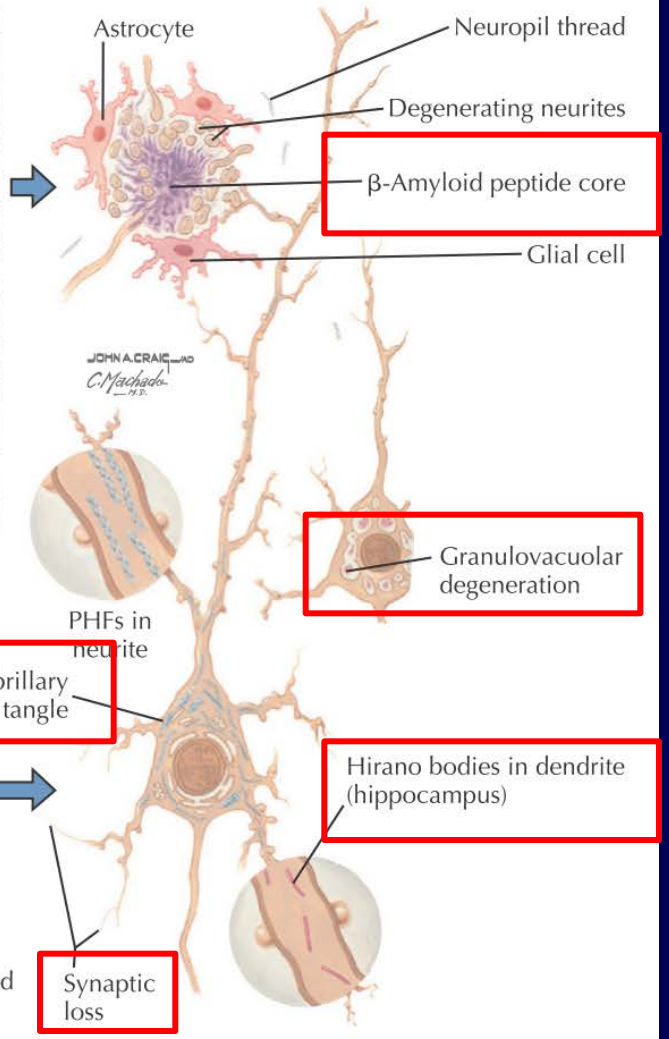
Senile plaque composed of dystrophic neuritic process, β-amyloid peptide, microglial cells, and astrocytes and their processes

- Senile plaques
- Neurofibrillary tangles
- Hirano bodies
- Granulovascular degeneration
- Synaptic loss



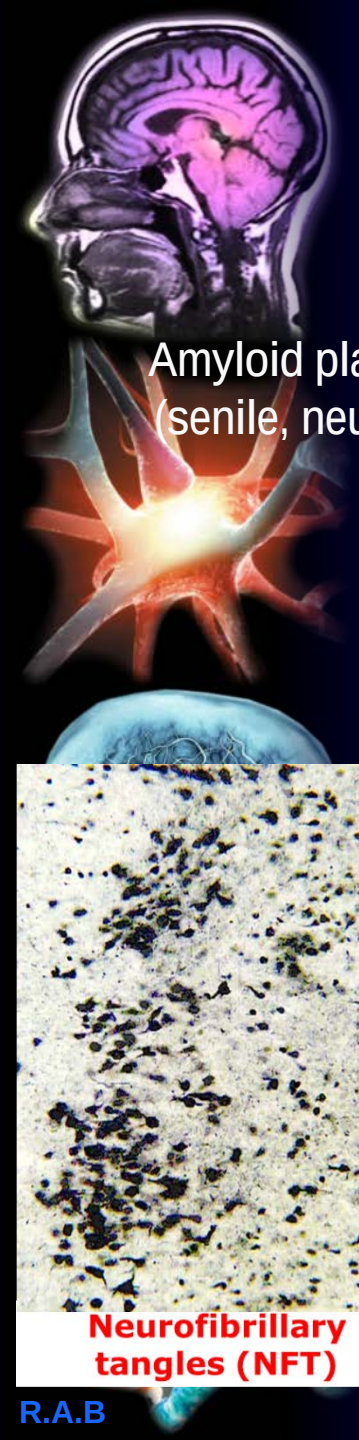


Neurofibrillary tangle composed of paired helical filaments (PHFs) of hyperphosphorylated tau protein

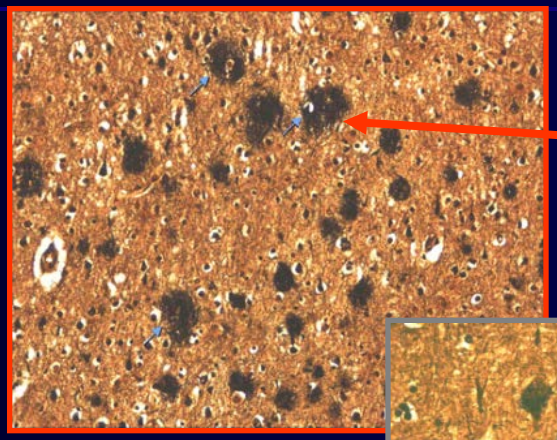


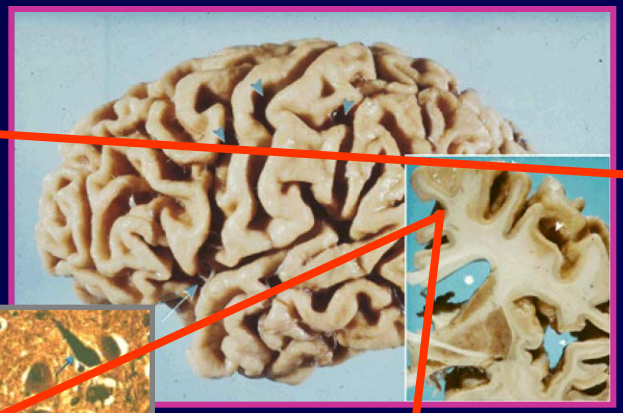
R.A.B

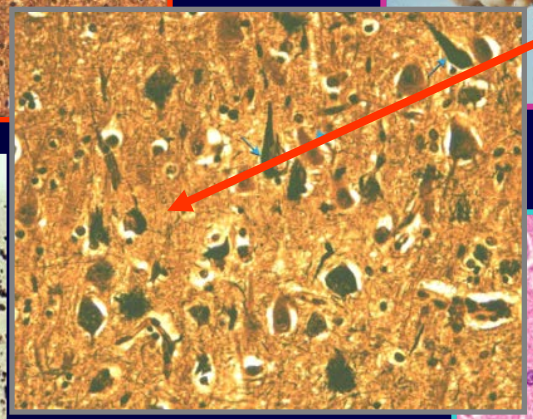
Microscopic alterations in AD



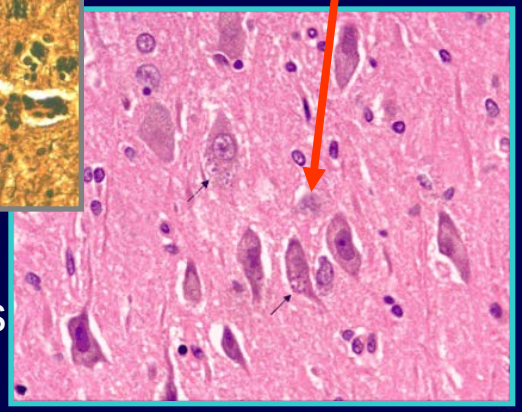
Amyloid plaques
(senile, neuritic))





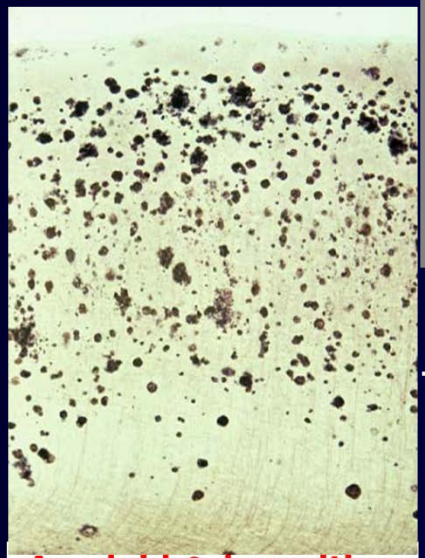


Neurofibrillary tangles
-filamentous inclusions



Granulovacuolar
Degeneration

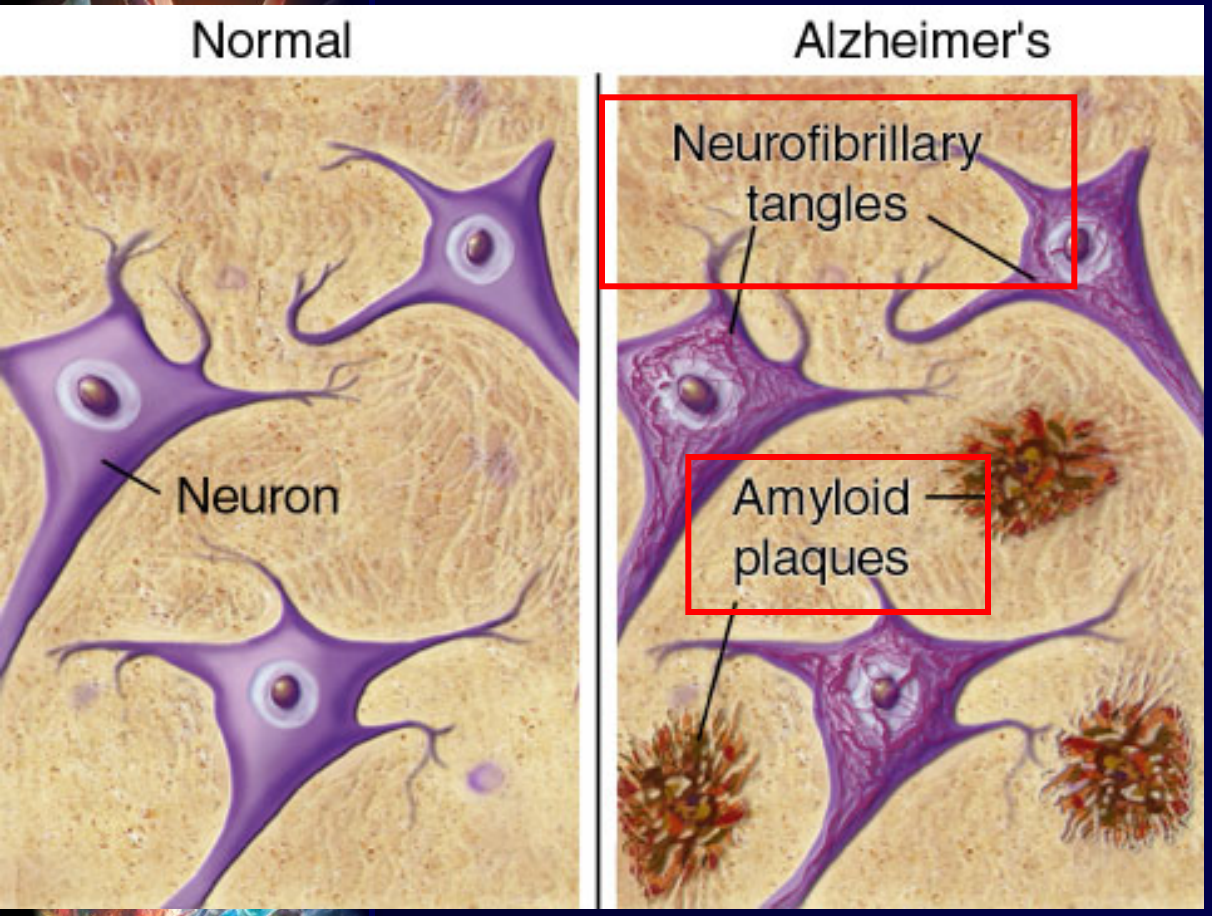
Neurofibrillary tangles (NFT)



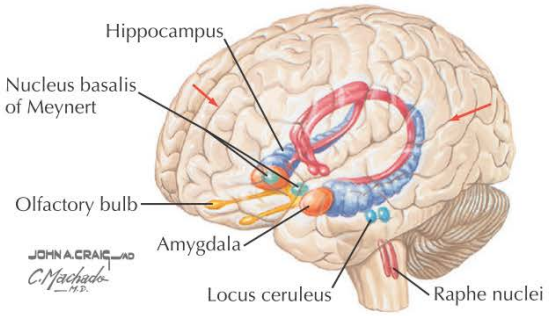
Amyloid-β deposition (Aβ)

R.A.B

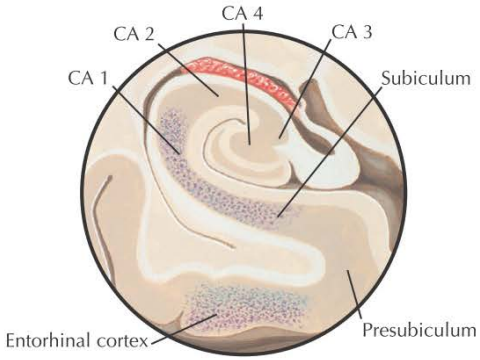
Micromorphologic view



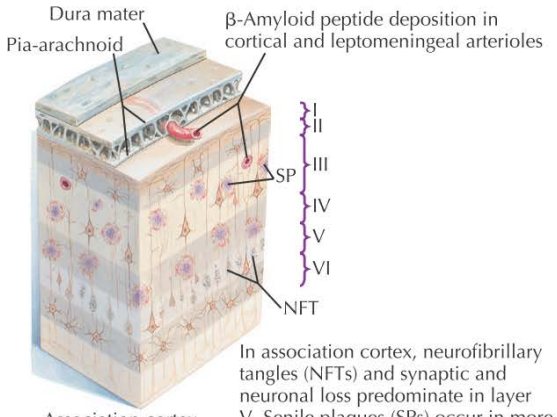
In neocortex, primary involvement of association areas (especially temporoparietal and frontal) with relative sparing of primary sensory cortices (except olfactory) and motor cortices



Pathologic involvement of limbic system and subcortical nuclei projecting to cortex



In hippocampus, neurofibrillary tangles, neuronal loss, and senile plaques primarily located in layer CA1, subiculum, and entorhinal cortex



In association cortex, neurofibrillary tangles (NFTs) and synaptic and neuronal loss predominate in layer V. Senile plaques (SPs) occur in more superficial layers.

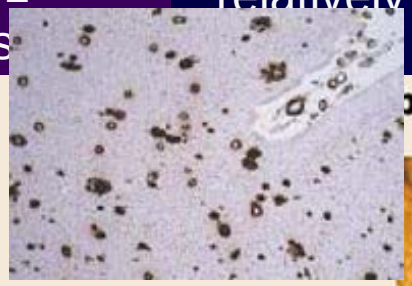
Figure 18-2 Distribution of Pathology in Alzheimer Disease.

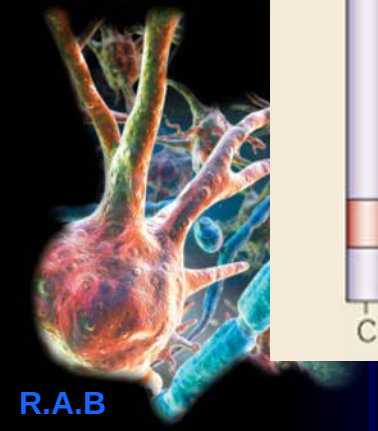
R.A.B

Beta amyloid plaque

- 1984 β-Amyloide detected in extracell senile plaques
- β-Amyloid short fragment 40–42 AA ← amyloid precursor protein (APP) Ch21 (help regulate synaptic function from excitotoxic activity of glutamate)
- APP is processed at membrane by secretases: α-, β-, and γ, : presenilin 1 (Ch14) and presenilin 2 (Ch1) compris
  active do
  secretas

- starting in the hippocampus and basal forebrain corelate with earliest sign= short-term memory loss., gradually spread to gray matter of the temporal, parietal, frontal, and, eventually, occipital cortex.
- Subcortical nuclei become involved relatively late in the process.





