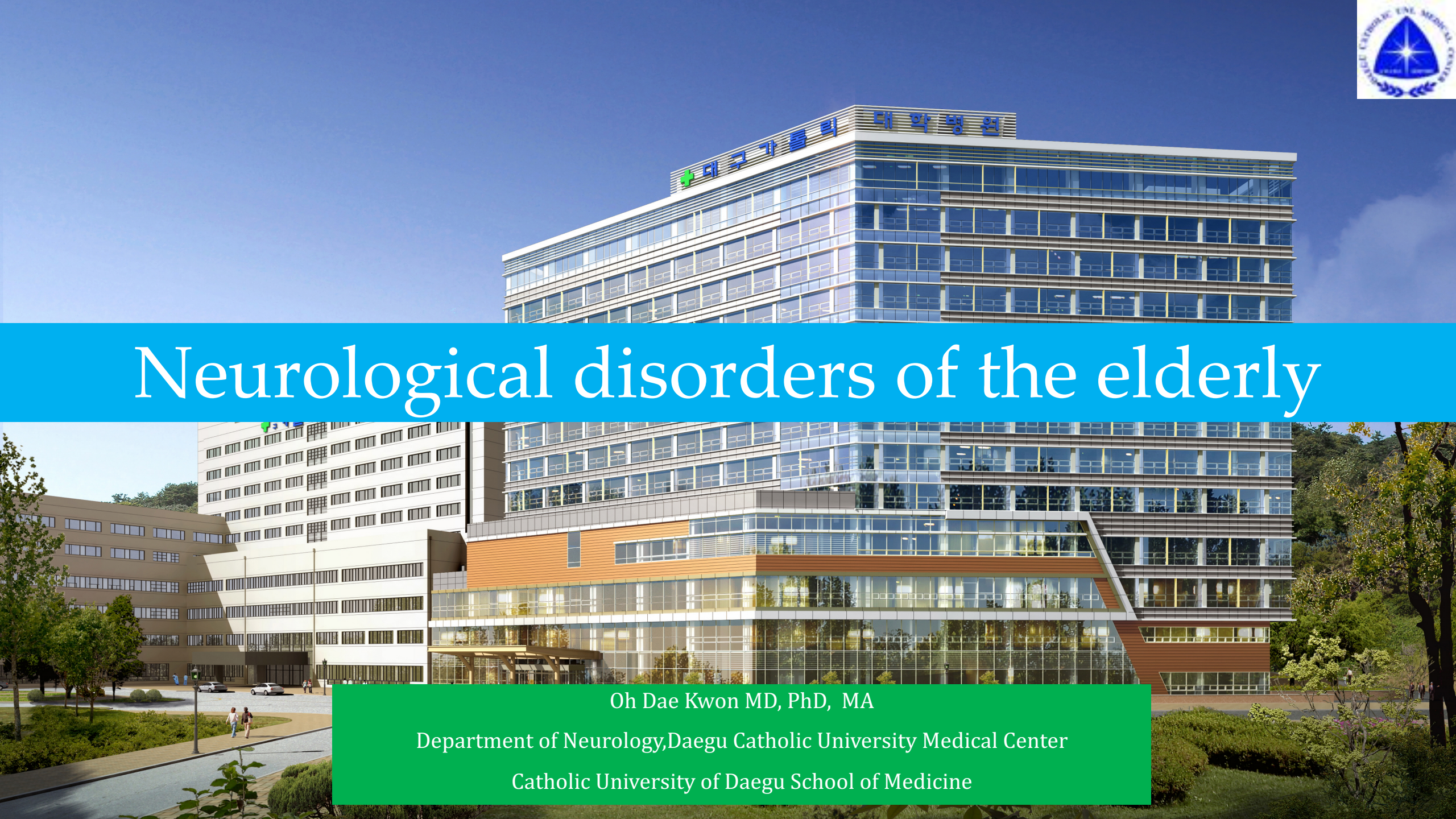

Neurological disorders of the elderly

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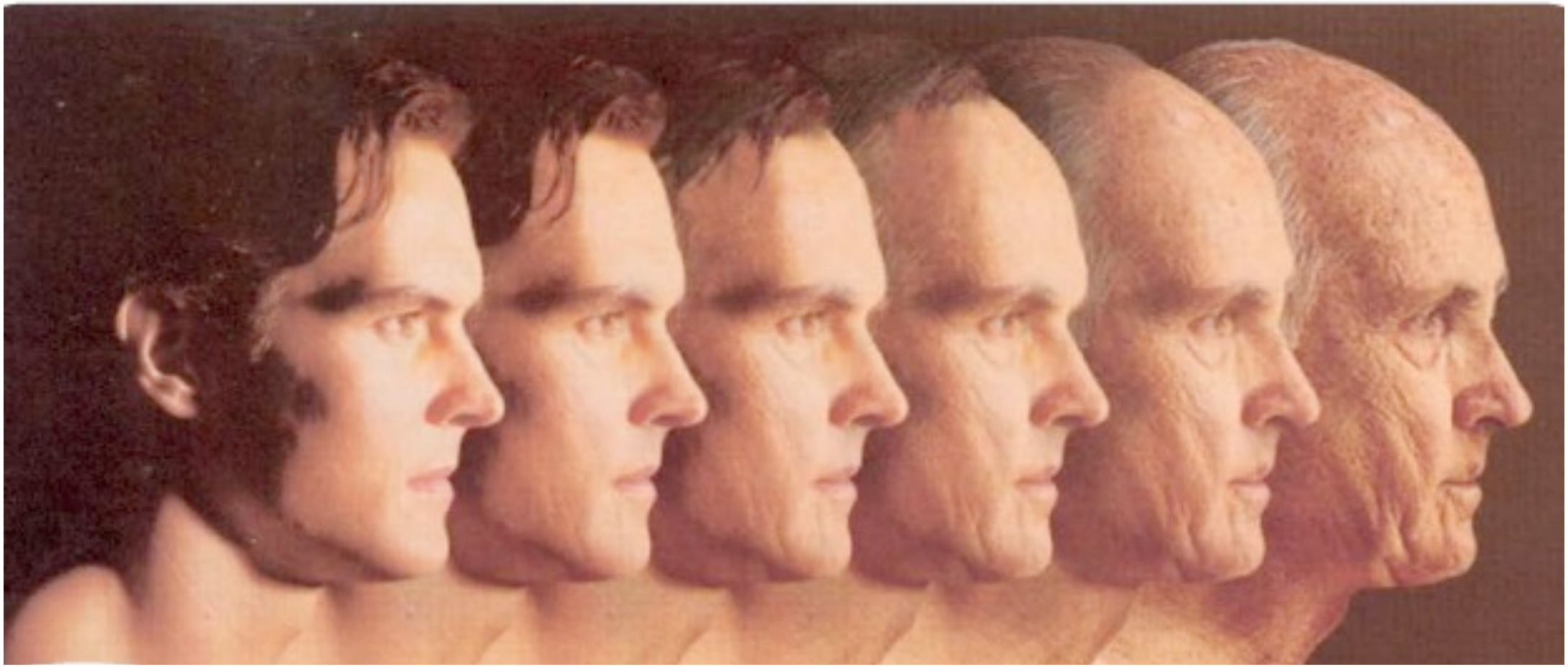
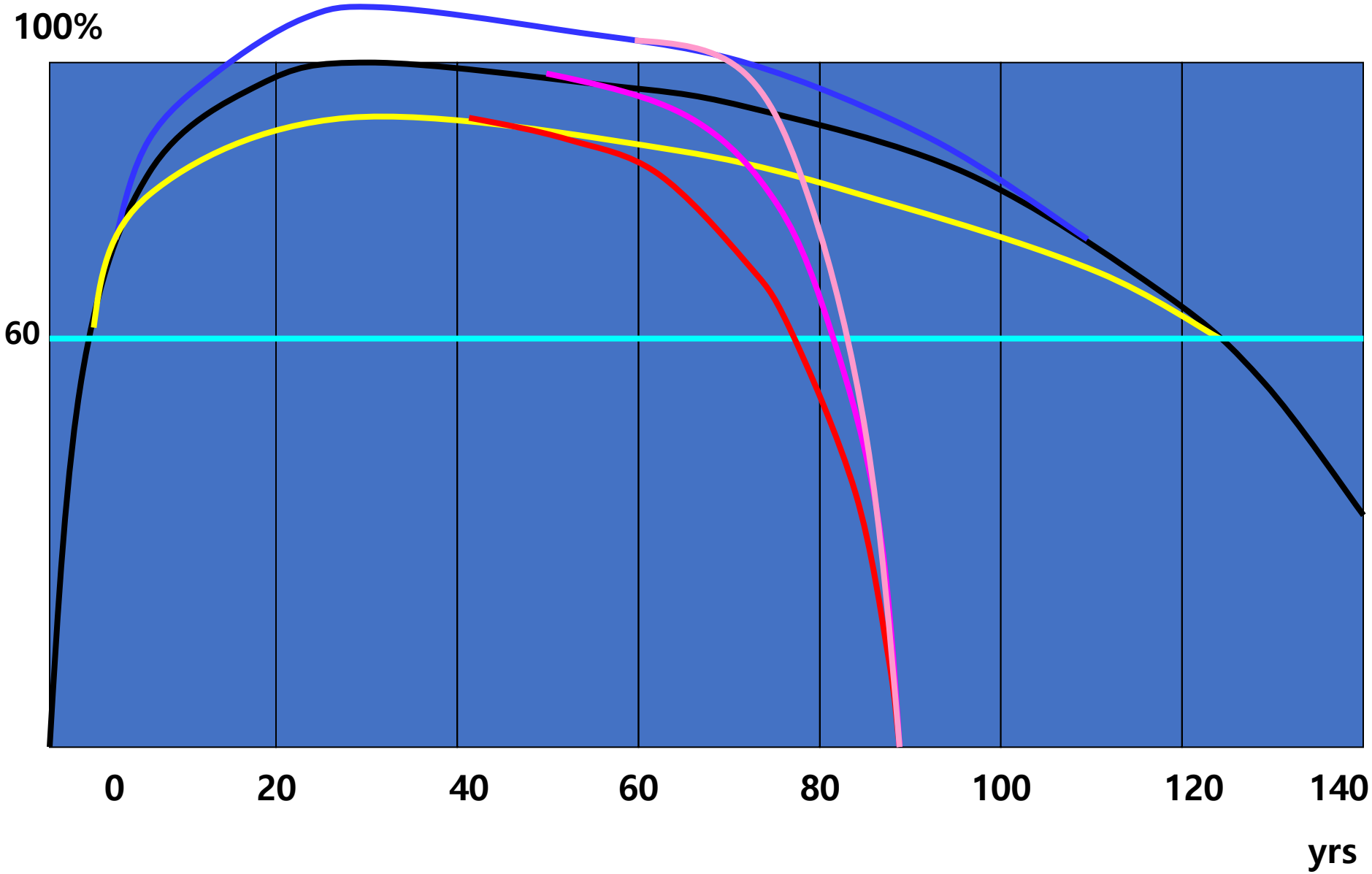
Catholic University of Daegu School of Medicine



Nervous system

- Central Nervous System (CNS)
- Peripheral Nervous System (PNS)
- Autonomic Nervous System (ANS)

Development & Degeneration of Nervous system



Definition

- **Degeneration**: rapid process of cell or tissue breakdown, the degradative products of which evoke a more vigorous reaction of phagocytosis and cellular gliosis

- **Atrophy**: gradual wasting and loss of cells, leaving no degradative products and only a sparsely cellular, fibrous gliosis

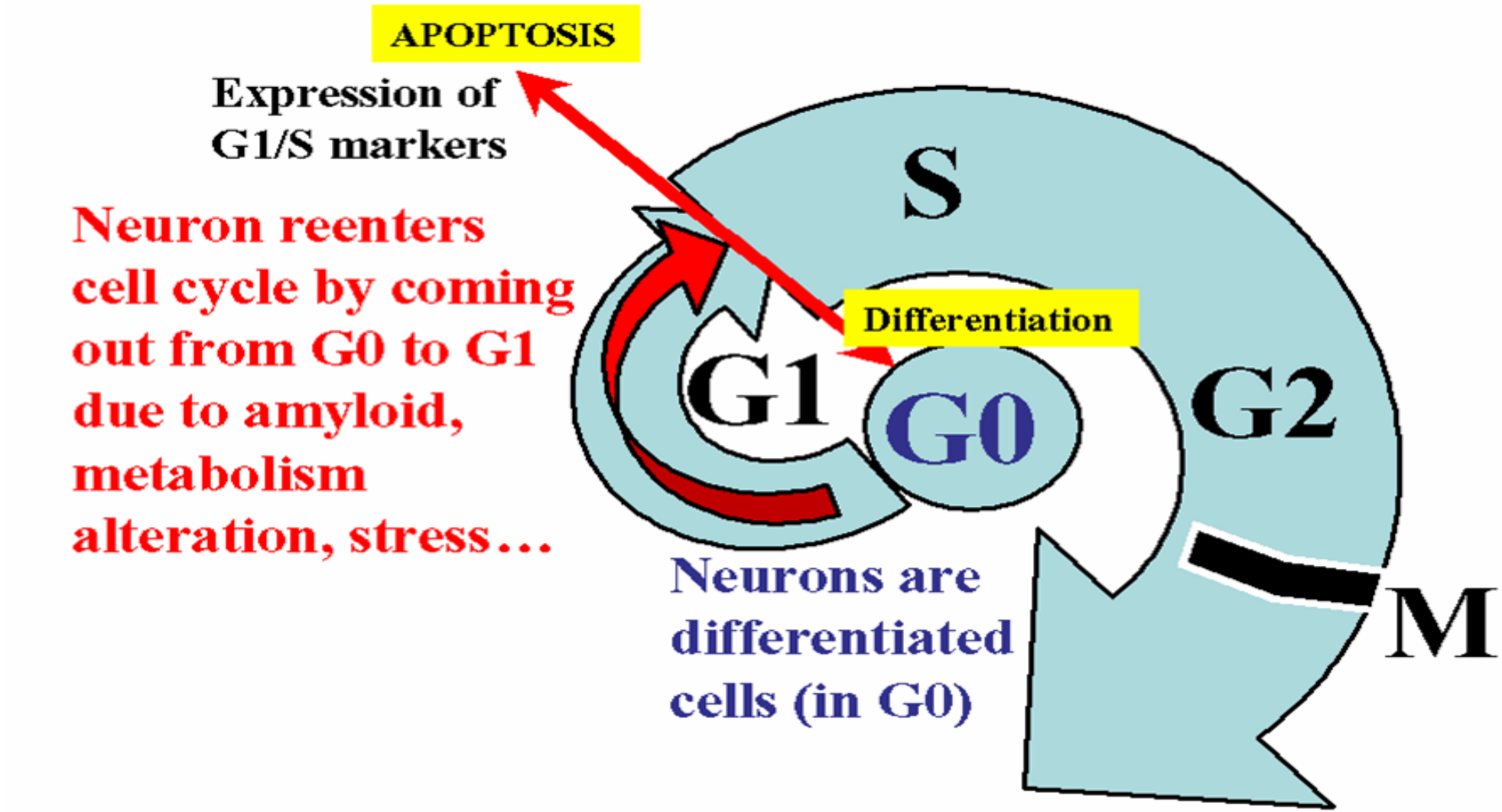
- **Apoptosis**: naturally occurring cell death in the CNS during development or some stressful conditions

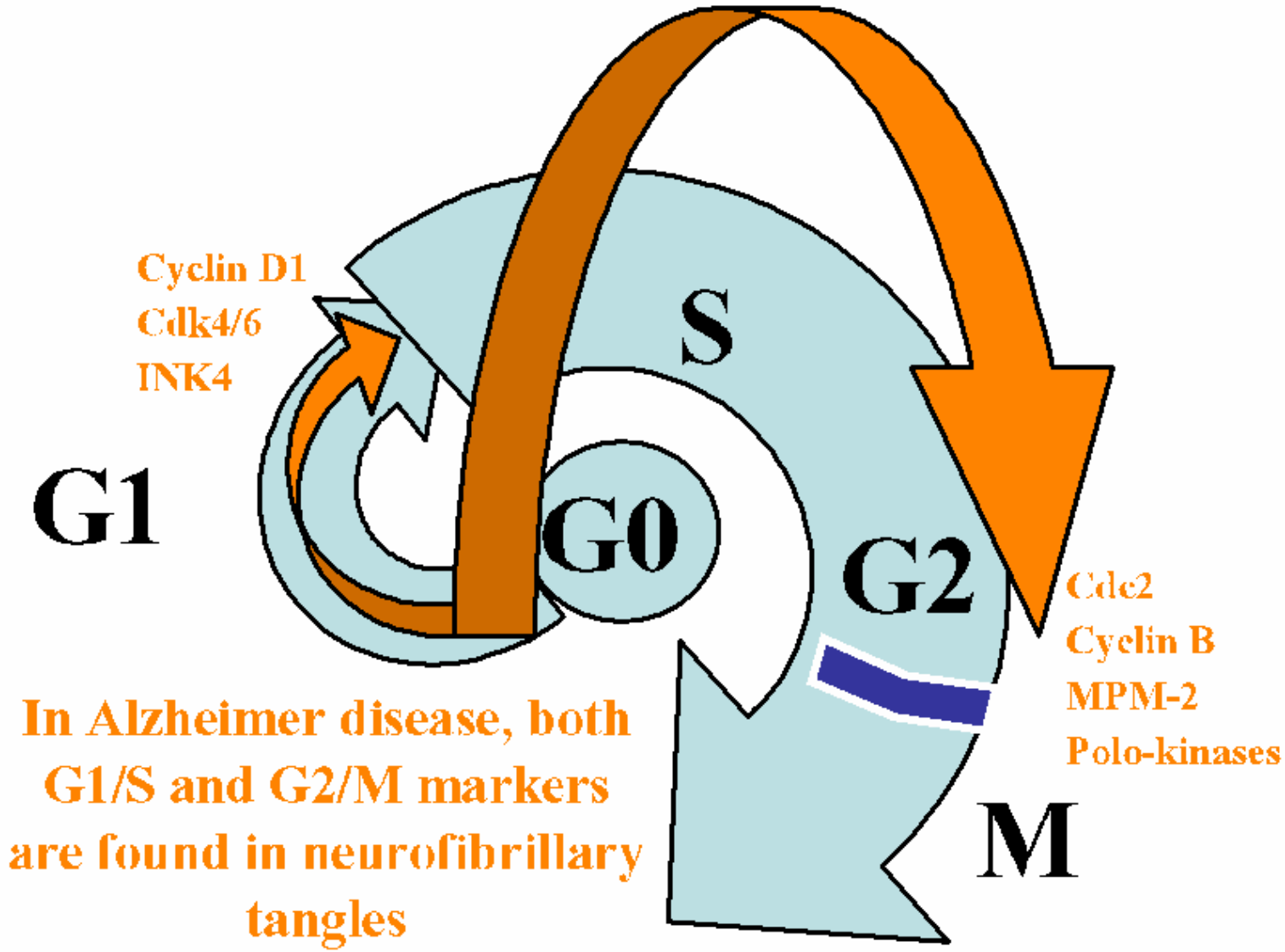
Mechanism of neurodegeneration

- Extracellular vs. intracellular Aβ:
  - Oxidative damage through H_2O_2
  - An ionophoric peptide, disrupting lipid packing and/or formation of an ion channel
- Tau polymerization(tangles, neurites)
- Inflammation/glial activation
- Mitochondrial failure
- Apoptosis

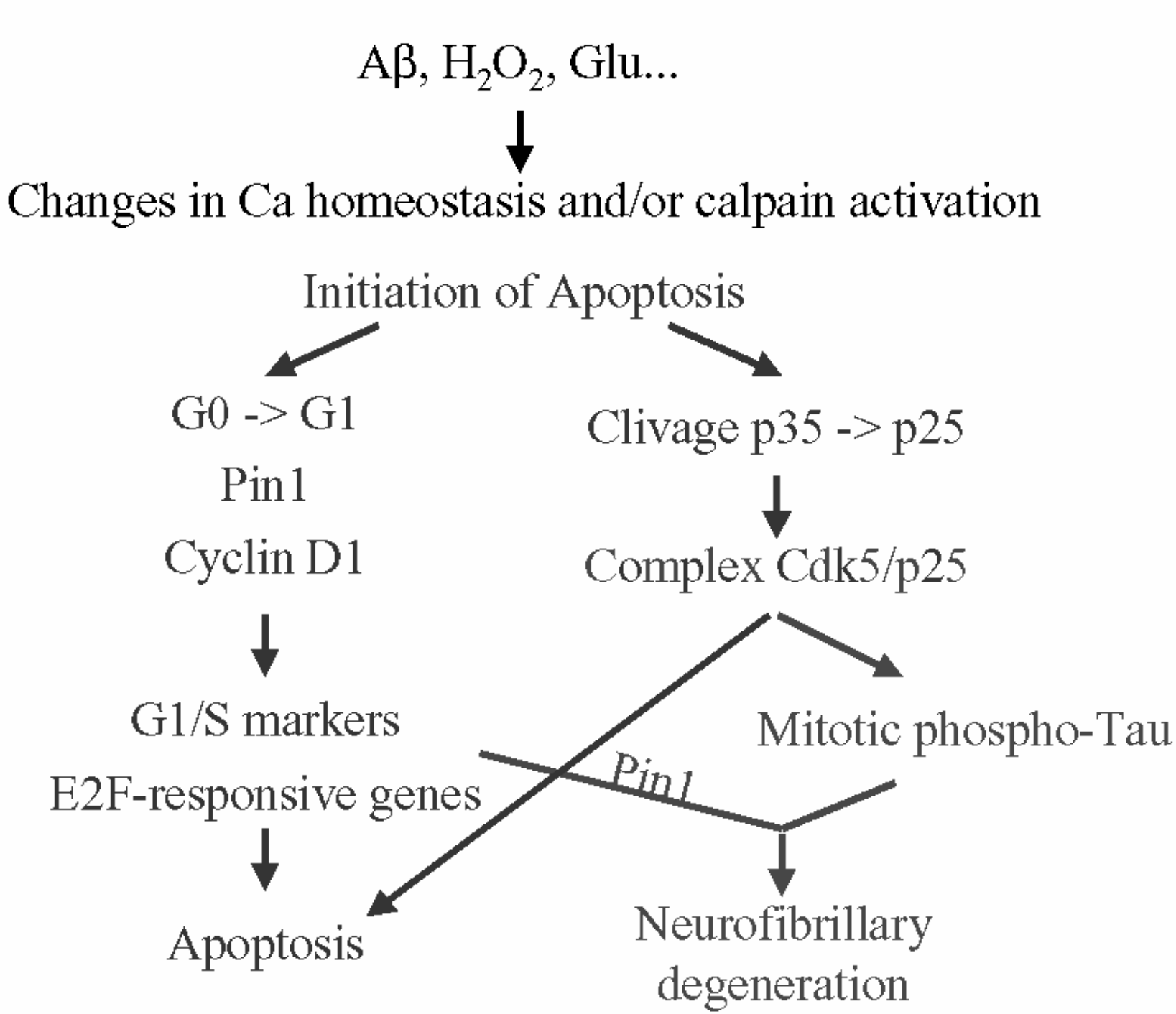
Apoptosis

- Programmed cell death
- Auto-digestion of cell
- Activation of intracellular protease
- No inflammatory reaction
- Cytoskeletal disruption, Cell shrinkage, Membrane blebbing


APOPTOSIS
Expression of
G1/S markers
Neuron reenters
cell cycle by coming
out from G0 to G1
due to amyloid,
metabolism
alteration, stress…
S
Differentiation
G1
G0
G2
M
Neurons are
differentiated
cells (in G0)



In Alzheimer disease, both G1/S and G2/M markers are found in neurofibrillary tangles


Aβ, H_2O_2, Glu...
Changes in Ca homeostasis and/or calpain activation
Initiation of Apoptosis
G0 -> G1
Pin1
Cyclin D1
G1/S markers
E2F-responsive genes
Apoptosis
Clivage p35 -> p25
Complex Cdk5/p25
Mitotic phospho-Tau
Pin1
Neurofibrillary degeneration

Apoptosis III

- Neurodegenerative disease:

  Alzheimer disease: temporoparietal lobe

  Parkinson's disease: SNc

  Amyotrophic lateral sclerosis: motor neuron

  Retinitis pigmentosa: retina

  Spinal muscular dystrophy: anterior horn cell

Apoptosis IV

Causative factor

- Oxidative stress
- Calcium toxicity
- Mitochondrial defect
- Excitatory toxicity
- Deficit of survival factor

cf: apoptotic threshold of cell

Treatment of Apoptosis

- Antioxidant
- CDK2/4 inhibitor(p21,p16 gene tx)
- Survival growth factor
- Gene therapy
- Deferoxamine

Characteristics of Degenerative disease

- Begin insidiously
- After a long period of normal function
- Ceaselessly progressive course
- Bilateral symmetry

  exception: early PD
- May continue for many years

Degenerative disease I

- Pathology

  Selective involvement of anatomically and physiologically related systems of neurons

  ex) ALS, FRDA

- Radiology

  no change initially

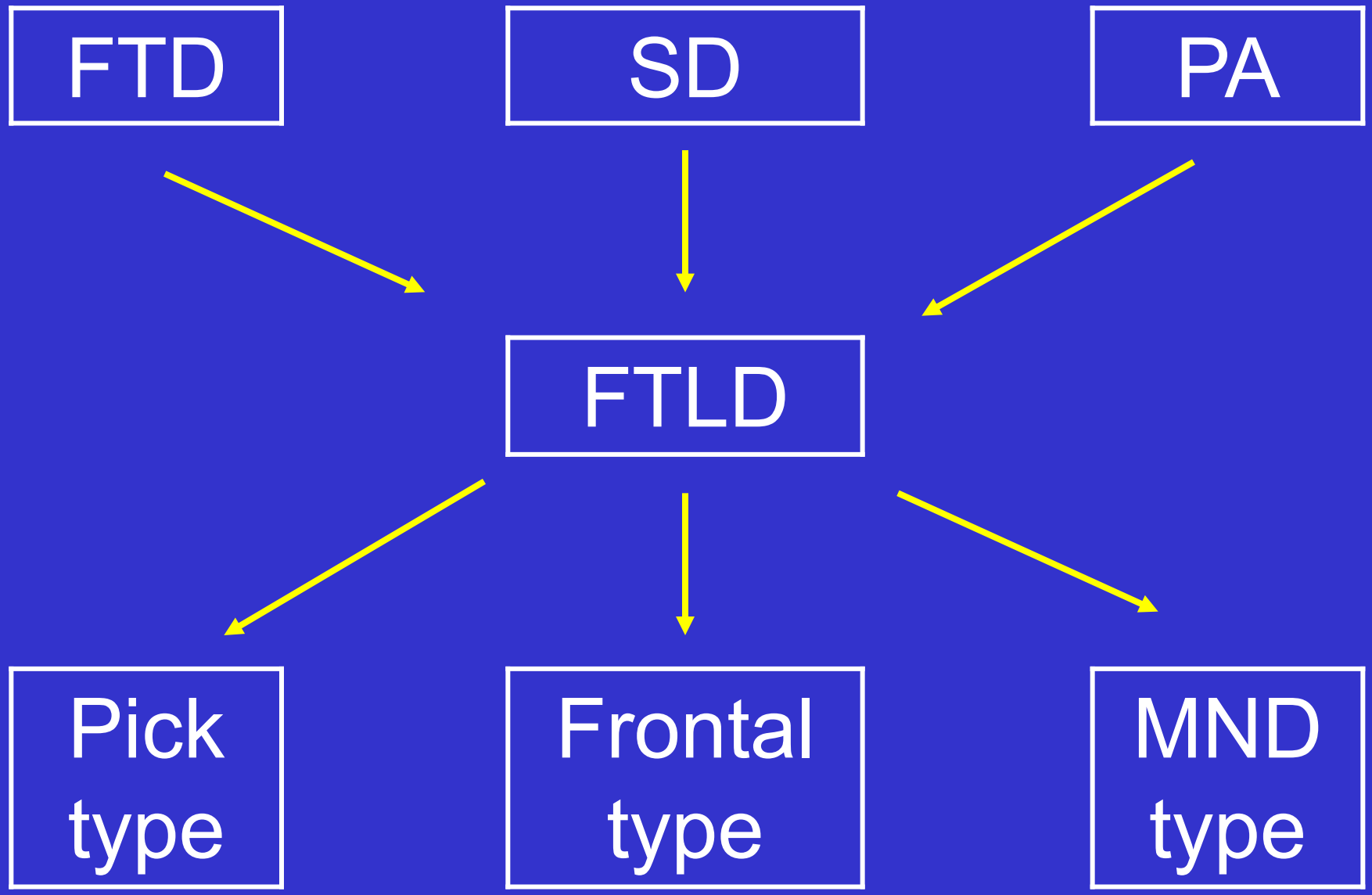
  volumetric reduction

  metabolic reduction

Degenerative disease II

Classification is based on

- Clinical syndrome
- Pathologic anatomy
- Genetic abnormality


FTD
SD
PA
FTLD
Pick type
Frontal type
MND type

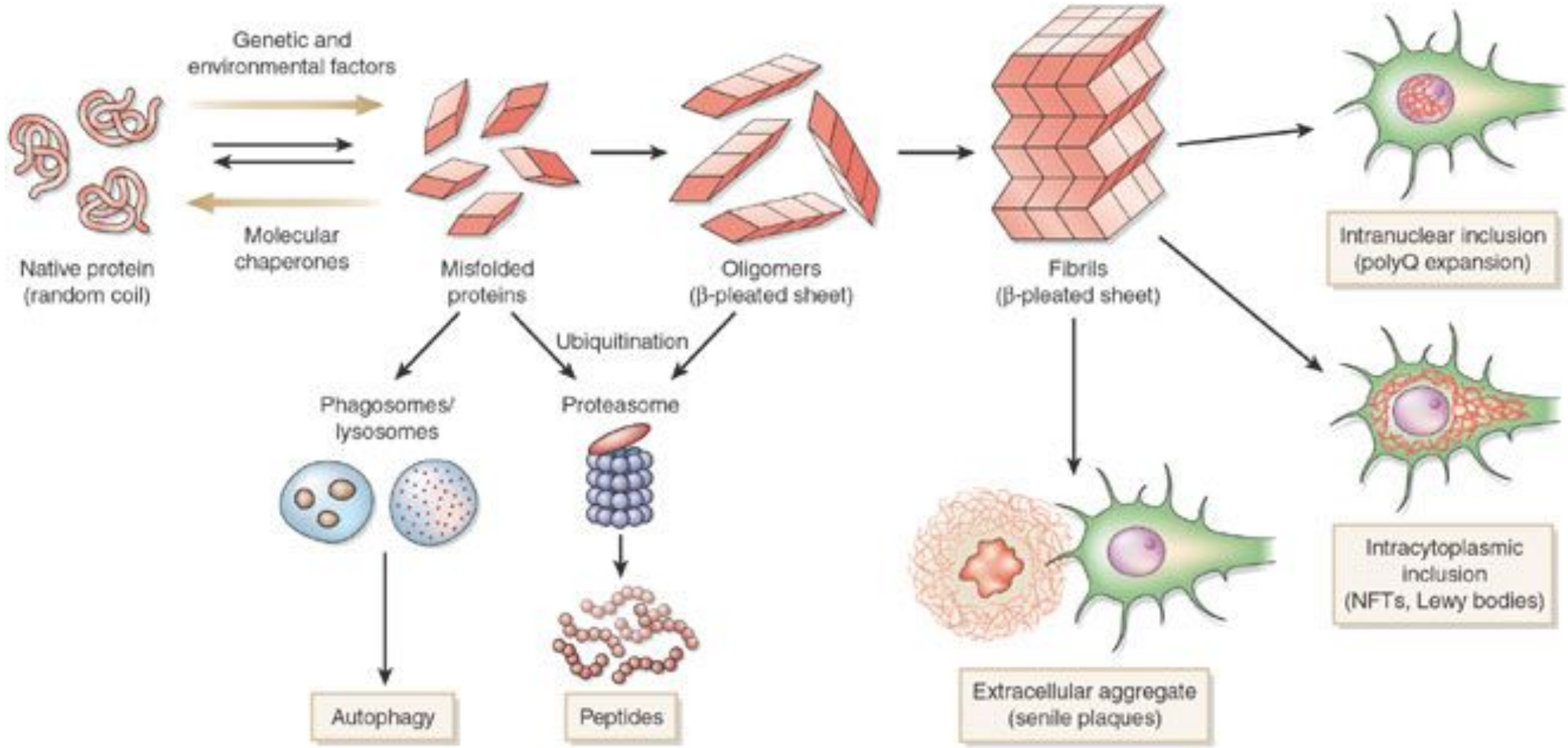
Classification of Neurodegenerative Diseases

