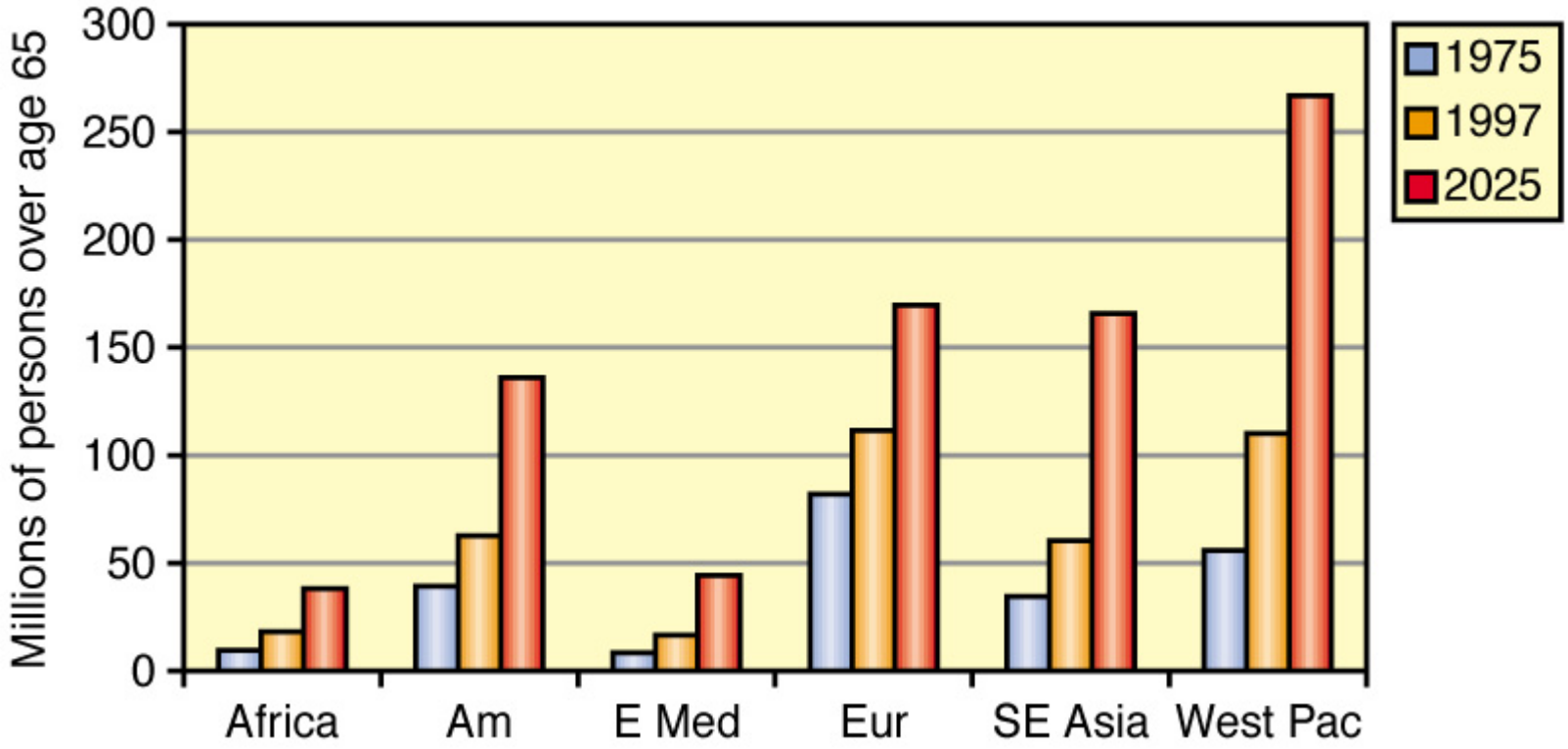
- **AGING and DEMENTIAS (4/13/2006)**

- **Canonical changes during aging**
- **Classification of dementias**
- **Symptoms of dementia**

- **ALZHEIMER'S DISEASE**
- **Clinical manifestations**
- **Cellular pathology**
- **Cholinergic deficits, relationship between cholinergic loss, pathological lesions and dementia**
- **Other neuropathological-neurochemical abnormalities**
- **Progression of the disease**
- **Pathology of the aging brain in relation to AD**
- **Clinical-pathological correlations**
- **Etiology and genetics**
- **Transgenic mice models**
- **Pathogenesis**
- **Therapy in AD**

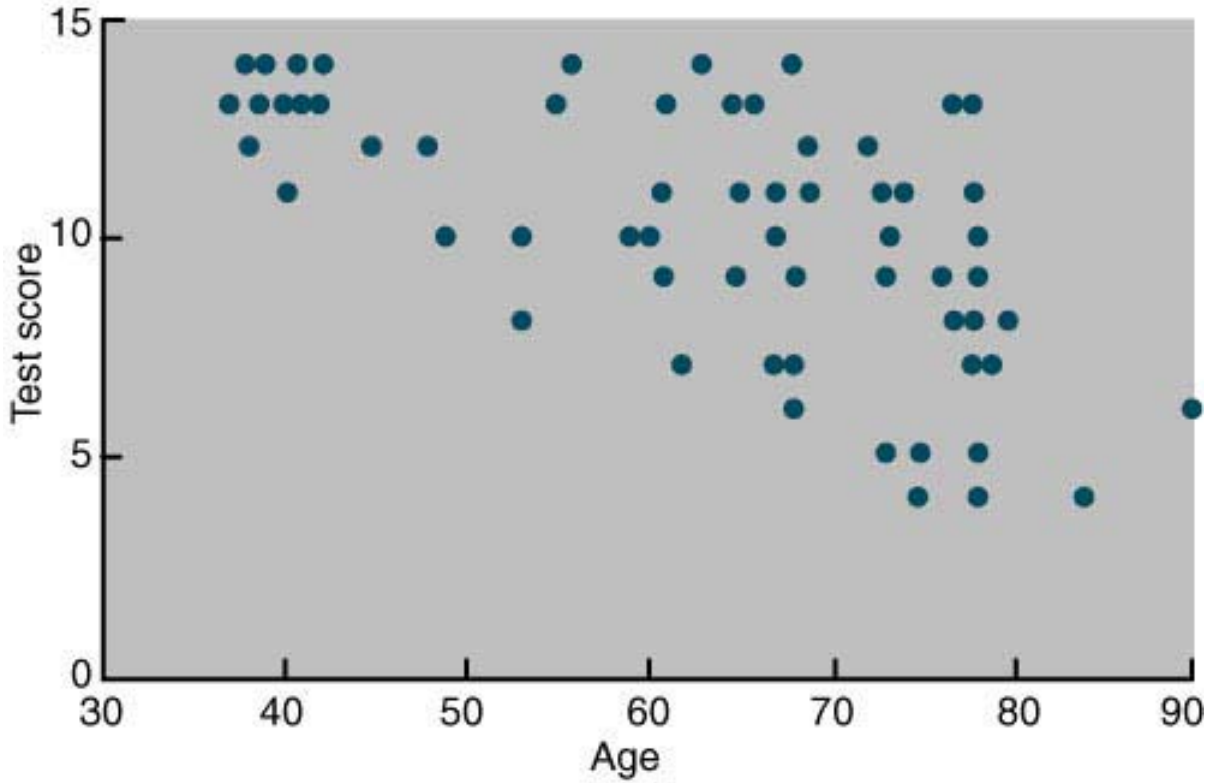
AGING, RISK FACTORS, PREVENTION of AGING-RELATED NEURODEGENERATIVE DISEASES

Millions of persons over the age of 65 for the years 1975, 1997, 2025



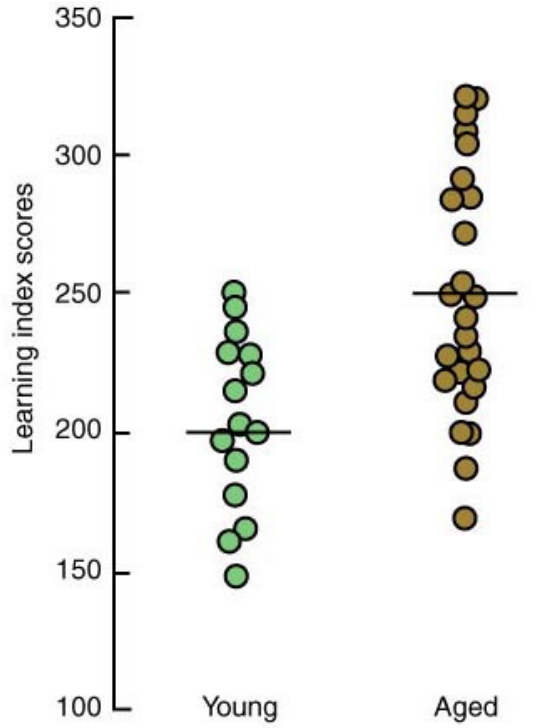
Am= Americas (North and South America, Canada, and Mexico), E Med= Eastern Mediterranean (including all nations of the Middle East), Eur=Europe, SE=South East Asia (including India), West Pac Western Pacific (including China).