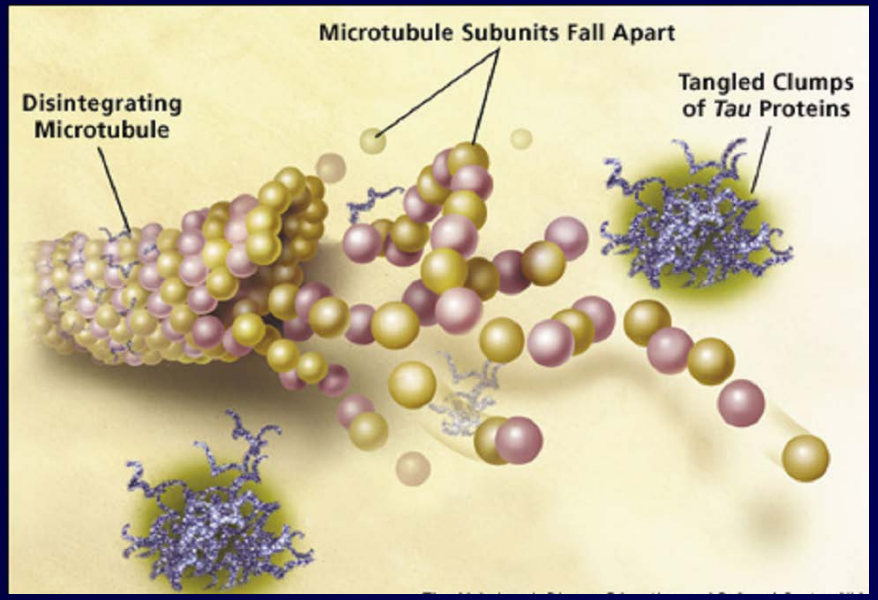
R.A.B

Beta amyloid plaque

- β-Amyloid (fragment of the APP, 40–42 AA) insoluble β-pleated sheet accumulates outside the cell
- (1) Diffuse plaques or immature plaques (silver-staining techniques). are not sufficient to produce demen tia; many nondemented elderly patients have substantial depositions of diffuse plaques throughout the cortex, a condition termed pathologic aging.
- (2) Senile neuritic plaques (matured) non diffuse (+ infmmation): dementia becomes more likely; consist of: β-amyloid, central core of β-amyloid surrounded by synaptic proteins, inflammatory proteins, neuritic threads, activated glial cells other substances
- Senile plaque are distributed diffusely in the cortex and correlate with increasing loss of synapses;

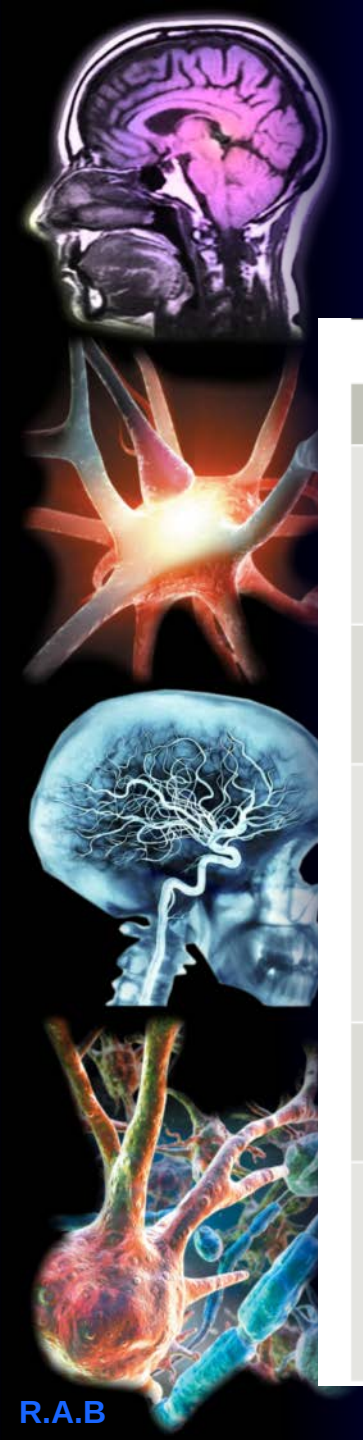
Neurofibrillary Tau protein

- Tau protein intracellular, microtubule-associated protein (role in the maintenance of microtubules)
- hyperphosphorylated tau dissociates from cytoskeleton --> accumulate (paired helical filaments) curls & tangles
- Since neurons can't get nutrients down length of axon…die
- Pin-1 (an enzyme), causes the bending of tau in Alz; block Pin-1 --> block problematic tau?



Neurofibrillary tangle' lesions conform to an anatomic pattern that correlates with the clinical syndrome; the number and distribution of tangles are directly related to the severity and clinical features of the dementia.

R.A.B

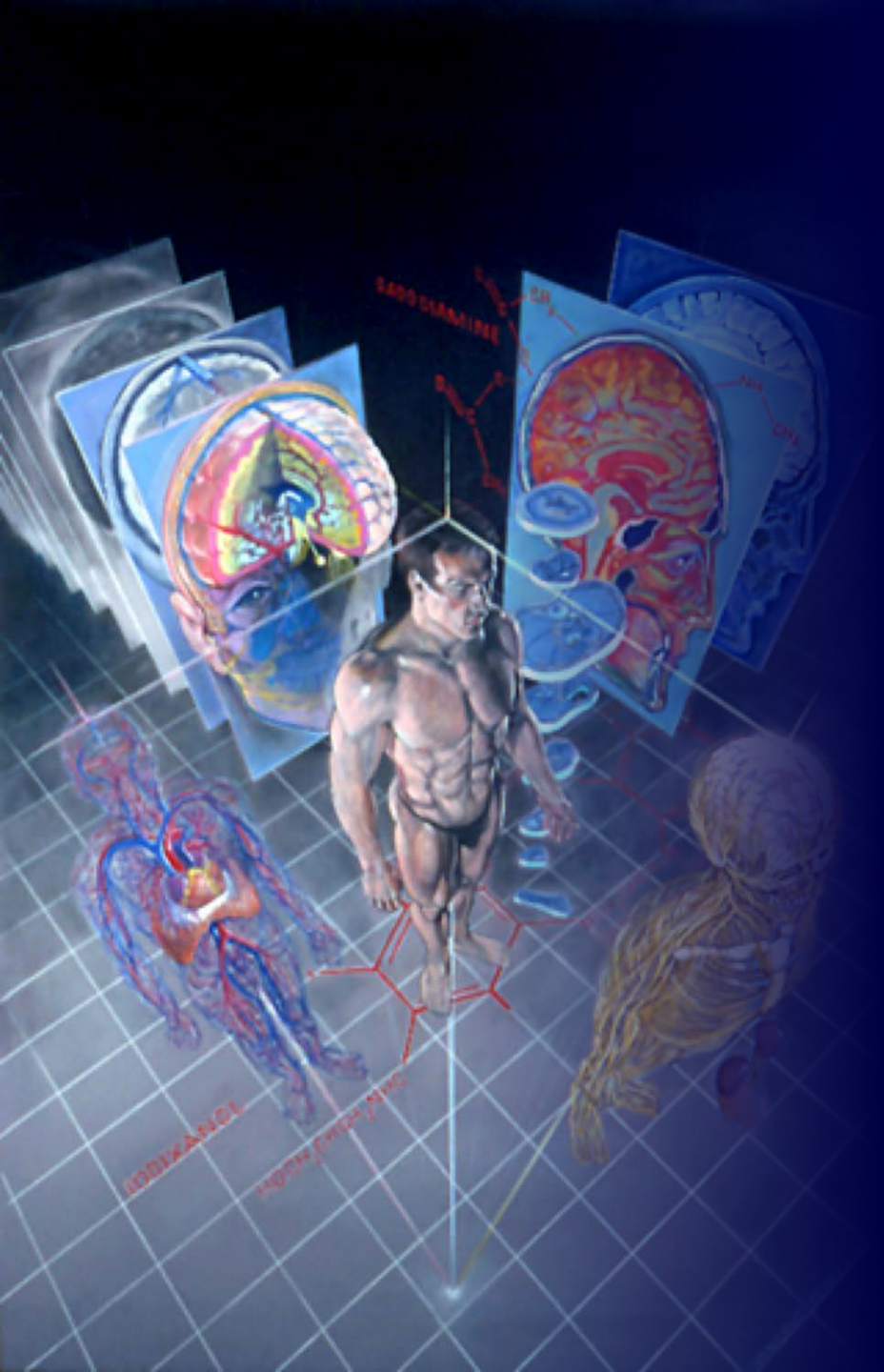


Biomarkers o AD

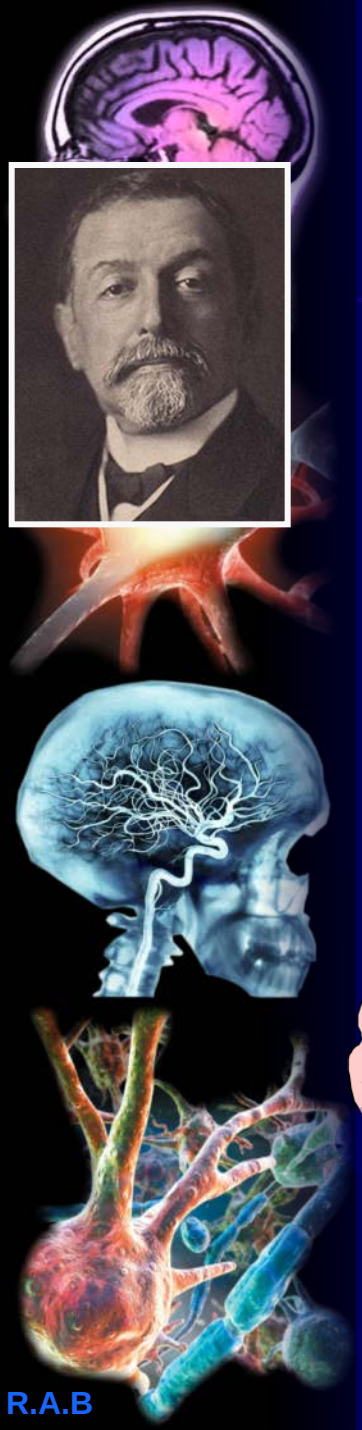
Table 1 | **Alzheimer disease processes, biomarkers and therapeutic agents**

Disease process	Biomarkers	Therapeutic agents
Aβ pathology	• Aβ PET* • CSF $A\beta_{42}$ and $A\beta_{40}$* • Others	• Antibodies and vaccines‡ • BACE inhibitors‡ • γ-Secretase modulators • Anti-aggregants
Tau pathology	• Tau PET* • CSF total tau and phospho-tau* • Others	• Antibodies‡ • Anti-aggregants
Neurodegeneration	• Structural MRI* • FDG PET* • Other MRI and PET measures • CSF neurogranin and SNAP-25 • CSF, plasma and serum NfL • Others	• Protective agents • Neurotrophic agents • Bioenergenic agents
Neuroinflammation	• TSPO PET • CSF soluble TREM2 • Others	• Targeted anti-inflammatory agents
Other processes	• Genetic tests* • Other imaging measurements • Other CSF, blood and eye tests • Cognitive and behavioural tests	• Synaptic transmission modulators • Brain stimulation • Diets and lifestyles • Repurposed drugs and supplements • Other agents

R.A.B

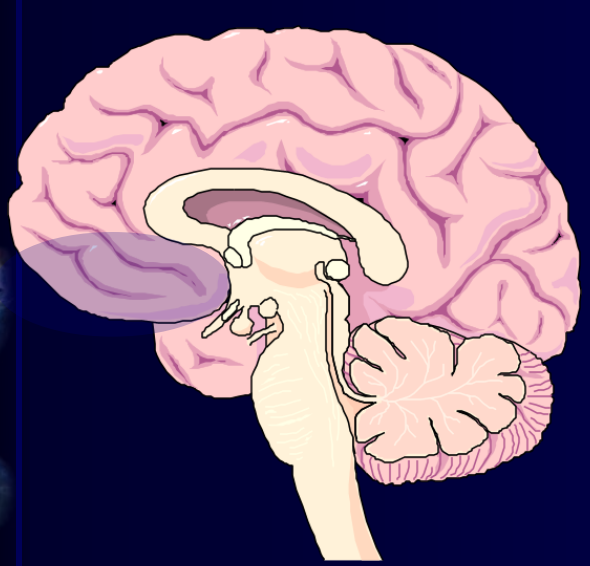


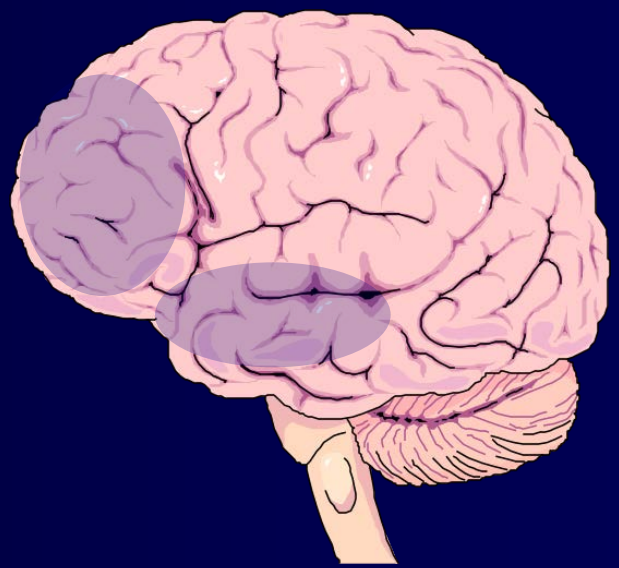
Pick disease



Pick disease

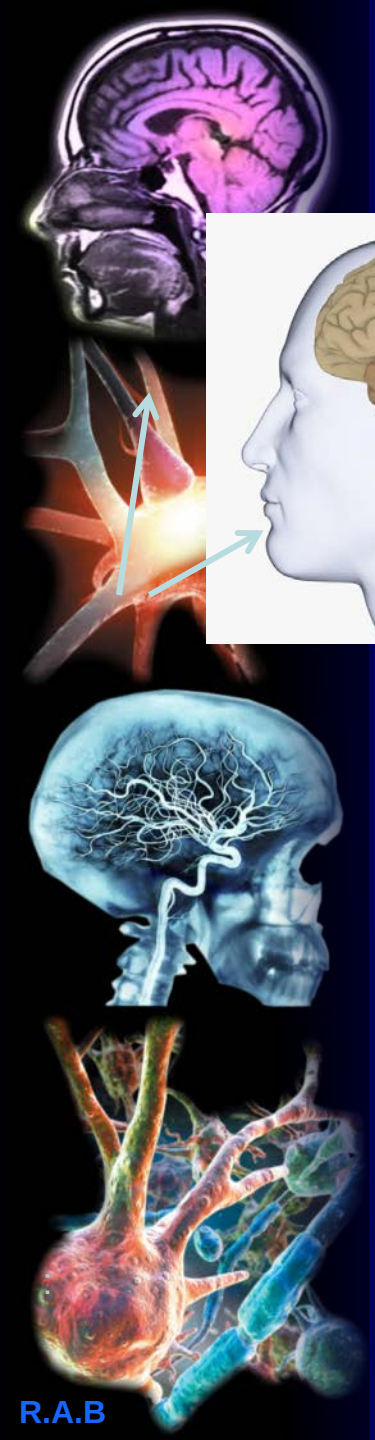
- **Def:** degenerative disease with fropntotemporal degeneration
- **Occ**: rare; 40-60r. age, sporadic and hereditary forms (males)
- **Path**: unbalanced, fronto-orbital cortex, temporal-basal
- - atrophy, gliosis, pick bodies (tau protein)
- **Sy:** in order different from Alzheimer's ch.
- 1. Behavioural disturbances (impulse control, Moria, gluttony)
- 2. Memory impairment, aphasia (palilalia, echolalia)
- 3. Focal manifestations of pyramidal
- 4. Deliberation of newborns. reflexes (grasping, sucking...)