- Progressive dementia: AD
- Dementia with other neurologic signs: HD
- Disorder of posture and movement: PD
- Ataxia: SCA
- Slowly developed muscular weakness: ALS
- Sensorimotor disorder: CMT
- Progressive blindness: Leber, Retinitis Pigmentosa
- Neurosensory deafness

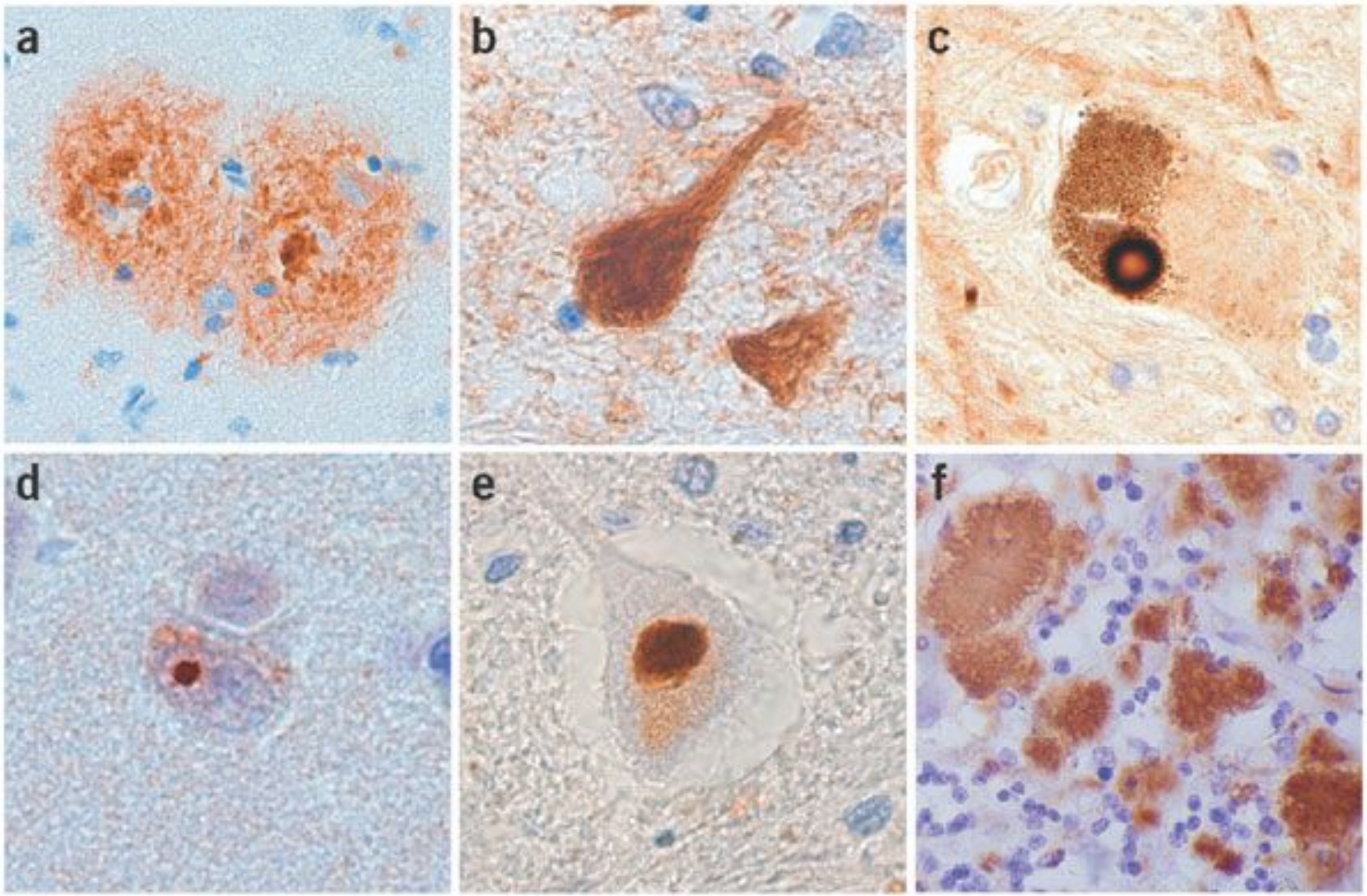
Proteins of Neurodegenerative Diseases(Nat Med, 2004)

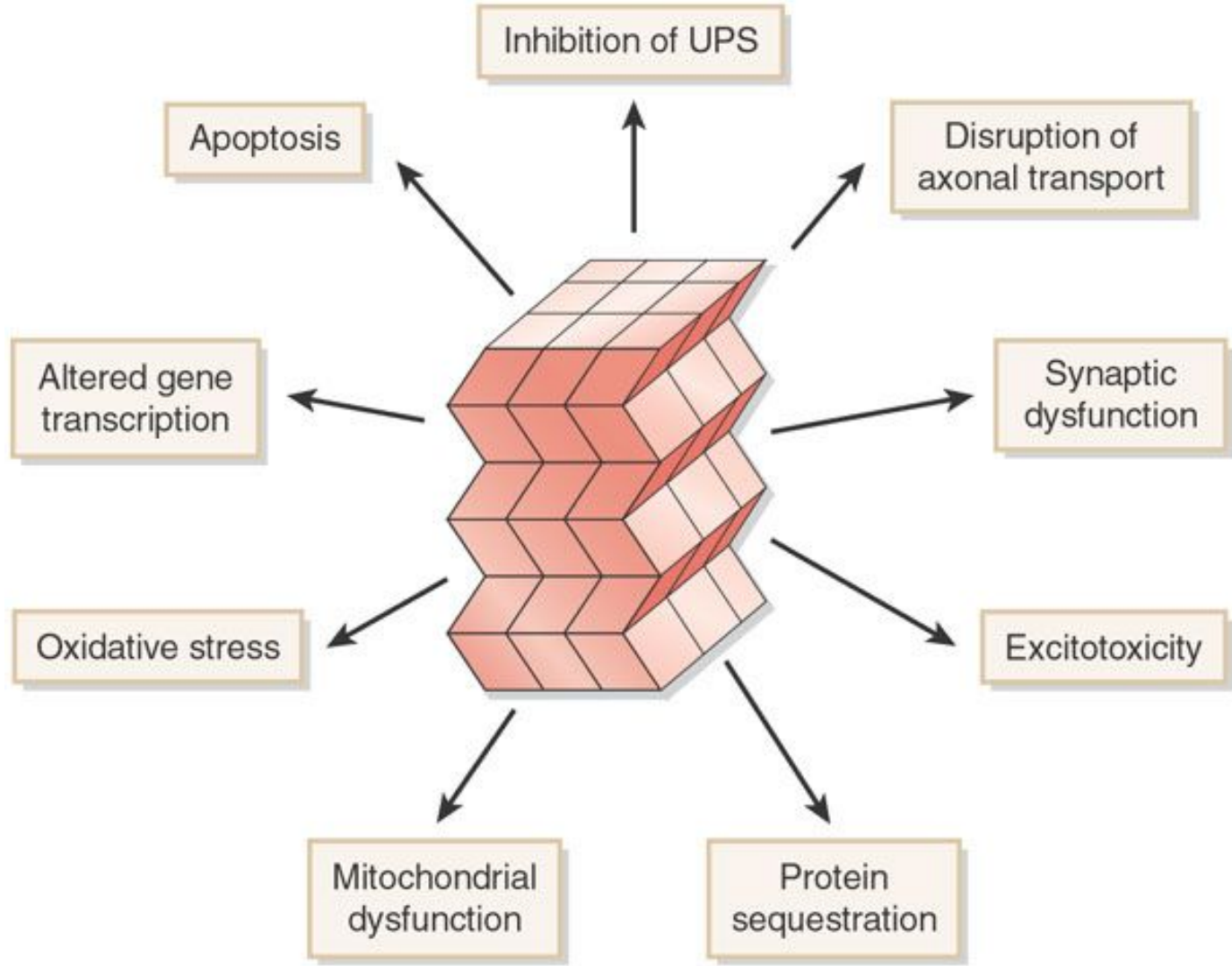
Toxic protein	Protein deposit	Familial disease	Gene mutated	Sporadic disease	Risk factor
β-amyloid	Senile plaques	FAD	*APP*	Alzheimer disease	*Apoe4*
			PS1, PS2		
Tau	Neuronal and glial inclusions	FTDP-17 inclusions	*MAPT*	AD and tauopathies[a]	*MAPT* haplotype
α-synuclein	Lewy bodies Lewy neurites	Familial PD[b]	*SNCA* (α-synuclein)	Lewy body disease[c]	*SNCA*polymorphism
				MAPT haplotype	
	Glial cytoplasmic inclusions	Not identified	Not applicable	Multiple system atrophy	Not identified
Polyglutamine repeat expansion	Nuclear and cytoplasmic inclusions	Huntington disease	*HD* (huntingtin)	Not applicable	Not identified
		Kennedy disease	*AR* (androgen receptor)		
		DRPLA	*DRPLA* (atrophin-1)		
		SCA1, 2,3	*ATXN1, 2,3*		
		SCA6	*CACNA1A*[d]		
		SCA7	*ATXN7* (ataxin-7)		
		SCA17	*TBP*		
PrP^{SC}	Protease-resistant PrP[e]	Familial prion protein disease[f]	*PRNP*	Sporadic prion protein disease[g]	*PRNP*polymorphism
SOD	Hyaline inclusions	Autosomal dominant familial ALS	*SOD1* (Cu/Zn SOD)	Sporadic ALS	Not identified
ABri/ADan	Amyloid plaques and angiopathy	Familial British/Danish dementia	*BRI*	Not identified	Not identified
Neuroserpin	Collins bodies	FENIB[h]	*SERPINI1*(neuroserpin)	Not identified	Not identified

Model of degeneration of nerve(Nat Med, 2004)



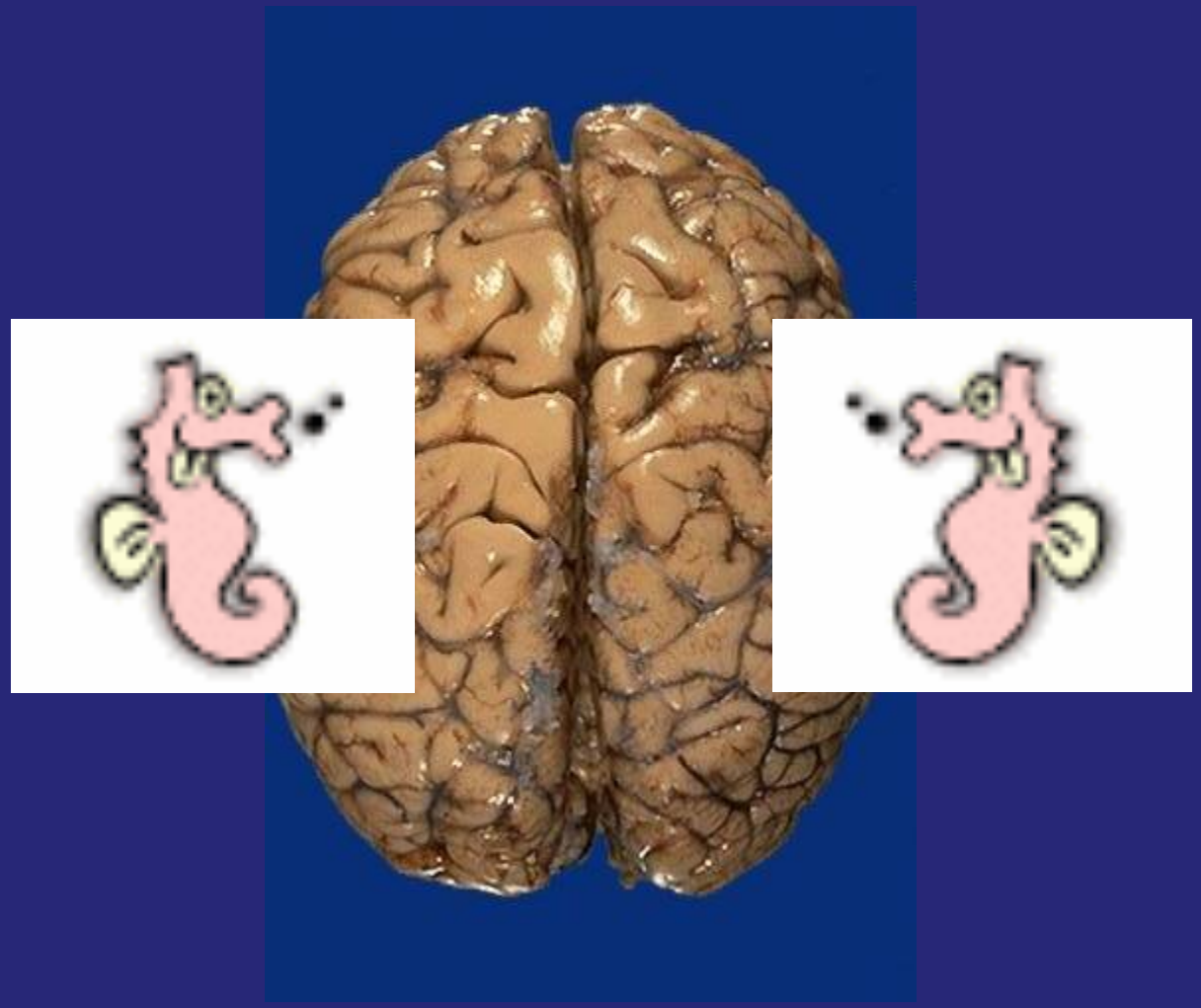
Protein aggregates in neurodegenerative diseases(Nigel Cairns)



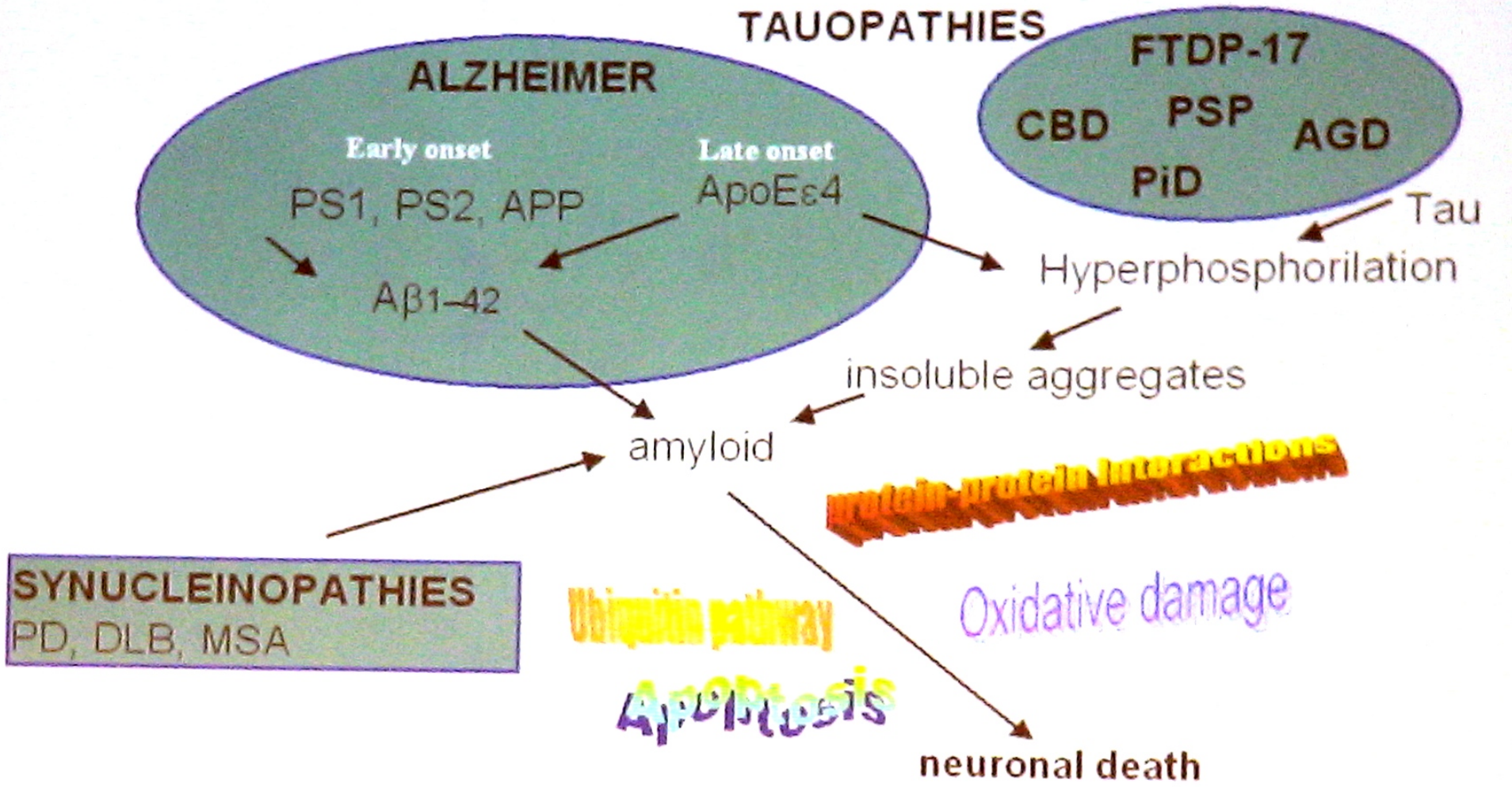

Inhibition of UPS
Apoptosis
Disruption of axonal transport
Altered gene transcription
Synaptic dysfunction
Oxidative stress
Excitotoxicity
Mitochondrial dysfunction
Protein sequestration

Progressive Dementia

Left



Neurodegenerative Dementias



FTDP-17 frontotemporal dementia and parkinsonism linked to chromosome 17 associated with Tau gene mutations.
CBD:Corticobasal degeneration PiD Pick's disease AGD Argyrophilic grain disease. PSP Progressive supranuclear palsy
PD Parkinson's disease, DLB Dementia with Lewy bodies MSA Multiple system atrophy

Table 1 Diseases with tau inclusions

Alzheimer's disease
Amyotrophic lateral sclerosis/parkinsonism-dementia complex
Argyrophilic grain disease
Chronic traumatic encephalopathy
Corticobasal degeneration
Diffuse neurofibrillary tangles with calcification
Down's syndrome
Familial British dementia
Familial Danish dementia
Familial frontotemporal dementia and parkinsonism
Gerstmann-Sträussler-Scheinker disease
Guadeloupean parkinsonism
Huntington's disease
Meningio-angiomatosis
Myotonic dystrophy
Neurodegeneration with brain iron accumulation
Niemann-Pick disease, type C
Non-Guamanian motor neuron disease with neurofibrillary tangles
Pick's disease
Postencephalitic parkinsonism
Progressive supranuclear palsy
SLC9A6-related mental retardation
Subacute sclerosing panencephalitis
Tangle-only dementia
White matter tauopathy with globular glial inclusions

doi:10.1093/brain/aww230 BRAIN 2017: 140; 266–278 | 266

BRAIN
A JOURNAL OF NEUROLOGY

REVIEW ARTICLE

Like prions: the propagation of aggregated tau and α-synuclein in neurodegeneration

Michel Goedert, Masami Masuda-Suzukake and Benjamin Falcon

The abnormal aggregation of a small number of known proteins underlies the most common human neurodegenerative diseases. In tauopathies and synucleinopathies, the normally soluble intracellular proteins tau and α-synuclein become insoluble and filamentous. In recent years, non-cell autonomous mechanisms of aggregate formation have come to the fore, suggesting that nucleation-dependent aggregation may occur in a localized fashion in human tauopathies and synucleinopathies, followed by seed-dependent propagation. There is a long prodromal phase between the formation of protein aggregates and the appearance of the first clinical symptoms, which manifest only after extensive propagation, opening novel therapeutic avenues.

Distribution of amyloid-b, tau, a-synuclein

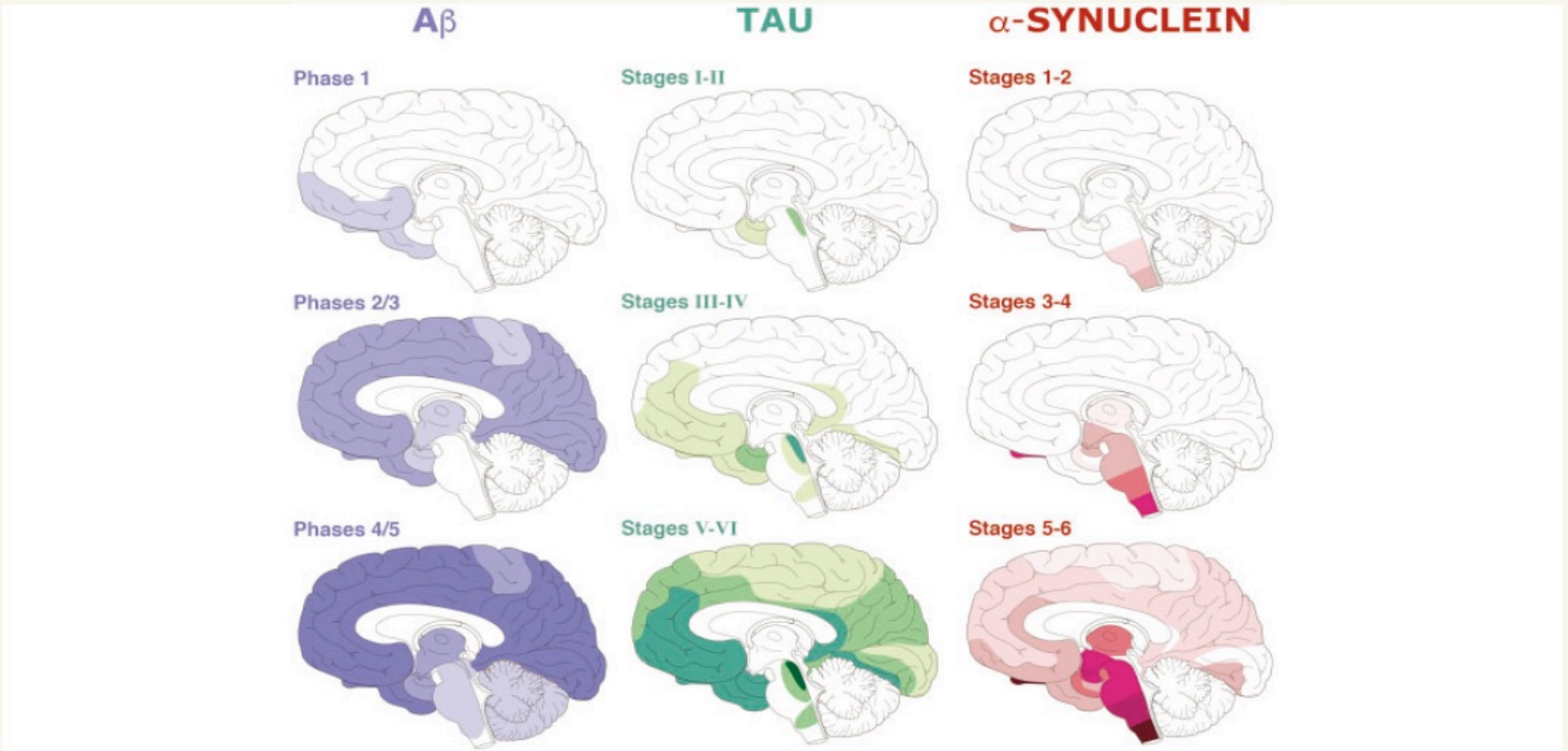


Figure 1 Distribution of amyloid-β, tau and α-synuclein inclusions in human brain. *Left*: Amyloid-β (Aβ) plaques develop first in basal temporal and orbitofrontal neocortex (Phase 1). They are observed later throughout the neocortex, hippocampal formation, amygdala, diencephalon and basal ganglia (Phases 2 and 3). In severe cases of Alzheimer's disease, amyloid-β plaques are also found in mesencephalon, lower brainstem and cerebellar cortex (Phases 4 and 5). *Middle*: Tau inclusions develop in the locus coeruleus, as well as in transentorhinal and entorhinal regions (Stages I and II). This is followed by their presence in the hippocampal formation and some parts of the neocortex (Stages III and IV), followed by large parts of the neocortex (Stages V and VI). *Right*: The first α-synuclein inclusions are present in the olfactory bulb and the dorsal motor nucleus of the vagal and glossopharyngeal nerves of the medulla oblongata (Stages 1 and 2). From the brainstem, the pathology ascends through the pons to midbrain and basal forebrain (Stages 3 and 4), followed by the neocortex (Stages 5 and 6). This figure is based on the work of Braak, Del Tredici, and collaborators. From Goedert (2015).

Brain 2017:140;266-278

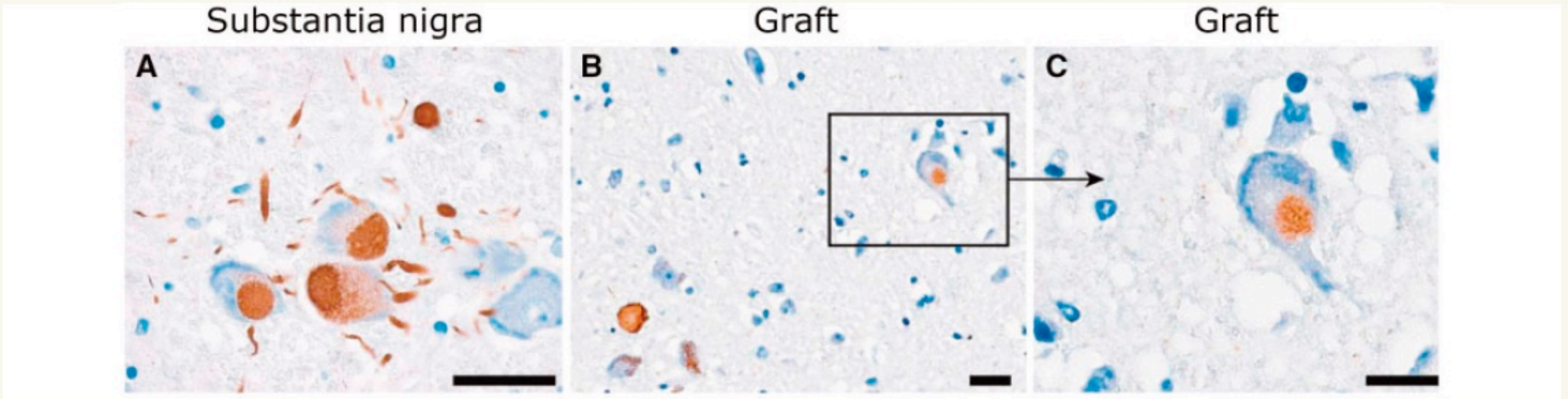


Figure 2 Possible host-to-graft spreading of Lewy pathology in Parkinson's disease. The patient received a transplant of foetal human mesencephalic dopaminergic nerve cells into the putamen 16 years previously. Immunohistochemistry for α-synuclein visualizes Lewy bodies and neurites in the host substantia nigra (**A**) and the transplant (**B** and **C**). Adapted from Li *et al.* (2008).

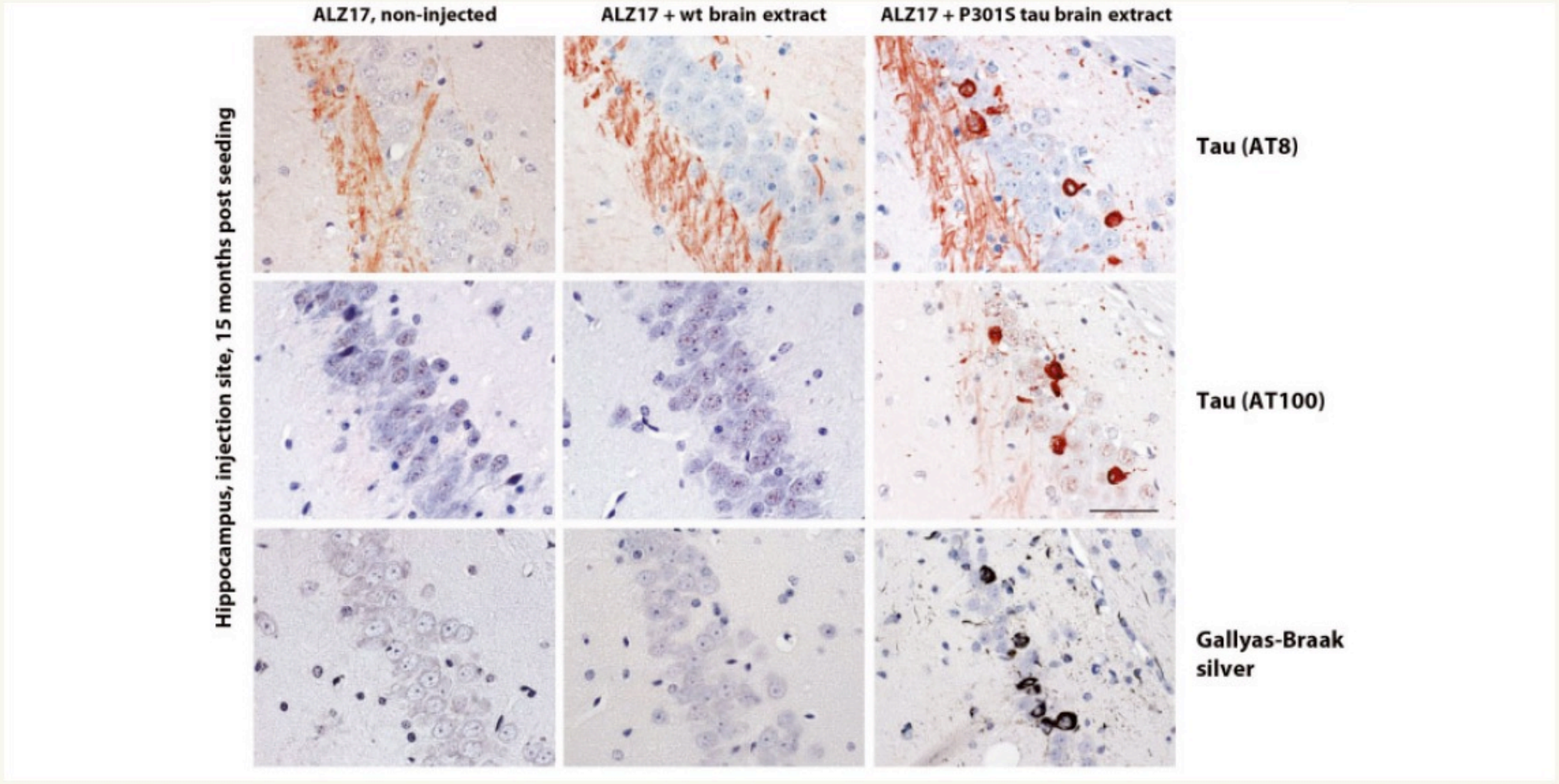


Figure 4 Induction of filamentous tau pathology in mice transgenic for one isoform of wild-type human tau (line ALZ17) following injection with brain extract from symptomatic mice transgenic for one isoform of human mutant P301S tau. Staining of the hippocampal CA3 region of 18-month-old ALZ17 mice with anti-tau antibodies AT8 and AT100 and Gallyas-Braak silver. Non-injected (*left*), 15 months after injection with brain extract from non-transgenic control mice (*middle*) and 15 months after injection with brain extract from 6-month-old mice transgenic for human P301S tau (*right*). The sections were counterstained with haematoxylin. Scale bar = 50 μm.