DELAYED RECALLS IN HEALTHY SUBJECTS



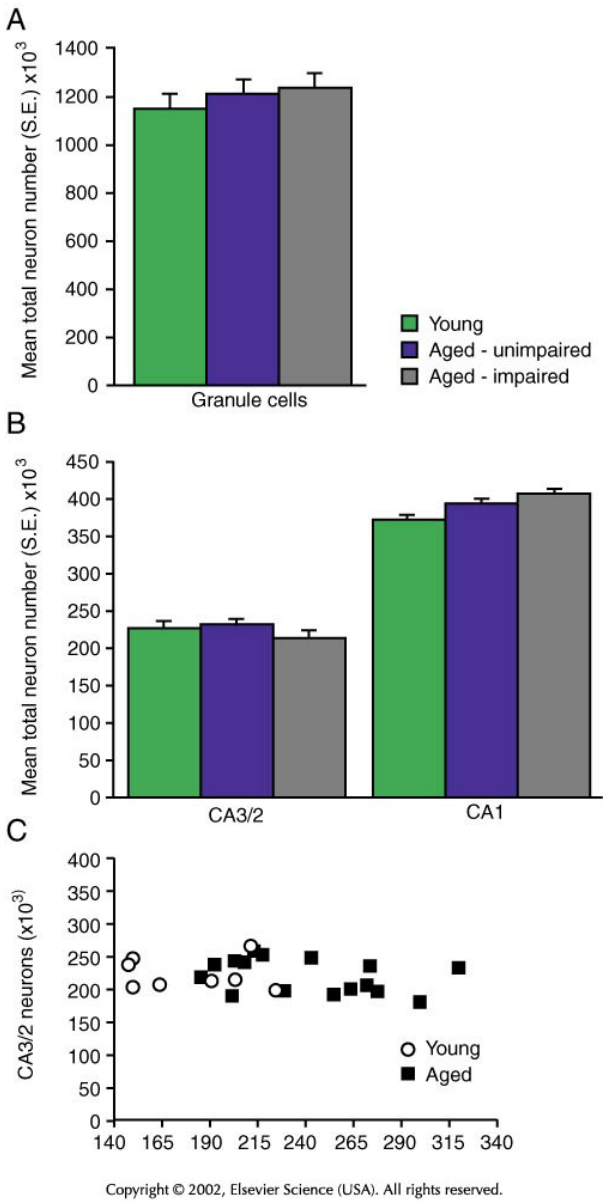
Scores for young adults and optimally healthy aged human subjects on a test of delayed recall that requires the integrity of the medial temporal lobe memory system. Note that although there is a significant overall decline with age, performance is highly variable across aged individuals. Data courtesy of M.S. Albert, Massachusett General Hospital, Harvard University

LEARNING SCORES FOR YOUNG AND AGED RATS IN A WATER MAZE TEST

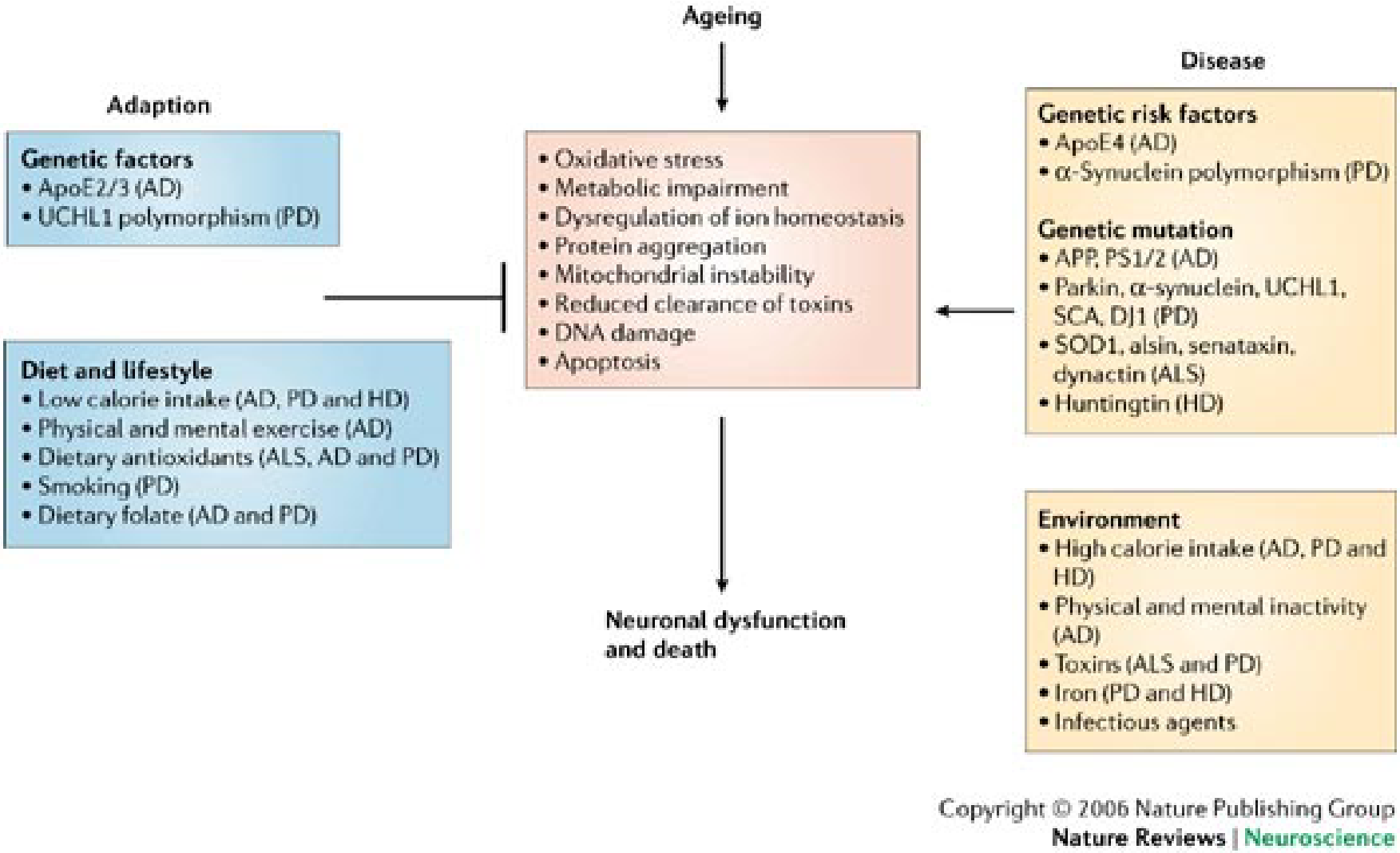


Learning scores for young adult and aged rats on a water maze test of spatial learning that requires the hippocampus. This measure of performance reflects the average distance of an animal from the goal location over the course of testing, and lower scores reflect better learning. Note that although the performance of the aged group is worse than for the younger cohort (compare group means represented by the horizontal bars), there is substantial variability among the aged rats and about half learn as well as young adults. Data courtesy of M. Gallagher, Johns Hopkins University.

NEURON NUMBER IN THE HIPPCOAMPUS IN BEHAVIORALLY TESTED RATS

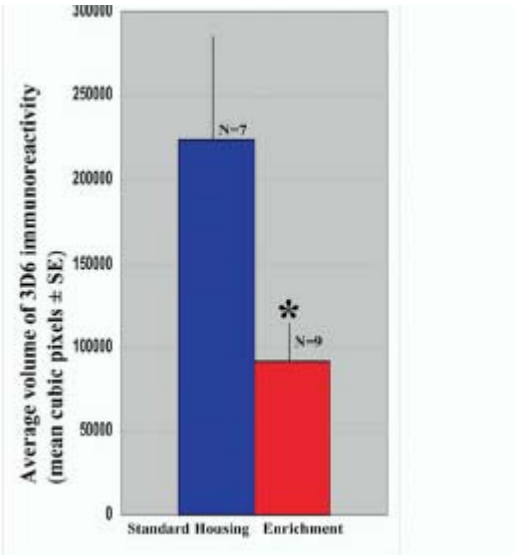


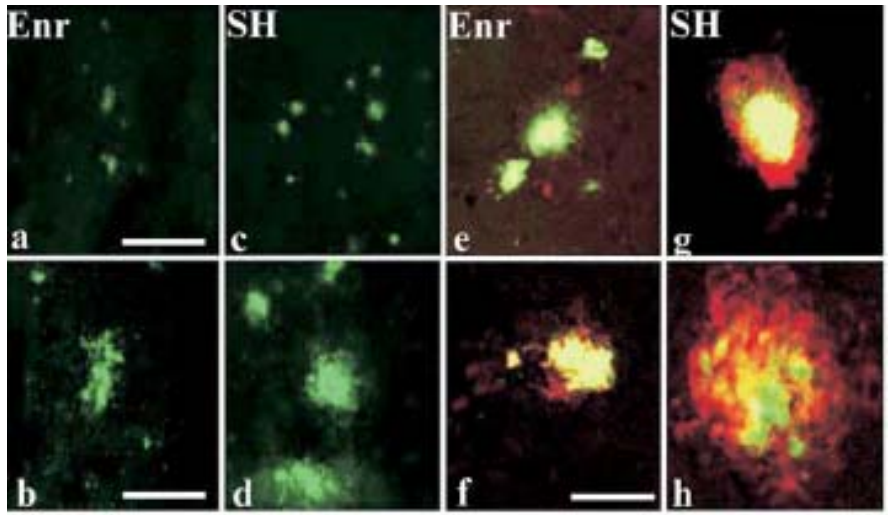
Values are for one hippocampus from each brain. Half of the aged rats exhibited substantial spatial learning deficits in the Morris water maze (aged impaired); the other half performed within the range of learning scores for the young group (aged unimpaired). (A) Mean estimated total neuron number (+standard error) in the granule cell layer for young, aged-unimpaired, and aged-impaired rats. Average granule cell number is comparable across the groups. (B) Mean estimated total neuron number (+SE) in CA3/2 (left) and CA1 (right) pyramidal cell fields of the hippocampus for behaviorally characterized young and aged rats. Neuron number does not differ with age or cognitive status. (C) Scatter plot of total neuron number in the CA3/2 hippocampal field for individual rats plotted as a function of spatial learning scores (lower values indicate better learning). Neuron number is stable with age and across a broad range of learning capacities. Rapp and Gallagher (1996).



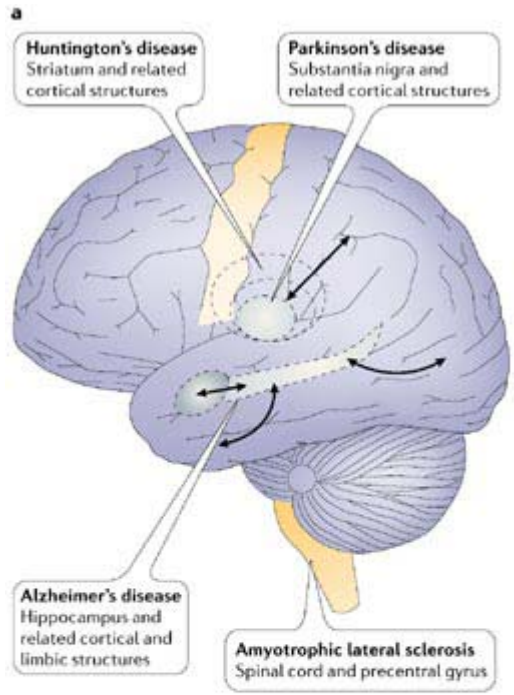
Mattson and Magnus, 2006

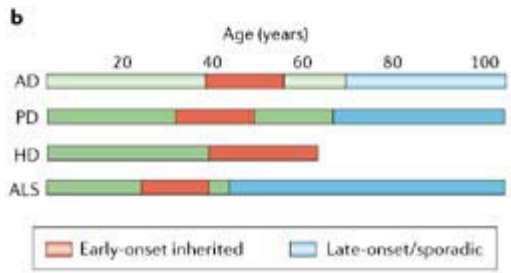
Environmental enrichment reduces BA levels and amyloid deposition in transgenic mice (Lazarov et al, 2005)