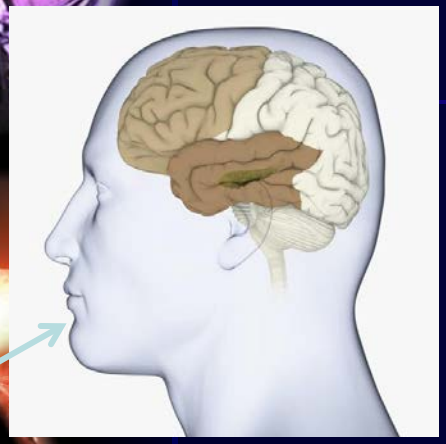


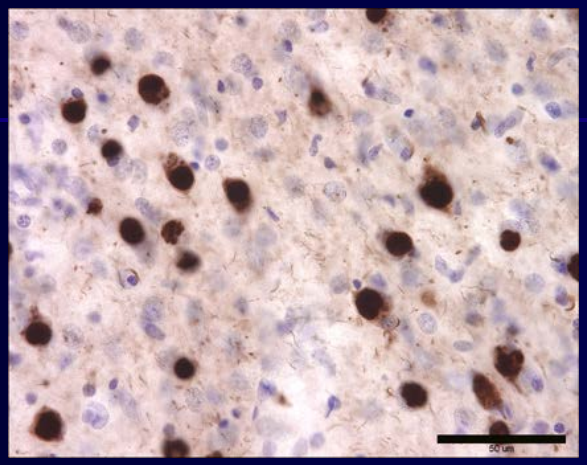


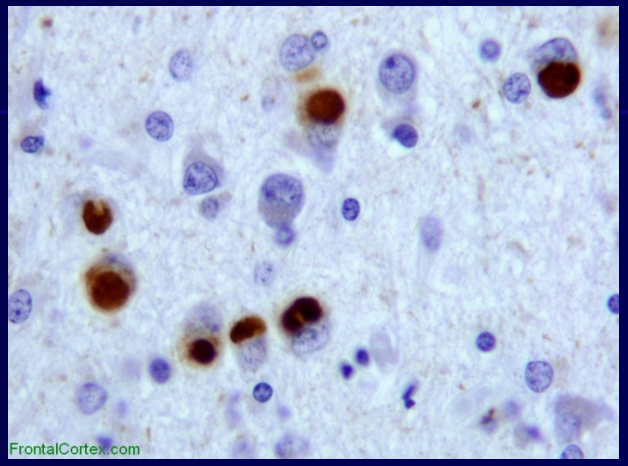
R.A.B

Pick disease

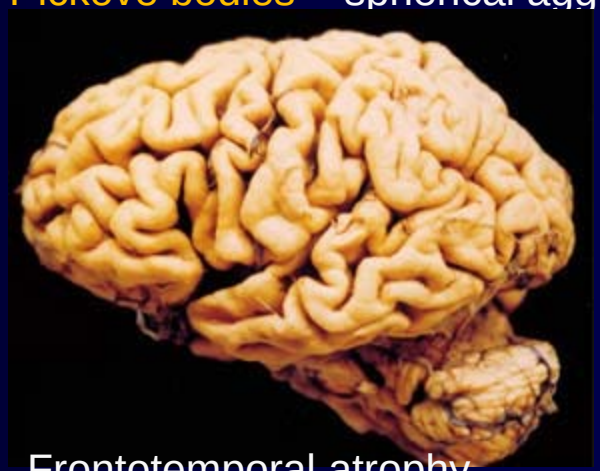




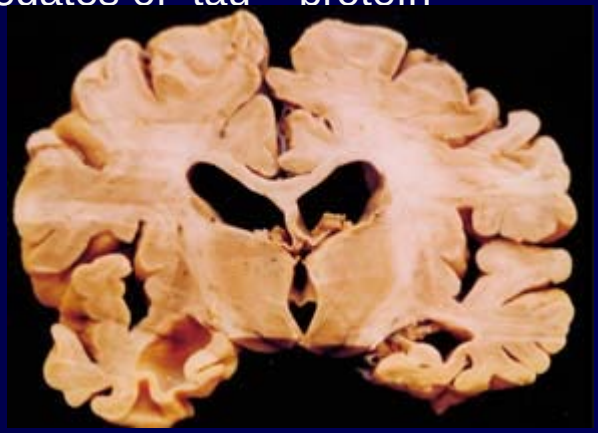




Pickove bodies = spherical aggregates of tau – proteín

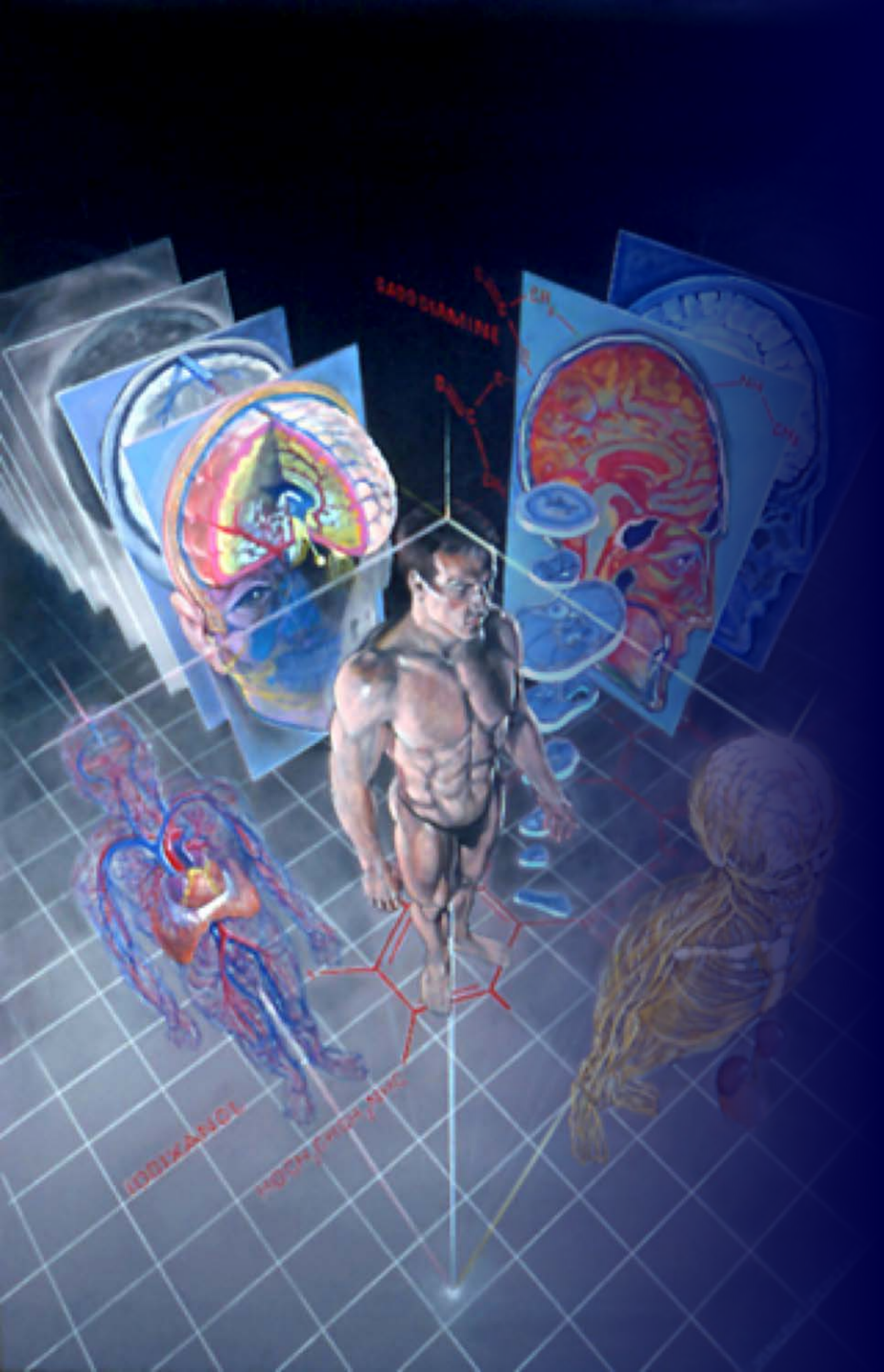


Frontotemporal atrophy in left hemisphere

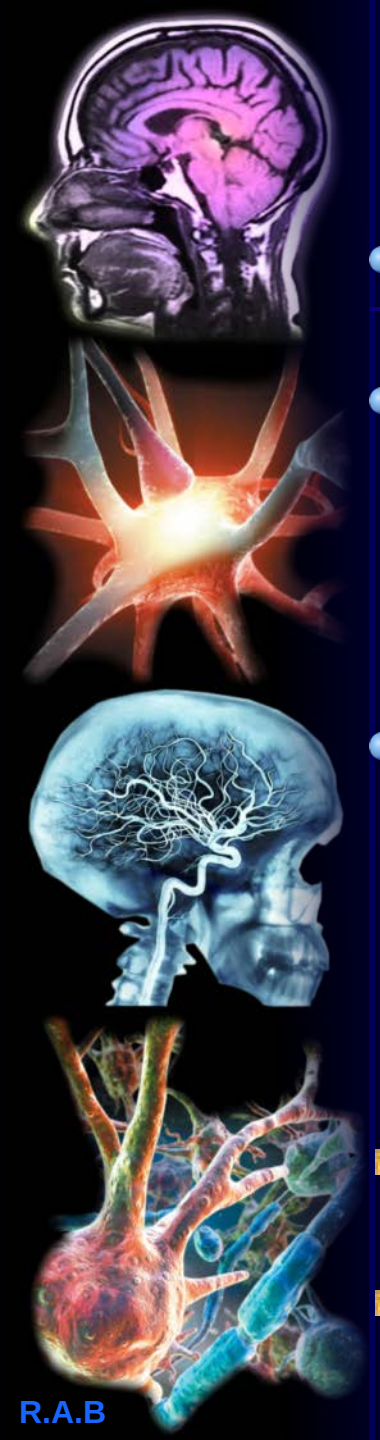


Atrophy of the left temporal hemisphere

R.A.B



Creutzfeld - Jacob disease

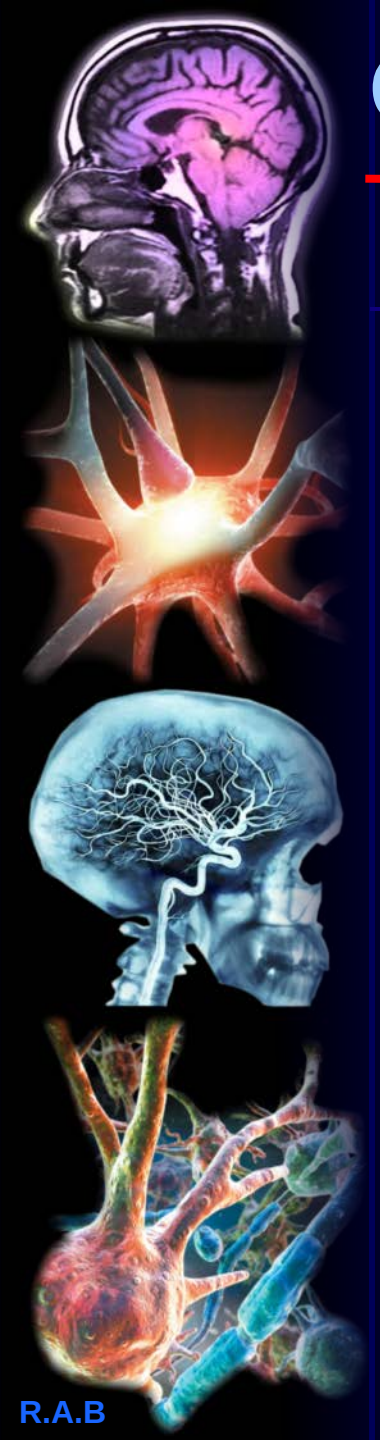


Creutzfeld-Jacob disease

- Def: fatal neurodegenerastic disease from the group of prionoses (the most significant, the most widespread,
- Otjer human prion diseases – Gerstmann-Sträussler-Sheinker syndrome (GSS), fatal familial insomnia (FFI) Great Britain 1986 epidemic of bovine spongiform encephalopathy (BSE – the disease originates: from scrapie or a sporadic case of BSE

- Forms:
  - Sporadic CJD (scjd): (80-85%) origin unclear
  - Iatrogenic CVD: (1-3%) : after therapeutic interventions (corneal transplantation; 1985 after growth hormone treatment (France) (extremely long incubation period of tens of years in peripheral disease; after dura mater transplantation (Japan)
  - Hereditary form: (10-15%) specific mutations, polymorphisms of the human prion gene (PRNP)
  - New variant disease (vCJch) 1996

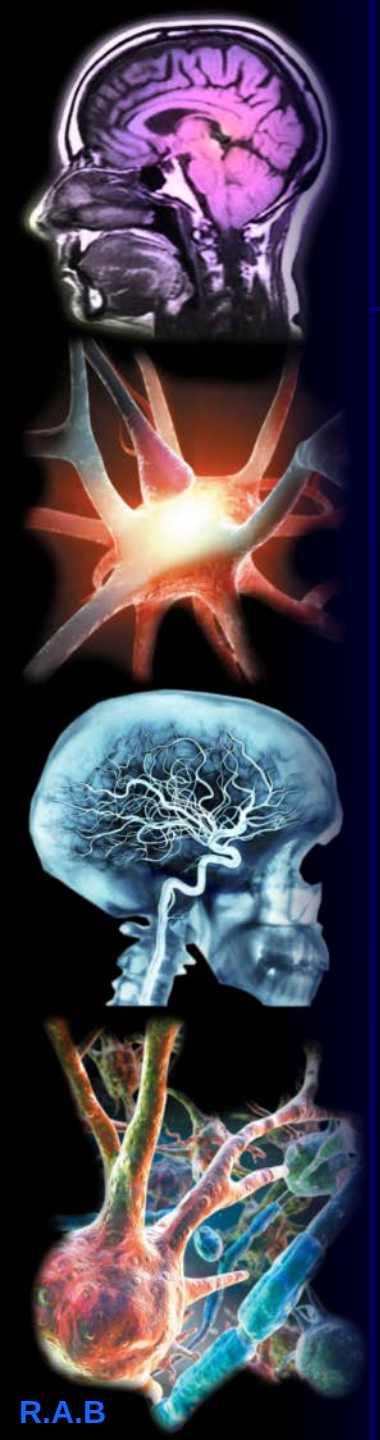
R.A.B



Creutzfeldova-Jacobova ch.