Conformation determines the seeding potencies and resistance to disaggregation of tau aggregates.

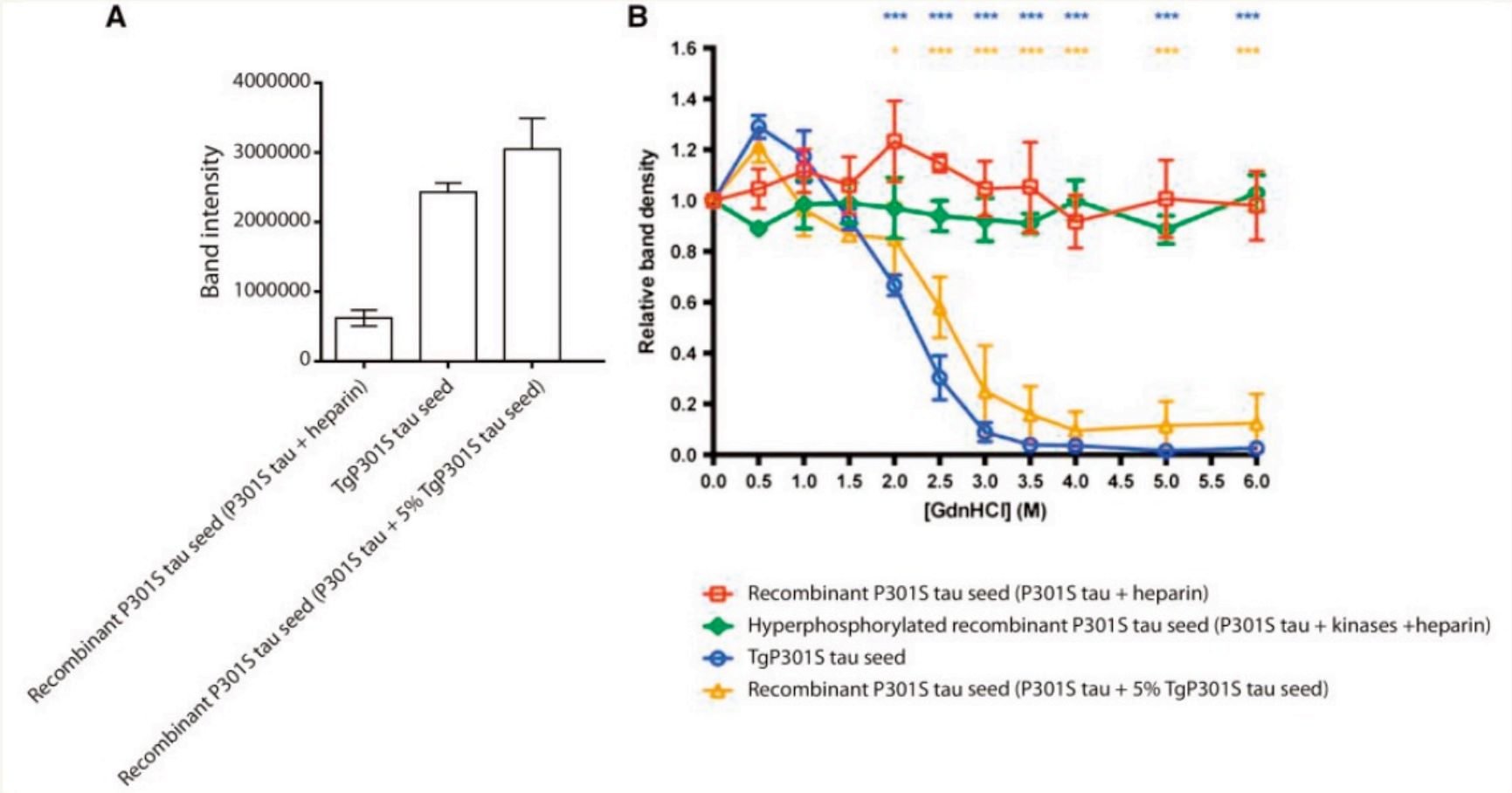
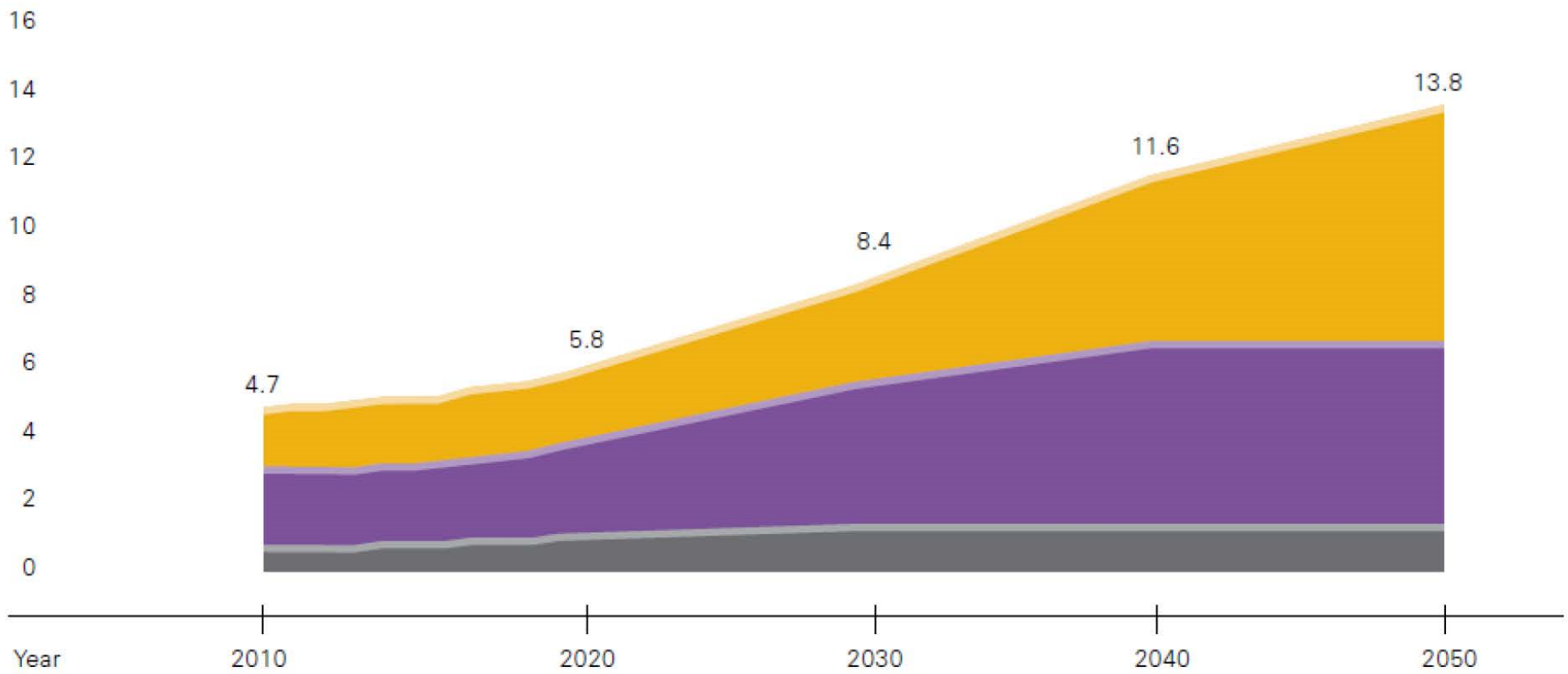


Figure 5 Conformation determines the seeding potencies and resistance to disaggregation of tau aggregates. (**A**) Quantitation by western blotting of insoluble fraction from tau-expressing HEK cells seeded with equivalent amounts of aggregated recombinant P301S tau (P301S tau + heparin), TgP301S tau aggregates and aggregated P301S tau (P301S tau + 5% TgP301S tau aggregates). (**B**) Guanidine hydrochloride (GdnHCl) treatment of tau seeds.

Patients

FIGURE 4	PROJECTED NUMBER OF PEOPLE AGE 65 AND OLDER (TOTAL AND BY AGE GROUP) IN THE U.S. POPULATION WITH ALZHEIMER'S DISEASE, 2010 TO 2050

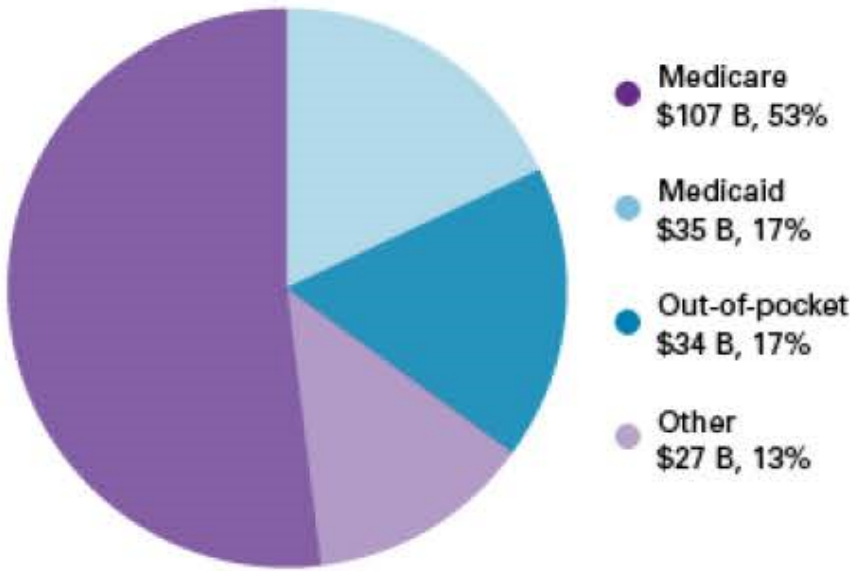


Created from data from Hebert et al.[B3], A10

Cost

FIGURE 10	AGGREGATE COSTS OF CARE BY PAYER FOR AMERICANS AGE 65 AND OLDER WITH ALZHEIMER'S DISEASE AND OTHER DEMENTIAS, 2013*

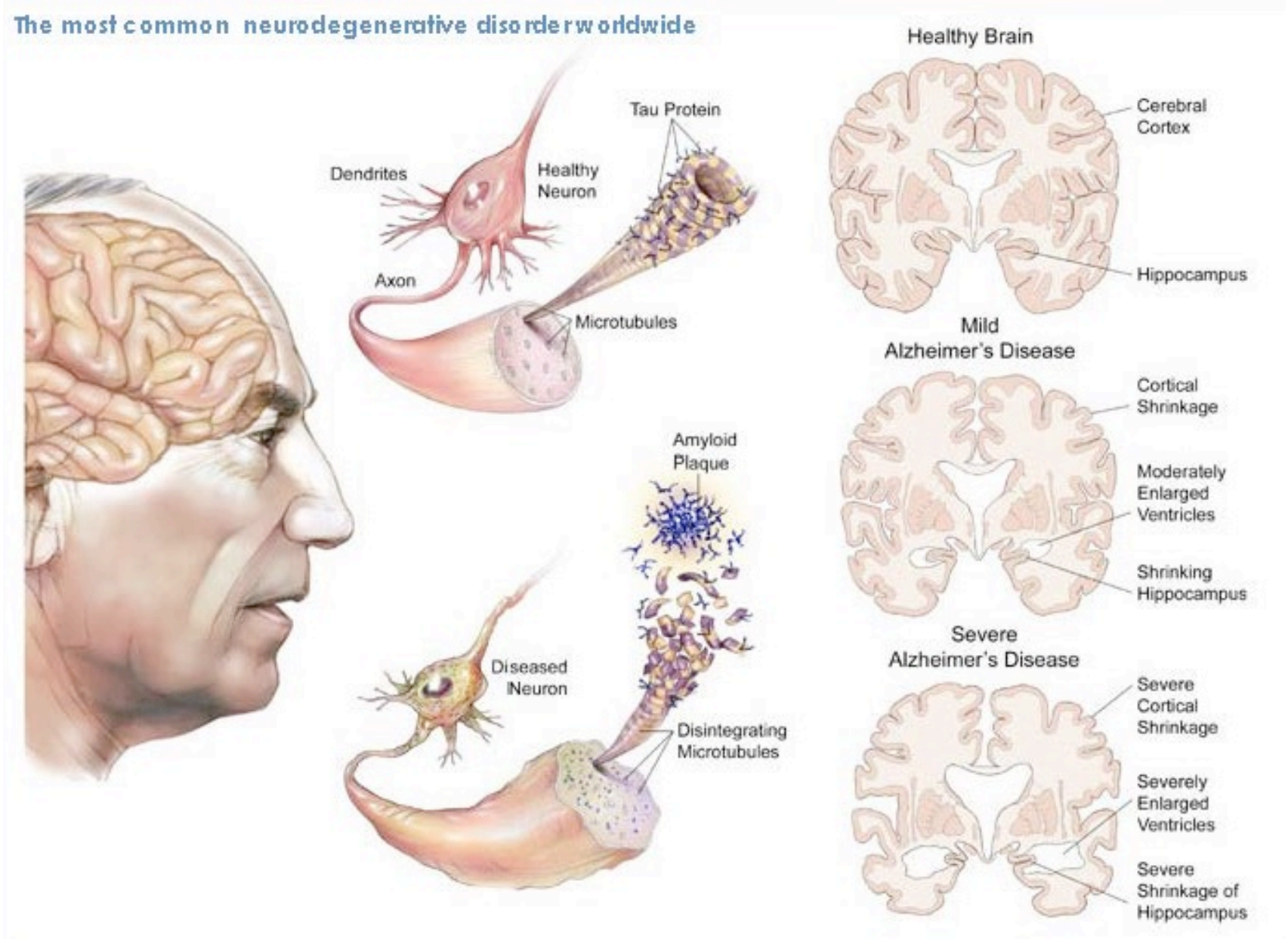
Total cost: $203 Billion (B)



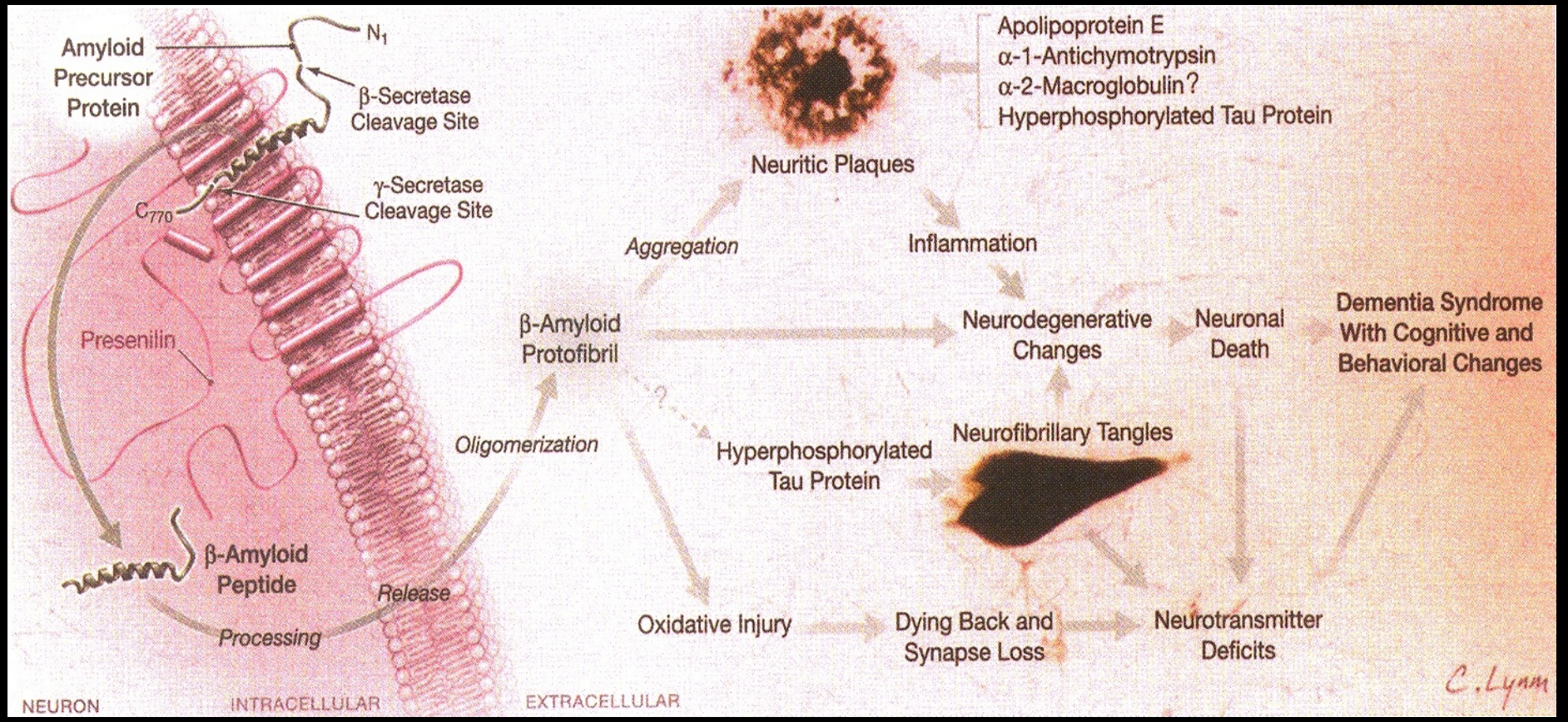
*Data are in 2013 dollars.

Created from data from the application of The Lewin Model[A19] to data from the Medicare Current Beneficiary Survey for 2008.[I21] "Other" payment sources include private insurance, health maintenance organizations, other managed care organizations and uncompensated care.

Alzheimer’s disease(AD)

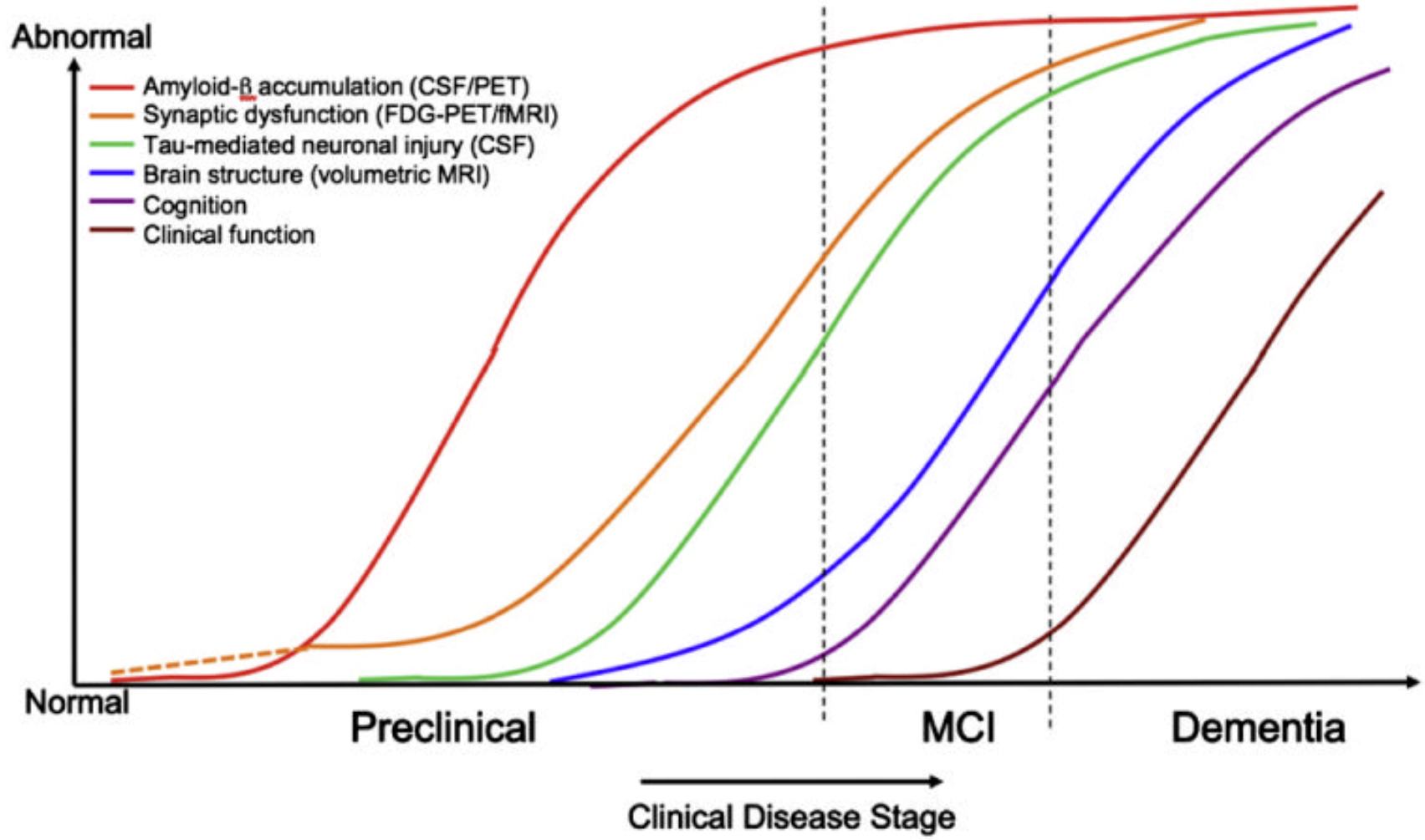


Ab Pathogenesis of AD

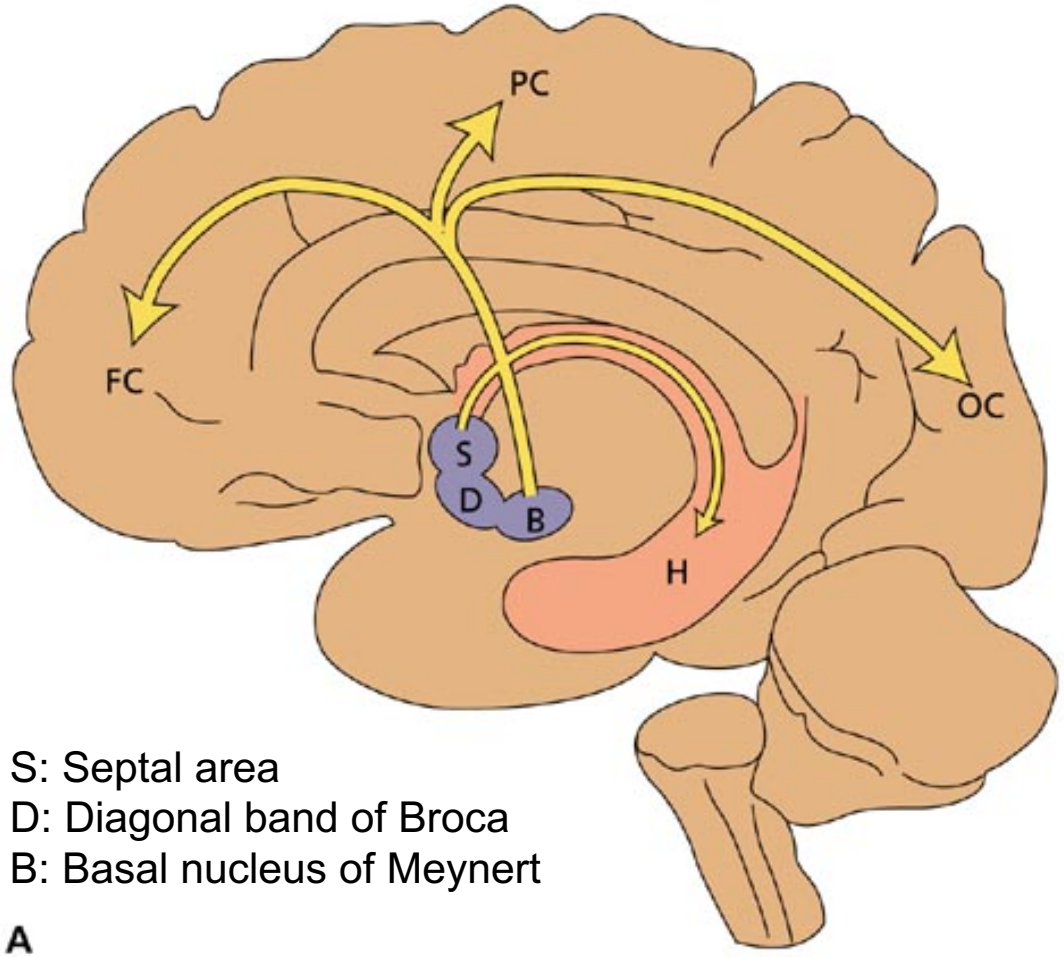


Cummings & Cole, 2002'

Biomarkers of Alzheimer's Disease



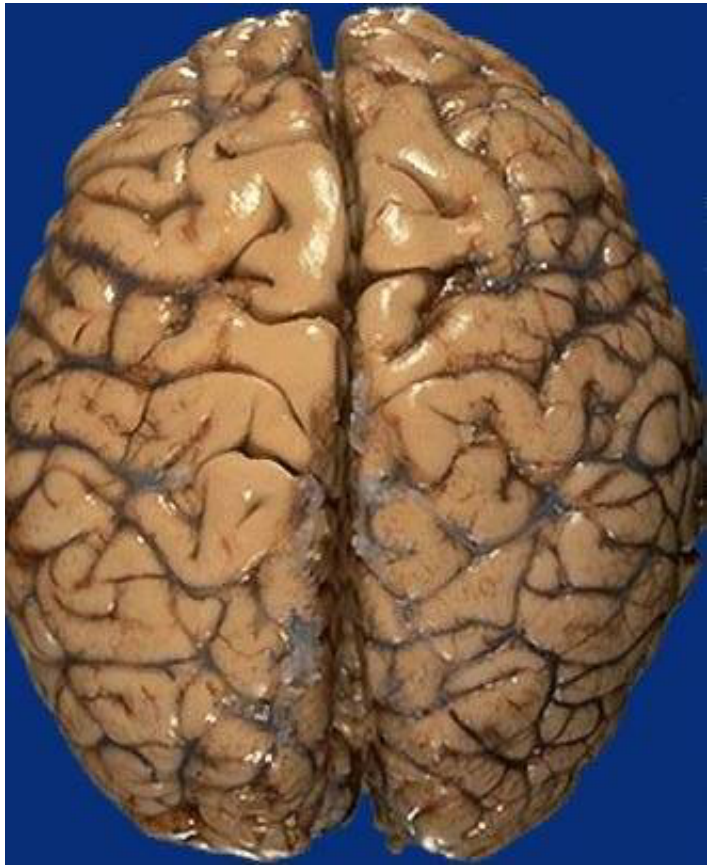
Cholinergic hypothesis of Dementia



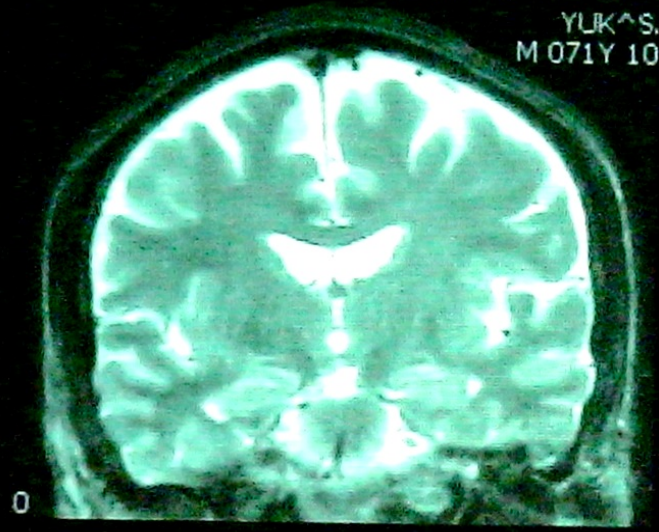
S: Septal area
D: Diagonal band of Broca
B: Basal nucleus of Meynert