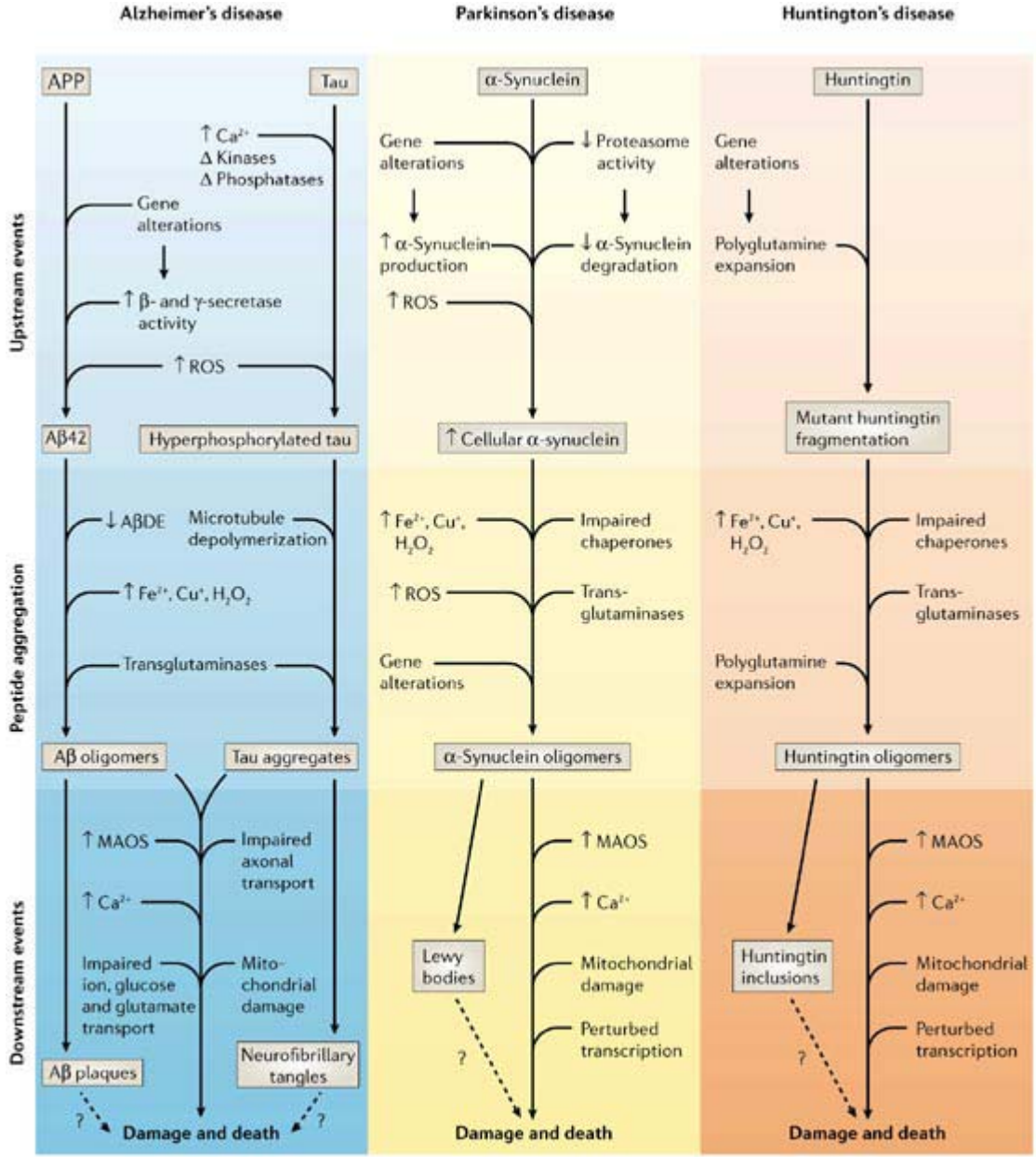




Quantitative analysis of volume of amyloid burden in brains of standard housingand enriched mice. Volume is in arbitrary units (mean cubic pixels ± SE, ANOVA, p % 0.0374).
Reduced number and size of thioflavineS-stained amyloid deposits in the hippocampus and cortex of enriched versus standard housing mice. Thioflavine S-positive amyloid deposits in brain sections of enriched (Enr; Ca, Cb, Ce, and Cf) and standard housing mice (SH; Cc, Cd, Cg, Ch). Size and abundance of thioflavine-positive structures in enriched (a = low power; b = high power) is reduced compared to standard housing mice (c = low power; d = high power). For (Ca) and (Cc), scale bar, 250 m. For (Cb) and (Cd), scale bar, 120 m. Double labeling with thioflavine S and anti-Aβ 3D6 antibodies reveals overlap staining at the core of the amyloid deposits, while the periphery of the deposit is stained mostly with anti-Aβ 3D6 antibodies (Cg and Ch). In contrast, the vast majority of amyloid deposits in brain sections of enriched mice had little 3D6-positive peripheral staining (Ce and Cf). Scale bar, 60 um.







Box 9.1 Classification of degenerative dementias and rel disorders based on protein abnormalities

Amyloidopathy (with limited tauopathy and alpha-synucleinopathy)

- Alzheimer's disease
  - Sporadic
  - Familial with amyloid precursor protein mutation
  - Familial with presenilin 1 mutation
  - Familial with presenilin 2 mutation
  - Down's syndrome with Alzheimer's disease (trisomy 21)

Tauopathies

- Frontotemporal lobar degeneration
  - Pick's disease
  - Frontotemporal lobar degeneration with parkinsonism lin chromosome 17
  - Frontotemporal lobar degeneration lacking distinct histop features
  - Frontotemporal lobar degeneration with motor neuron di
  - Hereditary disinhibition dysphasic dementia
- Pallidopontonigral degeneration
- Progressive supranuclear palsy
- Guamanian amyotrophic lateral sclerosis-parkinsonism demen
- Corticobasal degeneration
- Secondary tauopathies
  - Alzheimer's disease
  - Dementia with Lewy bodies
  - Dementia pugilistica
  - Hallervorden-Spatz disease
  - Creutzfeldt-Jakob disease
  - Gerstmann-Straussler-Scheinker disease
  - Neimann-Pick disease (type C)
  - Subacute sclerosing panencephalitis

Synucleinopathies

- Parkinson's disease
  - Sporadic
  - Familial with alpha-synuclein mutations
  - MPTP-induced
- Dementia with Lewy bodies (with amyloidopathy and limited tauopathy
- Cortical Lewy body disease
- Multiple system atrophy
  - Shy-Drager syndrome
  - Olivopontocerebellar atrophy
  - Striatonigral degeneration
- Neurodegeneration with brain iron accumulation
  - Hallervorden-Spatz disease
  - Neuroaxonal dystrophy
- Secondary synucleinopathies
  - Alzheimer's disease
  - Traumatic brain injury
  - Amyotrophic lateral sclerosis

Prion protein disorders

- Creutzfeldt-Jakob disease
  - Sporadic
  - Familial
  - New variant
  - Iatrogenic
- Kuru
- Fatal familial insomnia
- Sporadic fatal insomnia
- Gerstmann-Straussler-Scheinker disease
- Familial progressive subcortical gliosis

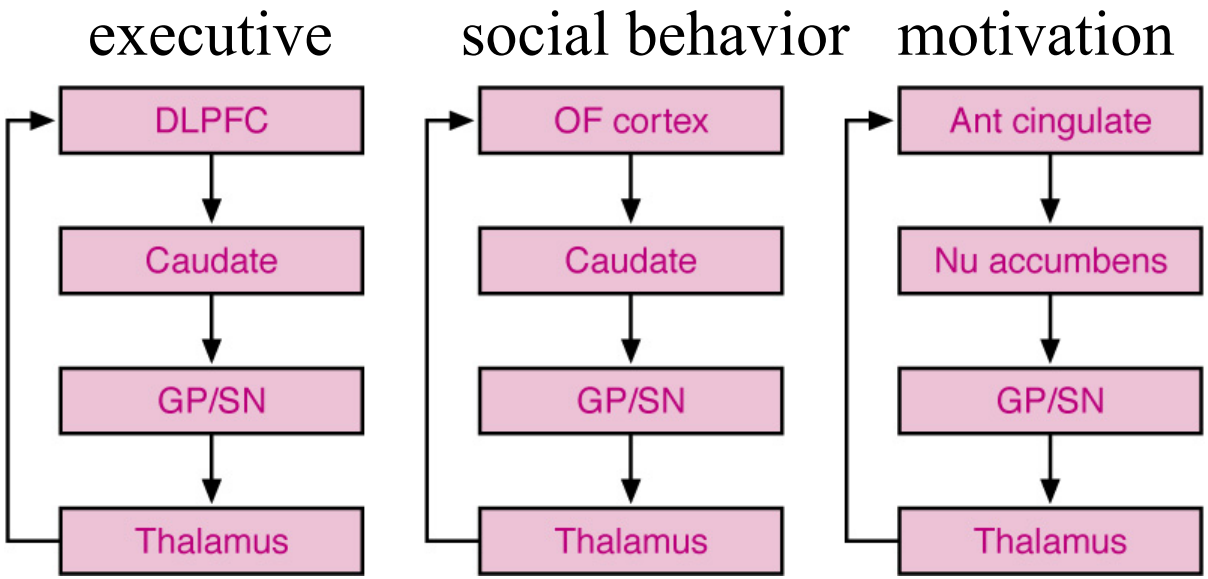
MPTP, 1-methyl-1-phenyl-1,2,3,6-tetrahydropyridine.

continued

Table 1 | Phenotypes of neurons vulnerable to age-related neurodegenerative disorders