- Hereditary form: (10-15%) specific mutations, polymorphisms of the human prion gene (PRNP)
  - codon 200 (E200K) the most common and significant mutation (in Slovakia it accounts for up to 75%) - the presence of "healthy" carriers of the e200k mutation or genetic testing of corneal donors
  - codon 129 in the normal population on both alleles Met, or Val (homozygotes), **Met-Met** increases the predisposition to iatrogenic infection; in heterozygotes (**Met-Val**) mutation Met 129 → fatal familial insomnia, mutation on the allele with Val →familial form of CJch.
  - A new variant of the disease (vCJch) discovered in 1996 in zoonosis-disease of milled cows; younger age of the affected, longer clinical course, more pronounced psychological changes, persistent pain delayed development of dementia

R.A.B

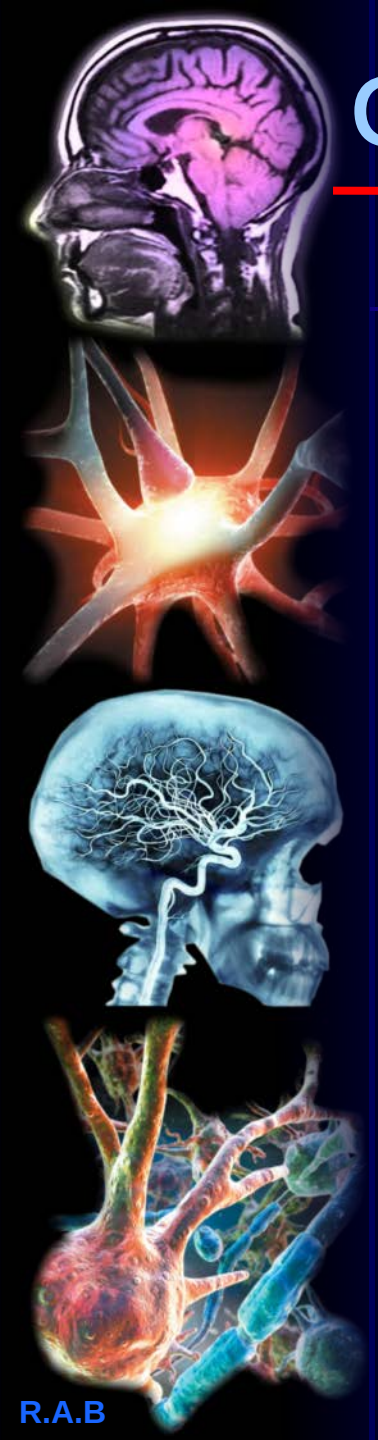


Creutzfeld-Jacob disease

- Lab A:
  - CT→ to exclude vascular, tumor, inflammatory, demyelinating) etiology;
  - EEG finding of 0.5-2Hz generalized, synchronized bi- / triphasic complexes (80% pac.)
  - MRI - vCJch je so-called. "pulvinar symptom" and for sCJch a conspicuous signal in cauda nc. caudati and in putamen.
  - CT

  Lab B:
  - CSM: examination of protein 14-3-3 in liquor- "marker of neuronal death" (Western blot) specificity and sensitivity of the matode in the range of 78-95% in sCJch. False positives in Alzheimer's ch. and with some encephalitis herpes zoster .
  - polymorphism on codon 129.
- Histol: presence of prion in biopsy tonsil tissue

R.A.B

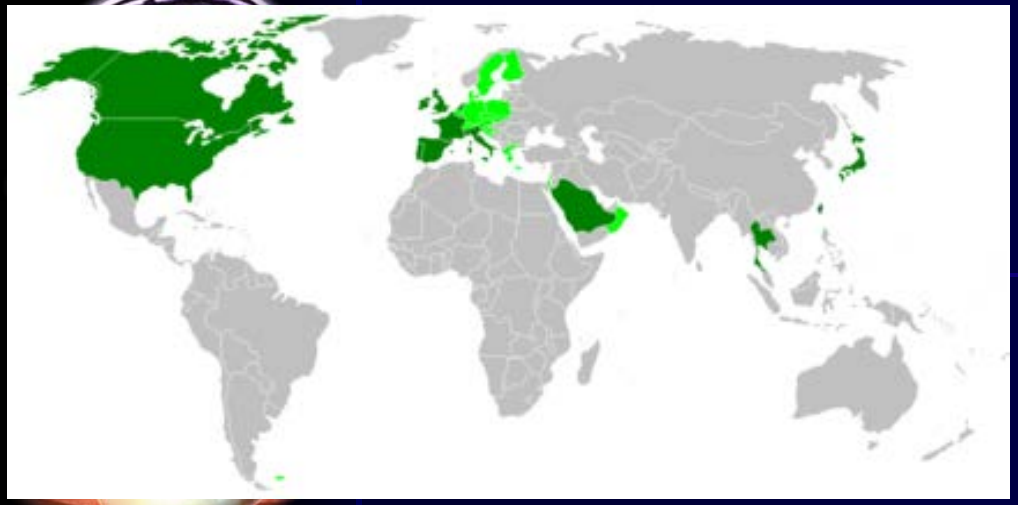


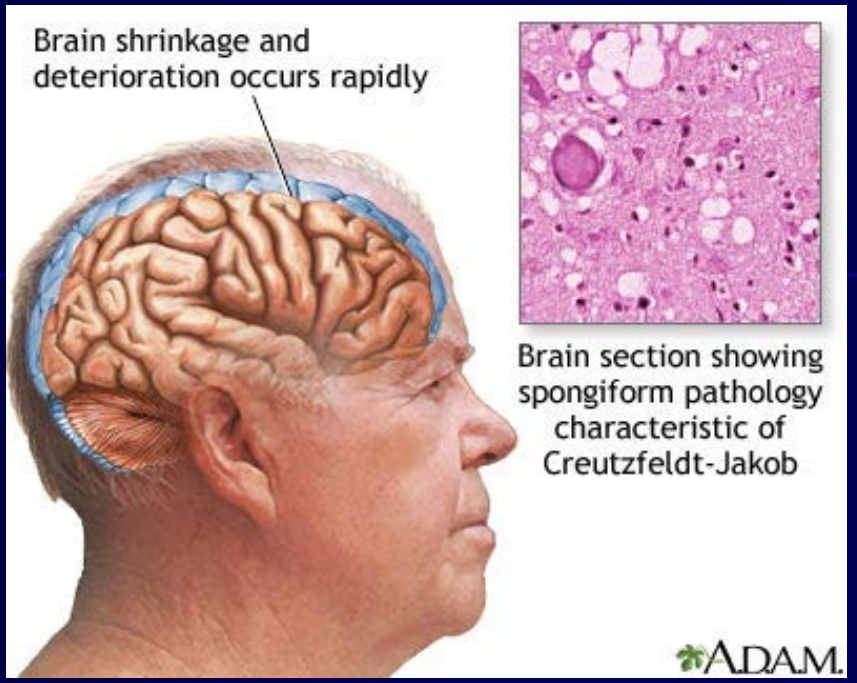
Creutzfeld – Jacob disease

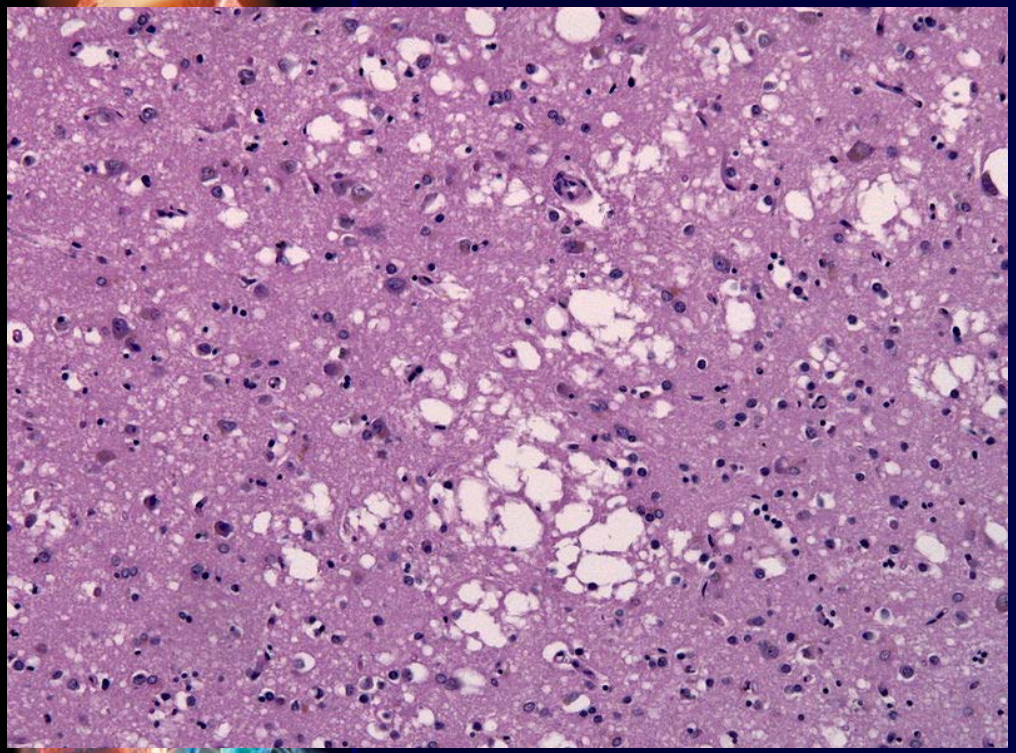
Manifestations:

1. In the prodromal stage: sleep disorders, restlessness, anxiety, sometimes hallucinations
2. Early variable manifestations: ataxia, visual disturbances, bulimia, which contrasts strikingly with gradual cachectisation; skin itching without superficial finding, similar to scrapie
3. The main symptoms: rapidly progressing dementia (99.9%) and myoclonus (80%) pyramidal and extrapyramidal symptoms, sometimes central blindness, rigidity increases, the patient becomes unable to move and is increasingly dependent on the environment.
4. Terminal manifestations: akinetic mutism, death occurs usually as a result of an associated Infection, The Manifest phase of CLD lasts no more than 4.5–5 months, exceptionally longer than a year

R.A.B

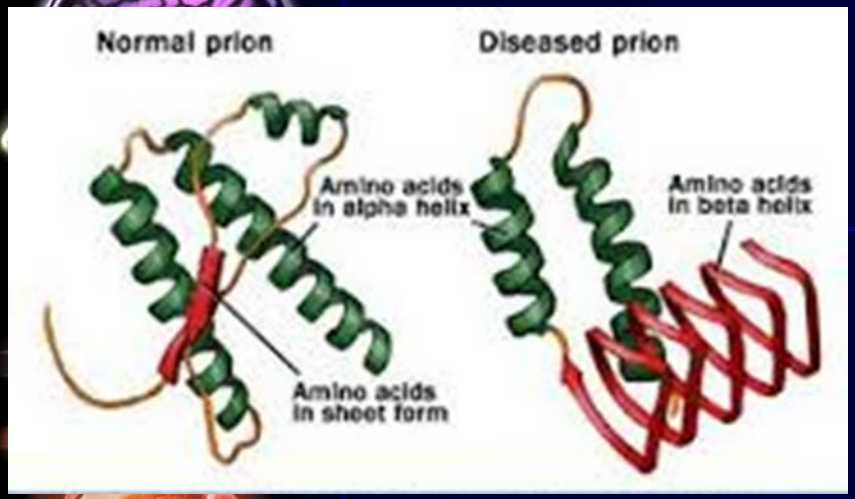


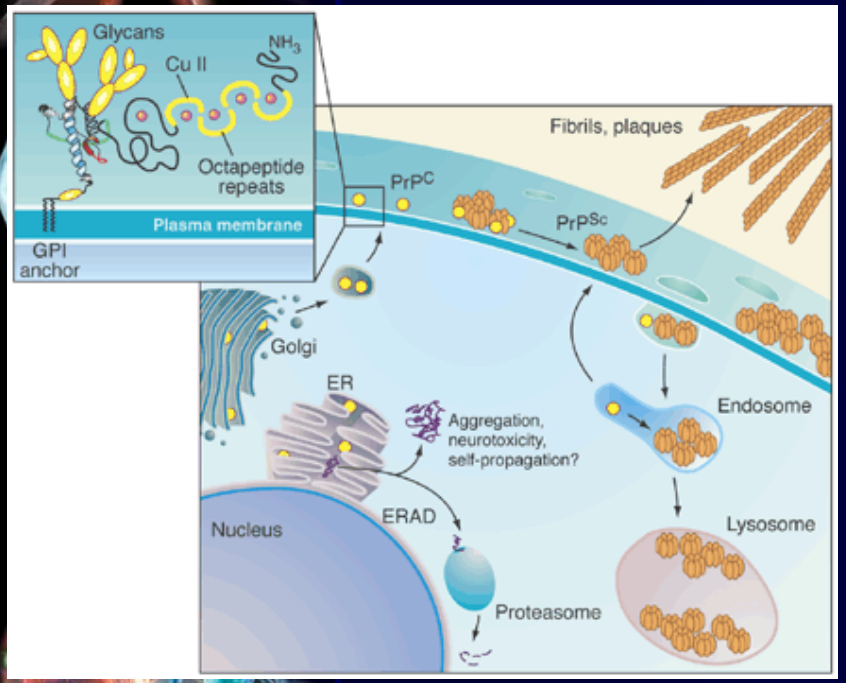




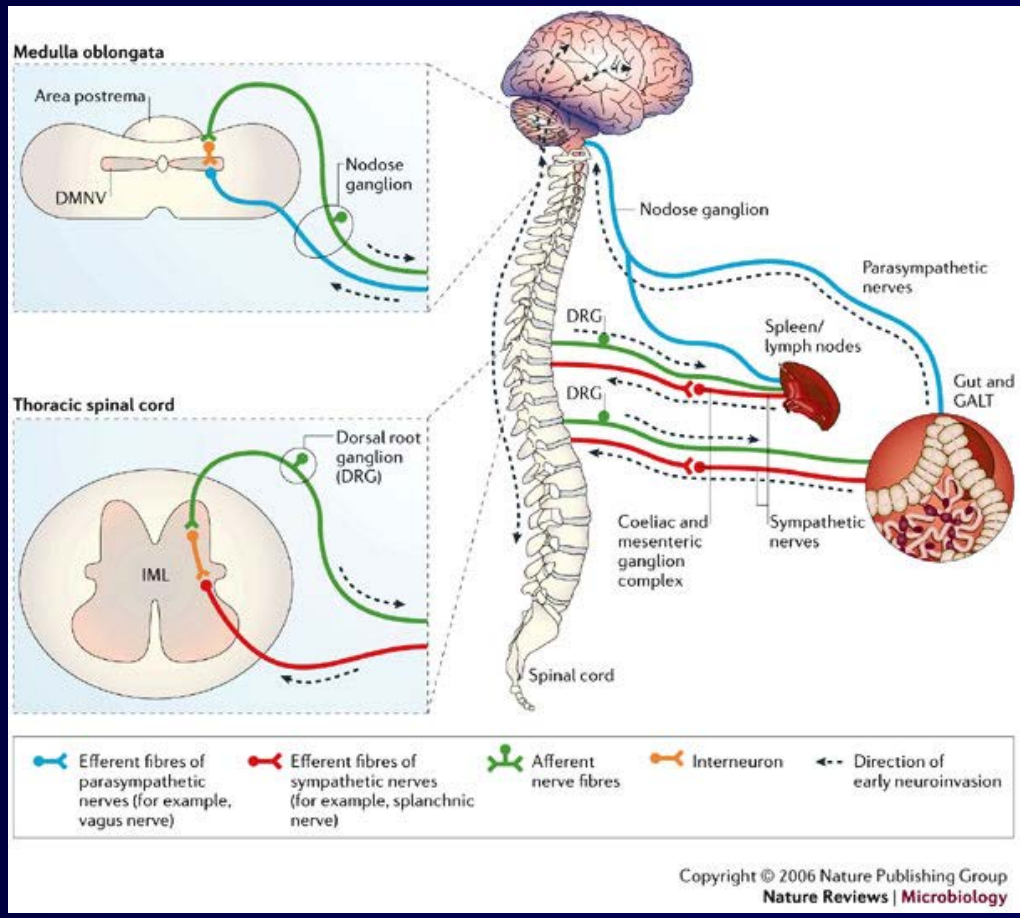
http://disruptinghomeostasis.weebly.com/creutzfeldt-jakob-disease.html
https://es.m.wikipedia.org/wiki/Archivo:CJD_spongiosis_temporal_lobe.jpg

R.A.B

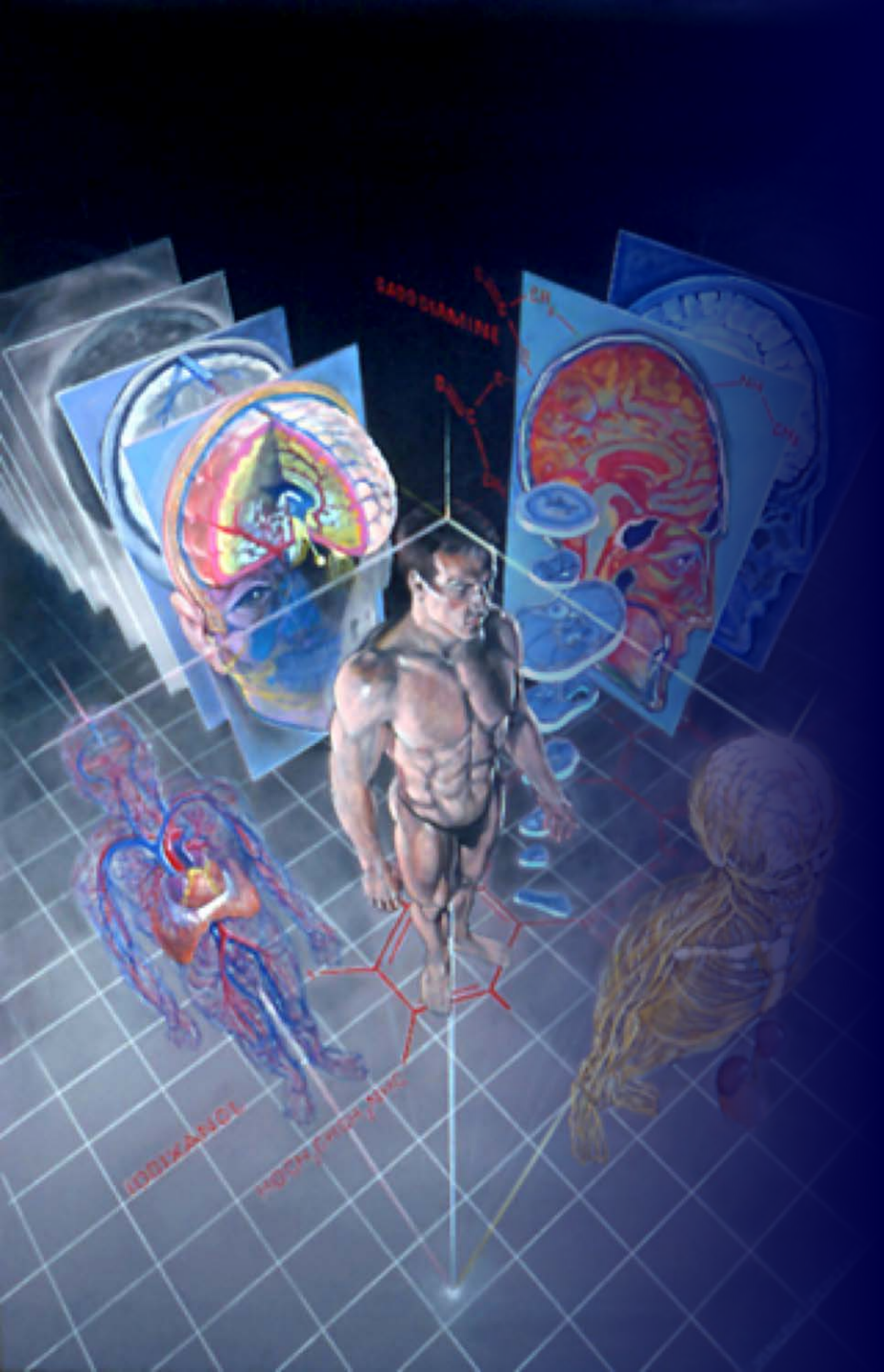




Prion replication and deposition (Priola et al., 2003 Science).