A

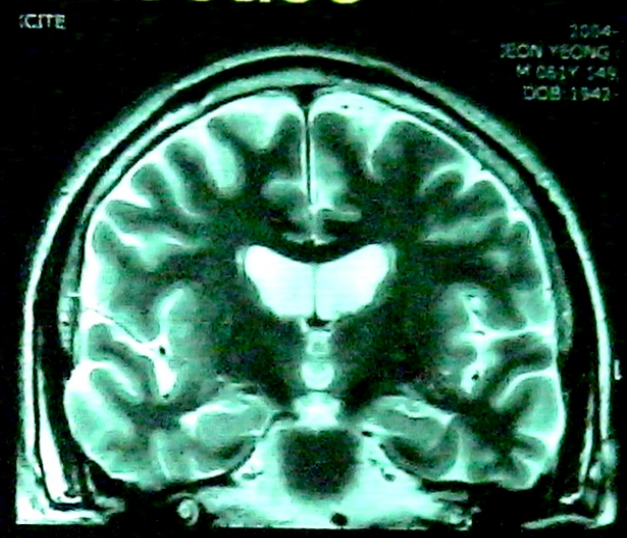
Neuroimagin of AD



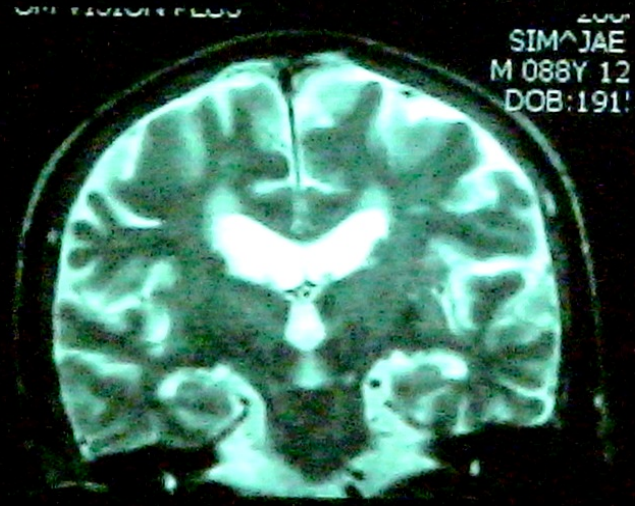
Alzheimer's Disease



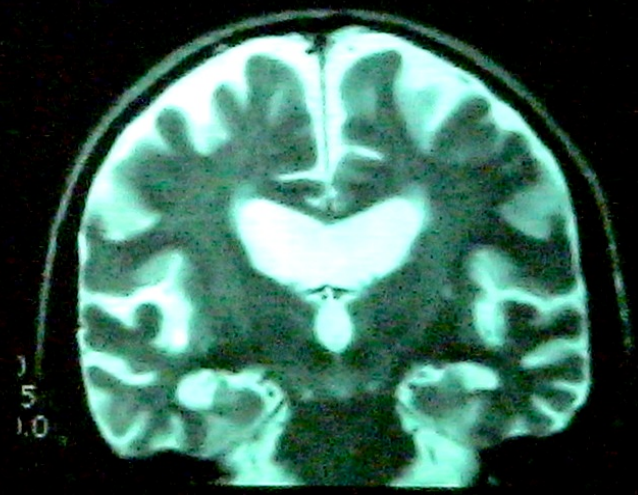
Normal



AD CDR0.5



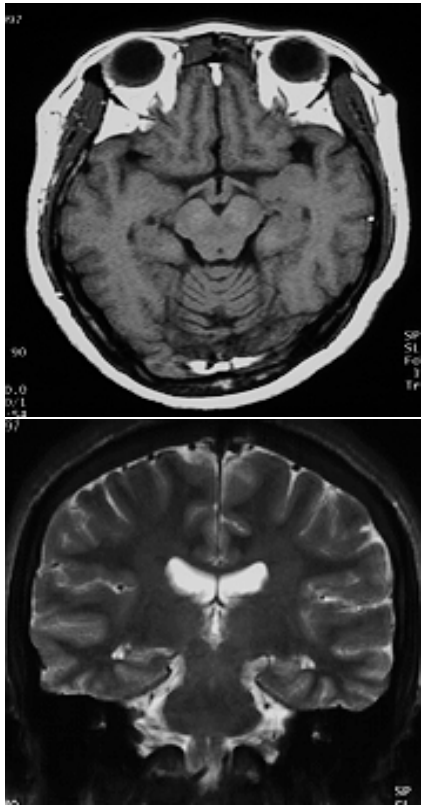
AD CDR 2



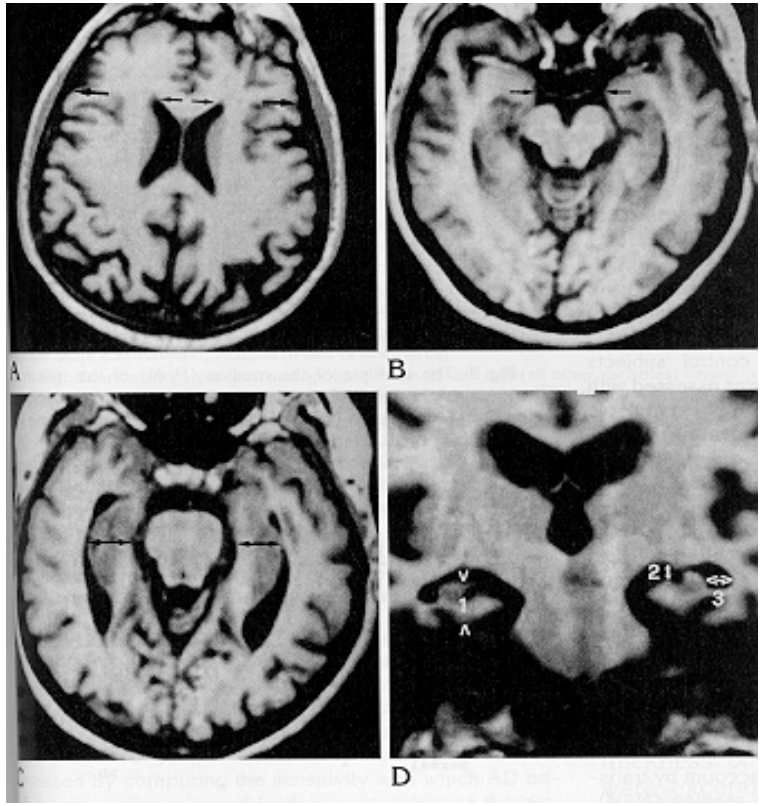
AD CDR3

Brain MRI of Normal and AD

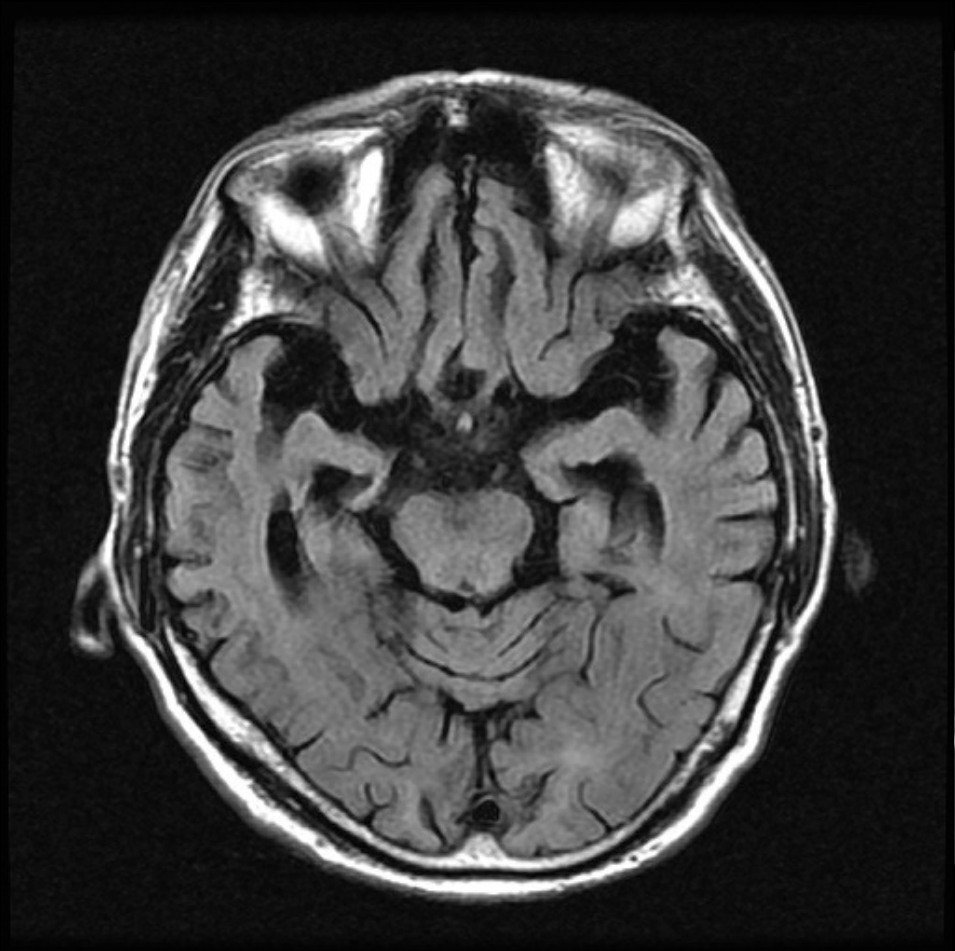
Normal

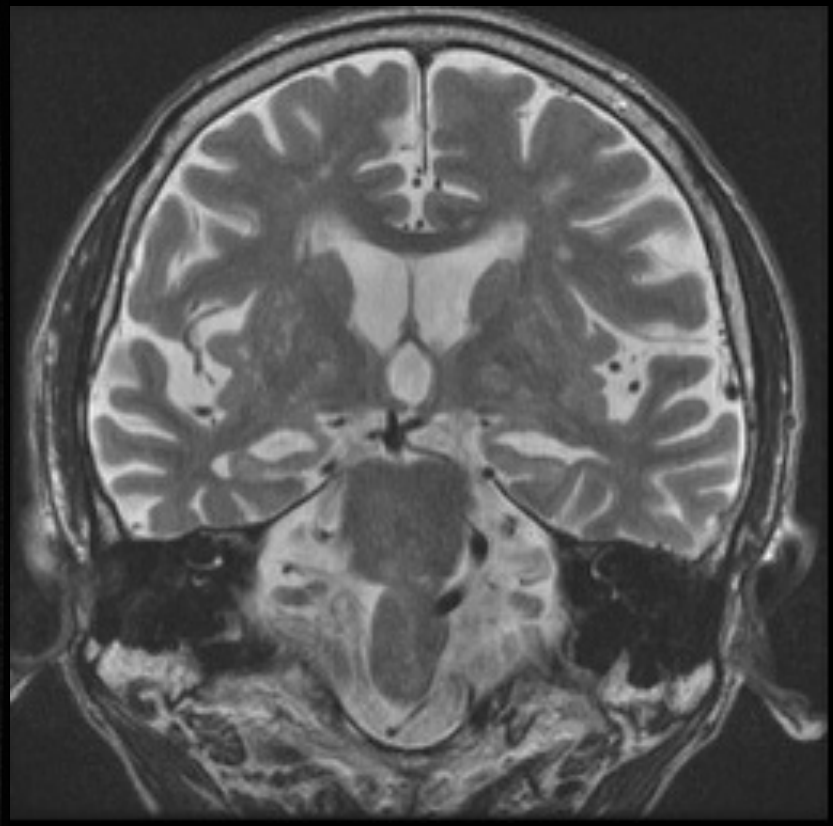


AD

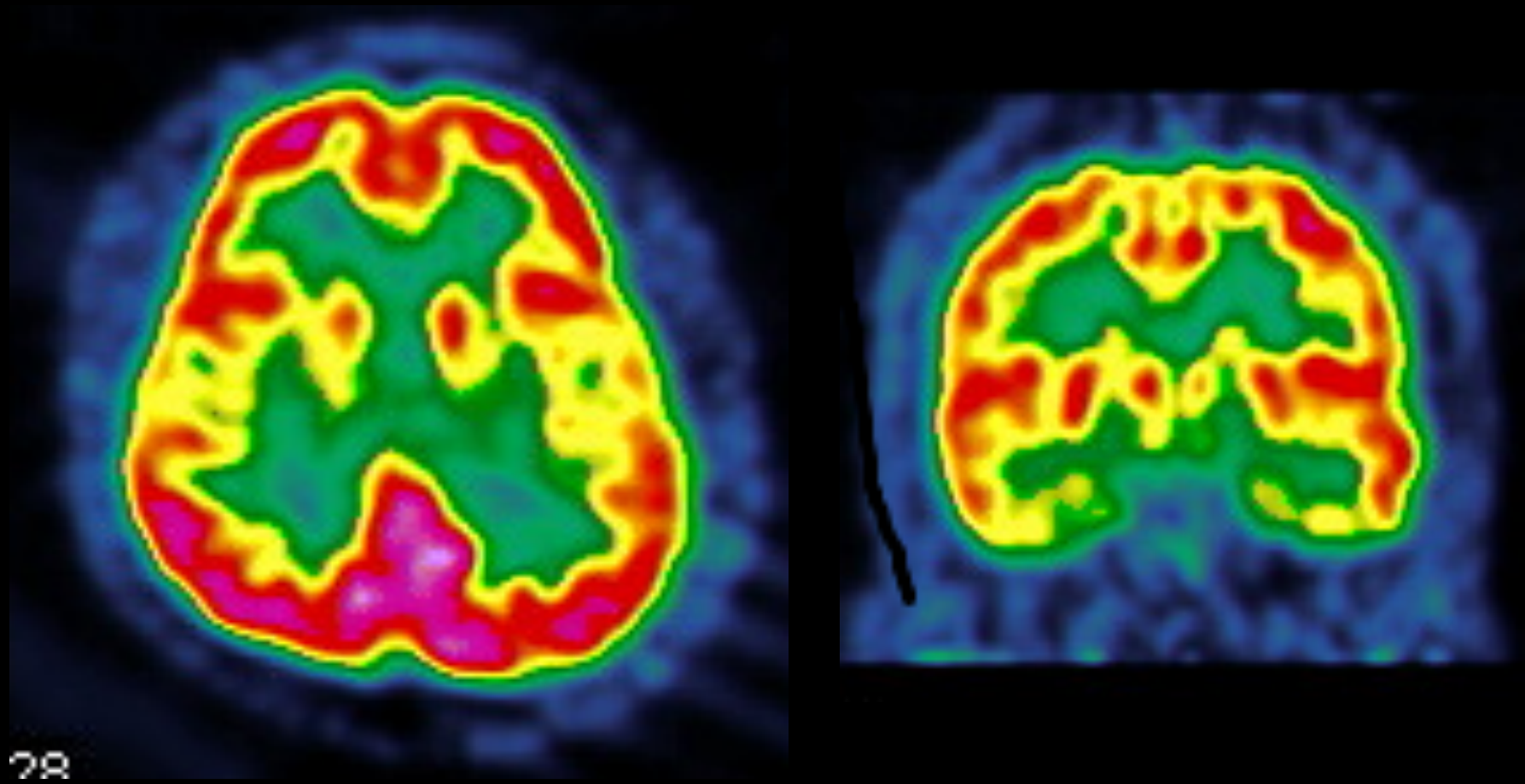


Brain MRI

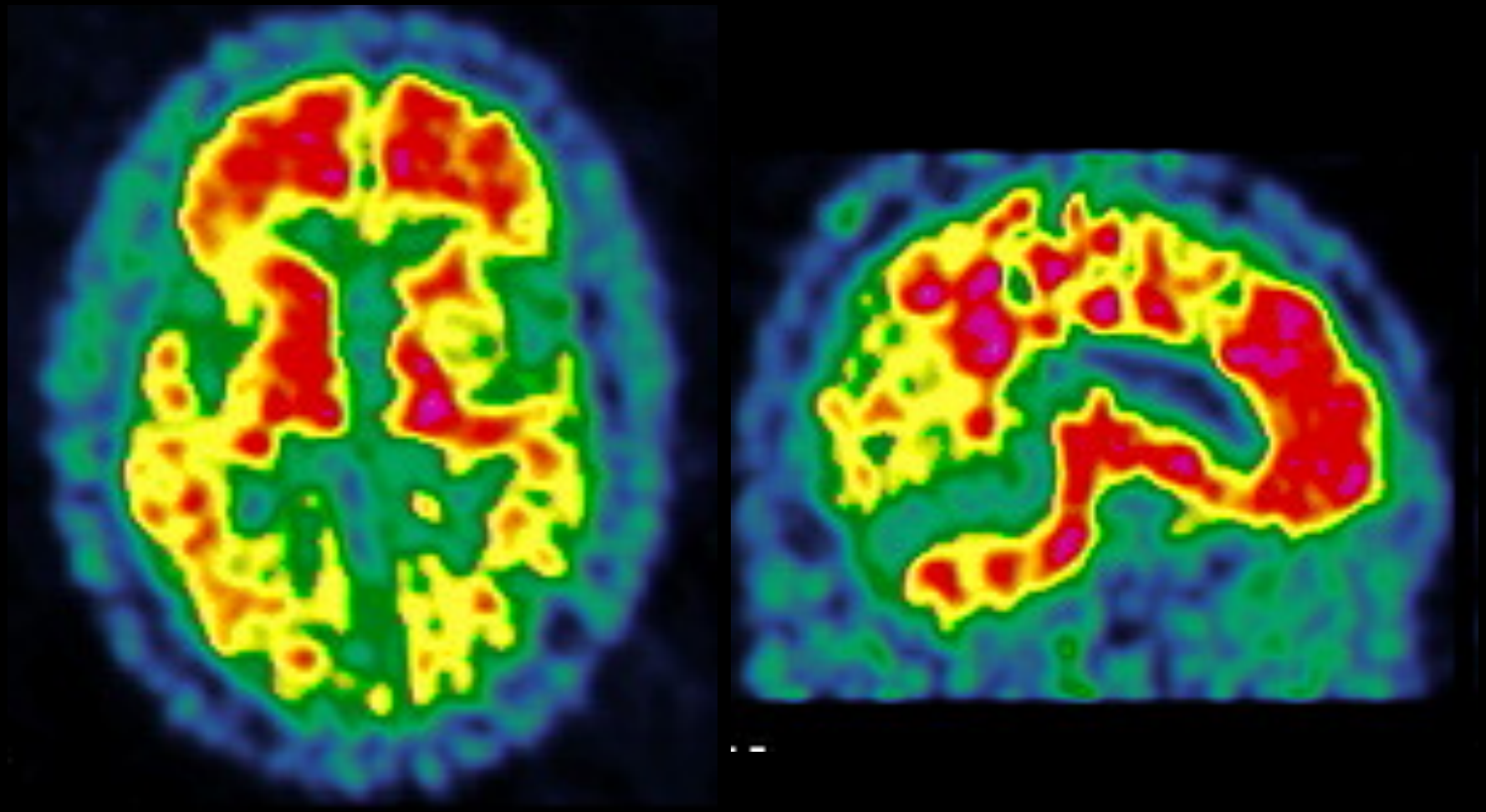




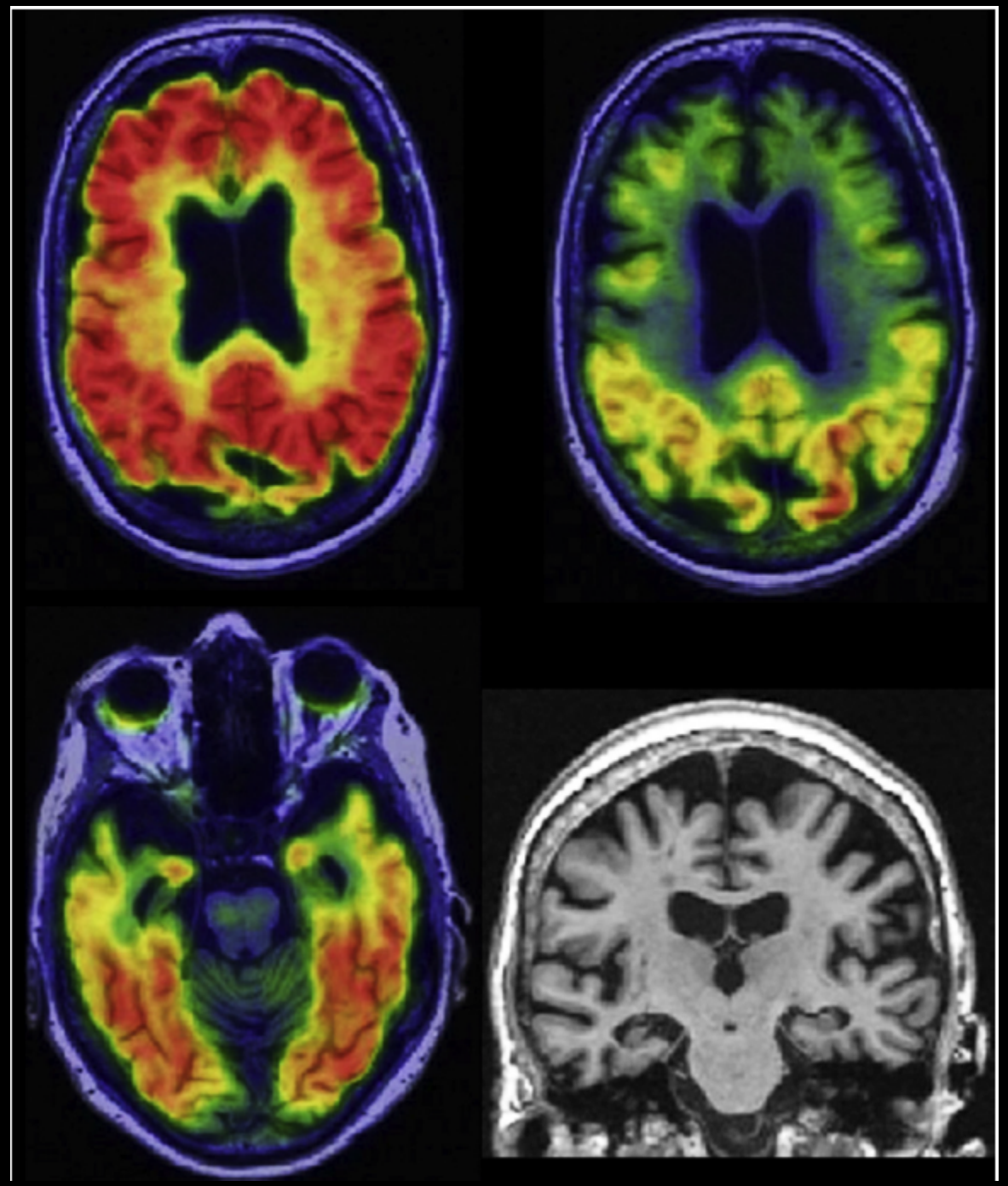
FDG PET



Amyloid Brain PET

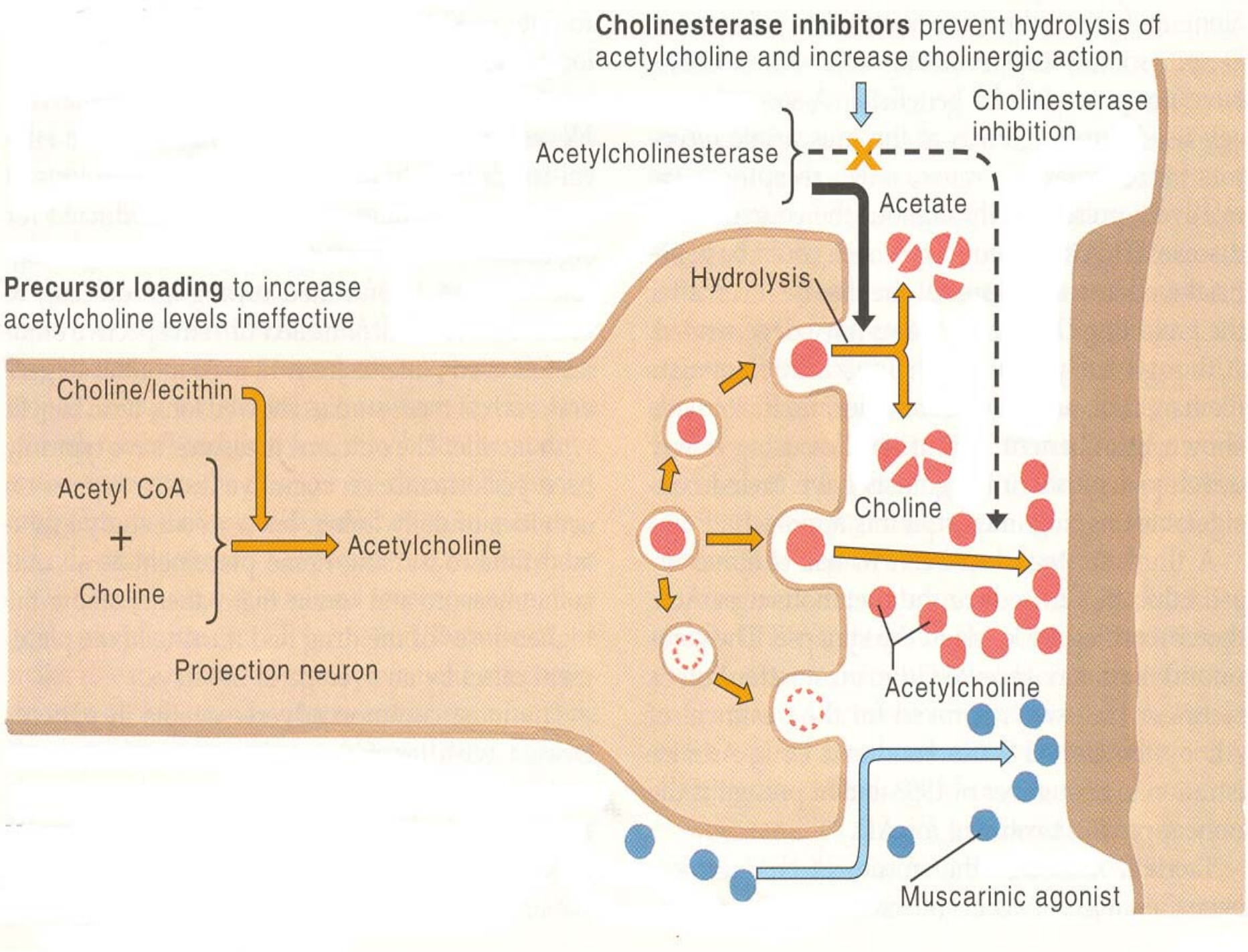


Tau PET



ATM
Staging

Treatment of AD


Cholinesterase inhibitors prevent hydrolysis of acetylcholine and increase cholinergic action
Cholinesterase inhibition
Acetylcholinesterase
Acetate
Hydrolysis
Precursor loading to increase acetylcholine levels ineffective
Choline/lecithin
Acetyl CoA
+
Choline
Acetylcholine
Projection neuron
Choline
Acetylcholine
Muscarinic agonist

Cholinergic hypothesis

- Reduced cortical choline acetyltransferase(CAT) activity
- Cholinergic neuronal loss in the Nucleus basalis of Maynert & other subcortical nuclei
- Cholinergic antagonists induced learning disability
- CAT level correlate with the No. of NP and with MMSE score
- Decreased presynaptic M2, Nicotinic rcp with relatively spared postsynaptic M1 rcp.

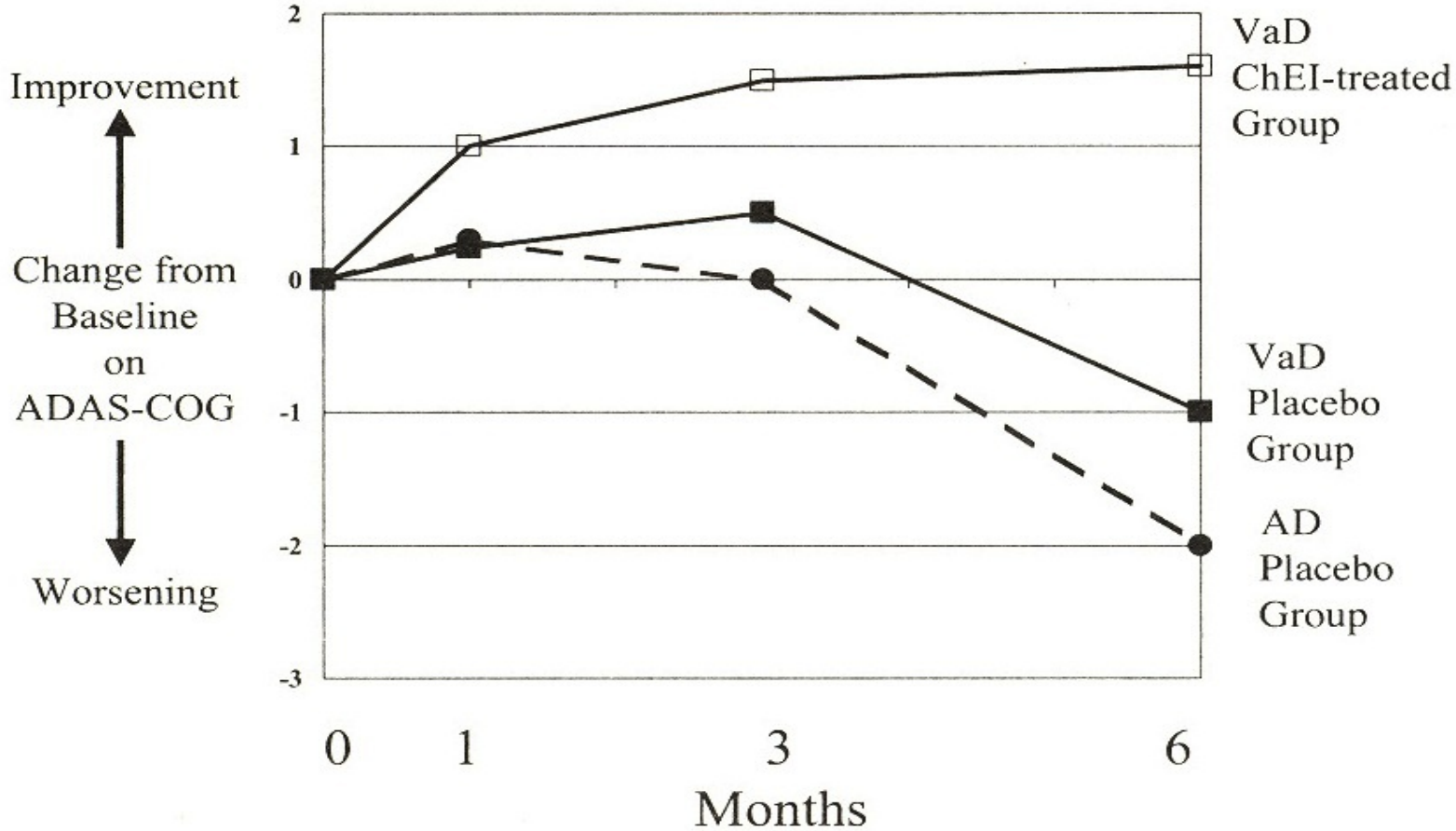
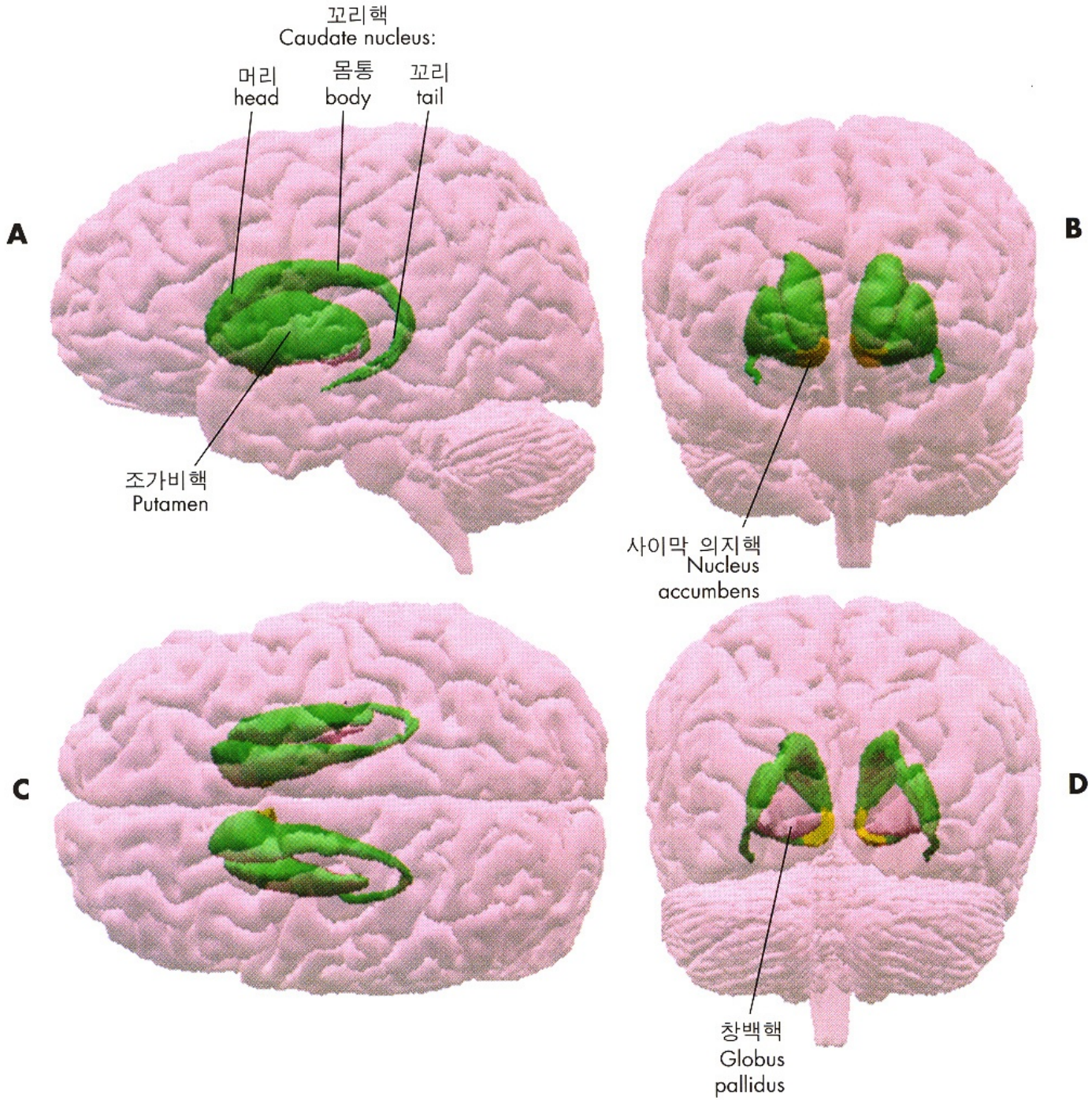