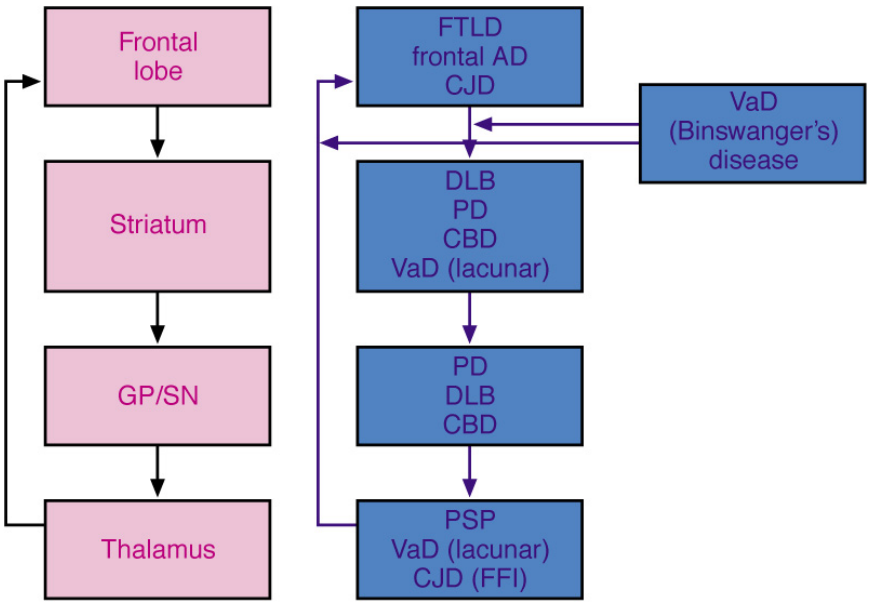
Disorder	Affected regions	Phenotypes
Alzheimer's disease	Entorhinal cortex, hippocampus, frontal cortex, basal forebrain, parietal lobe, occipital lobe, amygdala, locus coeruleus* and raphe nucleus*	Projection neurons; multiple transmitters (for example, glutamate, acetylcholine, noradrenaline and serotonin); and low CBPs
Parkinson's disease	Substantia nigra, frontal cortex, locus coeruleus* and raphe nucleus*	Projection neurons; primarily dopaminergic neurons; and low CBPs
Huntington's disease	Striatum, frontal cortex and locus coeruleus*	Projection neurons; and GABA-containing and glutamatergic neurons
Amyotrophic lateral sclerosis	Motor cortex and spinal cord	Projection neurons; cholinergic and glutamatergic neurons; and low CBPs
Stroke	Most CNS regions	Large neurons; and low CBPs

Mattson and Magnus, 2006



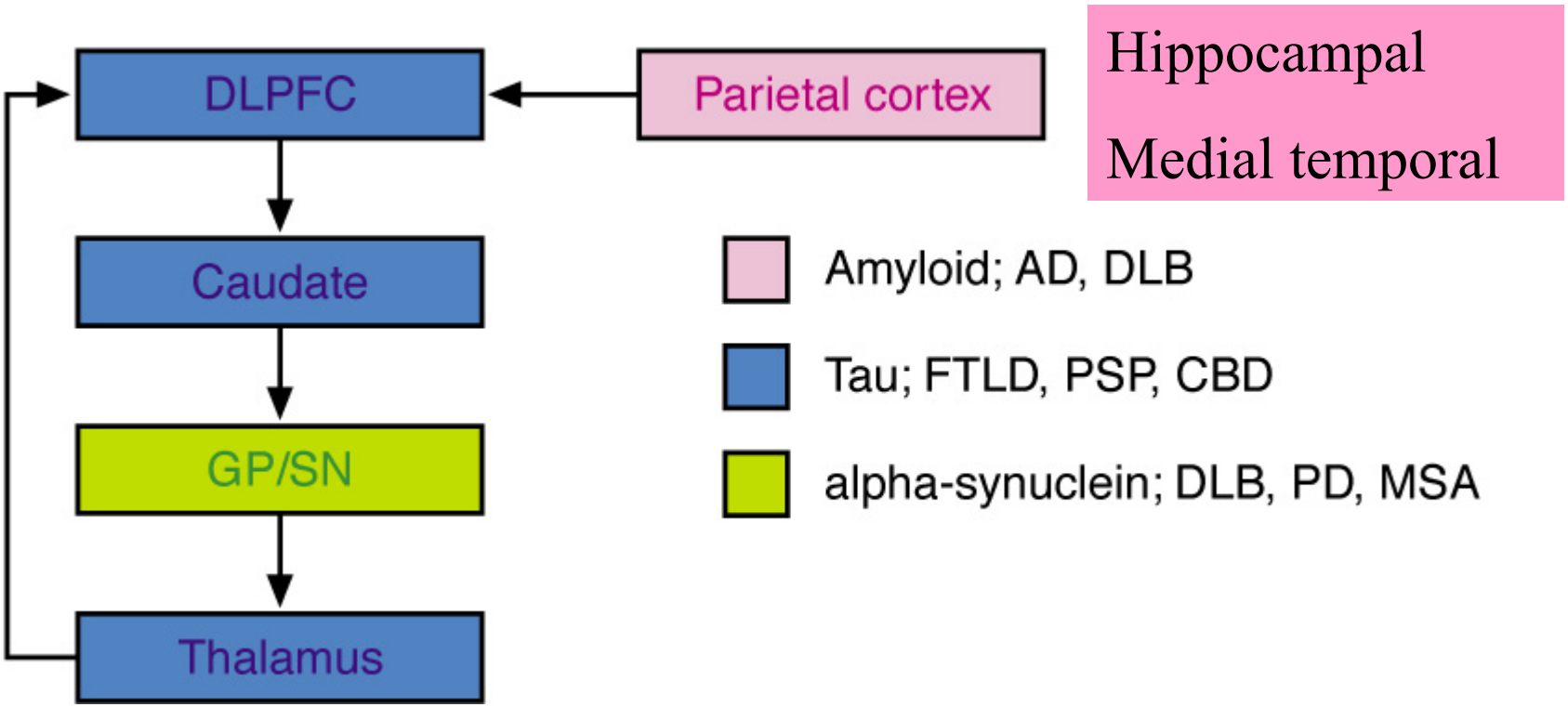
Three behaviorally relevant frontal-subcortical circuits.. DLPFC, dorsolateral prefrontal cortex; GP, globus pallidus; SN, substantia nigra; Nu accumbens, nucleus accumbens; Ant cingulate, anterior cingulate; OF, orbitofrontal.

Regional involvement of frontal-subcortical circuits by dementia syndromes



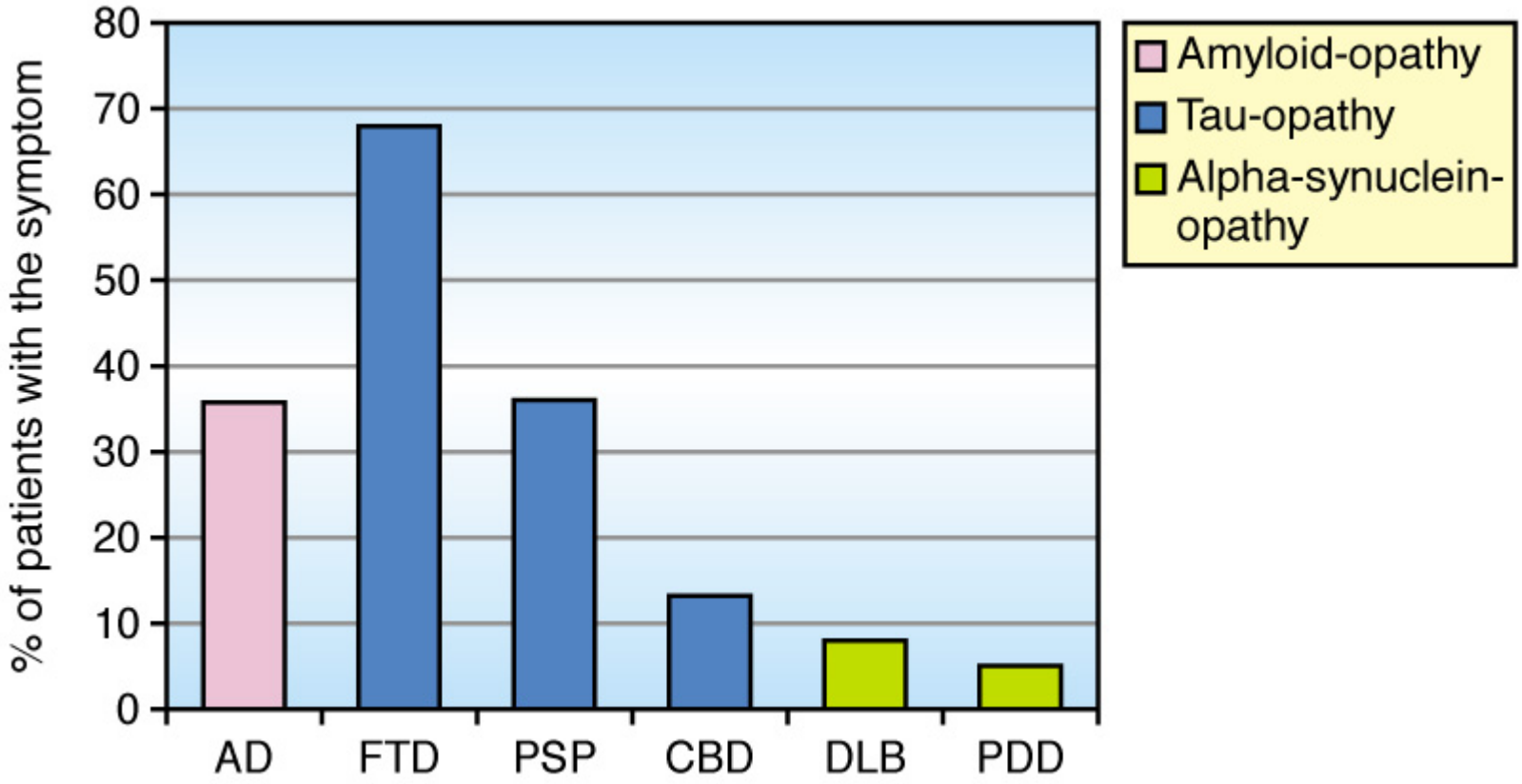
FTLD, frontotemporal lobar degeneration; AD, Alzheimer's disease; CJD, Creutzfeldt-Jakob disease; VaD, vascular dementia; DLB, dementia with Lewy bodies; PD, Parkinson's disease; CBD, corticobasal degeneration; PSP, progressive supranuclear palsy; FFI, fatal familial insomnia; GP/SN, globus pallidus/substantia.

Differential anatomic vulnerability to major types of protein metabolic abnormalities involved in dementing disorders



DLPFC, dorsolateral prefrontal cortex; GP/SN, globus pallidus/substantia nigra; FTLD, frontotemporal lobar degeneration; PSP, progressive supranuclear palsy; CBD, corticobasal degeneration; DLB, dementia with Lewy bodies; PD, Parkinson's disease; MSA, multiple system atrophies; AD, Alzheimer's disease.