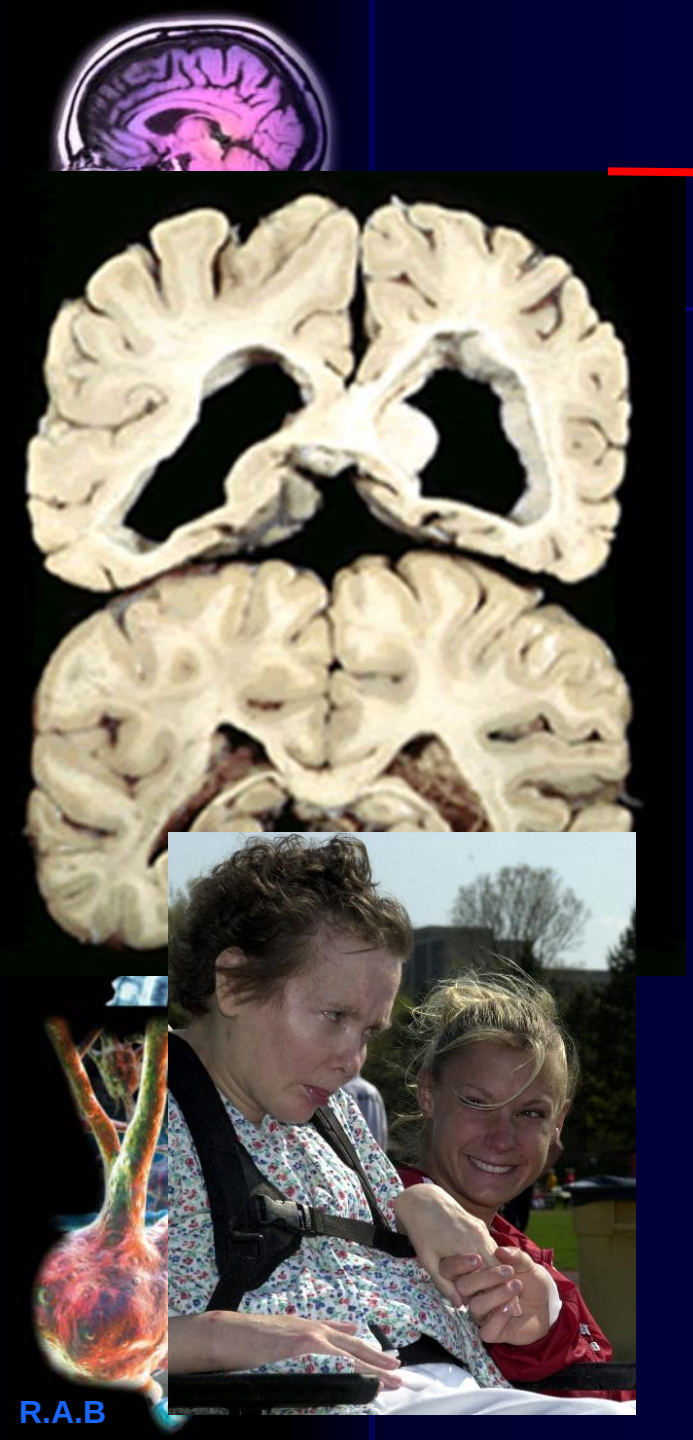


R.A.B



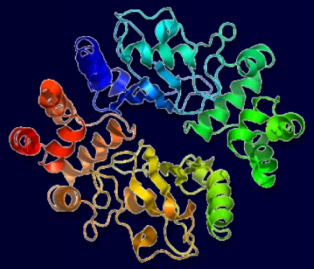
Huntington disease

Huntington disease

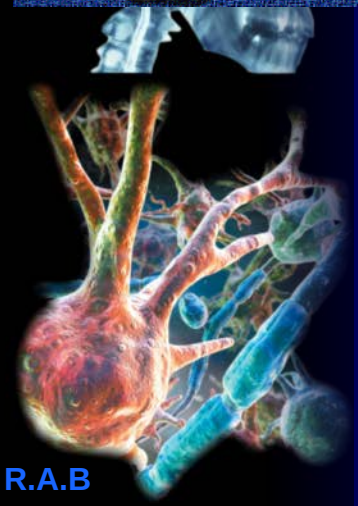


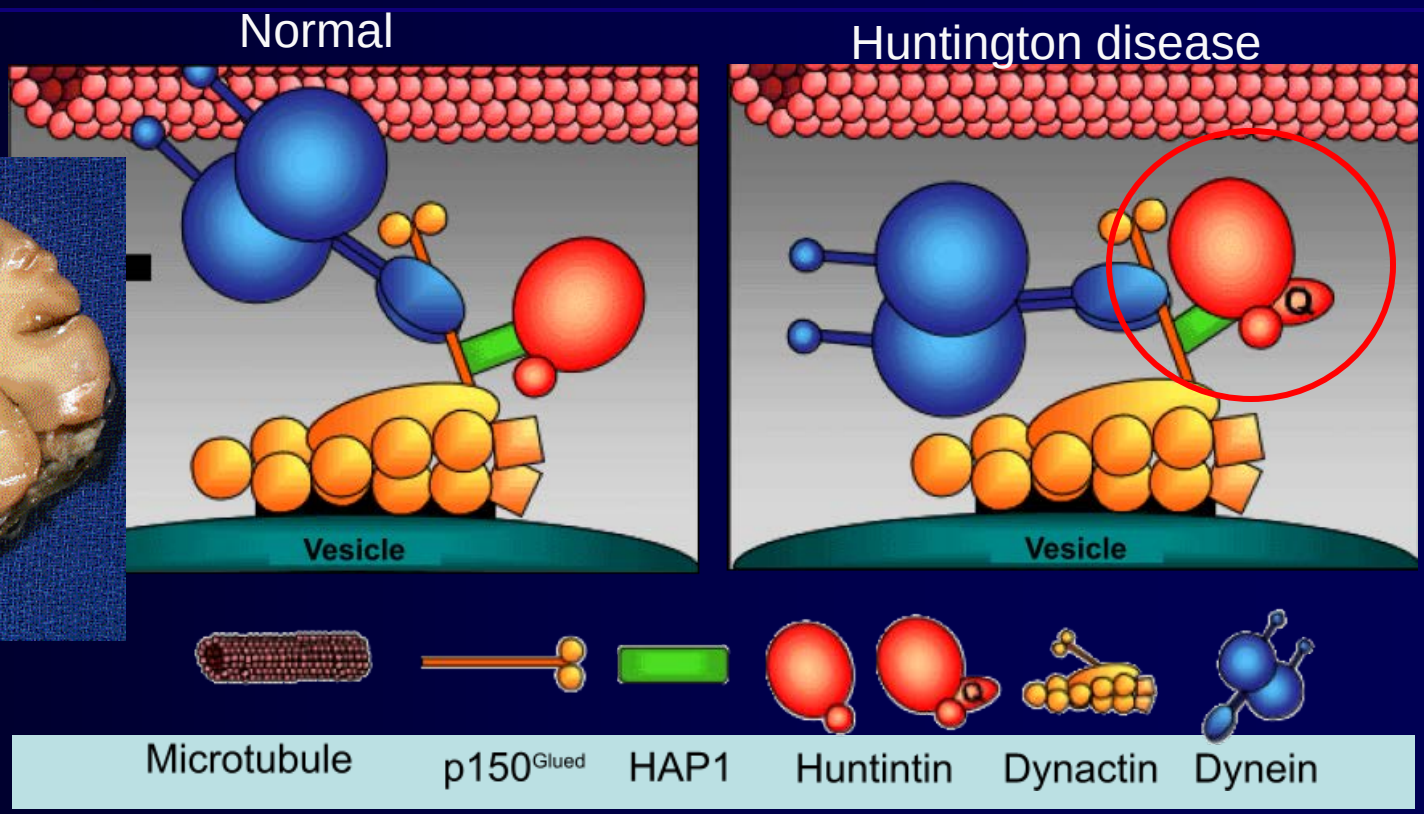
- Def: progressive AD-hereditary disease with dementia and chorea..
- Vy: : onset in the first 10 years, in others after 60. (average 30-40 r.); death on average 17 years after the appearance of the first symptoms
- Etio: dynamic mutations in it15 gene (Ch4p) for huntingtin protein (Htt) (350 kDa, 3144 AK) the gene contains normally 6-35 CAG repeats and thus many polymorphisms
- at the count > 36 and more (up to 250) an abnormal version with the manifestation of the disease arises
- Pa:
  - Cortico-Striate degeneration
  - Intranuclear inclusions of mutated form of huntingtin
  - aggegation - interacting proteins = huntingtin- AP: ubiquitin; huntingtin interacting protein 2 (HIP2)
  - Neurochemistry abundance of dopamine and lack of acetylcholine in striatum

R.A.B



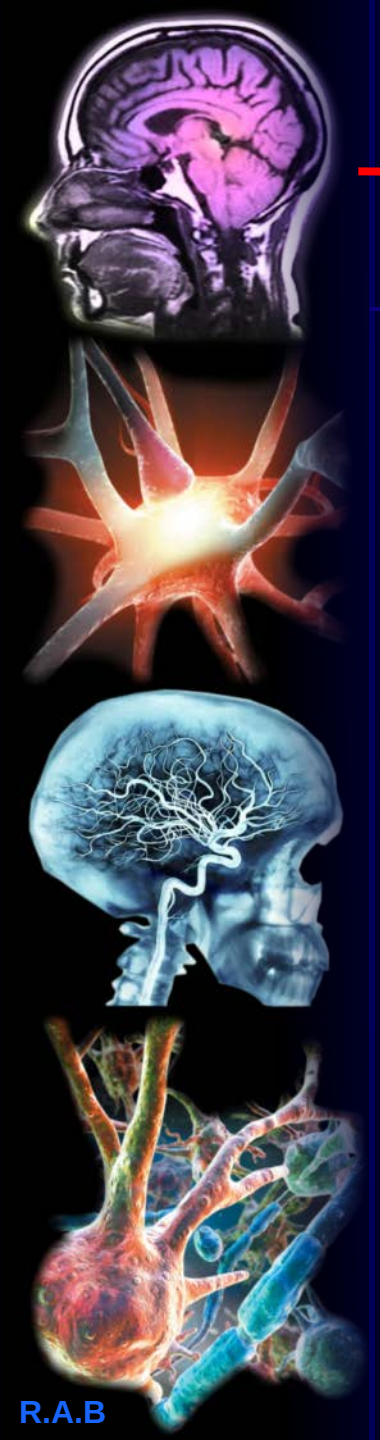
Huntingtin





- Interruption of axonal transport causes axonal and somatic death
- Huntingtin gene (IT15) - contains a polymorphic trinucleotide (CAG)n repeat longer than the normal - expanded and unstable. IThe severity of symptoms and early onset of the disease enhances with the increasing length of CAG repeats.
- HAP1, apopain and GAPD

R.A.B



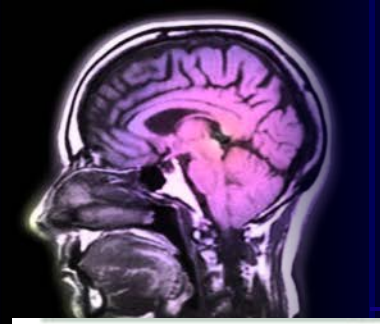
Huntington disease

Manifestations:

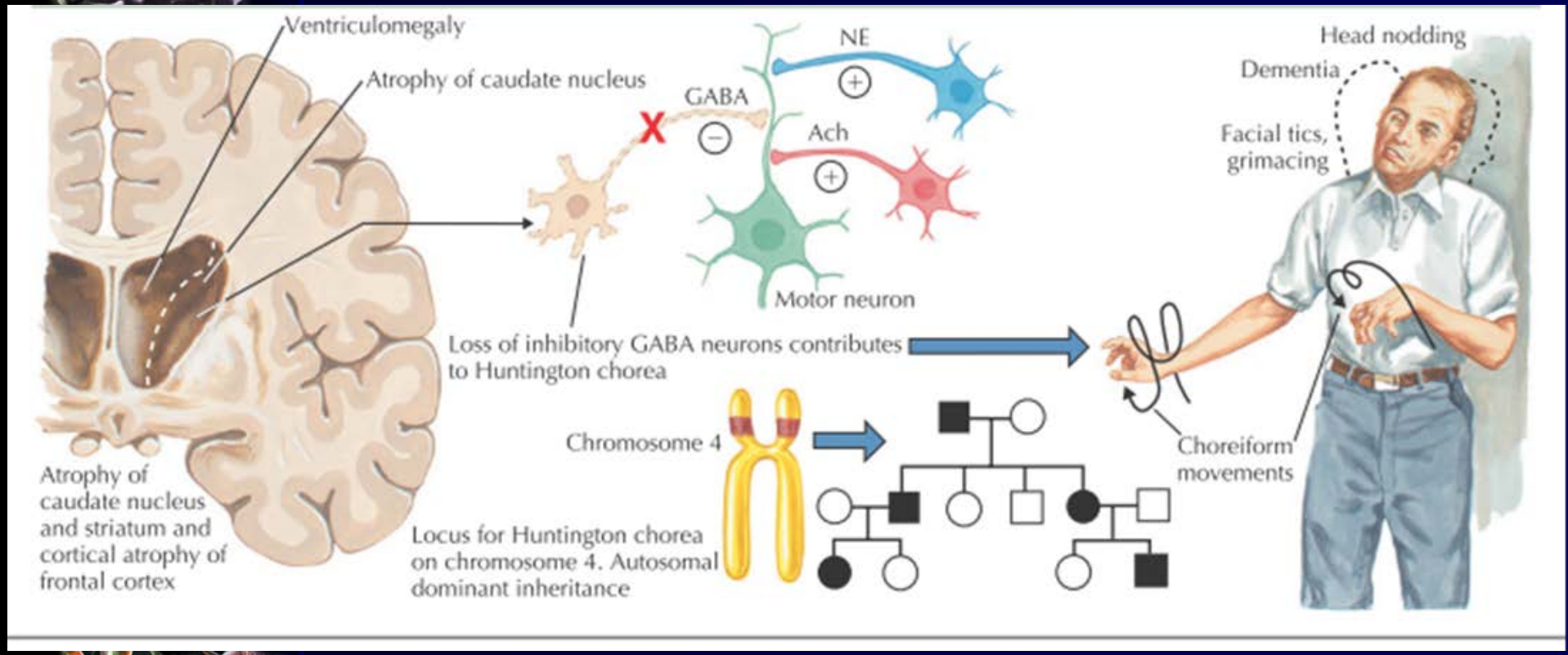
- Psychopathological changes: > 50% of cases as first personality disorders,
  - Mood swings, aggression and emotivity - higher feelings, depression, anxiety,
  - Changes in personality and behavior-paranoia, hallucinations, suicidal tendencies, loss of self-confidence and concentration, weakening of the intellect;
  - Disorders of cognitive functions: inability to plan and solve, slowed down, inexpedient thinking, decreased judgment, comprehensibility and criticality, disorders of both working and logical memory and learning;