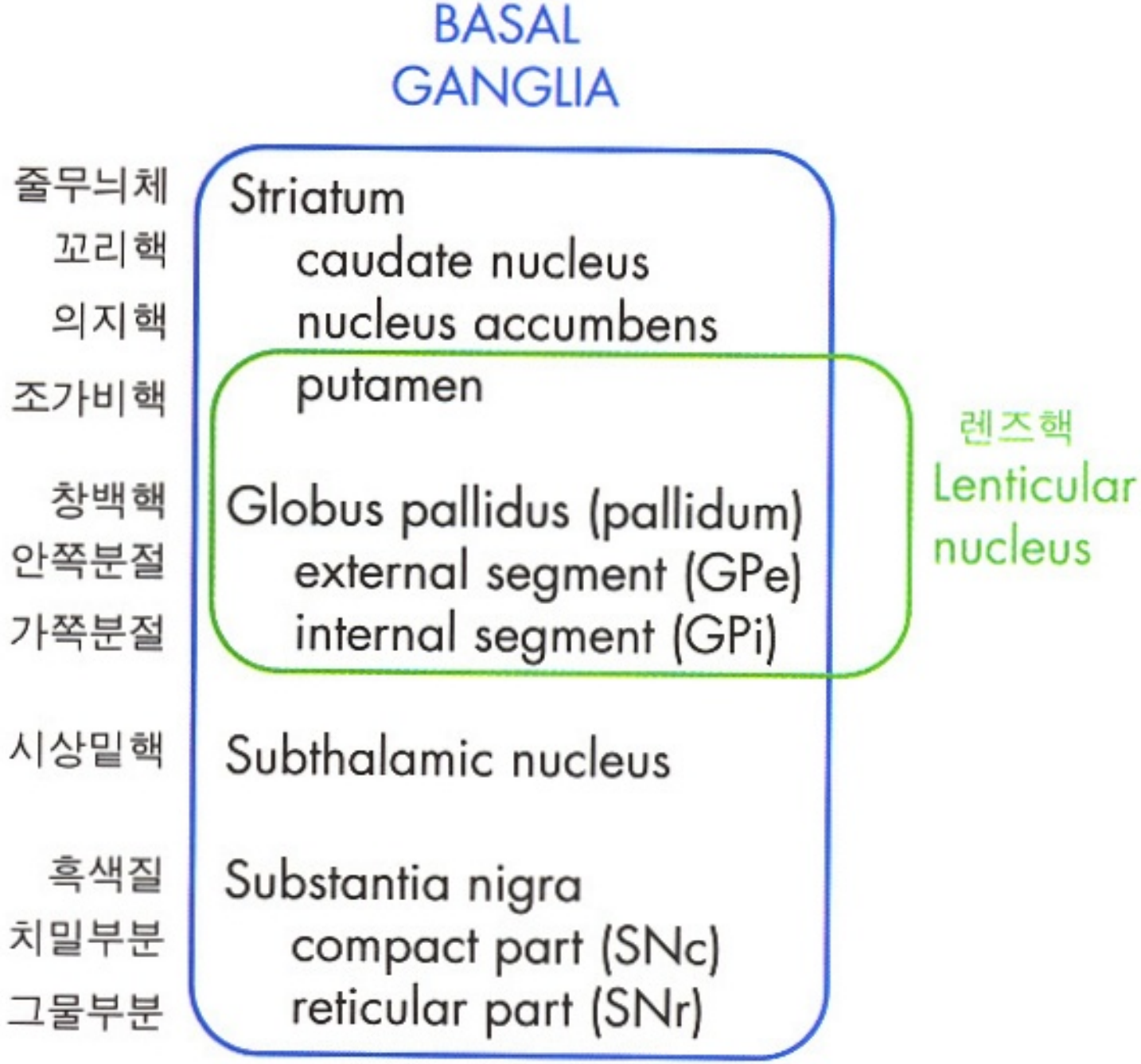
FIGURE 5-7 Data from a clinical trial with a cholinesterase inhibitor (ChEI) in vascular dementia (VaD). Both the treated group (*open squares, upper line*) and placebo group (*filled squares, middle line*) are shown,* as well as a placebo group (*filled circles, lower line*) from a similarly designed study with Alzheimer's patients. †The VaD placebo group did not decline as much as the Alzheimer's disease (AD) group.

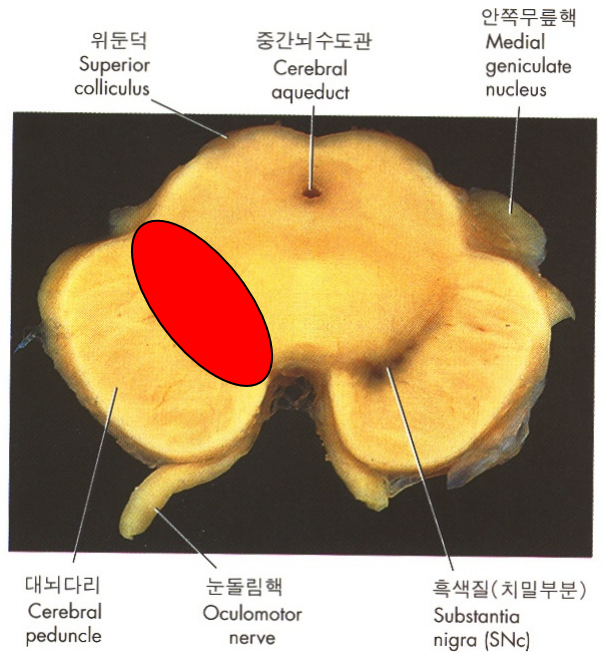
Erkinjuntti T(Lancet, 2002), Raskind MA (Neurology, 2000)

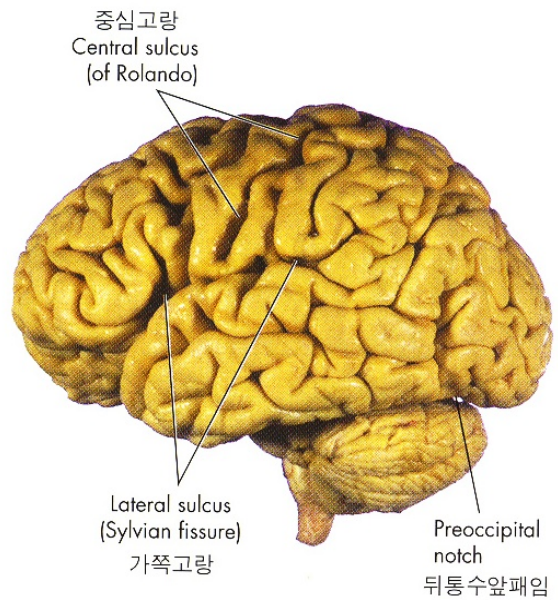
Movement disorders

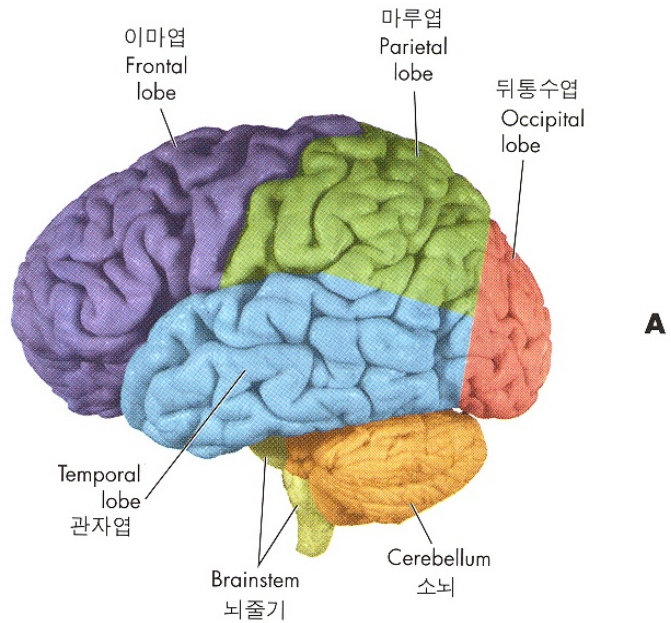
Oh-Dae Kwon
Department of Neurology
School of Medicine
Catholic University of Daegu


꼬리핵
Caudate nucleus:
머리
head
몸통
body
꼬리
tail
A
조가비핵
Putamen
B
사이막 의지핵
Nucleus
accumbens
C
D
창백핵
Globus
pallidus

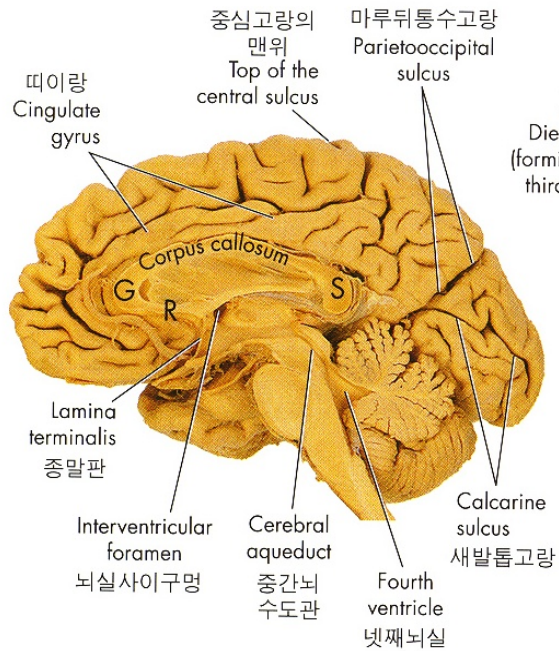

BASAL
GANGLIA
줄무늬체
Striatum
꼬리핵
caudate nucleus
의지핵
nucleus accumbens
조가비핵
putamen
렌즈핵
Lenticular
nucleus
창백핵
Globus pallidus (pallidum)
안쪽분절
external segment (GPe)
가쪽분절
internal segment (GPi)
시상밑핵
Subthalamic nucleus
흑색질
Substantia nigra
치밀부분
compact part (SNc)
그물부분
reticular part (SNr)

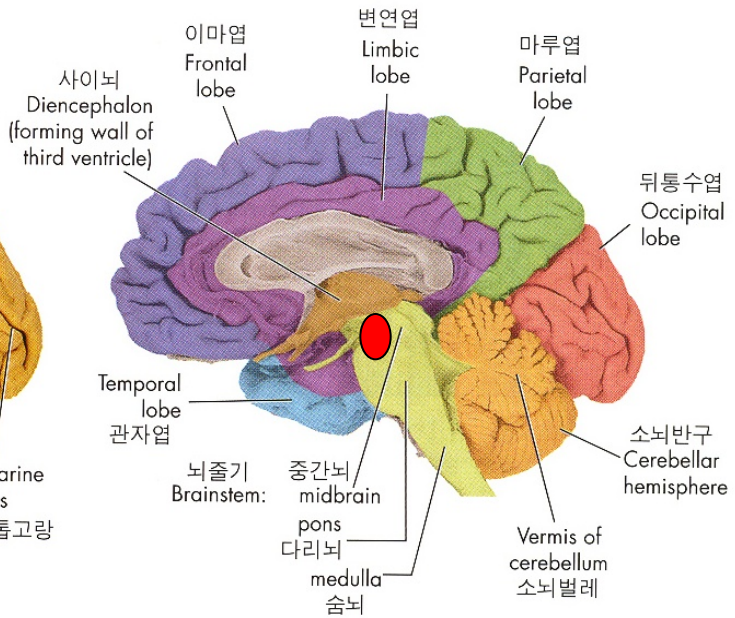

위둔덕
Superior colliculus
중간뇌수도관
Cerebral aqueduct
안쪽무릎핵
Medial geniculate nucleus
대뇌다리
Cerebral peduncle
눈돌림핵
Oculomotor nerve
흑색질(치밀부분)
Substantia nigra (SNc)


중심고랑
Central sulcus (of Rolando)
Lateral sulcus (Sylvian fissure)
가쪽고랑
Preoccipital notch
뒤통수앞패임

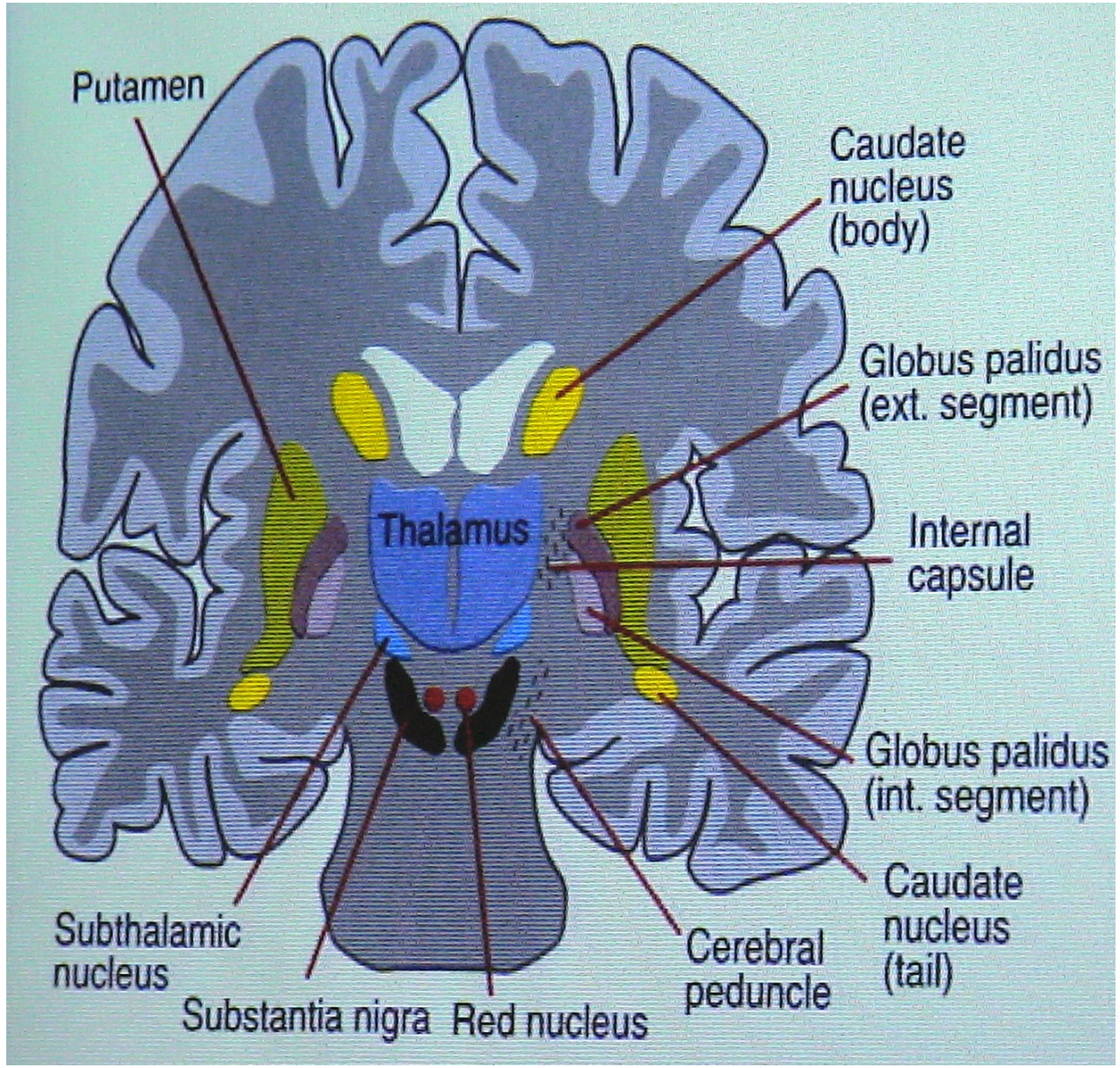

이마엽
Frontal lobe
마루엽
Parietal lobe
뒤통수엽
Occipital lobe
Temporal lobe
관자엽
Brainstem
뇌줄기
Cerebellum
소뇌

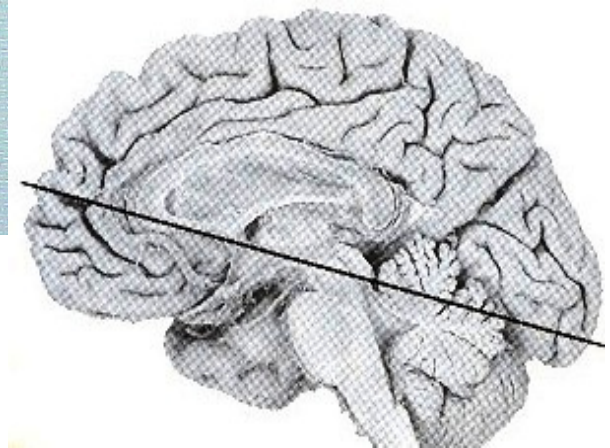
A

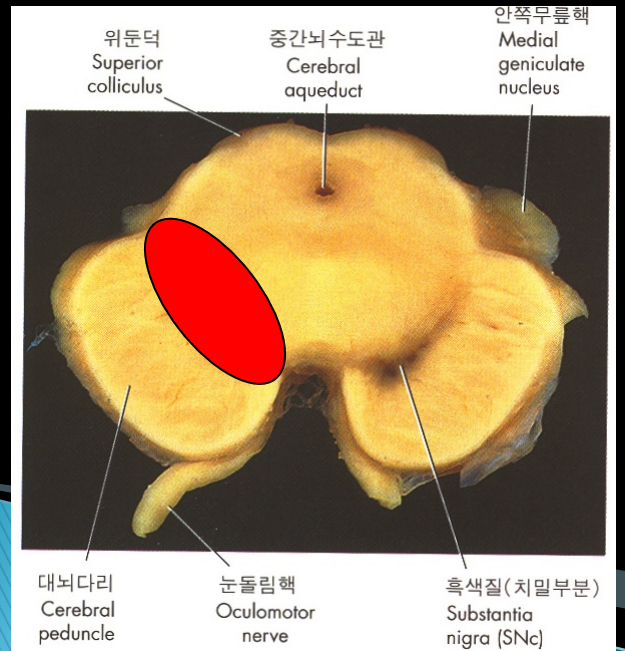

중심고랑의 맨위
Top of the central sulcus
마루뒤통수고랑
Parietooccipital sulcus
띠이랑
Cingulate gyrus
Corpus callosum
G
R
S
Lamina terminalis
종말판
Interventricular foramen
뇌실사이구멍
Cerebral aqueduct
중간뇌 수도관
Fourth ventricle
넷째뇌실
Calcarine sulcus
새발톱고랑

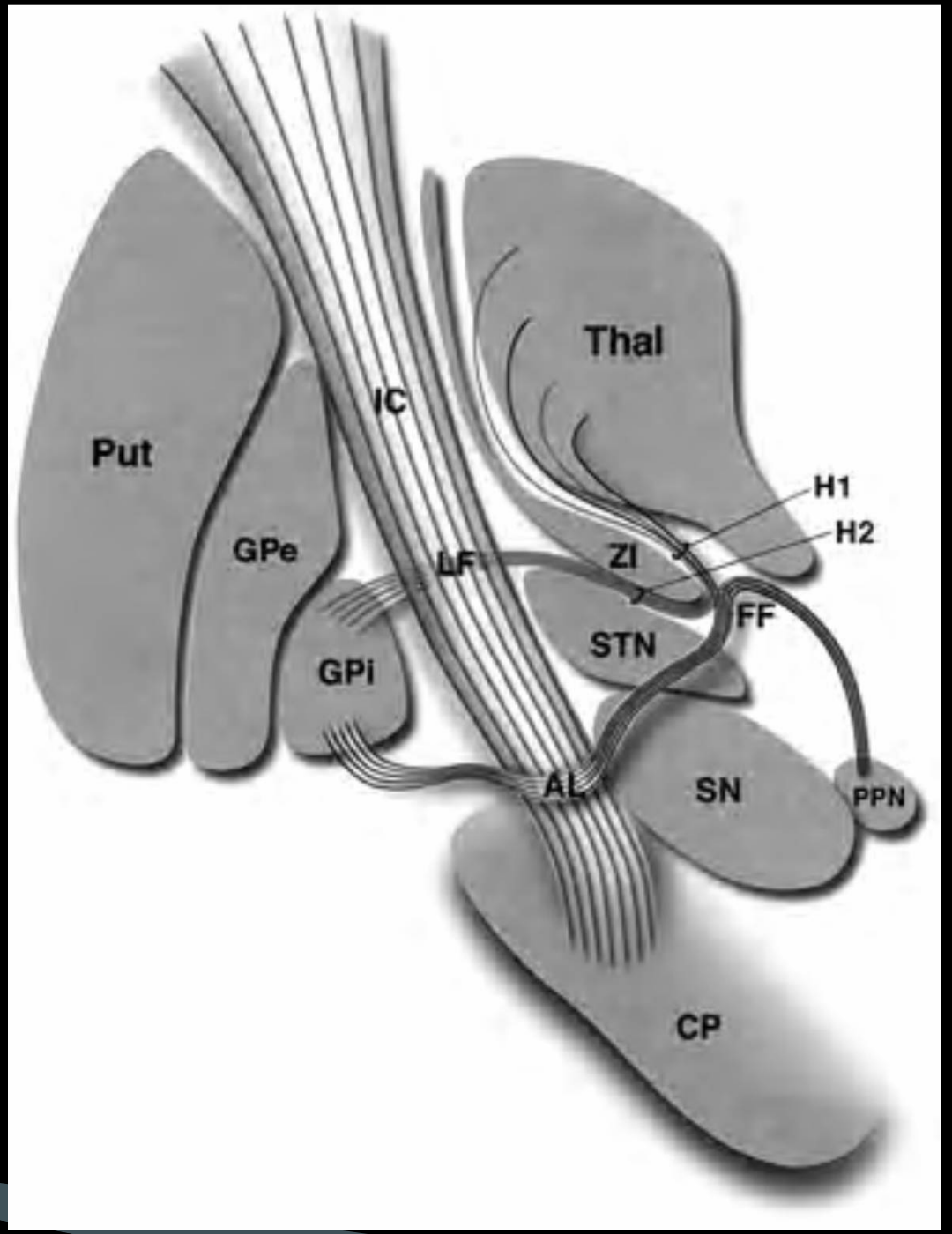

사이뇌
Diencephalon (forming wall of third ventricle)
이마엽
Frontal lobe
변연엽
Limbic lobe
마루엽
Parietal lobe
뒤통수엽
Occipital lobe
Temporal lobe
관자엽
뇌줄기
Brainstem:
중간뇌
midbrain
pons
다리뇌
medulla
숨뇌
소뇌반구
Cerebellar hemisphere
Vermis of cerebellum
소뇌벌레

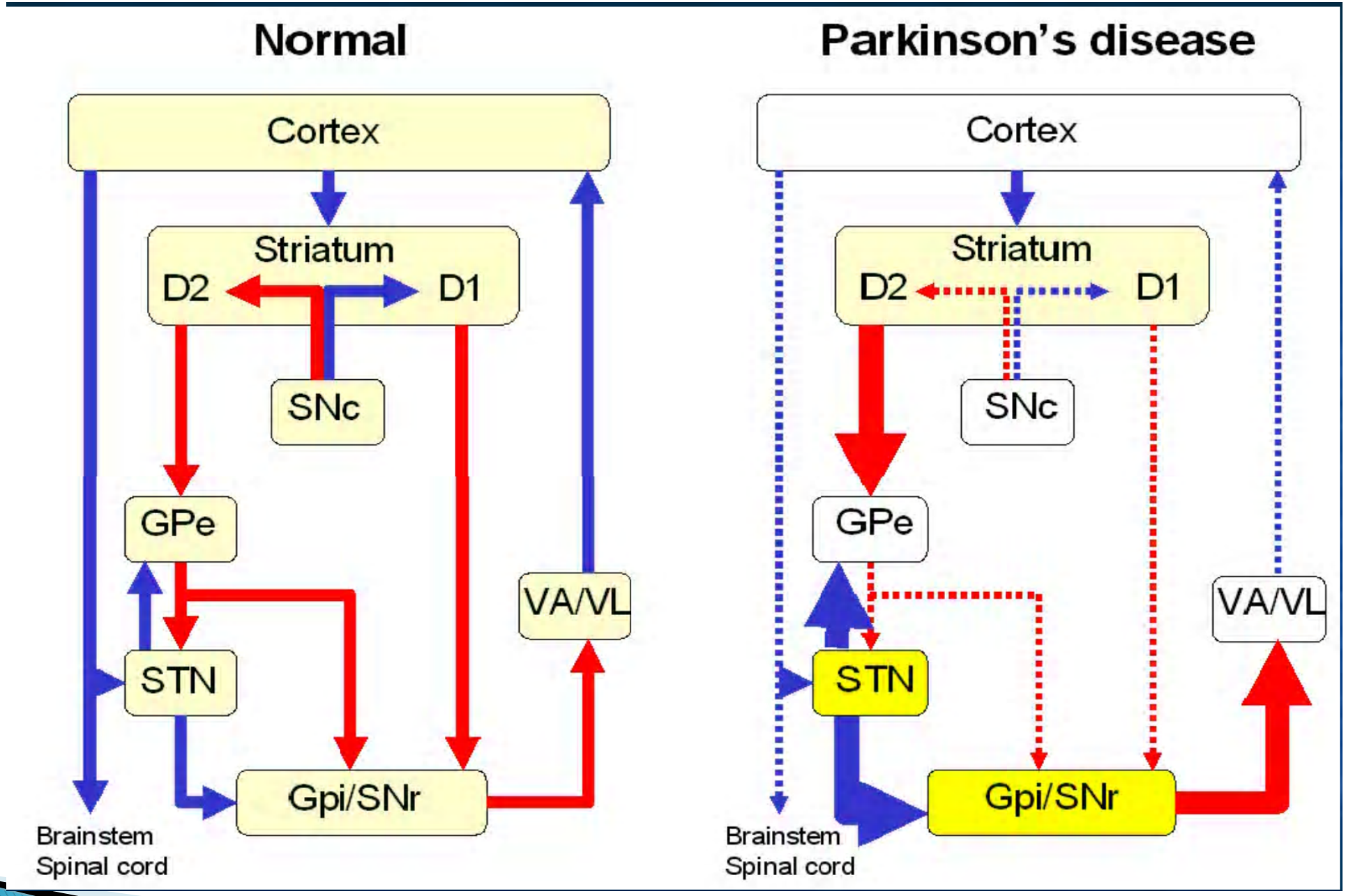
B


Putamen
Caudate nucleus (body)
Globus palidus (ext. segment)
Thalamus
Internal capsule
Globus palidus (int. segment)
Caudate nucleus (tail)
Subthalamic nucleus
Substantia nigra
Red nucleus
Cerebral peduncle




위둔덕
Superior colliculus
중간뇌수도관
Cerebral aqueduct
안쪽무릎핵
Medial geniculate nucleus
대뇌다리
Cerebral peduncle
눈돌림핵
Oculomotor nerve
흑색질(치밀부분)
Substantia nigra (SNc)


Put
GPe
GPi
IC
Thal
H1
H2
LF
ZI
FF
STN
AL
SN
PPN
CP


Normal
Parkinson's disease
Cortex
Striatum
D2
D1
SNc
GPe
STN
VA/VL
Gpi/SNr
Brainstem
Spinal cord
Cortex
Striatum
D2
D1
SNc
GPe
STN
VA/VL
Gpi/SNr
Brainstem
Spinal cord
Inhibitory effect
Excitatory effect