Disinhibition in protein metabolic abnormalities



FTLD and PSP are primary tauopathies; AD is a secondary tauopathy. AD, Alzheimer's disease; FTLD, frontotemporal dementia; PSP, progressive supranuclear palsy; CBD, corticobasal degeneration; DLB, dementia with Lewy bodies; PDD, Parkinson's disease with dementia (From Cummings, 2004)

The common types of dementing diseases and their relative frequency

Dementing disease	*Relative frequency, %*
Cerebral atrophy, mainly Alzheimer-senile dementia	50
Multi-infarct dementia	10
Alcoholic dementia*	5–10
Intracranial tumors	5
Normal-pressure hydrocephalus	6
Huntington chorea	3
Chronic drug intoxications	3
Miscellaneous diseases (hepatic failure; pernicious anemia; hypo- or hyperthyroidism; dementias with Parkinson disease, amyotrophic lateral sclerosis, cerebellar atrophy; neurosyphilis; Cushing syndrome, Creutzfeld-Jakob disease; multiple sclerosis; epilepsy)	7–10
Undiagnosed types	3
Pseudodementias (depression, hypomania, schizophrenia, hysteria, undiagnosed)	7

*Frequency varies with incidence of alcoholism in the population studied.

Source: Wells.

From Adams and Victor, 1993

Box 3.1 Criteria for definite, probable, and possible Alzheimer's disease (AD)

Definite AD

- Clinical criteria for probable AD
- Histopathological evidence of AD (autopsy or biopsy)

Probable AD

- Dementia established by clinical examination and documented by mental status questionnaire
- Dementia confirmed by neuropsychologic testing
- Deficits in two or more areas of cognition
- Progressive worsening of memory and other cognitive functions
- No disturbance of consciousness
- Onset between ages 40 and 90
- Absence of systemic disorders or other brain diseases capable of producing a dementia syndrome

Possible AD

- Presence of a systemic disorder or other brain disease capable of producing dementia but not thought to be the cause of the dementia
- Gradually progressive decline in a single intellectual function in the absence of any other identifiable cause (e.g. memory loss or aphasia)

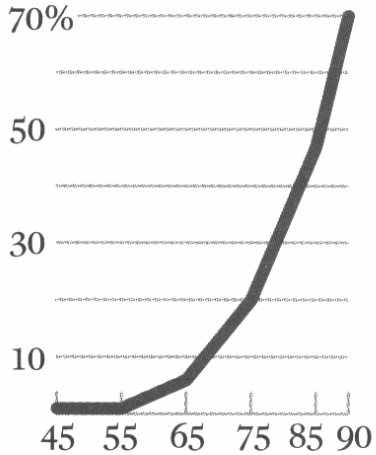
Unlikely AD

- Sudden onset
- Focal neurologic signs
- Seizures or gait disturbance early in the course of the illness

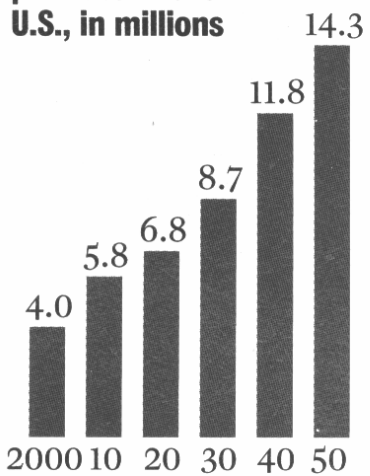
Cummings, 2004

The Growth

Alzheimer's prevalence in the U.S., by age, 1997



Projected Alzheimer's patients in the U.S., in millions



The Burden

Duration of illness after diagnosis, in years

Heart disease	3–4
Cancer	5–6
AIDS	5–6
Alzheimer's	**8–20**

Leading cause of death in the U.S., age 65 and older, 1997, in thousands

Heart disease	616
Malignant tumors	384
Vascular disease	142
Pulmonary diseases	96
Pneumonia/flu	80
Diabetes	47
Accidents	31
Alzheimer's	**22**
Kidney disease	22
Blood disease	18
All other causes	285

ALLGEMEINE ZEITSCHRIFT

FÜR

PSYCHIATRIE

UND

PSYCHISCH-GERICHTLICHE MEDIZIN

HERAUSGEGEBEN VON

DEUTSCHLANDS IRRENÄRZTEN

UNTER DER MITREDAKTION VON

BONHOEFFER BRESLAU · **CRAMER** GÖTTINGEN · **v. GRASHEY** MÜNCHEN · **KREUSER** WINNENTAL · **PELMAN** BONN · **SCHÜLE** ILLENAU

DURCH

HANS LAEHR
SCHWEIZERHOF

VIERUNDSECHZIGSTER BAND

NEBST EINEM BERICHT
ÜBER DIE PSYCHIATRISCHE LITERATUR IM JAHRE 1906

REDIGIERT VON

E. SCHULTZE und **O. SNELL**
GREIFSWALD LÜNEBURG

BERLIN

DRUCK UND VERLAG VON GEORG REIMER

1907

ALZHEIMER DISEASE AND ASSOCIATED DISORDERS, 1(1):7–8, 1987

ABOUT A PECULIAR DISEASE OF THE CEREBRAL CORTEX[1]

(Über eine eigenartige Erkrankung der Hirnrinde. *Allgemeine Zeitschrift für Psychiatrie und Psychisch-Gerichtliche Medizin* 64:146–148, 1907)

By Alois Alzheimer
Translated by L. Jarvik and H. Greenson

A. reports on his observation of a patient at the insane asylum in Frankfurt/Main whose central nervous system he examined at the request of Director Sioli. The picture he presents is of a case so deviant even on clinical grounds alone that it does not fit into any of the known disease categories, and the anatomical findings diverge from all currently known disease processes.

Case Presentation[2]

The first noticeable symptom of illness shown by this 51-year-old woman was suspiciousness of her husband. Soon, a rapidly increasing memory impairment became evident; she could no longer orient herself in her own dwelling, dragged objects here and there and hid them, and at times, believing that people were out to murder her, started to scream loudly.

On observation at the institution, her entire demeanor bears the stamp of utter bewilderment. She is completely disoriented to time and place. Occasionally, she remarks that she does not understand anything and is at her wits' end. Sometimes she greets the doctor as if he were a visitor and excuses herself that she has not finished with her work; on other occasions, she screams that he wants to cut her open[3]; on others yet, she dismisses him, full of indignation and with expressions indicating that she fears him as a threat to her honor as a woman. At times she is totally delirious, drags her bedding around, calls for her husband or daughter, and seems to have auditory hallucinations. Often she screams for many hours in a horrible voice.

With her inability to understand her situation, she bursts into loud screams each time she is approached to be examined. Only through constantly repeated efforts was it possible to eventually establish some limited information.

Clinical Evaluation

Her ability to encode information[4] is most severely disturbed. If one shows her objects, she usually names them correctly. Immediately thereafter, however, she has forgotten everything. In reading, she confuses lines, reads by spelling, or with senseless intonation. When writing, she repeats single syllables many times, omits others and gets stuck altogether very quickly. When speaking, she frequently uses phrases indicating perplexity or embarrassment, or single paraphasic expressions (milk pourer instead of cup); sometimes one observes that she is completely at a

loss for words. She clearly does not grasp some questions, and it seems that she no longer knows the use of certain objects.

Her gait is normal, and she can use her hands well. Patellar reflexes are present. Pupils react. Radial arteries are somewhat rigid; on percussion, there is no enlargement of cardiac dullness. Laboratory findings: No albumen.

Course of Illness

In the further course of illness, there appear what could be interpreted as focal symptoms, but they are very slight and variable—sometimes stronger, sometimes weaker. By contrast, general imbecility keeps progressing. The 4½ year illness ended in death. Terminally, the patient was totally dulled, lying in bed with legs drawn up, incontinent, and, despite all care, developed decubiti.

Autopsy

The autopsy reveals a consistently atrophic brain without macroscopic foci. The larger cerebral vessels show arteriosclerotic changes. Preparations stained with Bielschowsky's silver method reveal peculiar changes of the neurofibrils. Inside an otherwise apparently still normal cell, first one or more fibrils stand out prominently because of their unusual thickness and unusual ability to take up stain. Later on, there are many such fibrils lying next to each other, all changed in the same way. These are eventually seen clustering together in thick bundles which gradually emerge at the surface of the cell. Finally, the nucleus and the cell have fallen apart and only a tangled bundle of fibrils points to the place in which there once was a ganglion cell. Since these fibrils can be stained with methods other than those used to stain normal neurofibrils, a chemical change of the fibril substance must have taken place and might be the cause for the fibrils surviving the disintegration of the cell. The conversion of the fibril seems to go hand in hand with the storage of a pathologic metabolic product in the ganglion cell, a possibility which needs to be more deeply researched. About one-quarter to one-third of all ganglion cells in the cortex show such changes, and numerous ganglion cells, especially in the upper cell layers, have altogether disappeared.

Scattered over the entire cortex, and especially numerous in the upper layers, there are miliary foci distinguishable by the deposit in the cerebral cortex of a peculiar substance which can be recognized without stain and is, in fact, very refractory to staining.

The glia have formed abundant fibers, and many glial cells show large fatty sacs.

There is total absence of infiltration of the vessels; by contrast, one sees endothelial proliferation and also, occasionally, neovascularization.