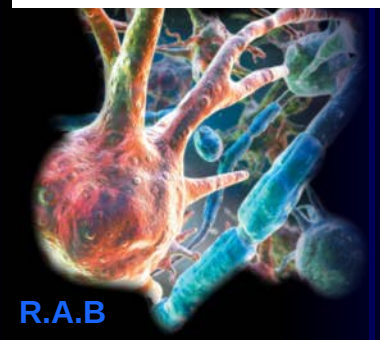
- Motor disorders – chorea („chorein - dancing“);
  - i inconspicuous twitching, twisting uncoordinated movements of the hands,
  - over time, motor restlessness - more intense, rough, impractical involuntary movements disappearing during sleep.
  - difficulty articulating-unintelligible speech, involuntary sounds bothering others, difficulty swallowing, groaning (risk of aspiration pneumonia) excessive salivation, sweating,
  - inability to perform basic work tasks (writing, buttoning buttons, everything falls out of the patient's hands, ...), walking reminds a drunk
  - loss of independence, mobility, basic hygiene principles.
  - the disease ends in death

R.A.B



Huntington disease





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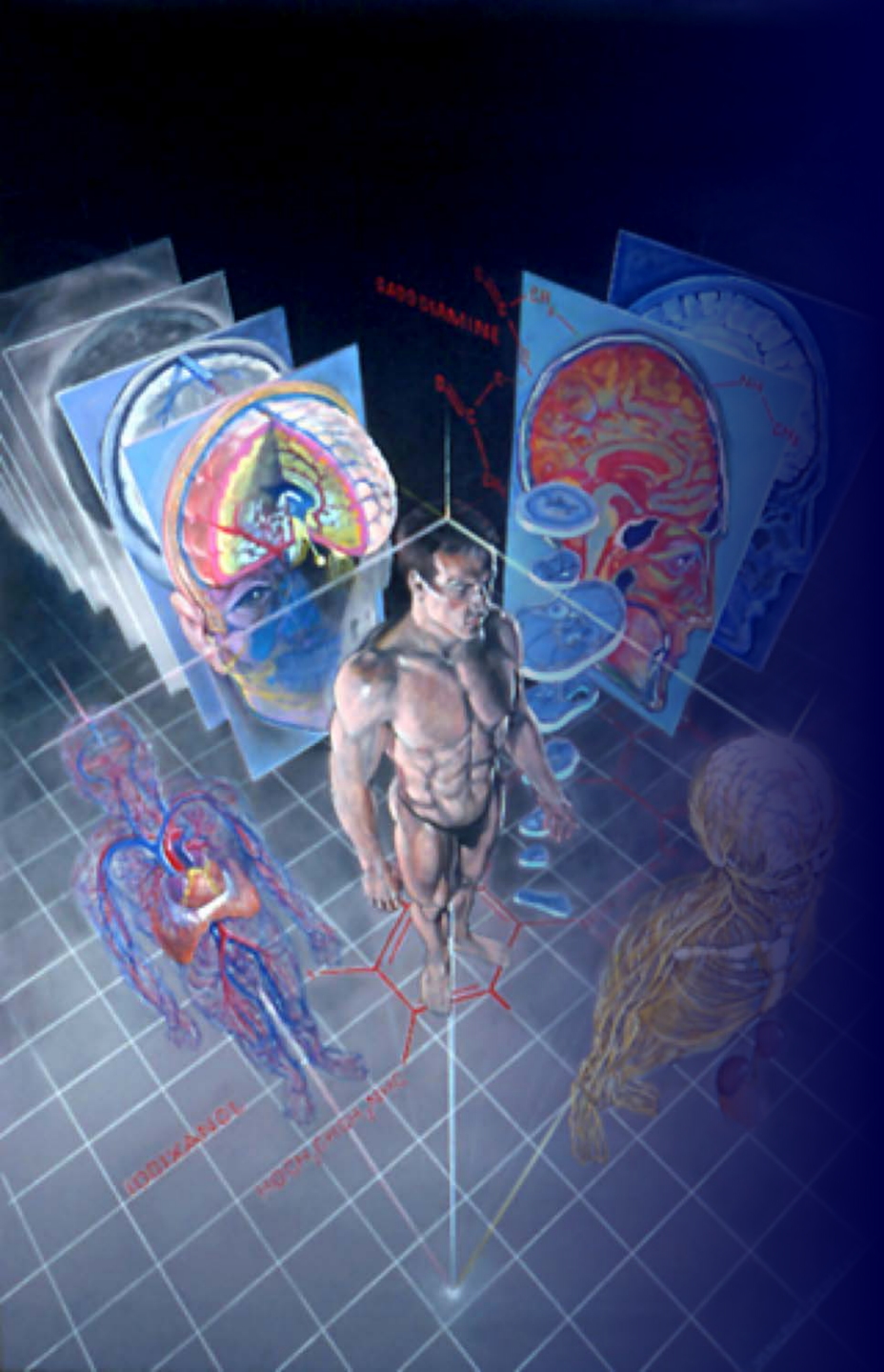
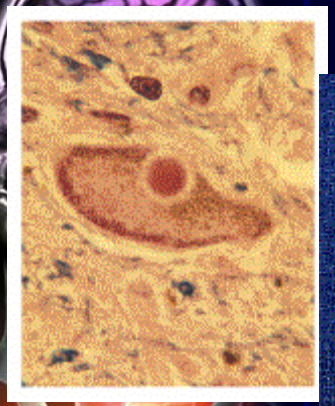


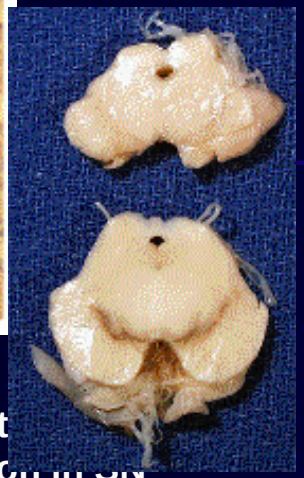
Parkinson disease

Parkinson disease (Paralysis agitans)

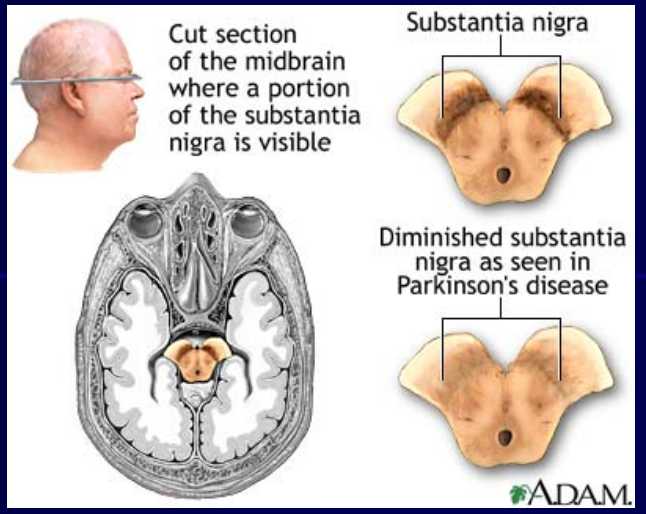
- Def: Progressive neurodegenerative disease with motor, vegetative, cognitive functions(memory impairment), personality and behavioral changes (1817 described by James Parkinson)
- Occ: Men > women; 50.- 60. year of life, progresses 10 - 20 r., affects ~ 0.1-1% of the population in industry. countries ; 3. most often neurol. disease; symptoms only in 60% of those affected; 2 most common neurodegenerative disease
- Etio: inhereted cases (heredtary + acquired (enviromental)
  - Inhereoted form – early familial form of PD (AD-transmitted; mutated gene for: :
    - Alfa - synucleín +Kinase rich on leucíne motifs type 2 (LRRK2).
  - Acquired form - Ekonomo encefalitís 1920th (infection?) Intoxikácia: Hg, Mn, Fe, Cu, MPTP (N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) contaminant in synthetic heroin (1982 San Francisco)
- Pathology: degeneration of DA neurons in the parc compacta sunstantia nigra and ventral tegmentum (symptom. evident after 80% loss)
  - degener. nucl. raphe (serotonin) & locus coeruleus (NA)
  - lesions of the nuclei. subthalamicus (sudden decrease in akinesia-bradykinesia, tremor and rigidity controlaterally)

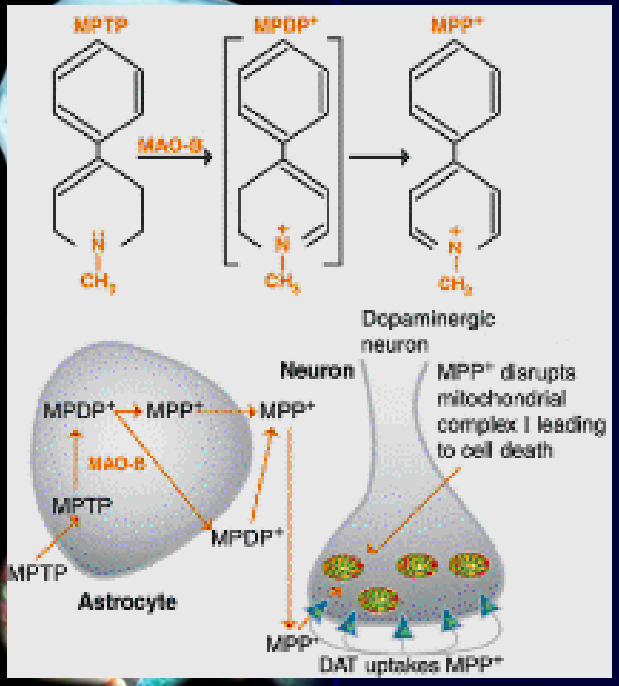
R.A.B





Lewy body in the cyt
pigmented DA neuron in SN

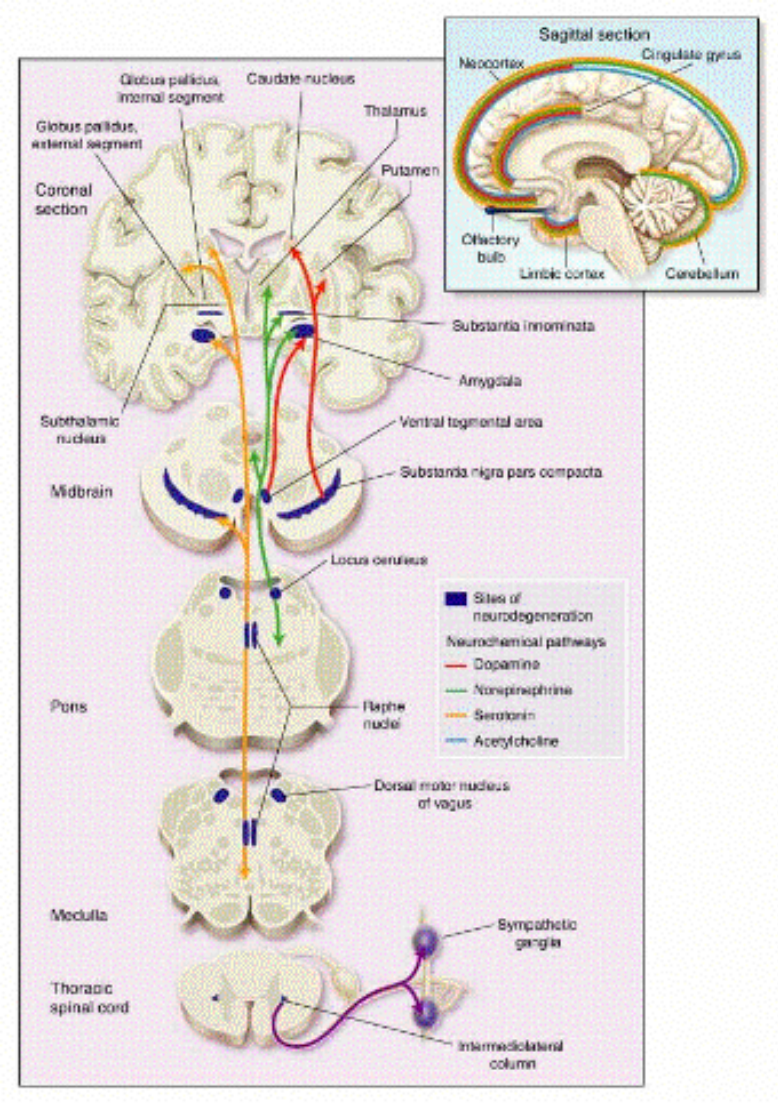




MPTP crosses the blood-brain barrier, it is converted into MPDP+, an intermediate product, by the enzyme MAO-B within brain astrocytes. MPDP+ can then spontaneously form MPP+ either within the astrocyte itself or after diffusion into the extracellular space. MPP+ is then specifically taken up into dopaminergic neurons via the dopamine transporter (DAT). Onc inside the dopaminergic neuron, MPP+ is taken up into the mitochondria via an energy-dependent transport process, where acts as a specific inhibitor of mitochondrial complex