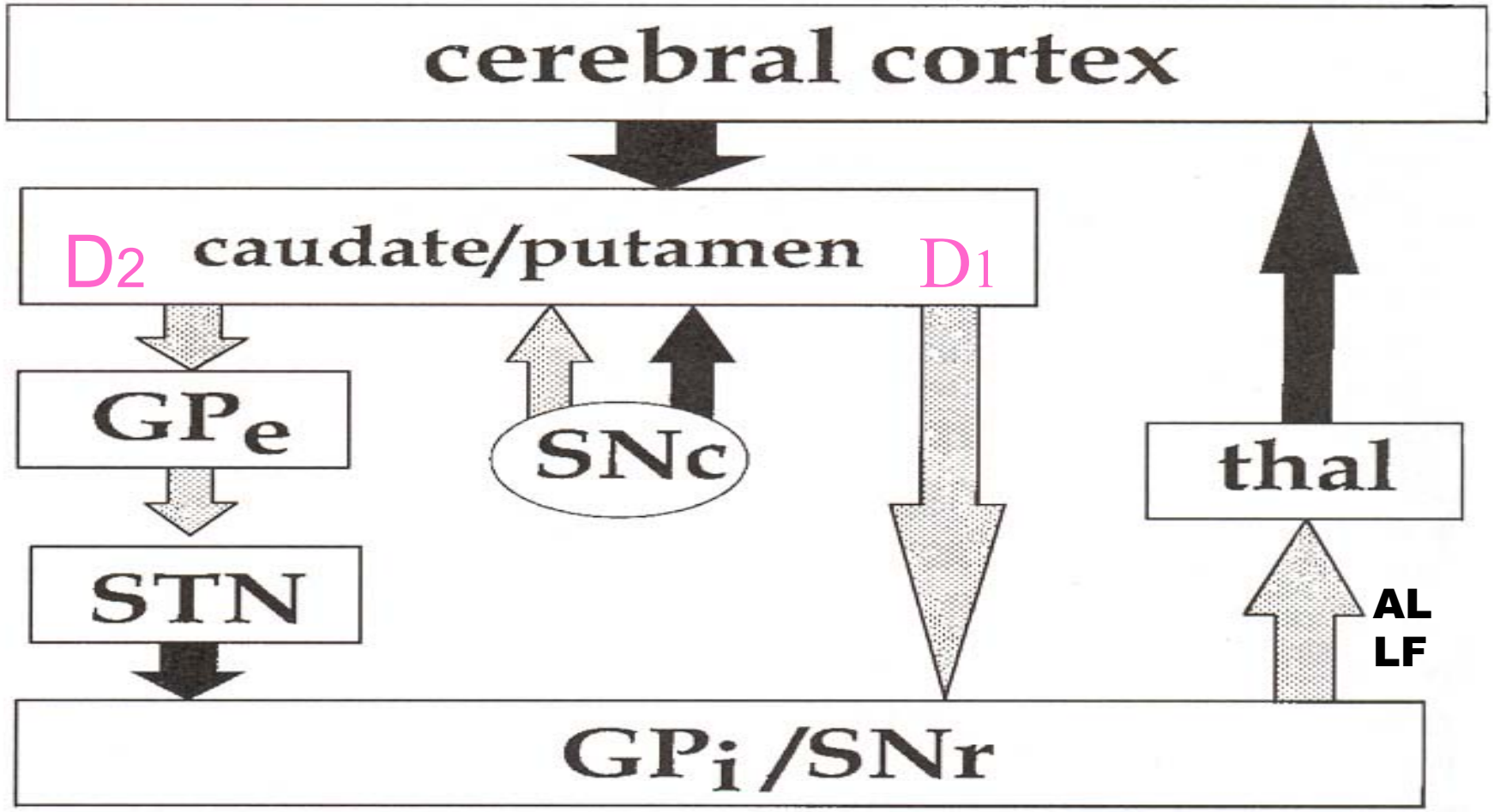
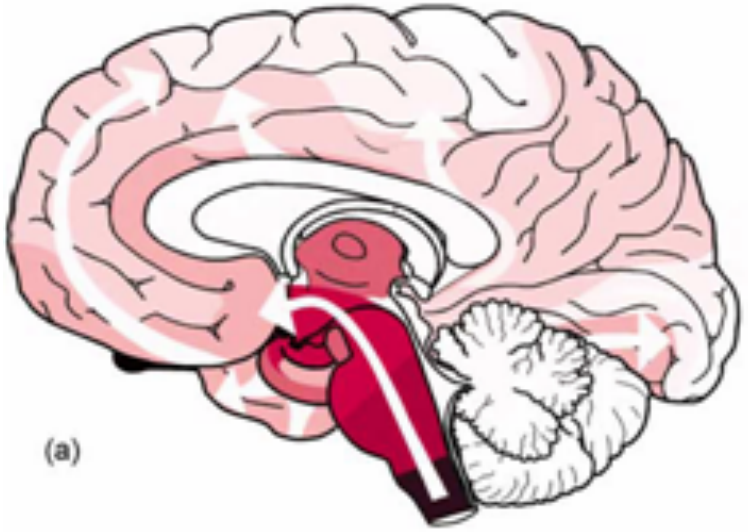
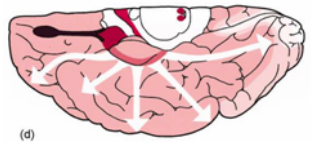
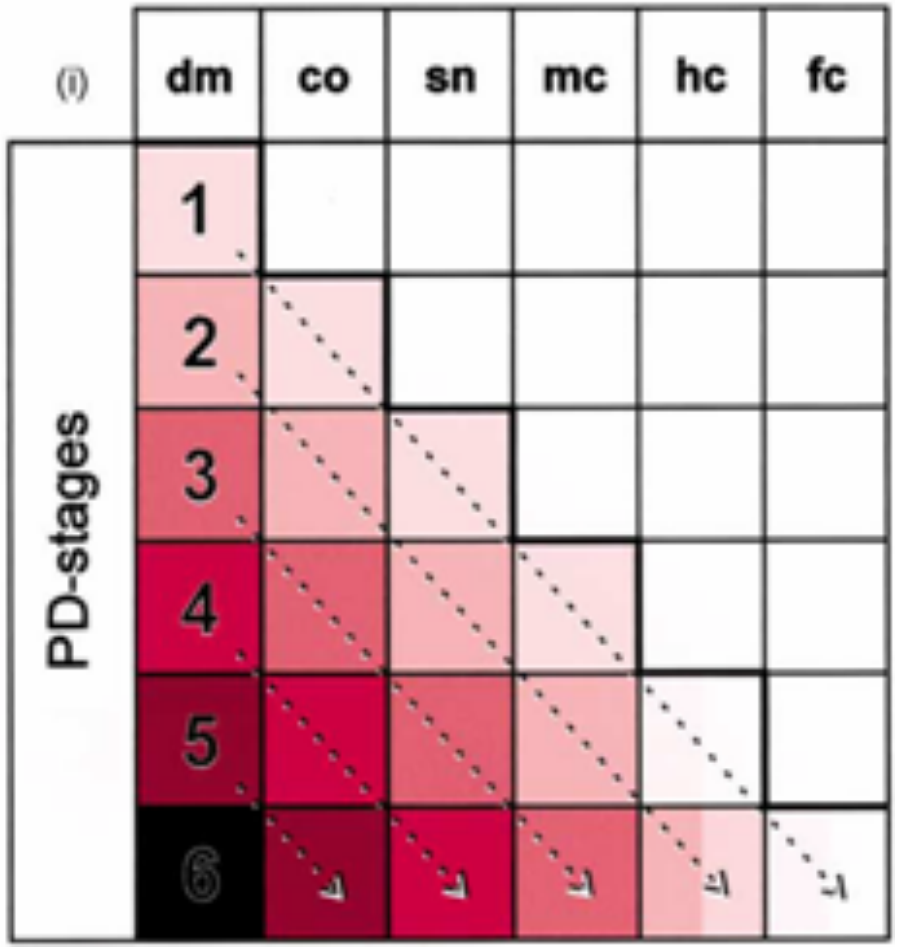


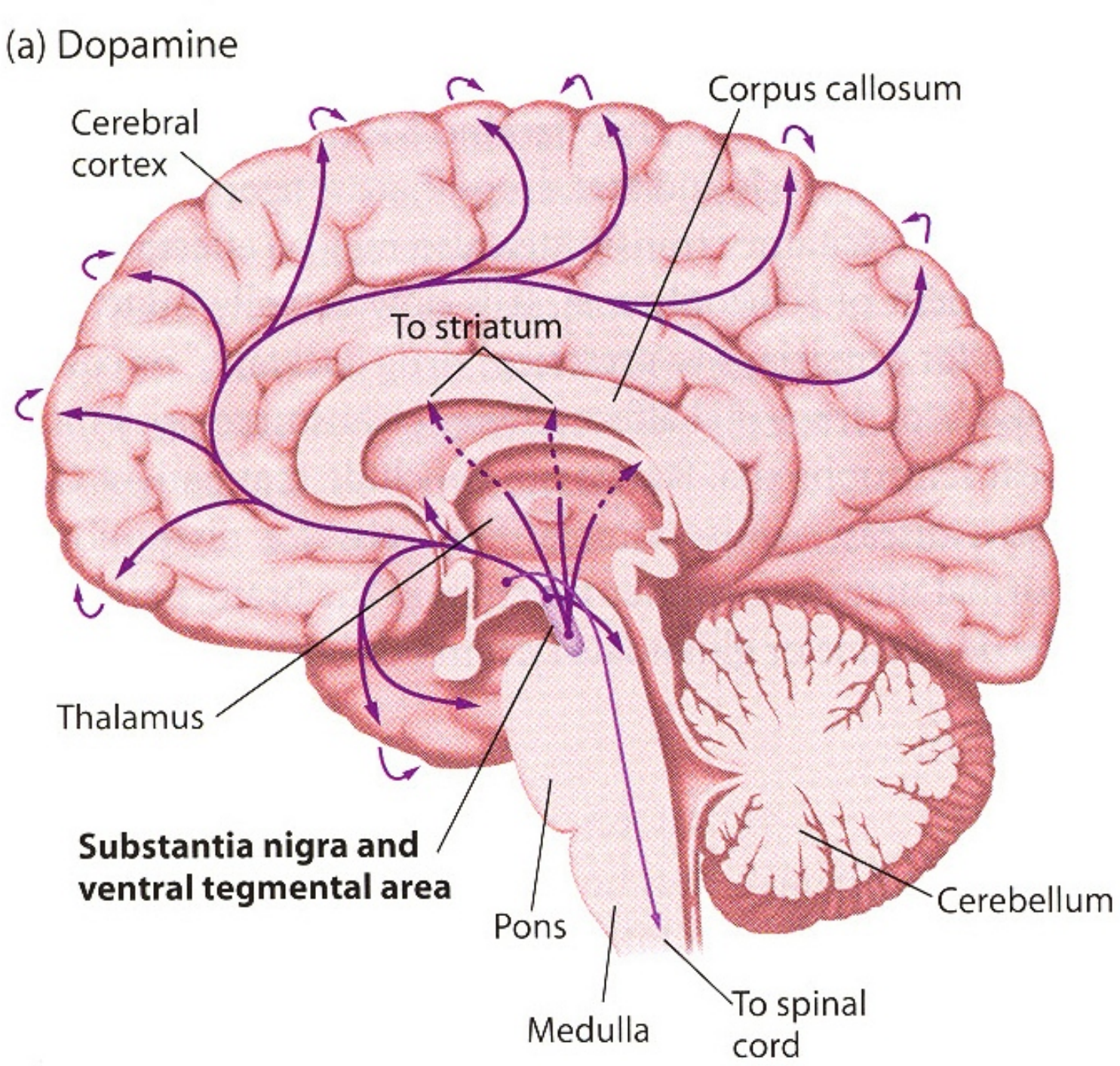
FIGURE 16–3. Schema of anatomical nuclei and pathways involving the basal ganglia. Black arrows represent excitation, and speckled arrows represent inhibition. Note the two primary pathways that leave the striatum—the "direct" pathway that flows monosynaptically to the GP_i and the "indirect" pathway that has intermediate synapses in the GP_e and the subthalamic nucleus. GP_i = globus pallidus internal segment; GP_e = globus pallidus external segment; STN = subthalamic nucleus; SNr = pars reticularis of the substantia nigra; SNc = pars compacta of the substantia nigra; thal = thalamus.

PD may begin in the medulla oblongata







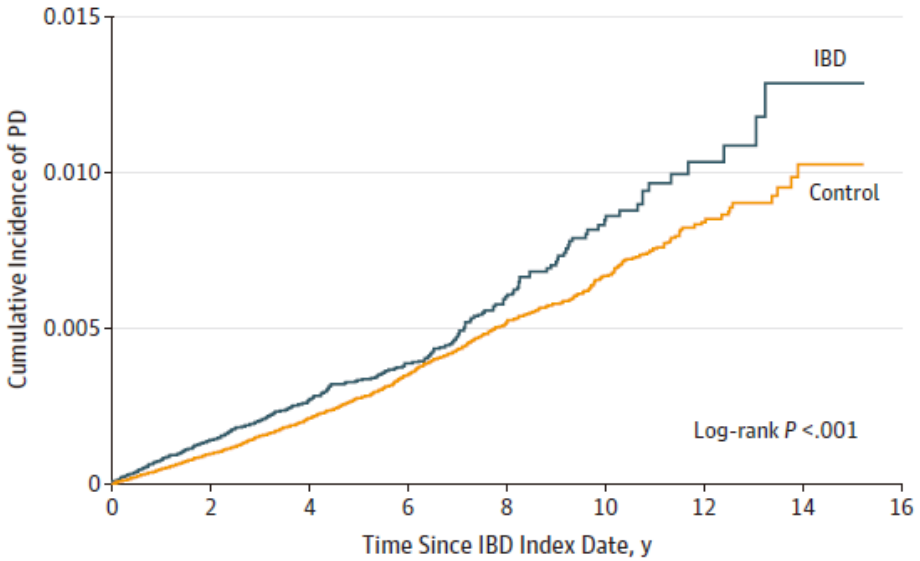

(a) Dopamine
Cerebral cortex
Corpus callosum
To striatum
Thalamus
Substantia nigra and ventral tegmental area
Pons
Medulla
To spinal cord
Cerebellum

Gut brain interaction in Movement disorders

Evidence of Gut brain interaction

- Gastric nervous plexus(Myenteric & Auerbach) show alpha-synuclein.
- LRRK2 and Inflammatory bowel disease(Crohn's disease) has association.
- Anti-TNF treatment in inflammatory bowel disease reduces risk of Parkinson's disease.(Hui et al. 2018)

Figure. Cumulative Incidence of Parkinson Disease (PD) Among Patients With or Without Inflammatory Bowel Disease (IBD)



No. at risk

IBD	144 018	86 557	46 261	25 505	13 275	6423	2250	440
Control	720 090	425 380	229 183	123 597	63 558	30 061	10 710	2202

Table 3. Incidence Analysis of PD Among Patients With IBD by Anti-TNF Exposure

				Univariate Poisson Model[c]		Multivariate Poisson Model[d]	
Anti-TNF Exposure[a]	PD Event	Person-years	Rate[b]	Crude IRR (95% CI)	*P* Value	Adjusted IRR (95% CI)	*P* Value
Yes	2	23 610	0.08	0.11 (0.03-0.45)	.002	0.22 (0.05-0.88)	.03
No	369	484 423	0.76	1 [Reference]		1 [Reference]	

Abbreviations: anti-TNF, anti–tumor necrosis factor; IBD, inflammatory bowel disease; IRR, incidence rate ratio; PD, Parkinson disease.

[a] Anti-TNF exposure status was defined as yes for all days from anti-TNF exposure index date to last date of anti-TNF exposure coverage or end of enrollment or PD index date, whichever was earliest; otherwise the anti-TNF exposure status was defined as no.

[b] Incidence rate per 1000 person-years.

[c] Unadjusted incidence ratio, offset by time.

[d] Model adjusted for time-varying age group and sex, and offset by time.

Inga Peter et al.JAMA Neurol. 2018

Hypothesis on Gut brain interaction

- Dual hit hypothesis on the pathology of Parkinson's disease in both olfactory nucleus and gut.

- Lewy body extracts from PD brains trigger alpha synuclein pathology and neurodegeneration in Mice and monkeys.(Ann Neurol 2014;75:351-362, 2015;78;522-528)

Objective: Mounting evidence suggests that a-synuclein, a major protein component of Lewy bodies (LB), may be responsible for initiating and spreading the pathological process in Parkinson disease (PD). Supporting this concept, intracerebral inoculation of synthetic recombinant a-synuclein fibrils can trigger a-synuclein pathology in mice. However, it remains uncertain whether the pathogenic effects of recombinant synthetic a-synuclein may apply to PD- linked pathological a-synuclein and occur in species closer to humans.

Methods: Nigral LB-enriched fractions containing pathological a-synuclein were purified from postmortem PD brains by sucrose gradient fractionation and subsequently inoculated into the substantia nigra or striatum of wild-type mice and macaque monkeys. Control animals received non-LB fractions containing soluble a-synuclein derived from the same nigral PD tissue.

Results: In both mice and monkeys, intranigral or intrastriatal inoculations of PD-derived LB extracts resulted in pro- gressive nigrostriatal neurodegeneration starting at striatal dopaminergic terminals. No neurodegeneration was observed in animals receiving non-LB fractions from the same patients. In LB-injected animals, exogenous human a- synuclein was quickly internalized within host neurons and triggered the pathological conversion of endogenous a- synuclein. At the onset of LB-induced degeneration, host pathological a-synuclein diffusely accumulated within nigral neurons and anatomically interconnected regions, both anterogradely and retrogradely. LB-induced pathogenic effects required both human a-synuclein present in LB extracts and host expression of a-synuclein.

Interpretation: a-Synuclein species contained in PD-derived LB are pathogenic and have the capacity to initiate a PD-like pathological process, including intracellular and presynaptic accumulations of pathological a-synuclein in different brain areas and slowly progressive axon-initiated dopaminergic nigrostriatal neurodegeneration.

ANN NEUROL 2014;75:351–362

Vagotomy and subsequent risk of Parkinson's disease.

OBJECTIVE:

Parkinson's disease (PD) may be caused by an enteric neurotropic pathogen entering the brain through the vagal nerve, a process that may take over 20 years. We investigated the risk of PD in patients who underwent vagotomy and hypothesized that truncal vagotomy is associated with a protective effect, whereas superselective vagotomy has a minor effect.

METHODS:

We constructed cohorts of all patients in Denmark who underwent vagotomy during 1977-1995 and a matched general population cohort by linking Danish registries. We used Cox regression to compute hazard ratios (HRs) for PD and corresponding 95% confidence intervals (CIs), adjusting for potential confounders.

RESULTS:

Risk of PD was decreased in patients who underwent truncal (HR = 0.85; 95% CI = 0.56-1.27; follow-up of >20 years: HR = 0.58; 95% CI: 0.28-1.20) compared to superselective vagotomy. Risk of PD was also decreased after truncal vagotomy when compared to the general population cohort (overall adjusted HR = 0.85; 95% CI: 0.63-1.14; follow-up >20 years, adjusted HR = 0.53; 95% CI: 0.28-0.99). In patients who underwent superselective vagotomy, risk of PD was similar to the general population (HR = 1.09; 95% CI: 0.84-1.43; follow-up of >20 years: HR = 1.16; 95% CI: 0.80-1.70). Statistical precision of risk estimates was limited. Results were consistent after external adjustment for unmeasured confounding by smoking.

INTERPRETATION:

Full truncal vagotomy is associated with a decreased risk for subsequent PD, suggesting that the vagal nerve may be critically involved in the pathogenesis of PD.

Ann Neurol 2015;78;522-528

Vagus nerve & IPD

- Propagation of alpha-synuclein pathology from gut to brain and vice versa(both direction are possible). (Goedert et al., 2017), (Tredici & Braak, 2016)

Table 1 Diseases with tau inclusions

Alzheimer's disease
Amyotrophic lateral sclerosis/parkinsonism-dementia complex
Argyrophilic grain disease
Chronic traumatic encephalopathy
Corticobasal degeneration
Diffuse neurofibrillary tangles with calcification
Down's syndrome
Familial British dementia
Familial Danish dementia
Familial frontotemporal dementia and parkinsonism
Gerstmann-Sträussler-Scheinker disease
Guadeloupean parkinsonism
Huntington's disease
Meningio-angiomatosis
Myotonic dystrophy
Neurodegeneration with brain iron accumulation
Niemann-Pick disease, type C
Non-Guamanian motor neuron disease with neurofibrillary tangles
Pick's disease
Postencephalitic parkinsonism
Progressive supranuclear palsy
SLC9A6-related mental retardation
Subacute sclerosing panencephalitis
Tangle-only dementia
White matter tauopathy with globular glial inclusions

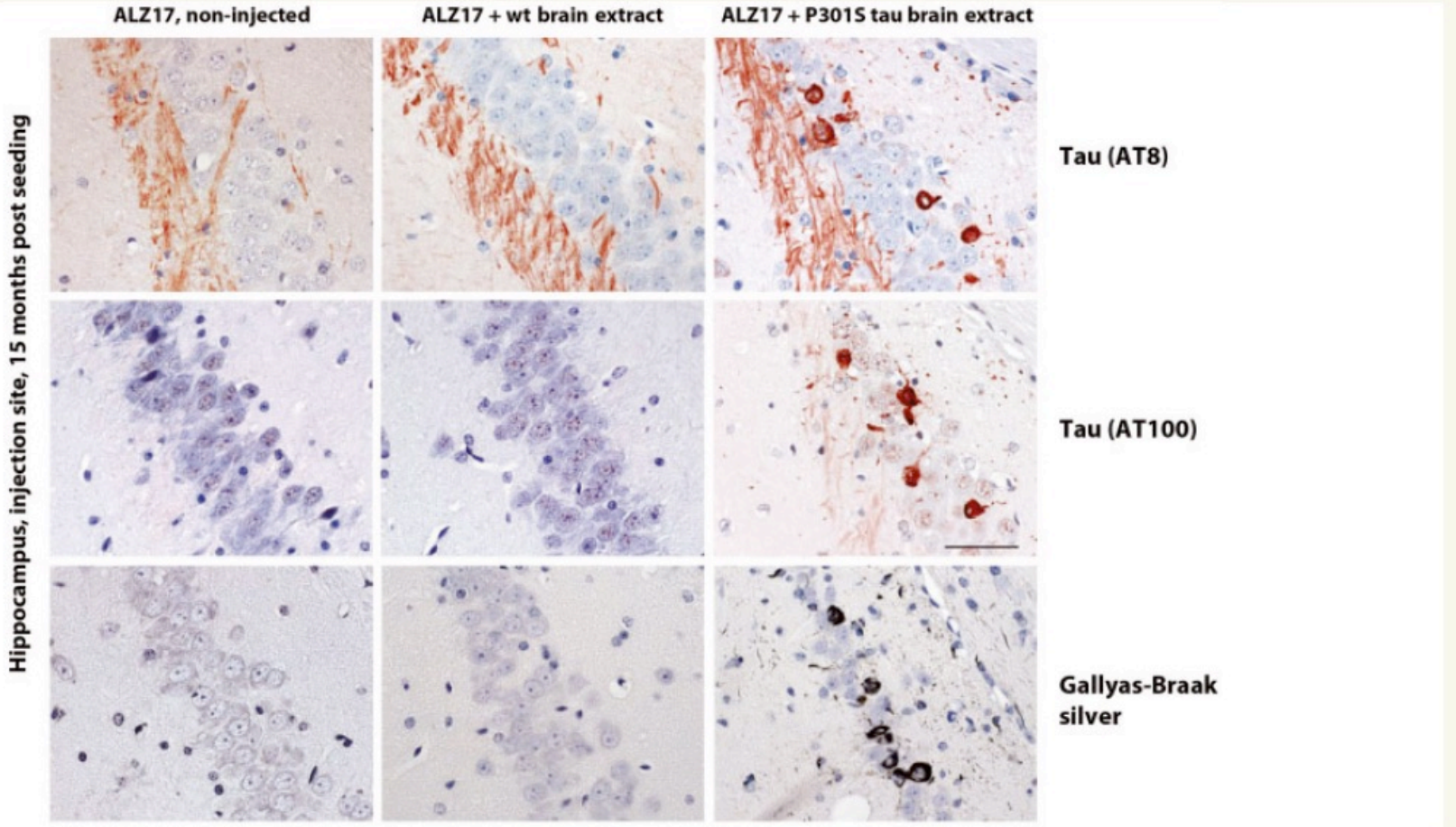


Figure 4 Induction of filamentous tau pathology in mice transgenic for one isoform of wild-type human tau (line ALZ17) following injection with brain extract from symptomatic mice transgenic for one isoform of human mutant P301S tau. Staining of the hippocampal CA3 region of 18-month-old ALZ17 mice with anti-tau antibodies AT8 and AT100 and Gallyas-Braak silver. Non-injected (*left*), 15 months after injection with brain extract from non-transgenic control mice (*middle*) and 15 months after injection with brain extract from 6-month-old mice transgenic for human P301S tau (*right*). The sections were counterstained with haematoxylin. Scale bar = 50 μm.

Conformation determines the seeding potencies and resistance to disaggregation of tau aggregates.

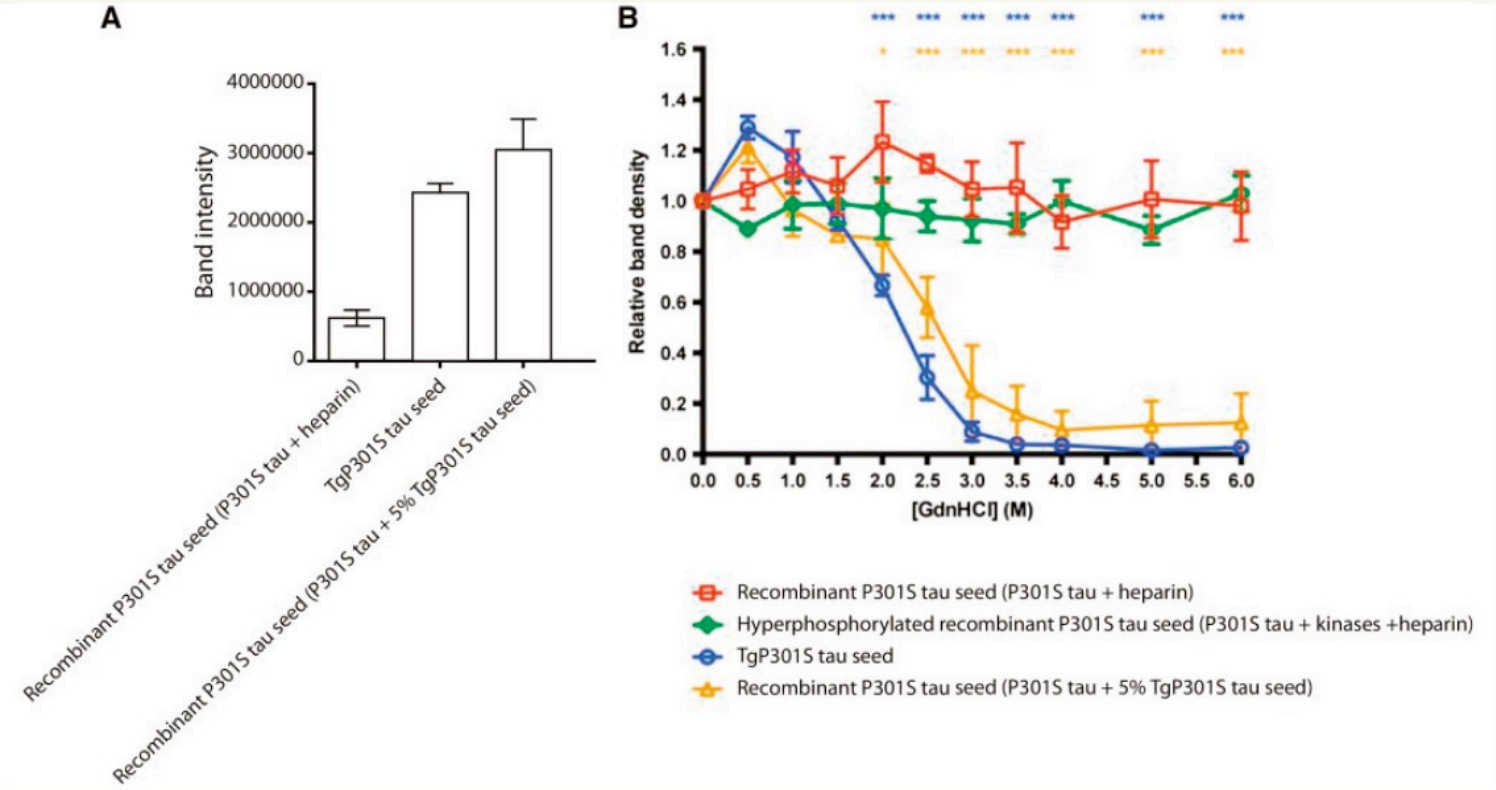
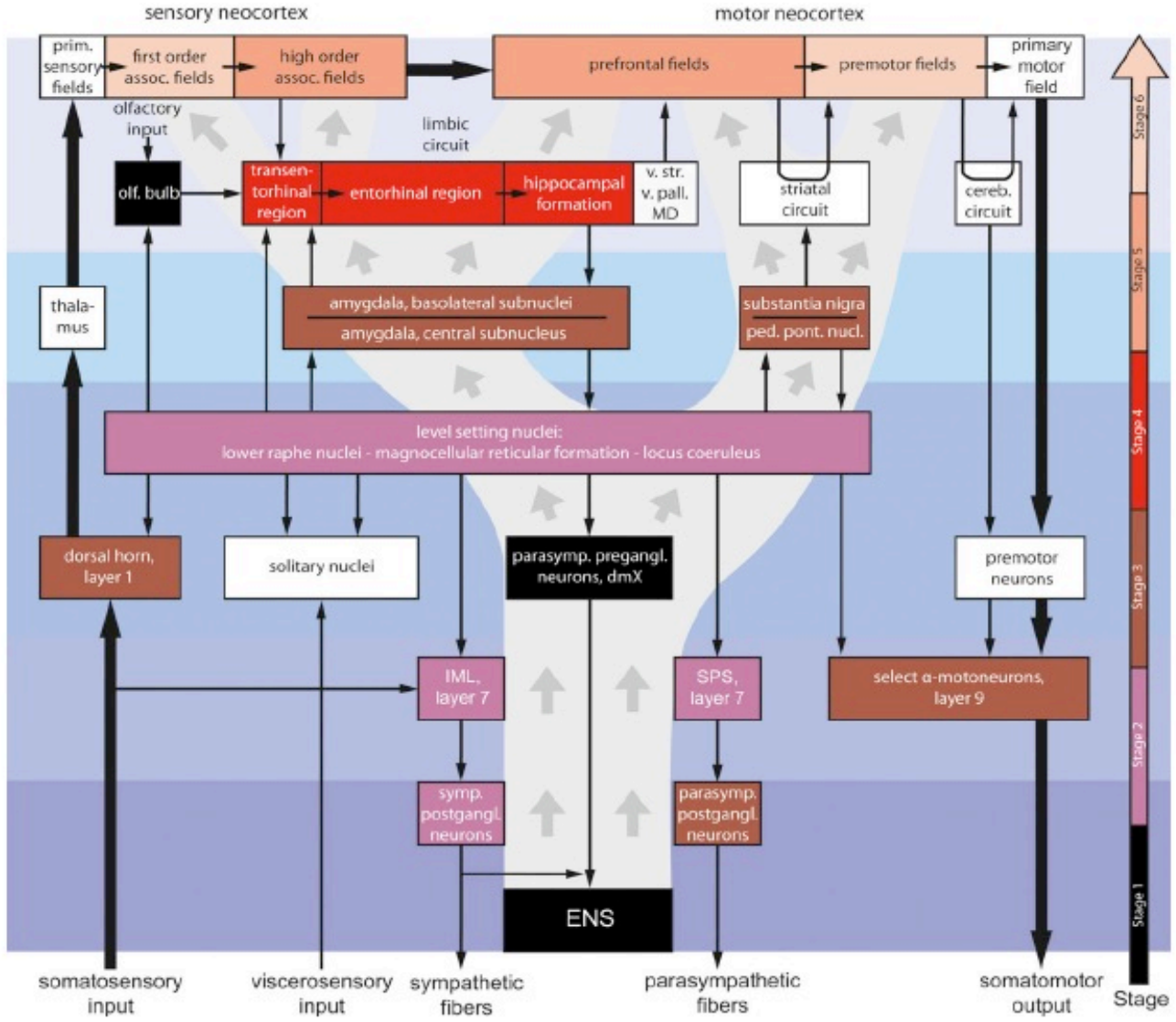


Figure 5 Conformation determines the seeding potencies and resistance to disaggregation of tau aggregates. (**A**) Quantitation by western blotting of insoluble fraction from tau-expressing HEK cells seeded with equivalent amounts of aggregated recombinant P301S tau (P301S tau + heparin), TgP301S tau aggregates and aggregated P301S tau (P301S tau + 5% TgP301S tau aggregates). (**B**) Guanidine hydrochloride (GdnHCl) treatment of tau seeds.