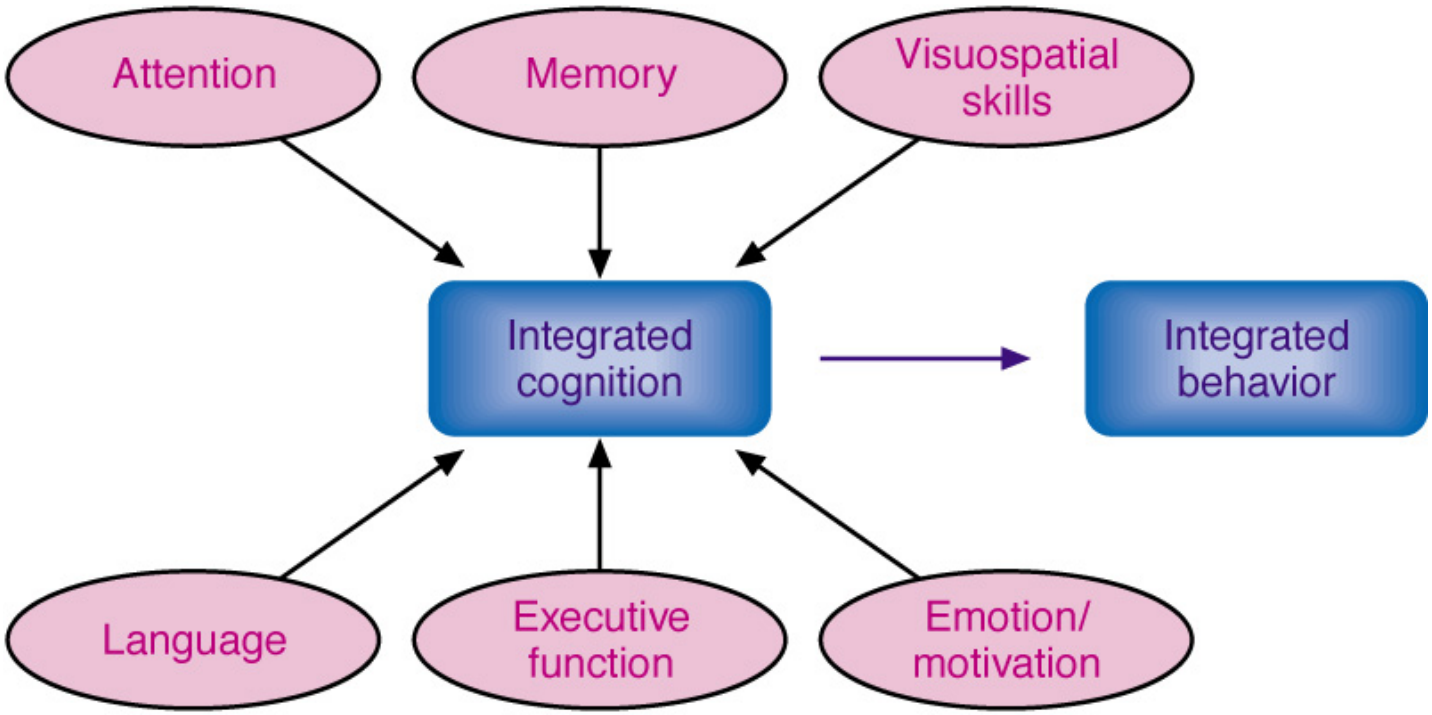
* * *

All in all, we have before us the evidence for a specific disease process. In recent years the ascertainable number of such specific disease processes has been increasing. As this case report demonstrates, it behooves us not to be satisfied with attempts to force, by means of painstaking efforts, clinically unclear observations to fit one of the disease categories familiar to us. There are without doubt many more psychiatric illnesses than our textbooks mention. In some instances, the uniqueness of the case will be established by subsequent histologic examination. Then, we will gradually arrive at the stage where we will be able to separate out individual diseases from the larger disease categories of our textbooks and sharpen their clinical definition.

inability to focus and direct cognitive processes and to resist distraction, unable to focus and sustain attention over a period of time

retrieval deficit with poor recall (frontal variant of AD); recognition (amnestic) for recently learned info (both semantic and episodic) [parietal-temp lesion]

difficulty copying complex figures, problems with route finding and dressing



anomia progressing to TCS aphasia; echolalia and palilalia late in course.
TCS: Disturbance of single word comprehension with relatively intact repetition

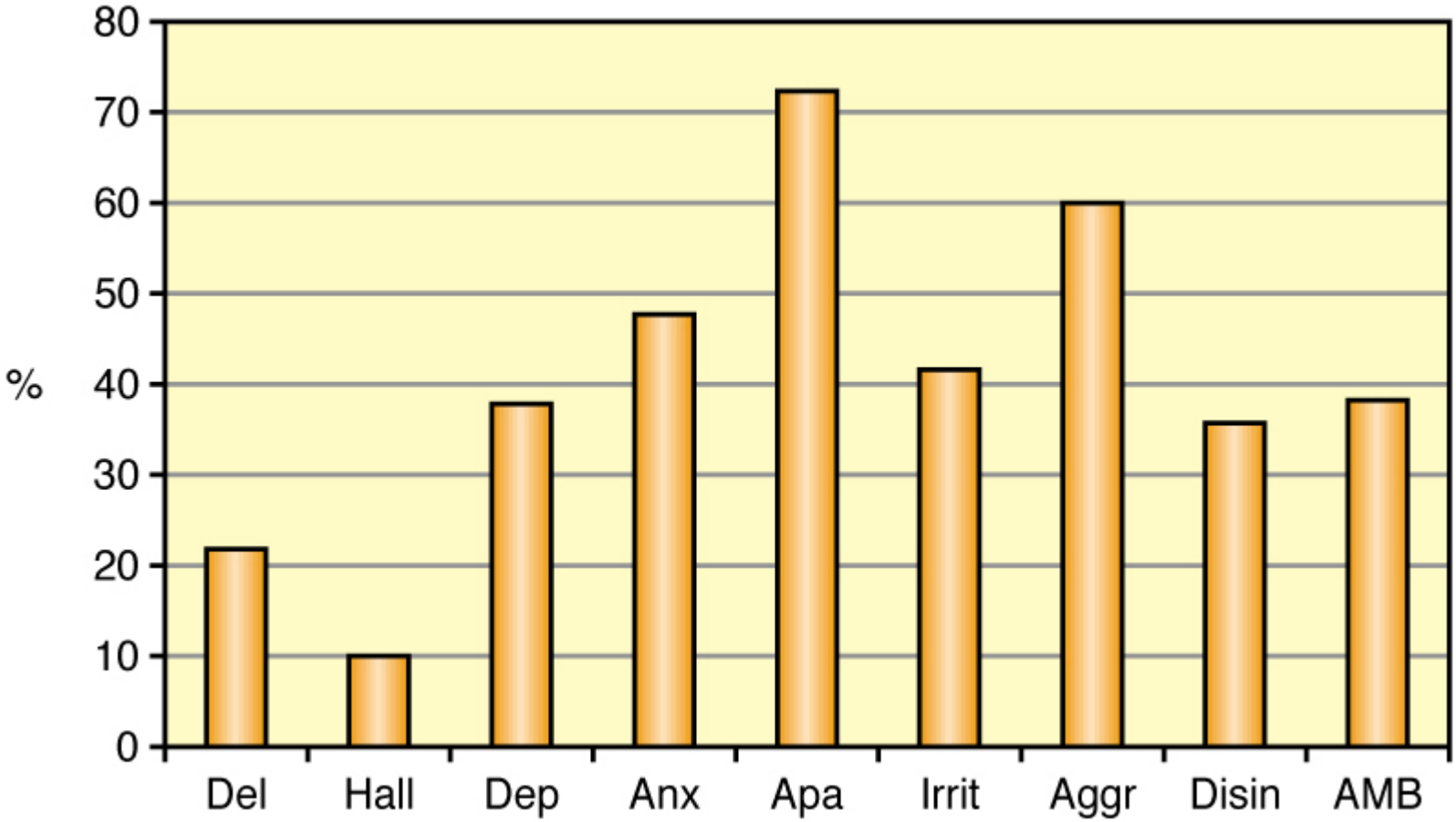
poor judgment, impaired insight, poor strategy, abstraction, planning inability to adjust to novelty, impaired motor programming, difficulties with set shifting, behavioral inhibition, reduced initiation, imitation, inability to withhold responses, distractibility, intrusions, perseveration, reduced responses to feedback

apathy, depression, agitation, anxiety, obsessive symptoms, sexual changes, euphoria, Psychosis (delusion, hallucinations)

Processing of emotional information in AD

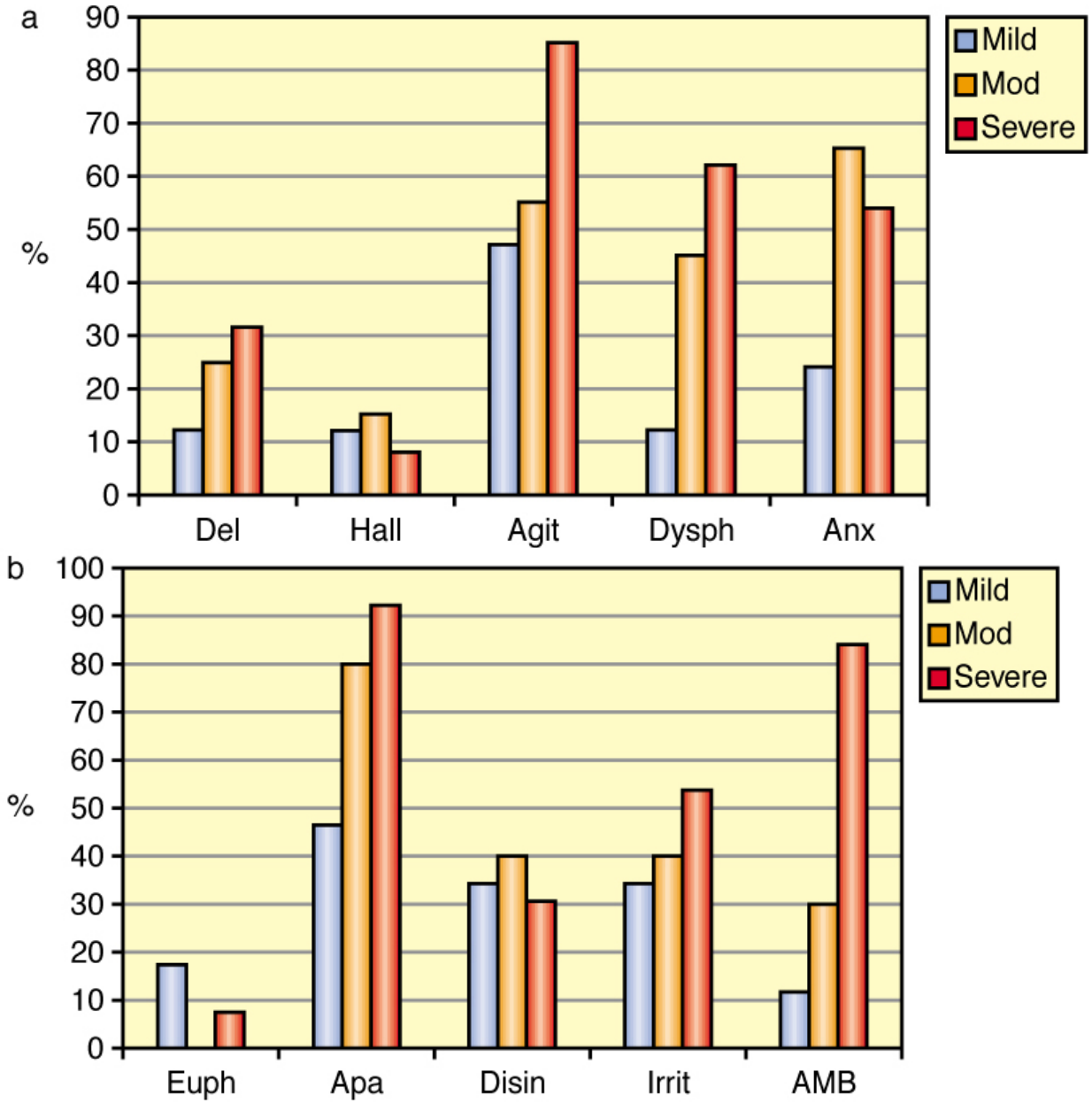
Images of a person drawn by a patient with AD over a 3-year period and showing progressive loss of the ability to reproduce the features of the face. The patient was copying the same target figure on each occasion. The progression is from left to right beginning at the top left. The diagnosis of AD was confirmed at autopsy (From Cummings, 2004)