R.A.B

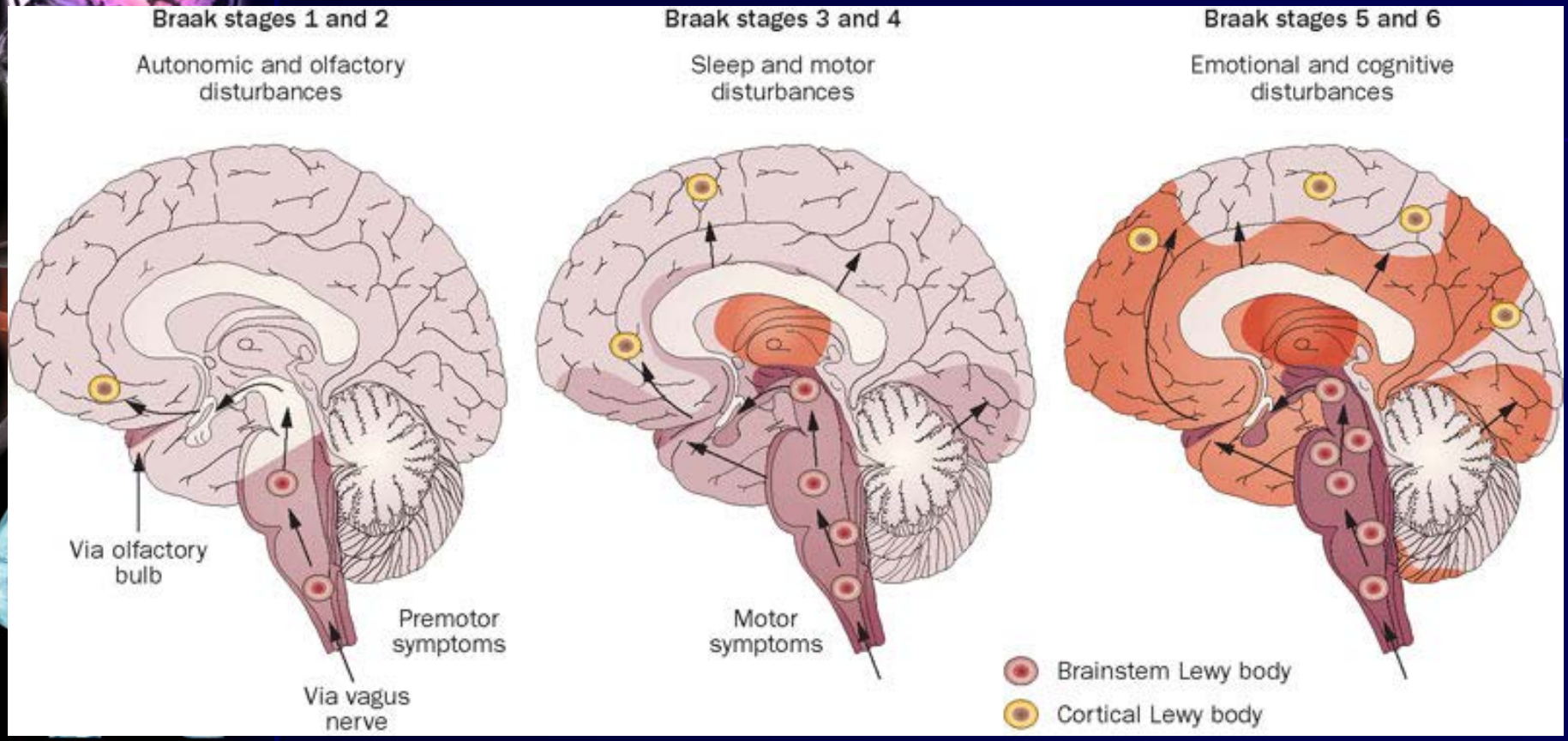
Parkinson's disease



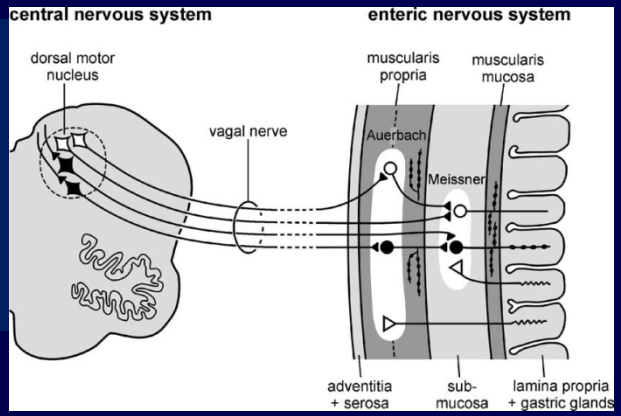
- Dopaminergic defect
- Serotoninergic defect
- Noradrenergic defect
- Acetylcholibergic defect
- substantia nigra pars compacta - DA - nigrostriatal pathway - striatum ventral tegmental area - DA - entorhinal cortex, olfactory tubercle, cingulate gyrus, and frontal cortex.
- locus ceruleus - NA - spinal cord, cerebellum, central gray matter of the midbrain, amygdala, substantia innominata, thalamus, limbic cortex
- raphe nuclei - SE - spinal cord cerebellum, substantia nigra, amygdala, striatum, and cortex.
- substantia innominata - nucleus basalis of Meynert - Ach
- intermediolateral column - preganglionic sympathetic fibers

R.A.B

Braag stages of Parkinson disease

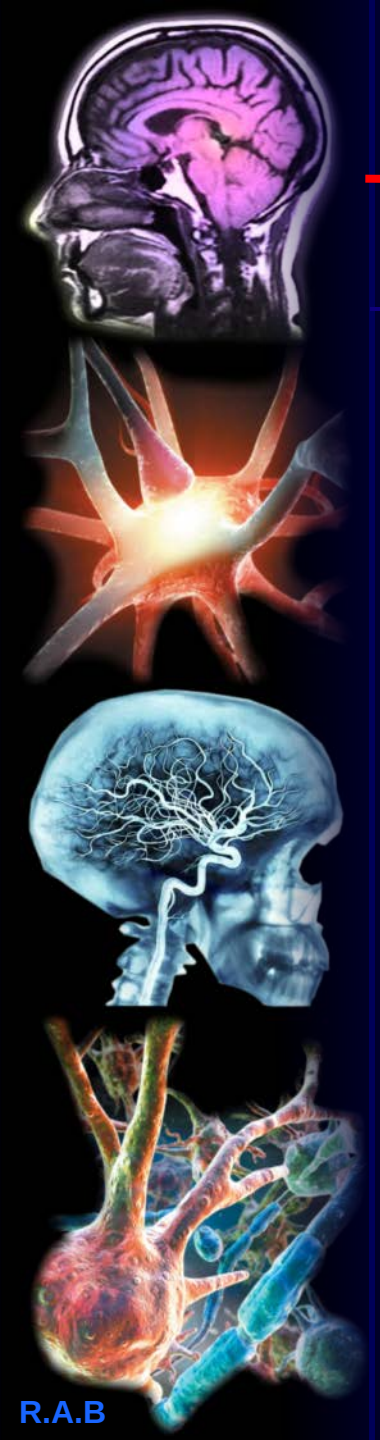


- Early stages PCh = disability dorzálne otorické kernel nX □ Pch starts penalties vagovej part of the ANS Braak stages of (Braak et al, 2003). alpha synuclein deposits
- ' gut to brain ' theory; alpha-synuclein in gut biopsies before PCh diagnosis.



https://scienceofparkinsons.com/2015/09/09/september-7-13th-2015/

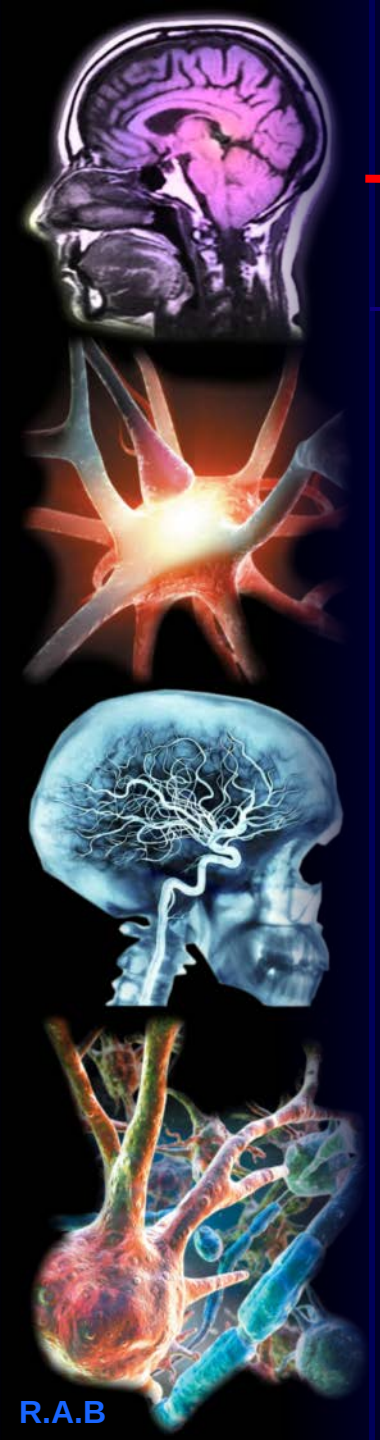
R.A.B



Parkinson disease

- Motor manigestations
  - Akinesia, hypokinesia, propulsions, retropulsions, HK articulation disorder, amimia, bradybasia
  - Bradykinesia-micrography, monotonous speech
  - Hypertonia-rigidity, gear phenomenon, posture-forward tilt, shoulder flexion
  - Quiet route
  - Oculomotor disorders, oculogyric crises, blepharospasm, respiratory distress
- Vegetatíve manifestations
  - Seborrhea-oily face, salivation, sweating,
  - Upper extremity anaemia, constipation
- Psychological changes
  - Affective lability, bradypsychia - > dementia

R.A.B



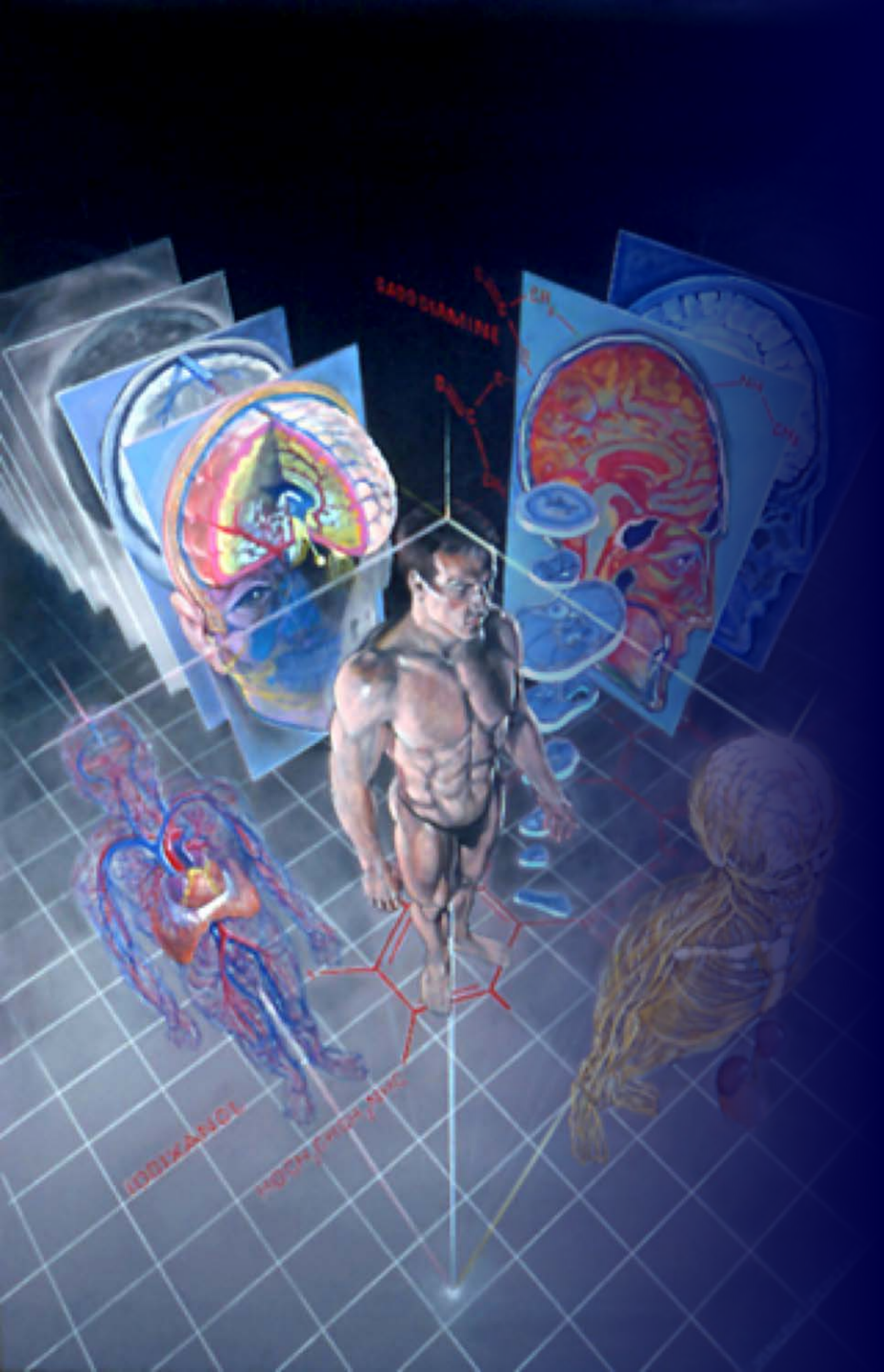
Parkinson disease

- Parkinsonism
  - Parkinson's disease (paralysis agitans) - akinesis + gentle tremor
  - Postencephalic Parkinsonism – vegetat.sy + dystonia, visual convulsions, tremor
  - Medicamentous Parkinsonism tremor (akinesia, rigor)
  - Arteriosclerotic (+idiopathic) Parkinsonism - bradykinesia, the fastest progression
  - Post-traumatický parkinsonizmus (punch-drunk)
  - Post-traumatic Parkinsonism (punch-drunk)
  - Intoxication (including MPTP) - tremor + torpid akinesia, rigor

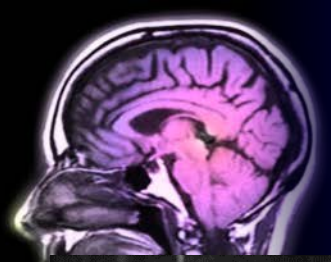
,

- Parkinsonism with dementia (M. Guam) rigor, akinesia, dementia
- Parkinsonimus with Levy bodies-dementia

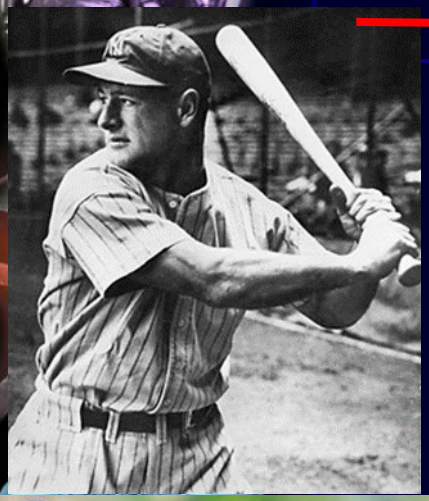
R.A.B

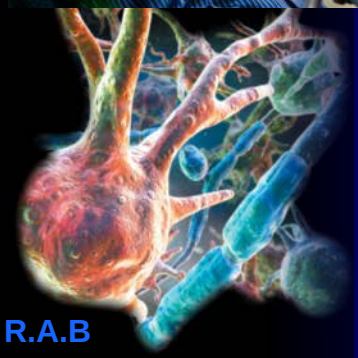


Motor neuron disease



Amyotrophic laterak sclerosis (ALS) Lou Gehring disease

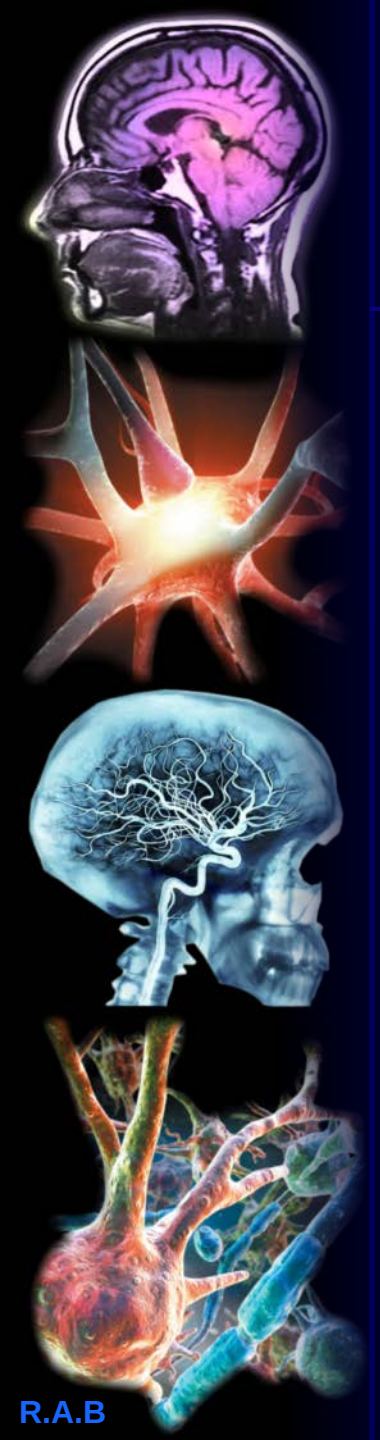




- Def: Amyotrophic lateral sclerosis (motor neurone disease (MND))
- progressive, fatal, neurodegenerative disease of the brain, causes degeneration of the motor neurons of the trunk and spinal cord with signs of muscle weakness, atrophy, paralysis, with preservation of menstrual functions
- Occ: prevalence 6:100000, incidence 2:100000; progression individual; duration of illness prim. 2-5 years, 25% pac. > 5 years, 8-16 % > 10 years, 5 % 20y
- Etio: hereditary + acquired; ; ALS and agricultural pesticides; A. **Sporadic form** - the most common, B. **Familial 5-10 %** M. Guam (v 50.r. 20.