Transmission of alpha synuclein in human nervous system



Tredici & Braak, 2016, NAN

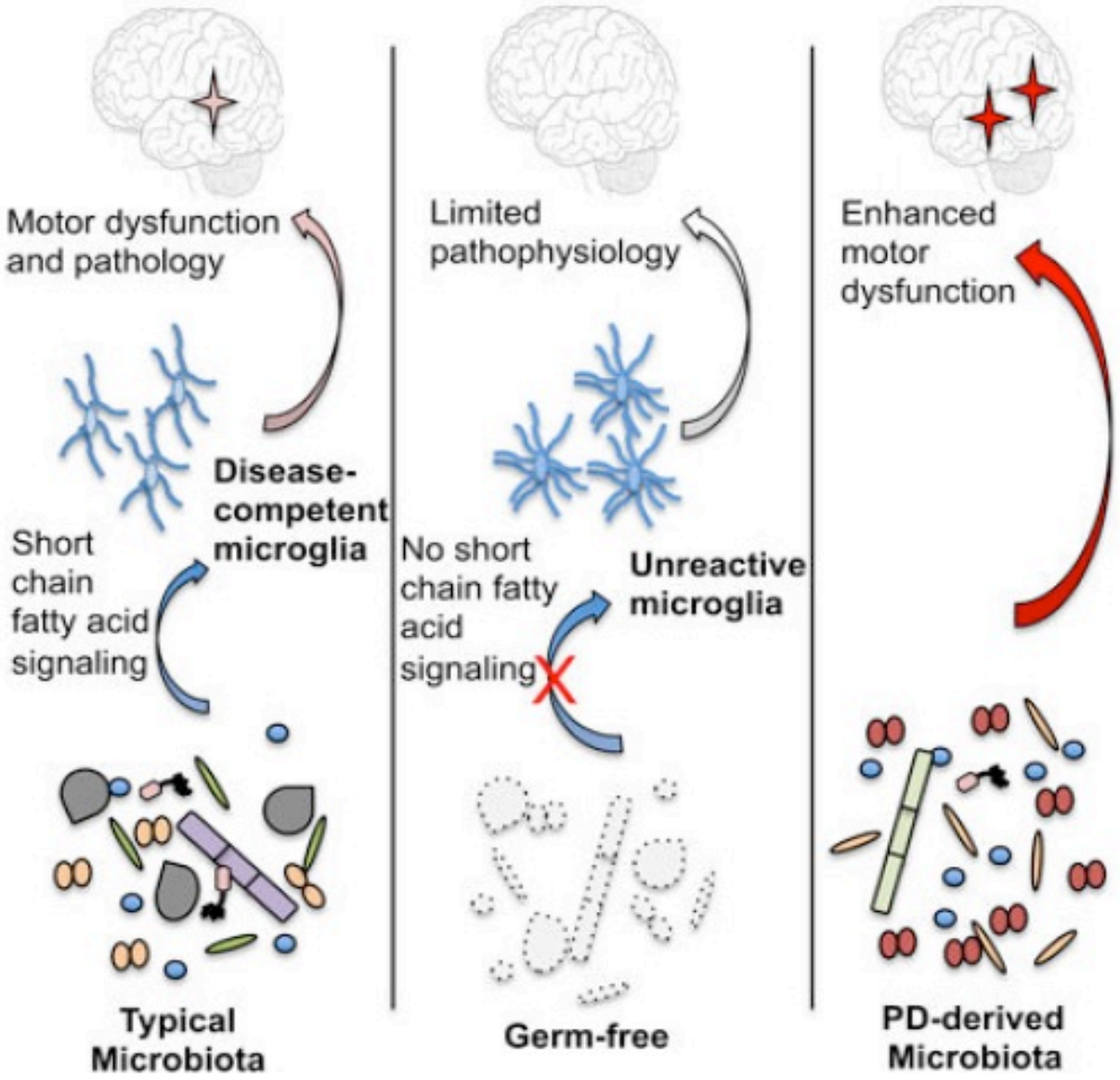
Animal study

- Animal study shows that injected alpha-synuclein in an animal gut propagated to brain. It indicates that gut microbiota modulates motor deficits & brain pathology in PD mice models. (Cell 2016;167:1469-1480)
- Neuronal alpha-synuclein in GI immunity → colonic inflammation and IPD → reduced short chain FA in PD

Gut Microbiota Regulate Motor Deficits and Neuroinflammation in a Model of Parkinson's Disease

- Gut microbes promote α-synuclein-mediated motor deficits and brain pathology
- Depletion of gut bacteria reduces microglia activation
- SCFAs modulate microglia and enhance PD pathophysiology
- Human gut microbiota from PD patients induce enhanced motor dysfunction in mice

Cell 2016;167:1469-1480



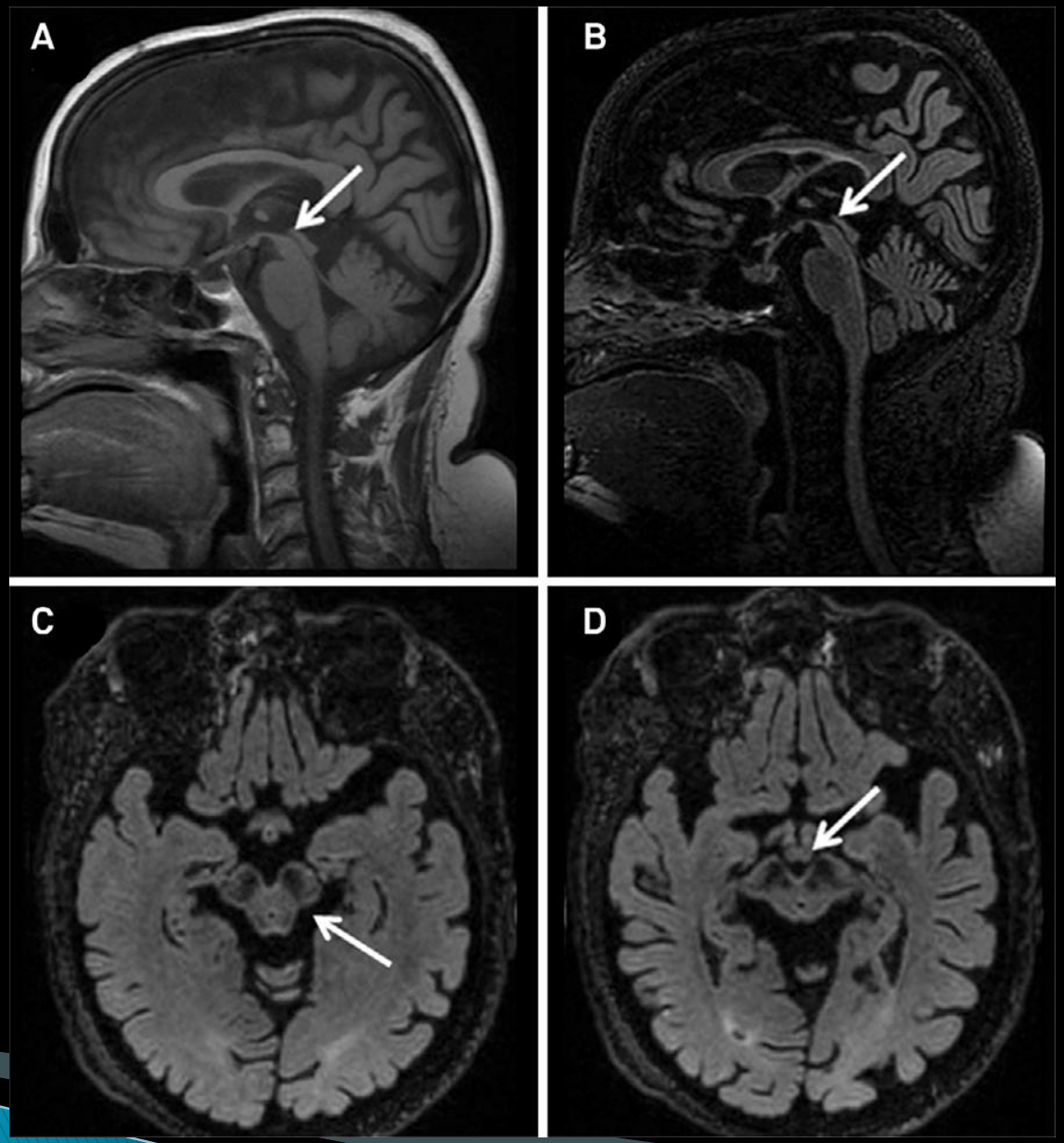
Cell 2016;167:1469-1480

Treatment of Gut brain interaction

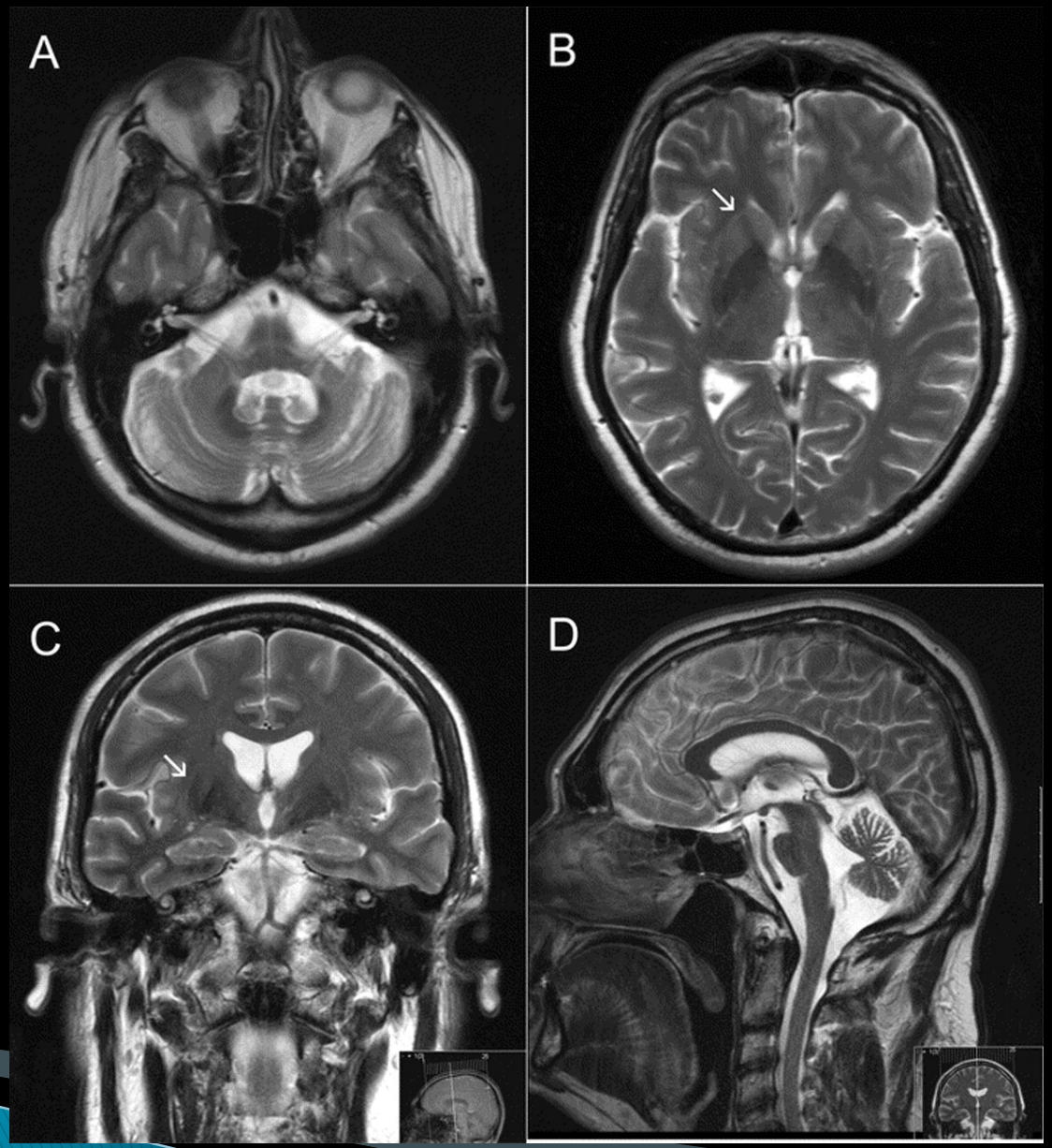
- Probiotics, prebiotics, synbiotics
- BMI
- Cigarette smoking
- Coffee
- probiotics

Imaging of Parkinsonism

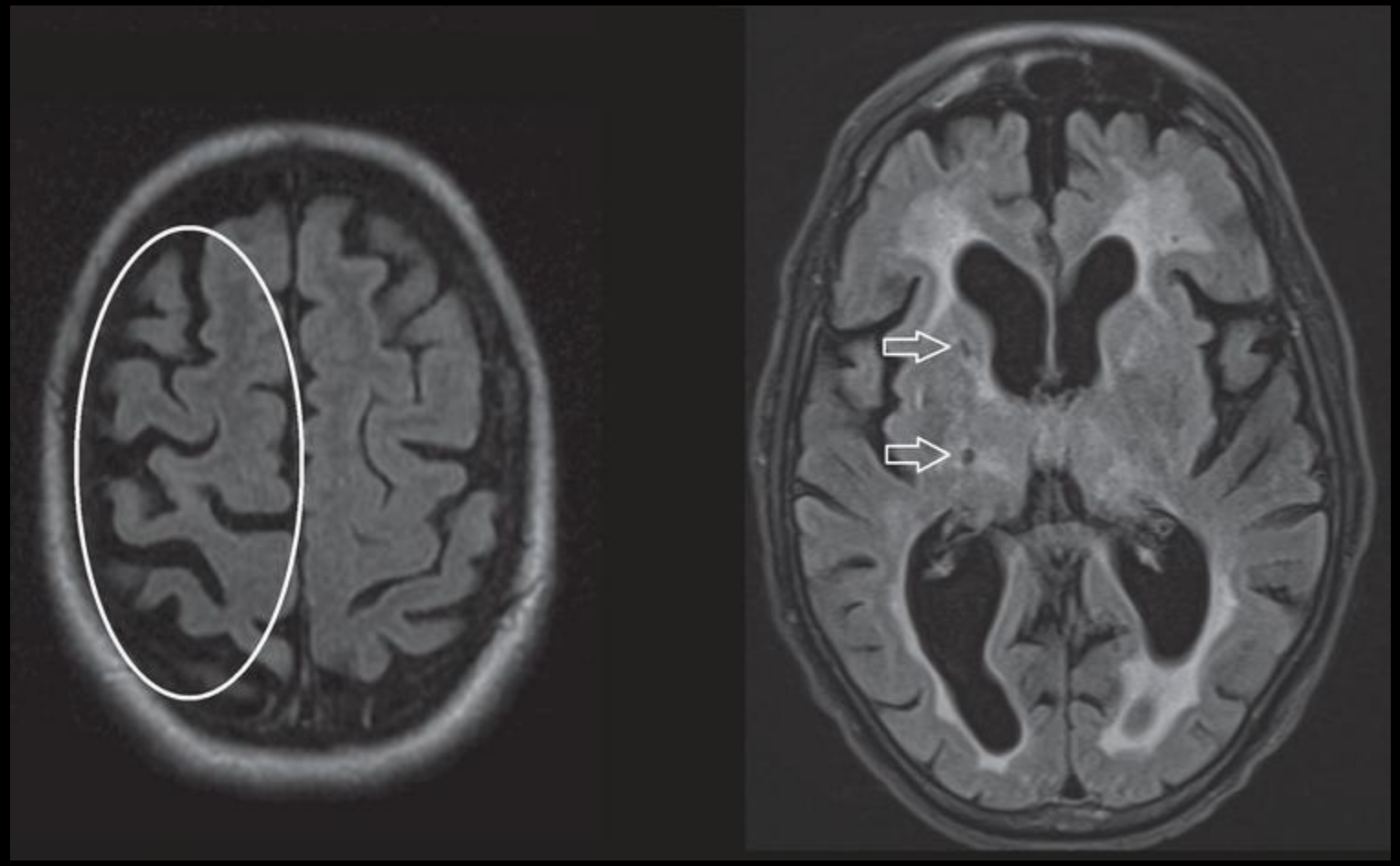
Progressive Supranuclear Palsy



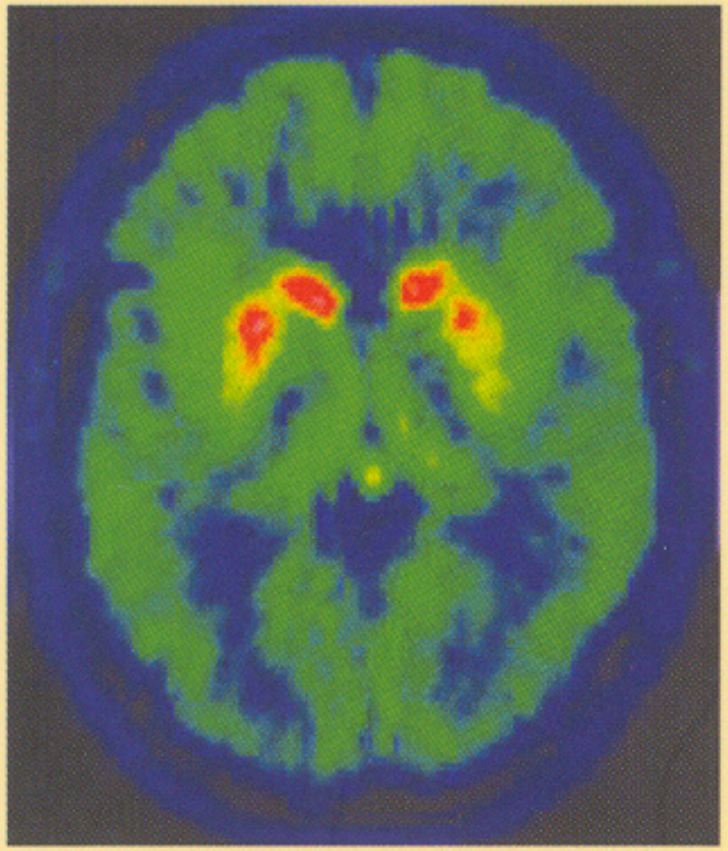
Multiple System Atrophy-P



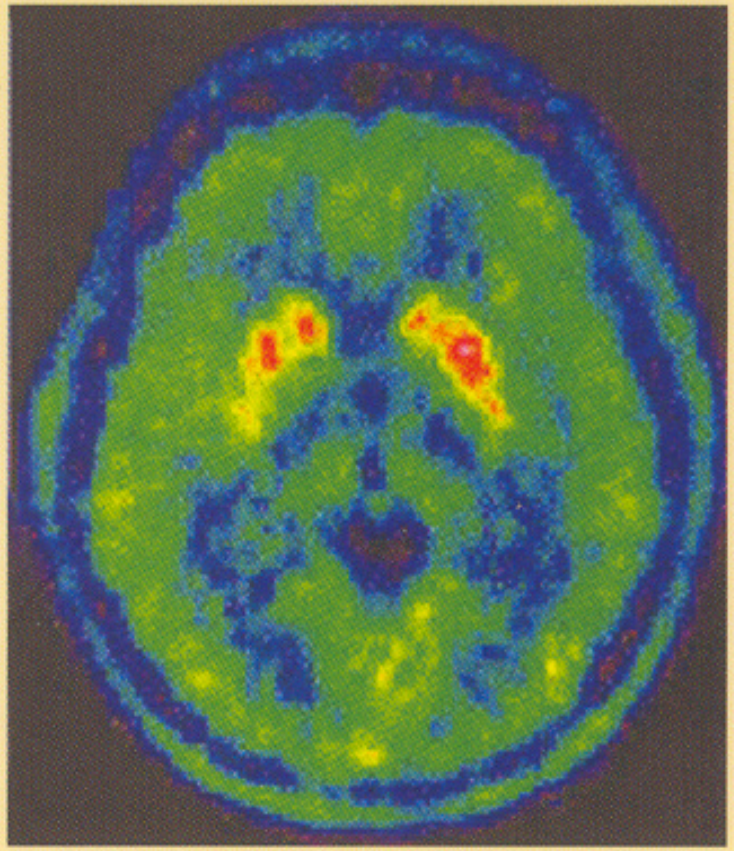
Corticobasal Degeneration



PET SCANNING IS A MARKER OF PD PROGRESSION

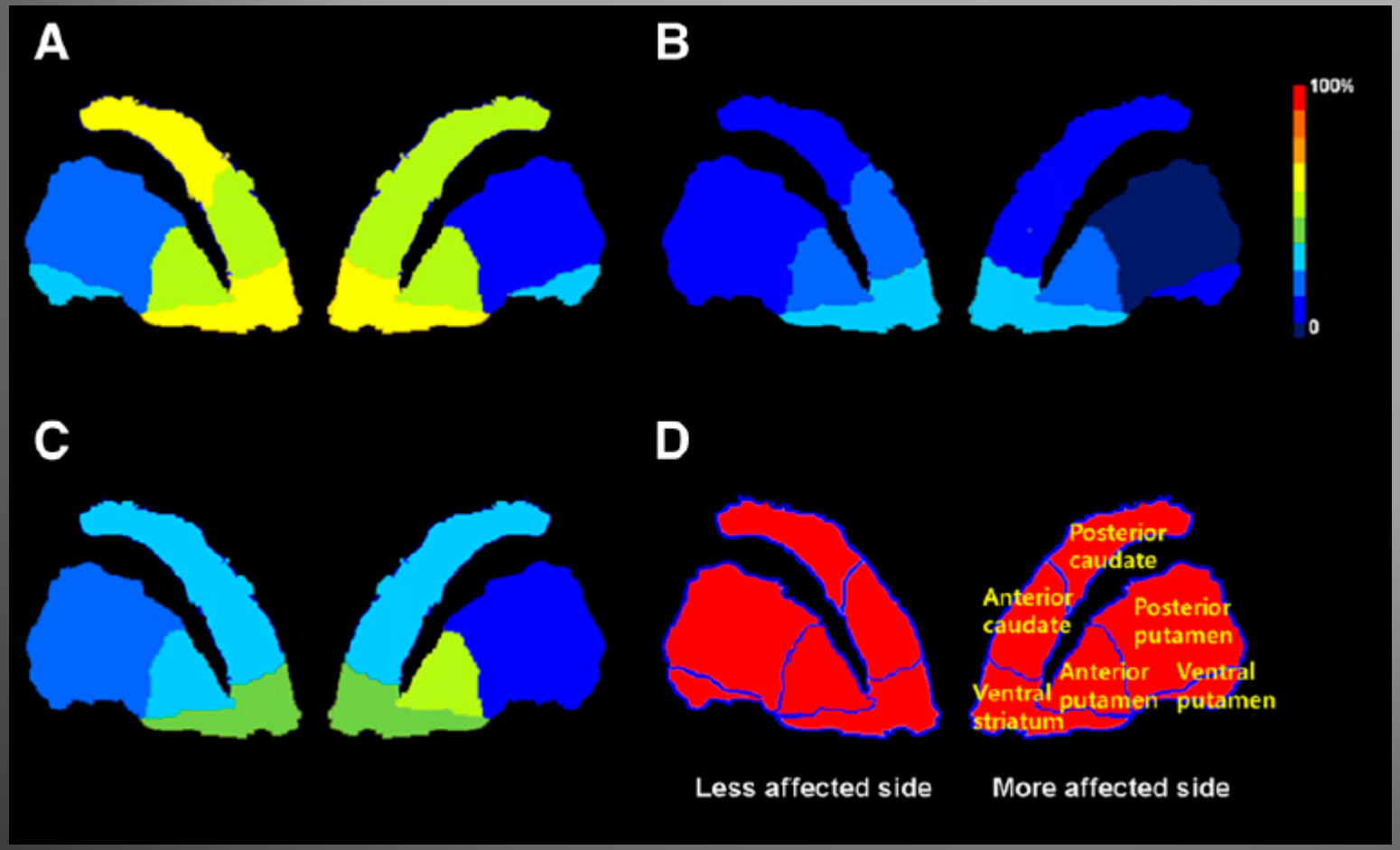


baseline



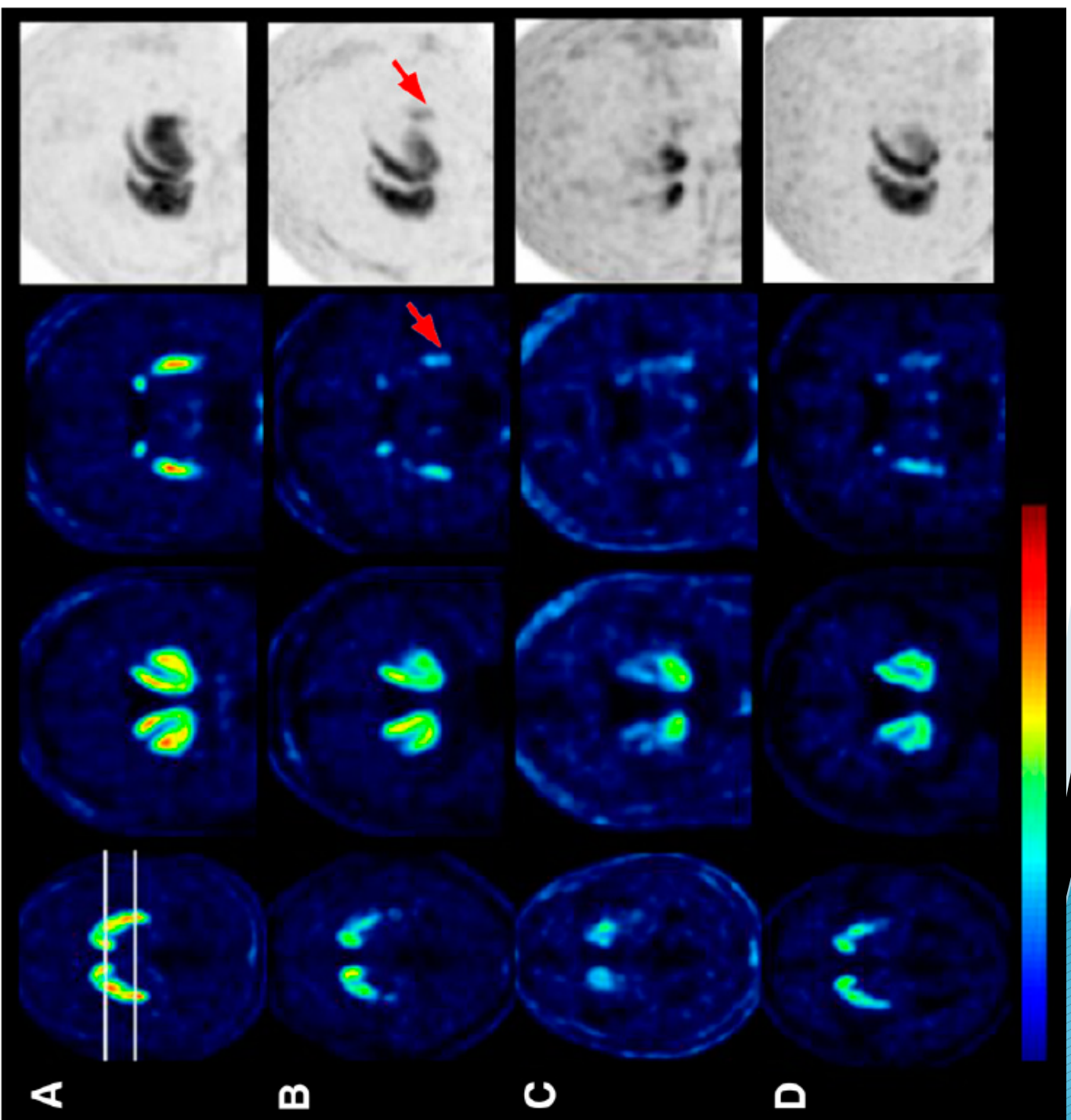
2 years

Diagram of age-corrected, normalized %BP of striatal subregion on 18F-FP-CIT PET for PD, PSP, MSA, Healthy control



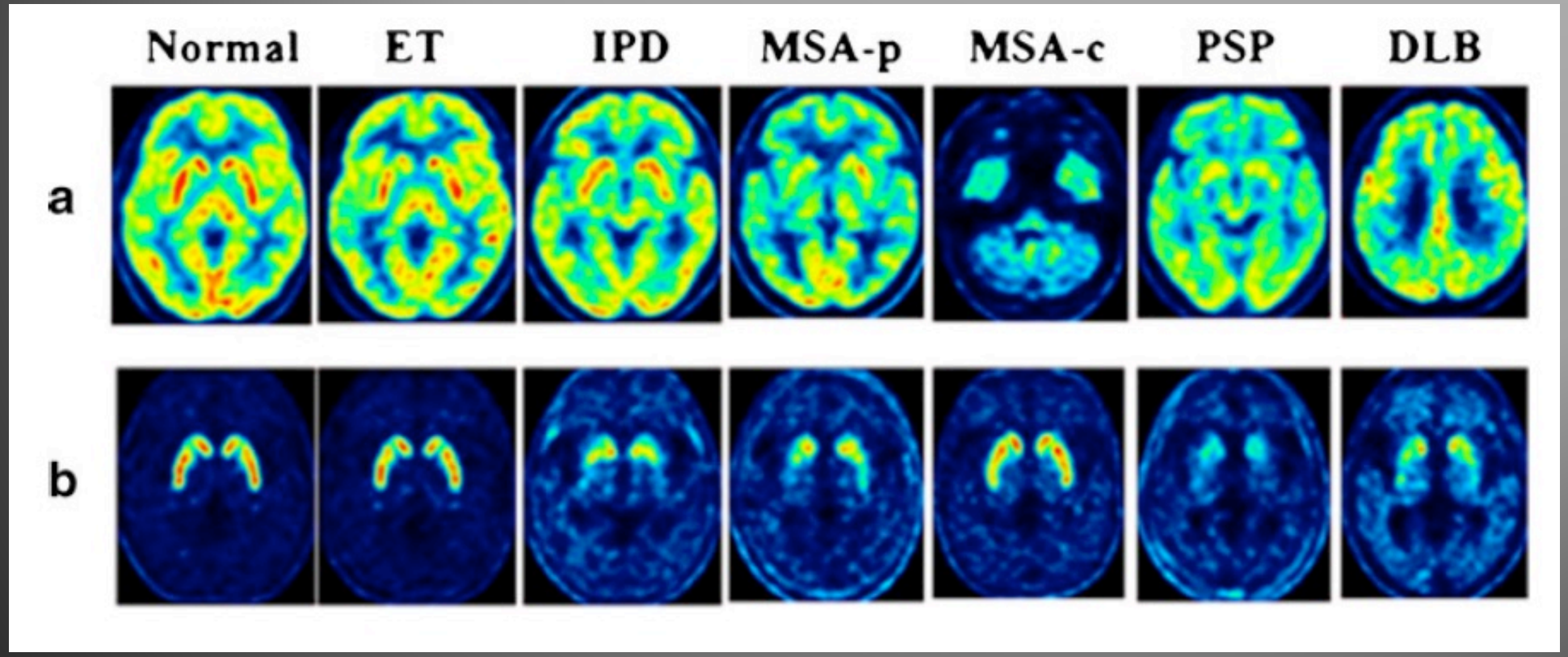
2012, Minyoung Oh, et al. Journal of Nucl Med