NEUROPSYCHIATRIC SYSMPTOMS IN AD

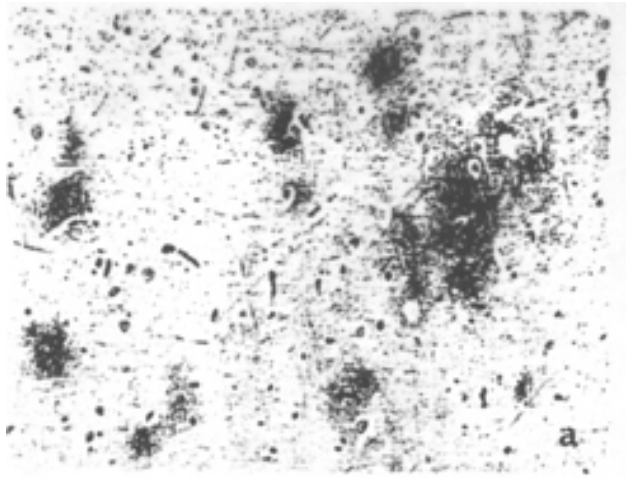


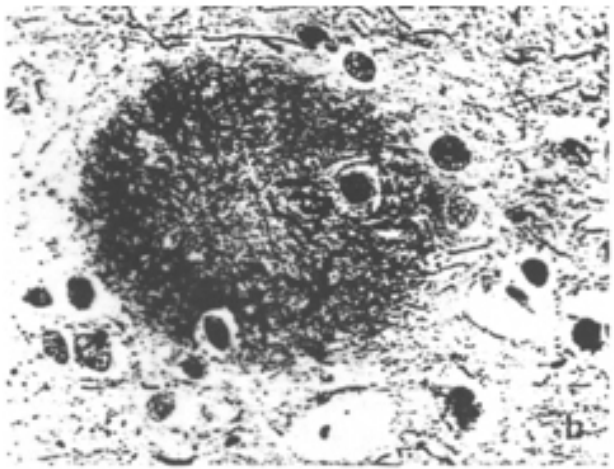
Percent of patients with scoreable symptoms on the Neuropsychiatric Inventory (n = 50). Del, delusions; Hall, hallucinations; Dep, depression; Anx, anxiety; Apa, apathy; Irrit, irritability; Aggr, aggression/agitation; Disin, disinhibition; AMB, aberrant motor behavior.

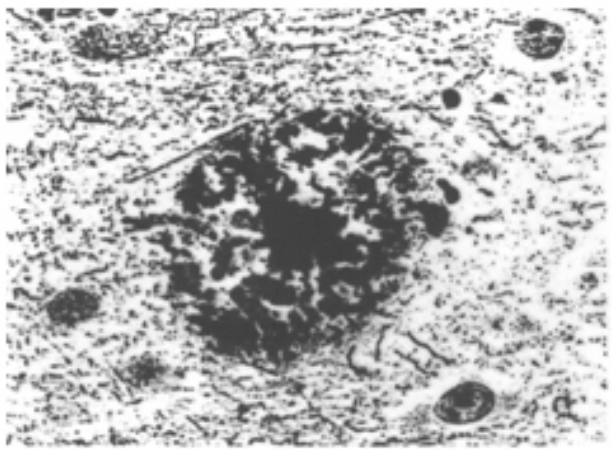
NEUROPSCHIATRIC SYMPTOMS IN AD ACCORDING TO DISEASE SEVERITY

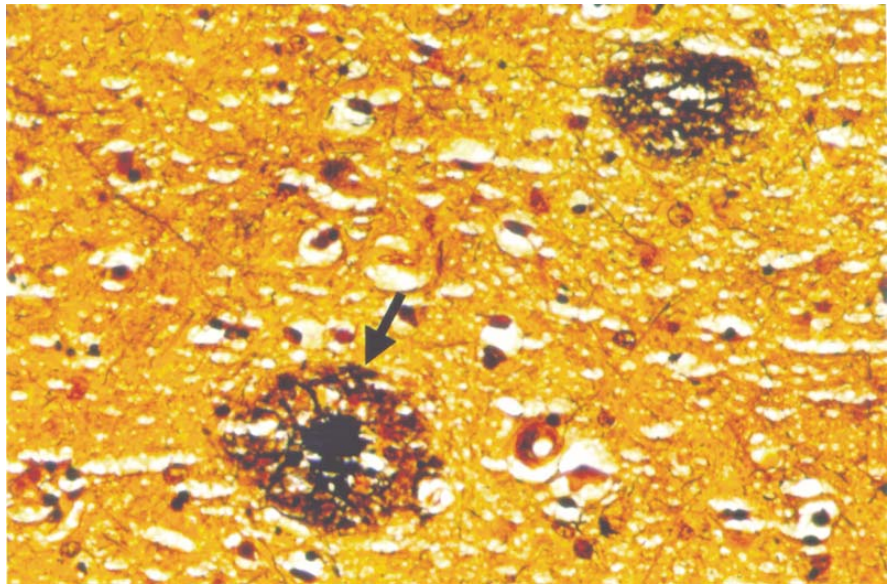


Mild, Mini-Mental State Examination (MMSE) scores 30-29; Moderate, MMSE scores 20-11; Severe, MMSE scores 10-0 (n = 50). Del, delusions; Hall, hallucinations; Agit, agitation; Dysph, dysphoria; Anx, anxiety; Euph, euphoria; Apa, apathy; Disin, disinhibition; Irrit, irritability; AMB, aberrant motor behavior.