1. Early manifestations: progressive muscle fatigue and weakness in the press and when moving the fingers on the hands, on the legs(dorsiflexia), when speaking (mumbling), swallowing, breathing individual. Pattern different from LMS; paralysis + muscle atrophy+ spasticity

R.A.B



Amyotrophic lateral sclerosis
Lou Gehring choroba

2. Late manifestations: disorders of chewing and swallowing (dysphagia), respiratory disorders (dyspnea); support needed; bilevel positive airway pressure (BiPAP) support during the night later in the day; threat: aspiration pneumonia;

- about 5% also have frontotemporal dementia.
- Most die from respiratory failure or aspiration pneumonia within 3-5 years after the onset of symptoms; the median survival time is 39 months, and only 4% survive longer than 10 years.
- Stephen Hawking - 50 years with the disease; is a rare thing
- Multisysemic proteinopathy = rarely ALS in complex with dementia, degen. muscle aches., degen. sick. bones,
- sensory functions preserved: hearing, vision, touch, smell, etc.

R.A.B

Amyotrophic lateral sclerosis (ALS)

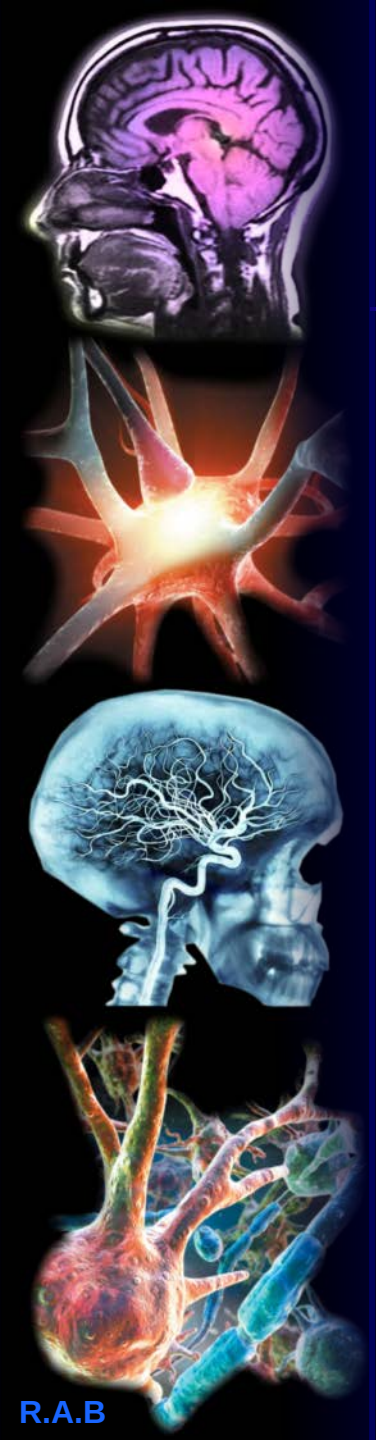
Table 1 | Genes associated with familial ALS

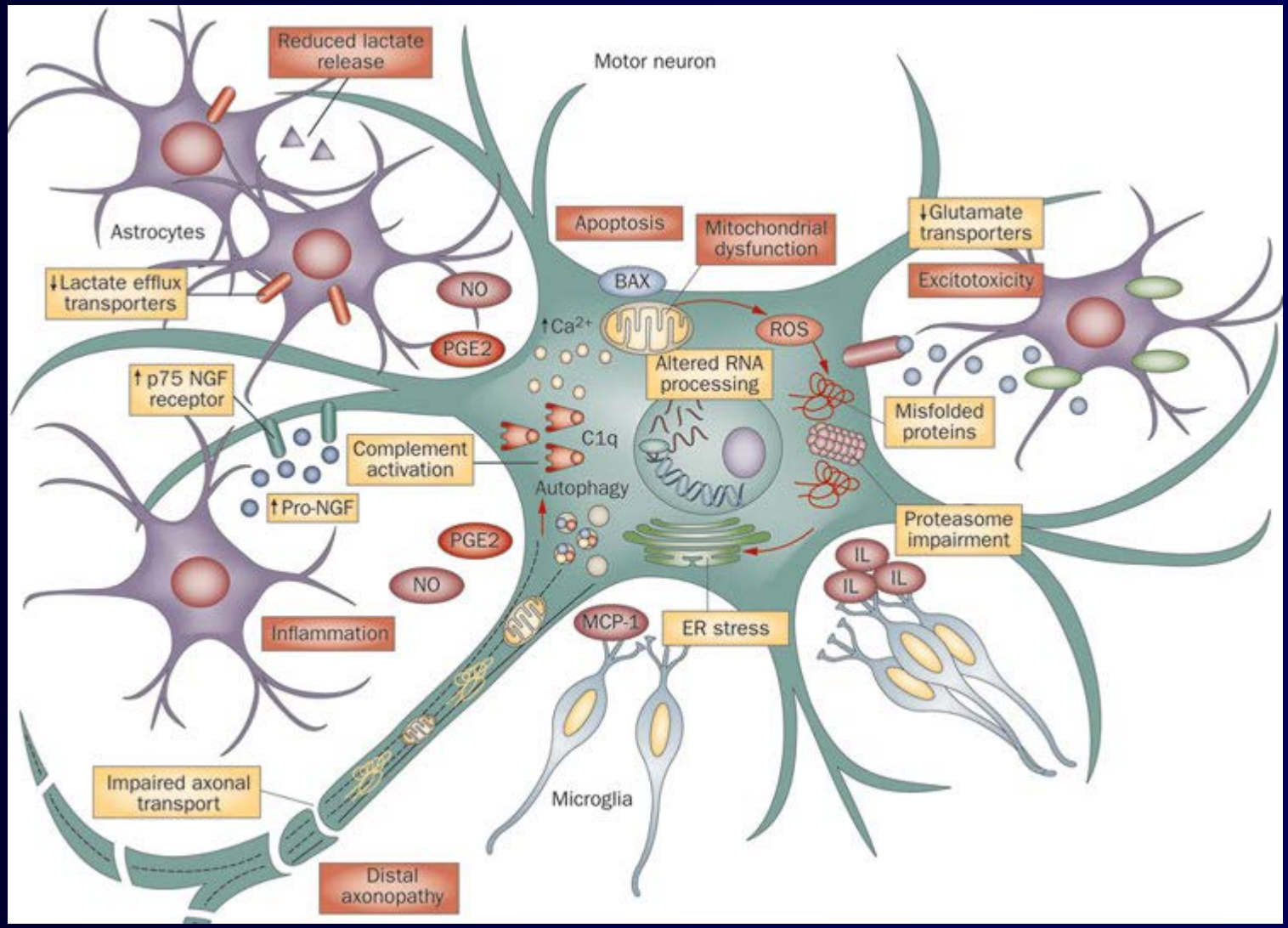
Genetic subtype	Chromosomal locus	Gene	Onset/ inheritance	Reference
Oxidative stress				
ALS1	21q22	Superoxide dismutase 1 (*SOD1*)	Adult/AD	Rosen (1993)[27]
RNA processing				
ALS4	9q34	Senataxin (*SETX*)	Juvenile/AD	Chen *et al.* (2004)[164]
ALS6	16p11.2	Fused in sarcoma (*FUS*)	Adult/AD	Kwiatkowski *et al.* (2009)[192] Vance *et al.* (2009)[193]
ALS9	14q11.2	Angiogenin (*ANG*)	Adult/AD	Greenway *et al.* (2006)[161]
ALS10	1p36.2	TAR DNA-binding protein (*TARDBP*)	Adult/AD	Sreedharan *et al.* (2008)[89]
Endosomal trafficking and cell signaling				
ALS2	2q33	Alsin (*ALS2*)	Juvenile/AR	Yang *et al.* (2001)[102]
ALS11	6q21	Polyphosphoinositide phosphatase (*FIG4*)	Adult/AD	Chow *et al.* (2009)[108]
ALS8	20q13.3	Vesicle-associated membrane protein-associated protein B (*VAPB*)	Adult/AD	Nishimura *et al.* (2004)[104]
ALS12	10p13	Optineurin (*OPTN*)	Adult/AD and AR	Maruyama *et al.* (2010)[105]
Glutamate excitotoxicity				
ND	12q24	D-amino acid oxidase (*DAO*)	Adult/AD	Mitchell *et al.* (2010)[79]
Ubiquitin/protein degradation				
ND	9p13–p12	Valosin-containing protein (*VCP*)	Adult/AD	Johnson *et al.* (2010)[99]
ALSX	Xp11	Ubiquilin 2 (*UBQLN2*)	Adult/X-linked	Deng *et al.* (2011)[101]
Cytoskeleton				
ALS–dementia–PD	17q21	Microtubule-associated protein tau (*MAPT*)	Adult/AD	Hutton *et al.* (1998)[120]
Other genes				
ALS5	15q15–q21	Spatacsin (*SPG11*)	Juvenile/AR	Orlacchio *et al.* (2010)[184]
ALS–FTD	9p13.3	σ Non-opioid receptor 1 (*SIGMAR1*)	Adult/AD Juvenile/AR	Luty *et al.* (2010)[185] Al-Saif *et al.* (2011)[186]
ALS–FTD	9q21–q22	Chromosome 9 open reading frame 72 (*C9ORF72*)	Adult/AD	Hosler *et al.* (2000)[24] Renton *et al.* (2011)[196] De Jesus-Hernandez *et al.* (2011)[197]
Unknown genes				
ALS3	18q21	Unknown	Adult/AD	Hand *et al.* (2002)[194]
ALS7	20ptel–p13	Unknown	Adult/AD	Sapp *et al.* (2003)[195]

Abbreviations: AD, autosomal dominant; ALS, amyotrophic lateral sclerosis; AR, autosomal recessive; FTD, frontotemporal dementia; PD, Parkinson disease.

Ferraiuolo, L. et al. (2011) Molecular pathways of motor neuron injury in amyotrophic lateral sclerosis
Nat. Rev. Neurol.
doi:10.1038/nrneurol.2011.152

Amyotrophic lateral sclerosis (ALS)





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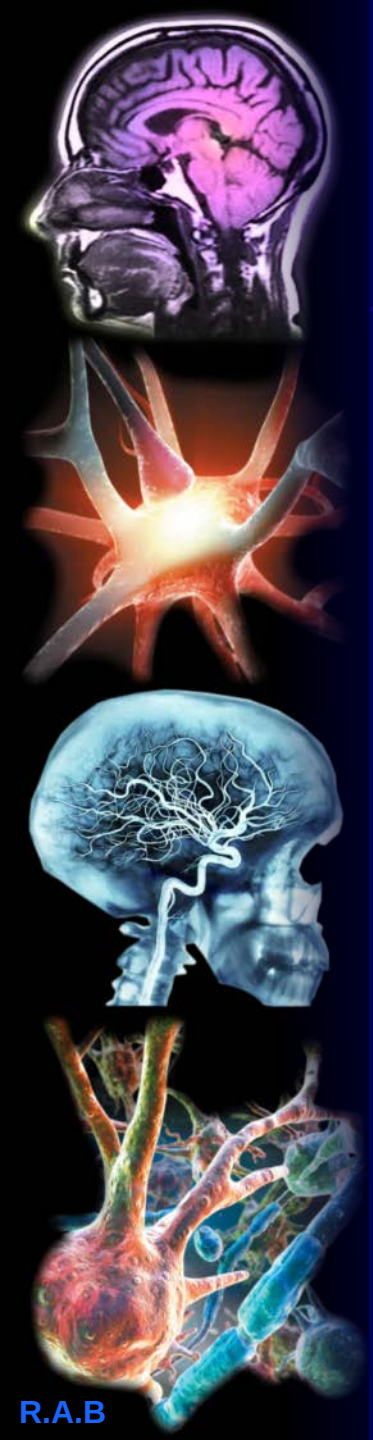

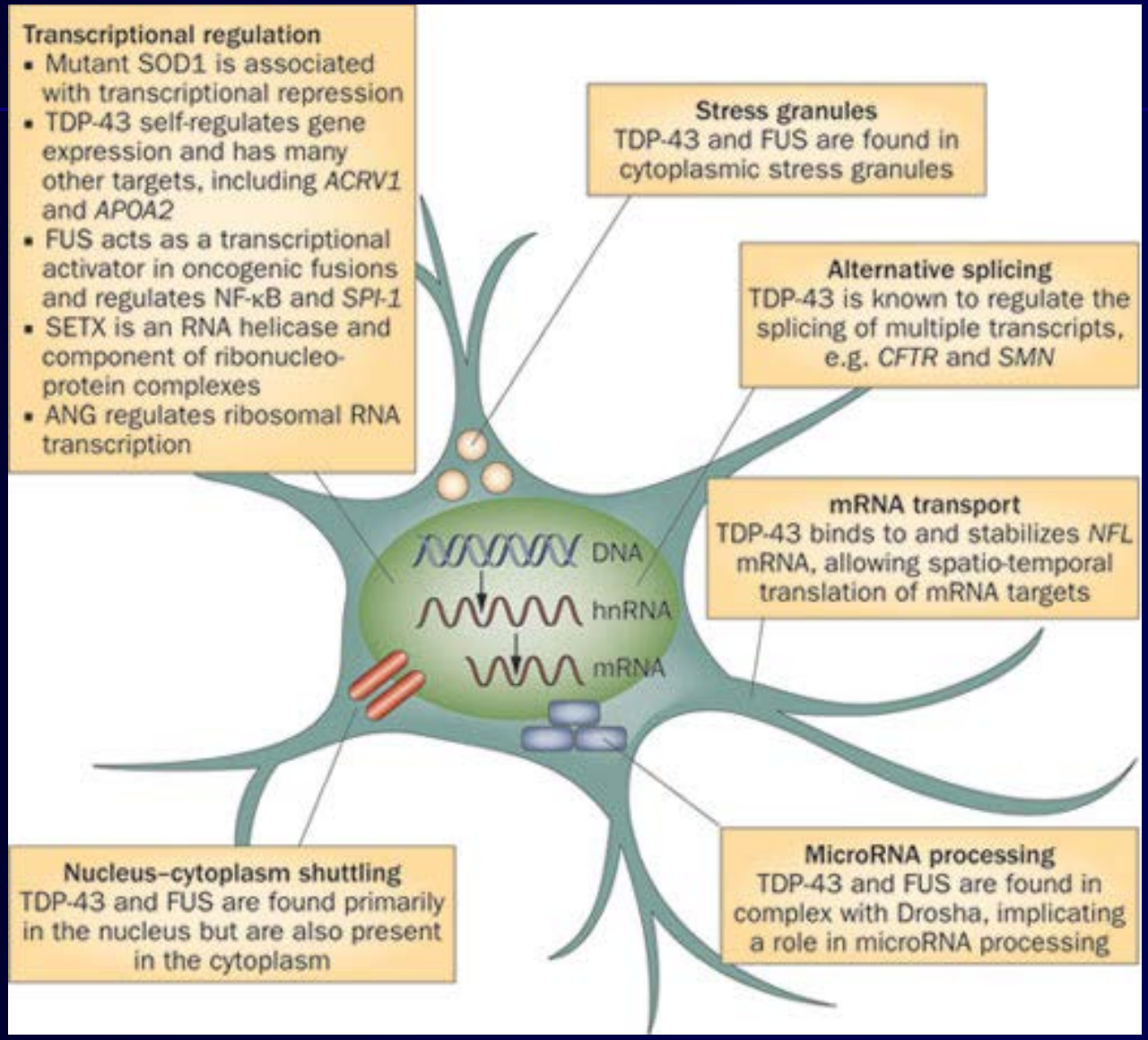
Transcriptional regulation
• Mutant SOD1 is associated with transcriptional repression
• TDP-43 self-regulates gene expression and has many other targets, including ACRV1 and APOA2
• FUS acts as a transcriptional activator in oncogenic fusions and regulates NF-κB and SPI-1
• SETX is an RNA helicase and component of ribonucleo-protein complexes
• ANG regulates ribosomal RNA transcription
Stress granules
TDP-43 and FUS are found in cytoplasmic stress granules
Alternative splicing
TDP-43 is known to regulate the splicing of multiple transcripts, e.g. CFTR and SMN
mRNA transport
TDP-43 binds to and stabilizes NFL mRNA, allowing spatio-temporal translation of mRNA targets
DNA
hnRNA
mRNA
Nucleus–cytoplasm shuttling
TDP-43 and FUS are found primarily in the nucleus but are also present in the cytoplasm
MicroRNA processing
TDP-43 and FUS are found in complex with Drosha, implicating a role in microRNA processing

R.A.B