Representative ration parametric axial images at level of around AP commissure,



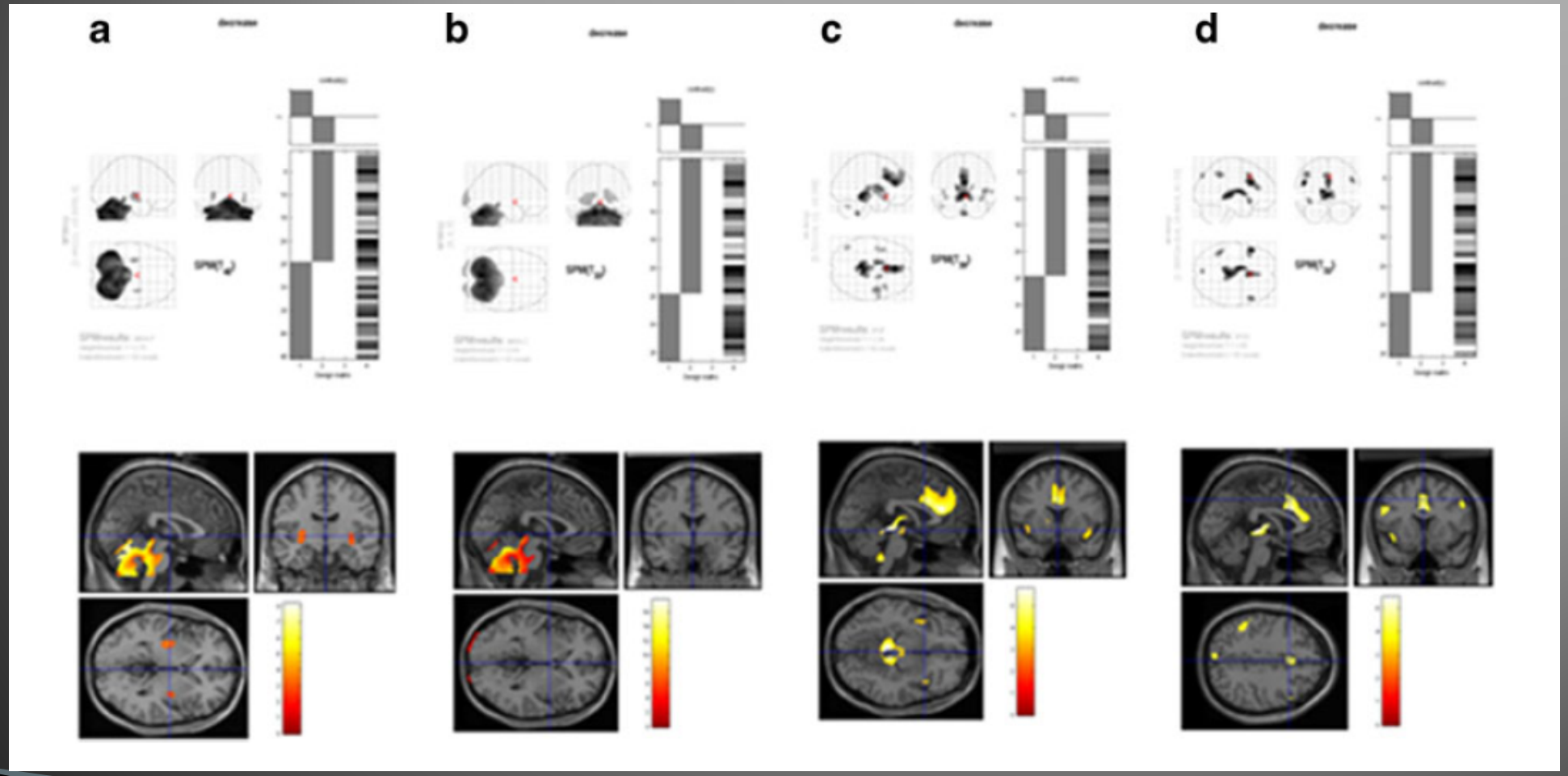
2012, Minyoung Oh, et al. Journal of Nucl Med

a early and **b** late phase F-18 FP-CIT-PET of Movement disorders and Normal



2013, Soyoung Jin et al. Nucl Med Mol Imaging

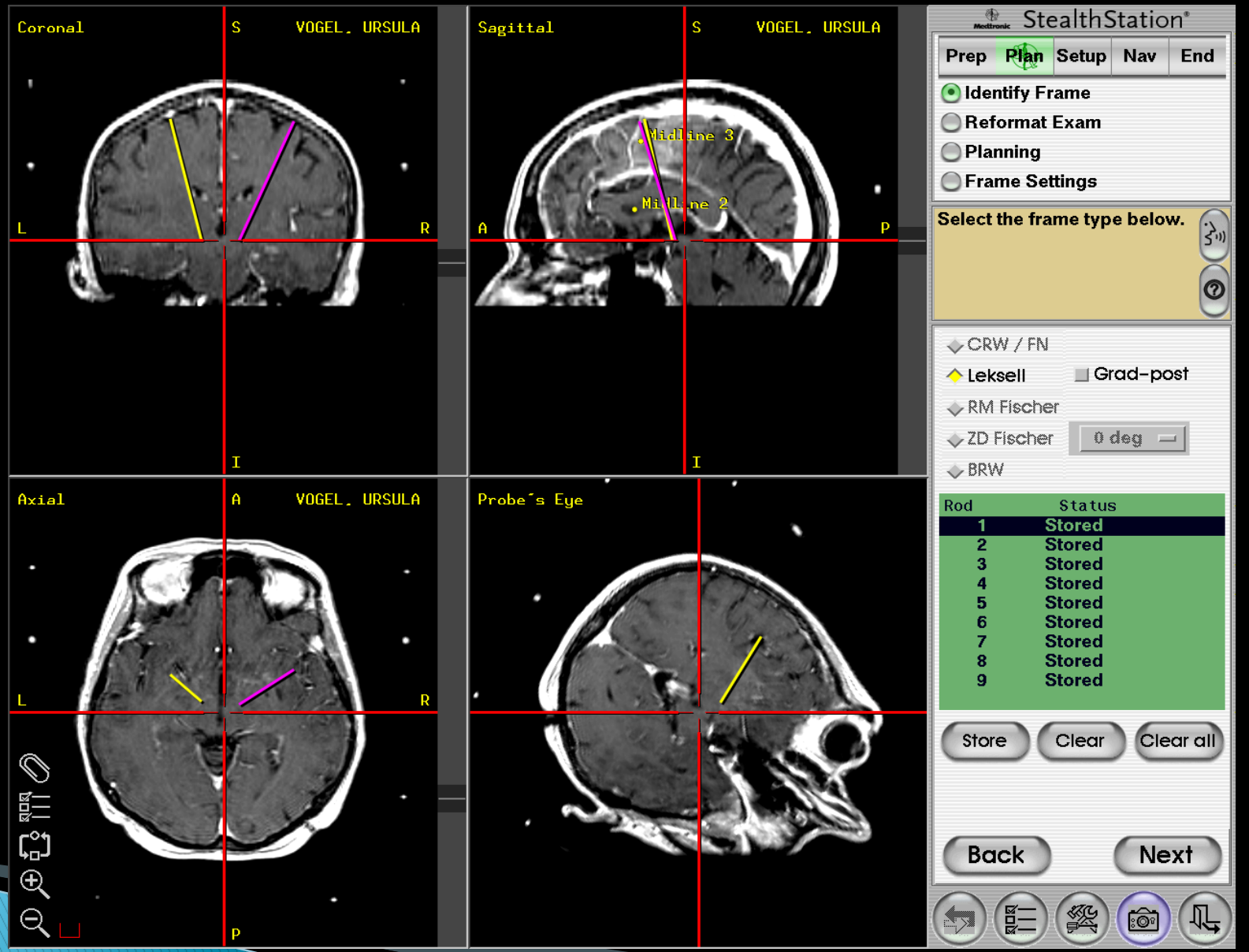
Difference of regional uptake in early phase image SPM of MSA-P, MSA-C, PSP, and DLB, compared with IPD (FDR<0.05)



2013, Soyoung Jin et al. Nucl Med Mol Imaging

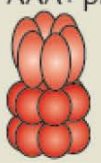
Peak dose dyskinesia

Deep brain stimulation



The molecular chaperon

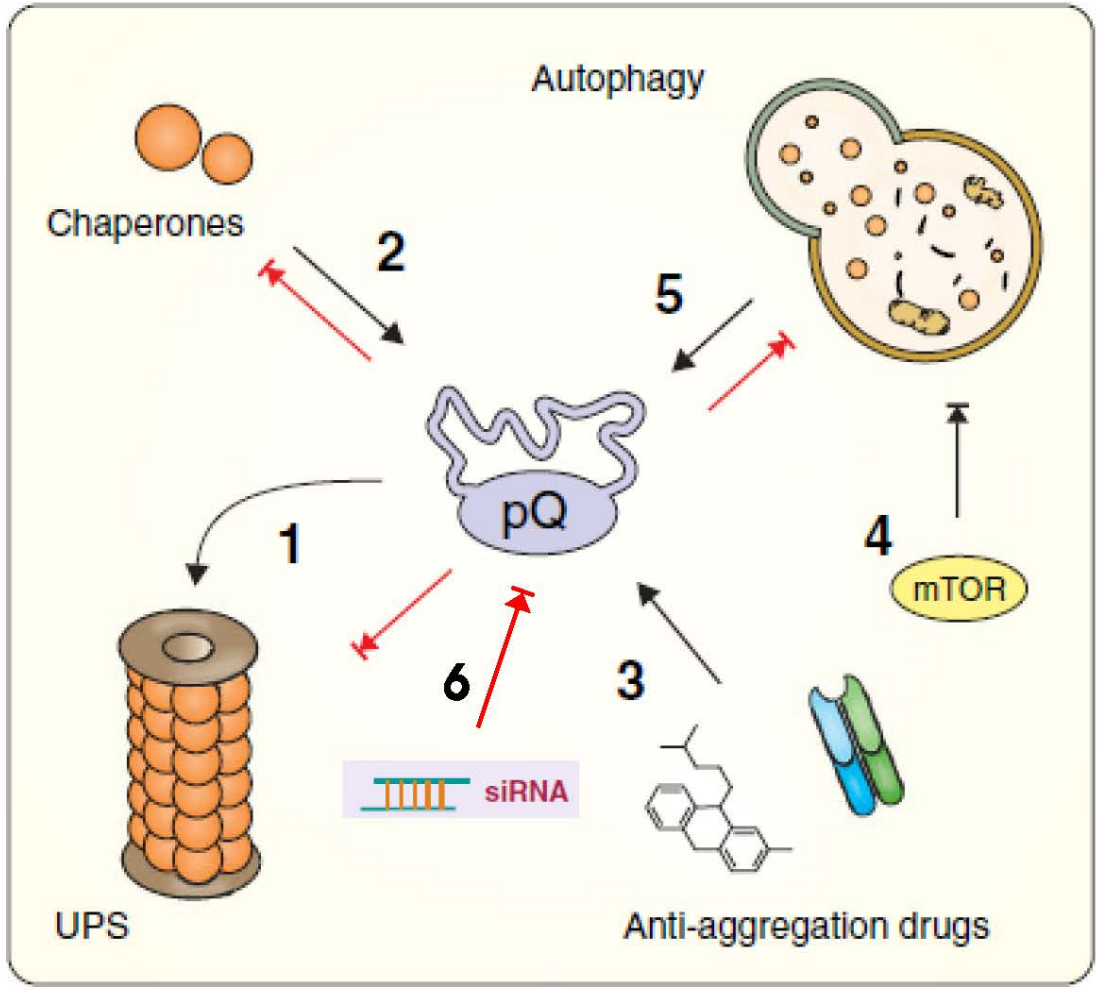
Table 1 | **Molecular chaperones and proteases implicated in protein disaggregation**

Chaperone	Organism	Structure and oligomeric state	ATP binding	Activity
ClpB or Hsp104 	Bacteria, yeast, plants and mitochondria of animals	Hexamer	Yes	Reactivation of aggregated proteins in cooperation with an Hsp70 chaperone system
Hsp70 	Bacteria, archaea and eukaryotes (cytosol, ER, mitochondria and chloroplasts)	Monomer	Yes	Prevention of aggregation, reactivation of aggregated proteins in cooperation with ClpB or Hsp104, and folding of newly synthesized proteins and misfolded protein species
sHSPs 	Bacteria, archaea and eukaryotes (cytosol)	8–24-mer	No	Prevention of irreversible protein aggregation
AAA+ proteases 	Bacteria and eukaryotes (mitochondria and chloroplasts)	Hexamer (for example, ClpA and ClpC) and heptamer (for example, ClpP)	Yes	Degradation of misfolded or aggregated protein species and of native proteins harbouring specific degradation tags
26S proteasome 	Eukaryotes (cytosol)	Hexamer (for AAA+ proteins) and heptamer (for α- and β-subunits)	Yes	Degradation of polyubiquitylated proteins (including misfolded and native proteins harbouring specific degradation tags)
VCP 	Eukaryotes (cytosol)	Hexamer	Yes	Degradation of misfolded ER proteins and membrane fusion

ER, endoplasmic reticulum; sHSP, small heat shock protein; VCP, valosin-containing protein.

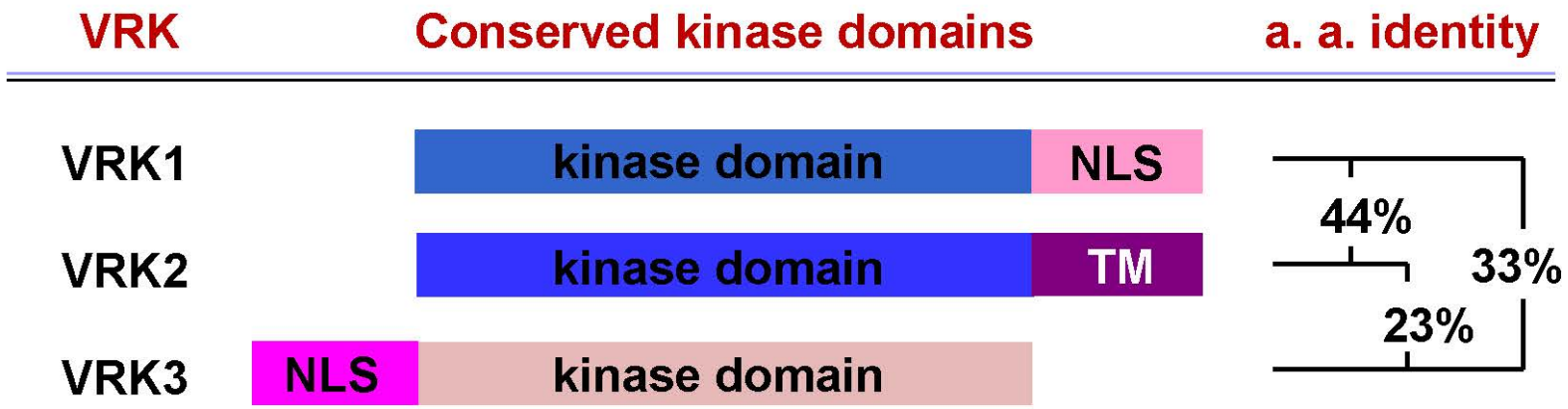
(*Nat rev mol cell biol*, 2010)

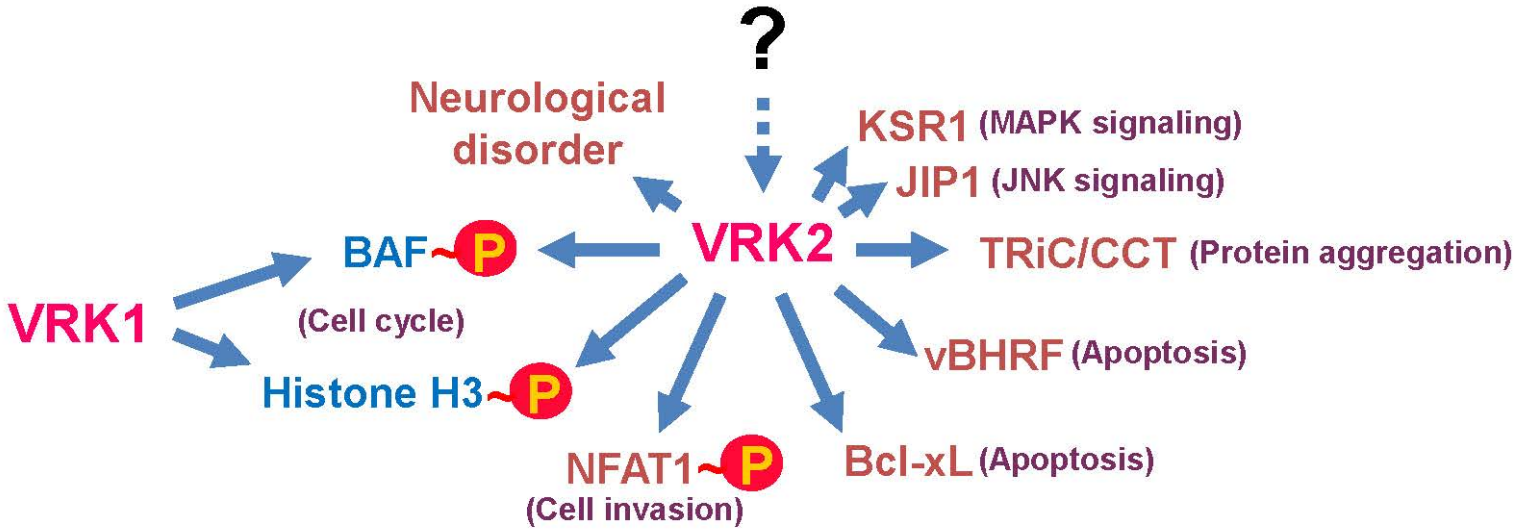
Strategy for clearance of aggregates



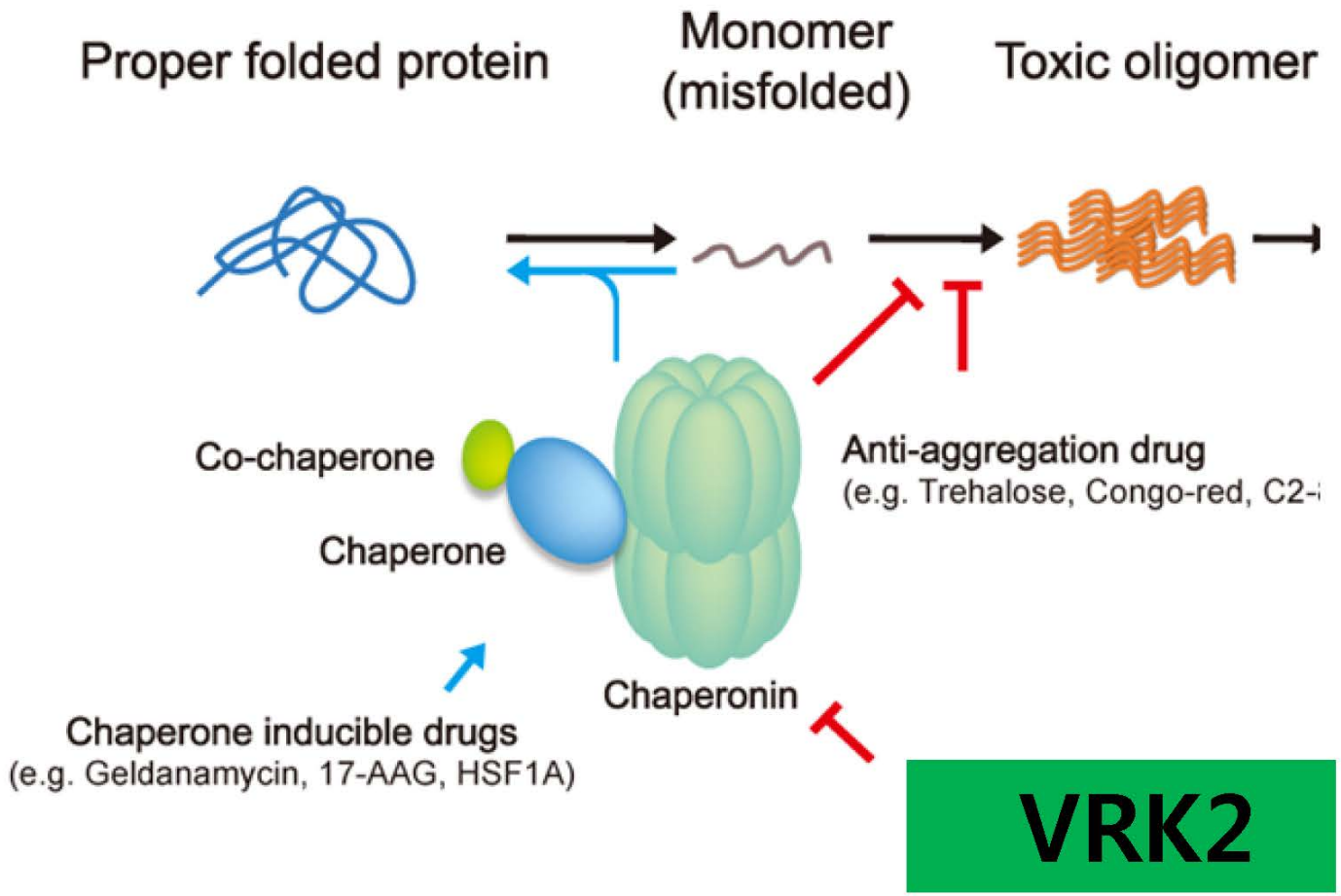
Vaccinia-related kinase (VRK) family

Vaccinia virus B1 kinase ⟷ VRK2 ~36 % a.a identity



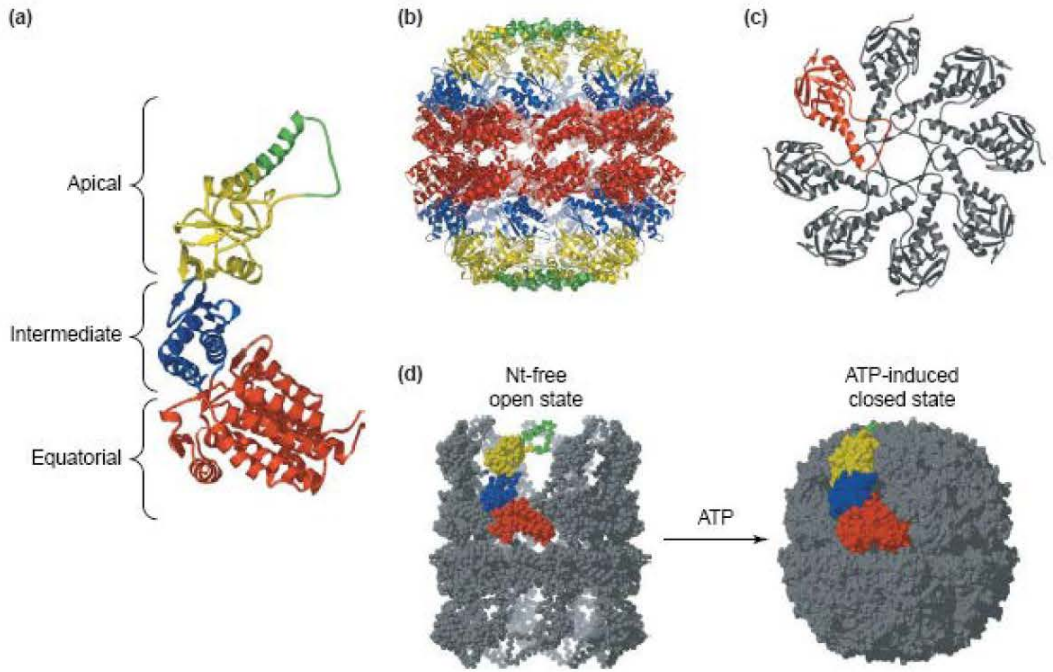


VRK2 & Chaperonin



The eukaryotic chaperonin TRiC

- Key components of the cellular chaperone machinery



- Chaperonin initially proposed to fold only actin and tubulin *(Cell,* 1992)

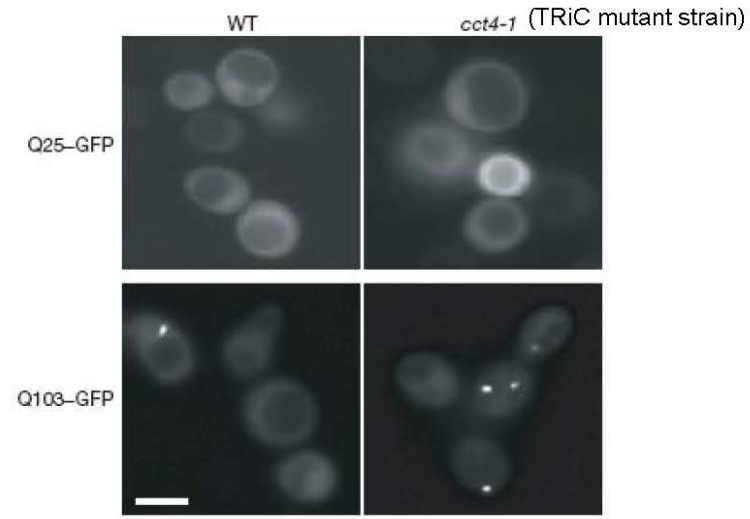
- Numerous non-cytoskeletal substrate proteins have been identified, including cyclin E, Cdc20 and the Von Hippel-Lindau tumor suppressor (VHL) *(Mol Cell,* 1999), (*Mol Cell,* 2001*), (Mol Cell Biol,* 1998*)*

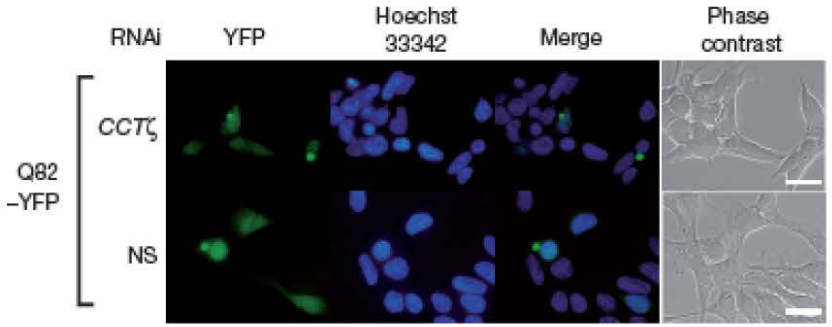
- Recently, chaperonin controls polyglutamin aggregation and toxicity *(Nat Cell Biol, 2006)*

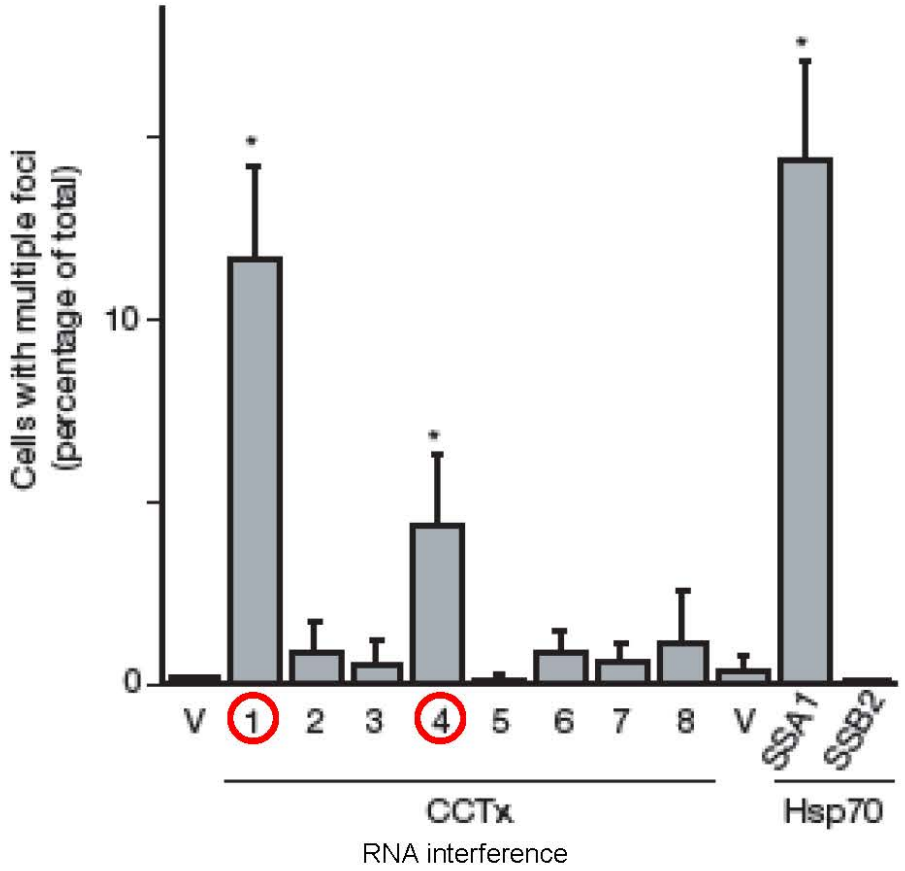
TRiC, TCP-1 Ring Complex
CCT, chaperonin containing TCP-1
TCP-1, tailless complex polypeptide 1

Chaperonin alleviates protein aggregation

Chaperonin TRiC control polyglutamine aggregates formation







(Nat Cell Biol, 2006)

Estimated life expectancy of Parkinson's disease patients compared with the UK population

Age at Onset	Life expectancy	Average age of death
25-39	38(49)	71(82)
40-64	21(31)	72(83)
65+	5(9)	88(91)

L Ishihara, A Cheesbrough, C Brayne, A Schrag JNNP 2007;78:1304-1309

AAD(average age of death)괄호속 숫자는 정상인의 경우임.

What can we do for the patients with neurological diseases?

Thank you for your attention