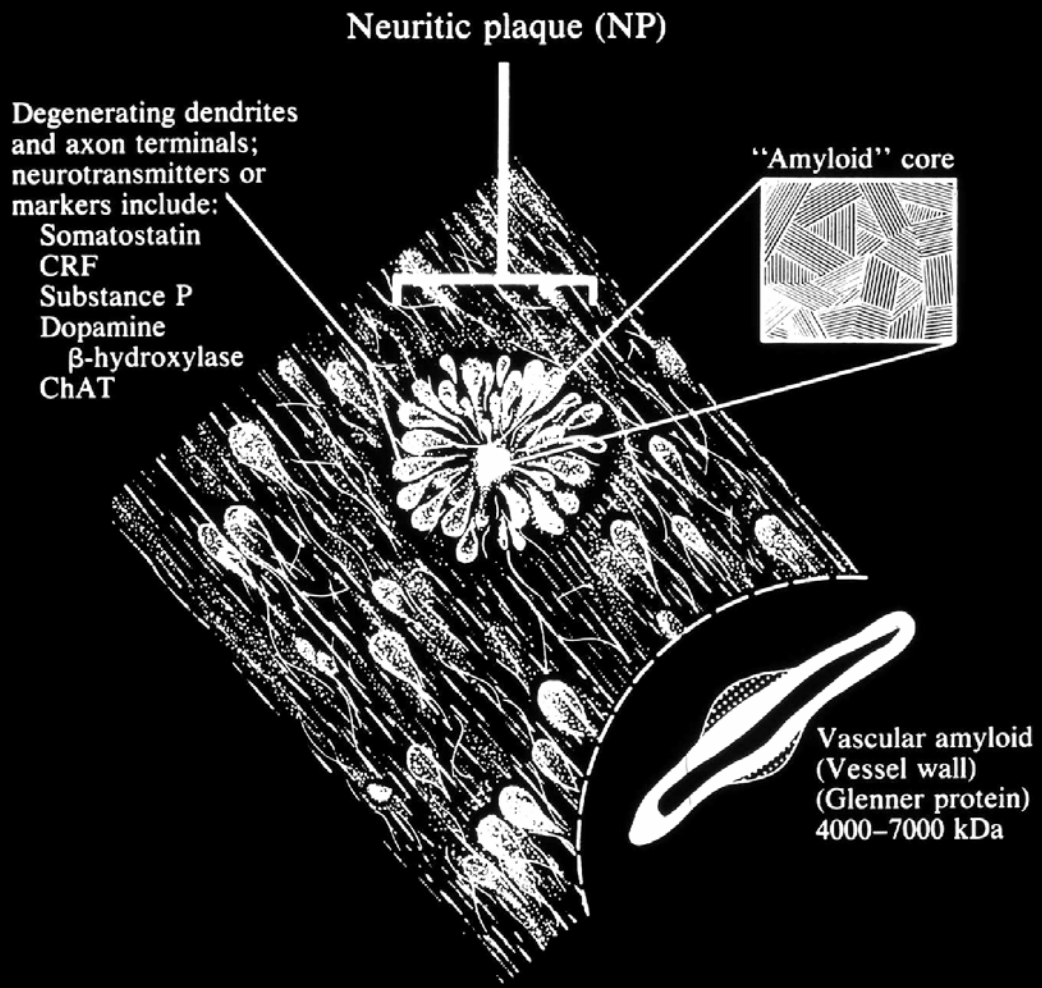




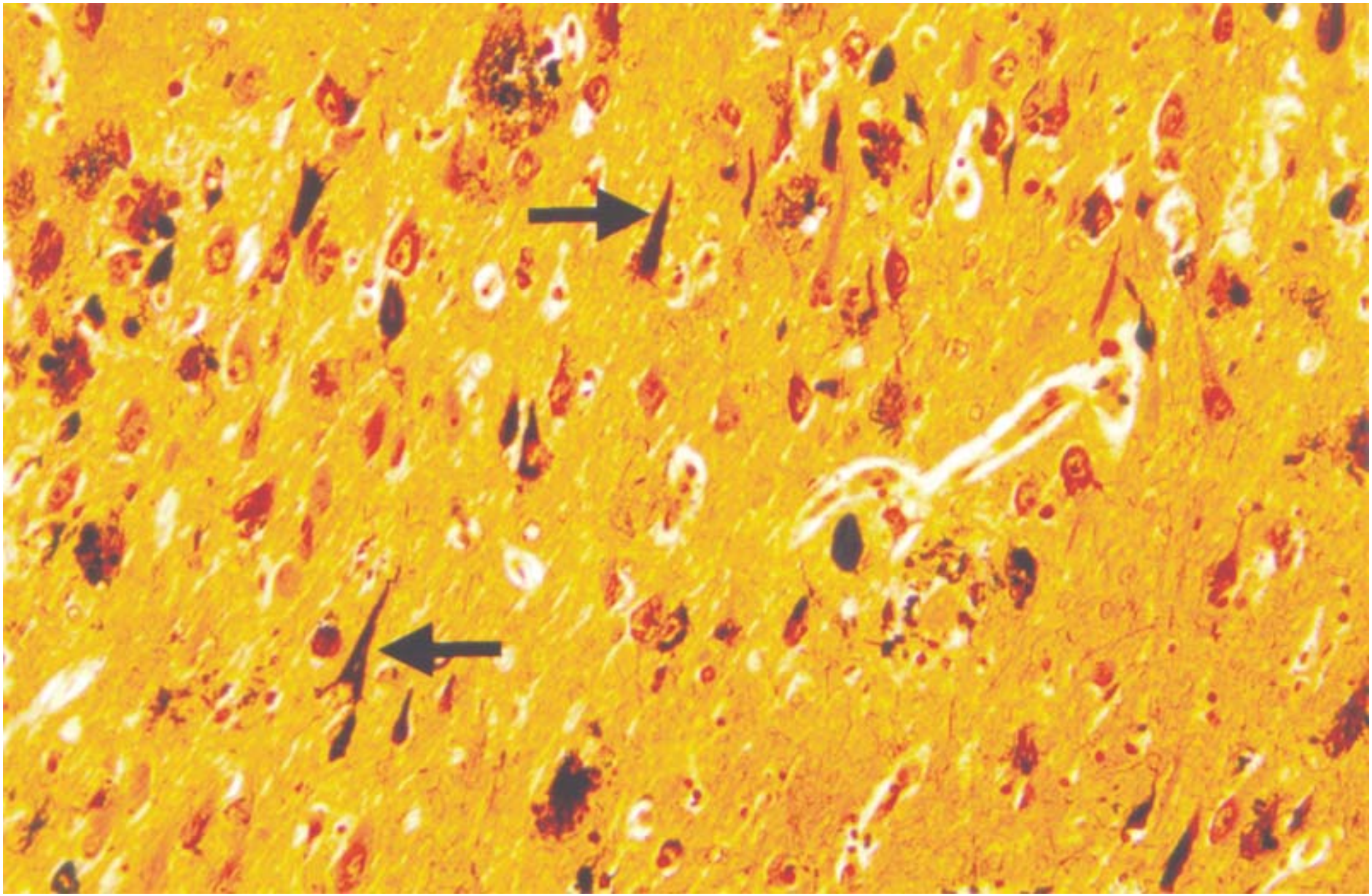
a: Diffuse β-amyloid deposits in the frontal cortex stained with monoclonal antibody 4G8 x 50. Braak and Braak

b: Primitive plaque without central amyloid core or dystrophic neurites. Modified Bielschowsky silver stain x 200. Braak and Braak.

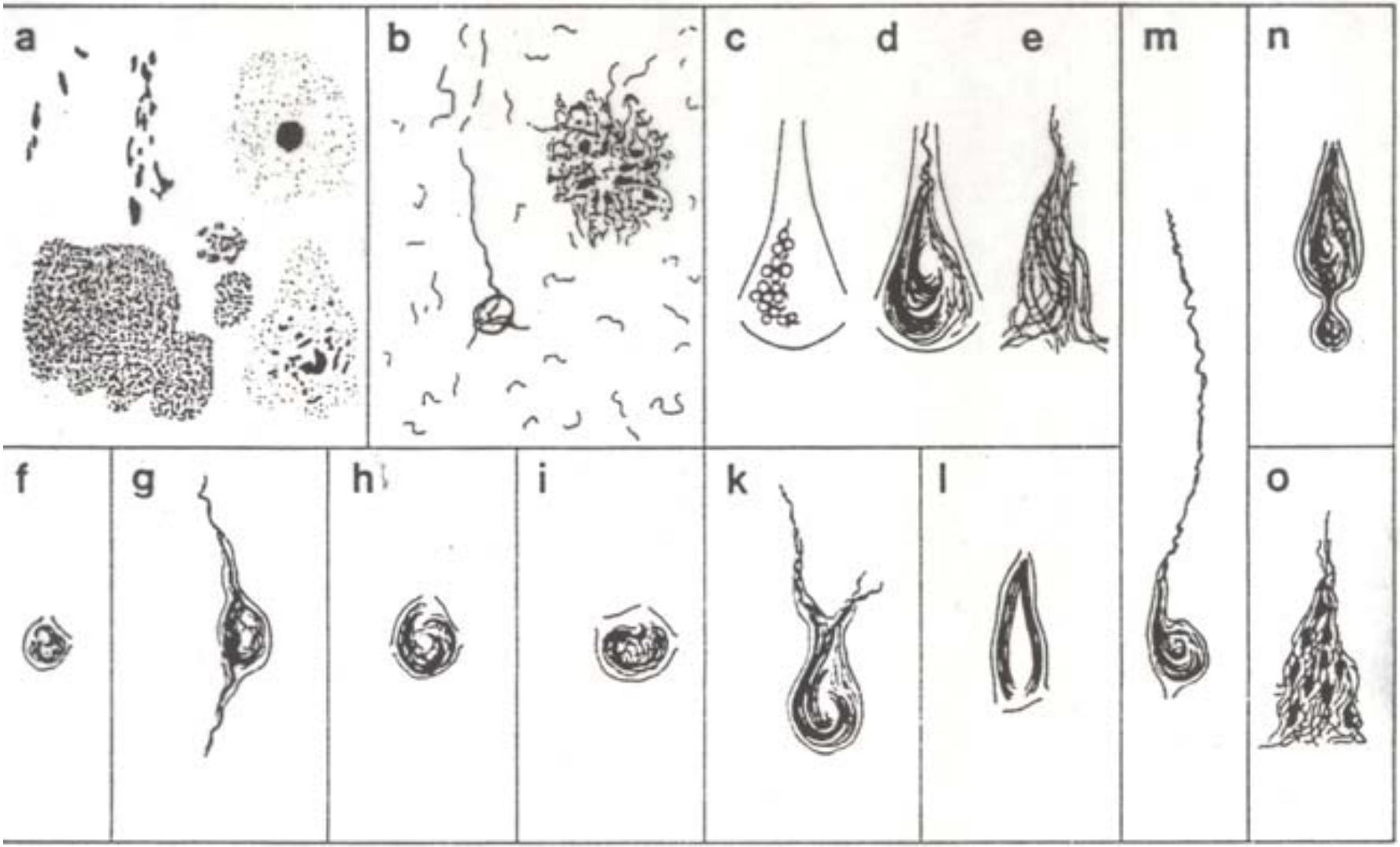
c: Classical plaque with central amyloid core and peripheral crown of dystrophic neurites. Modified Bielschowsky stain x 200 . Braak and Braak.


Neuritic plaque (NP)
Degenerating dendrites and axon terminals; neurotransmitters or markers include:
Somatostatin
CRF
Substance P
Dopamine β-hydroxylase
ChAT
"Amyloid" core
Vascular amyloid
(Vessel wall)
(Glenner protein)
4000–7000 kDa

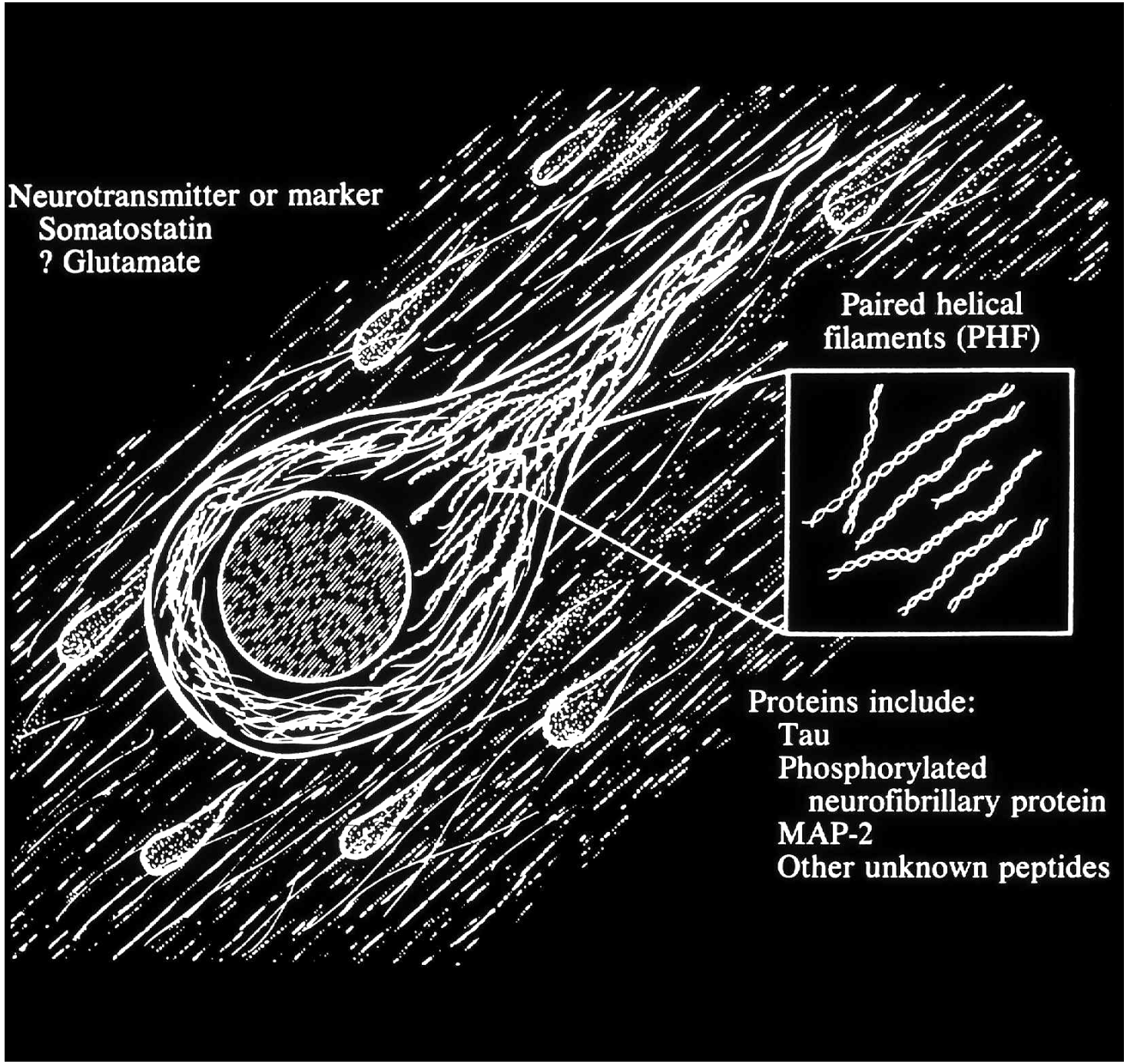
NEUROFIBRILLARY TANGLE IN AD

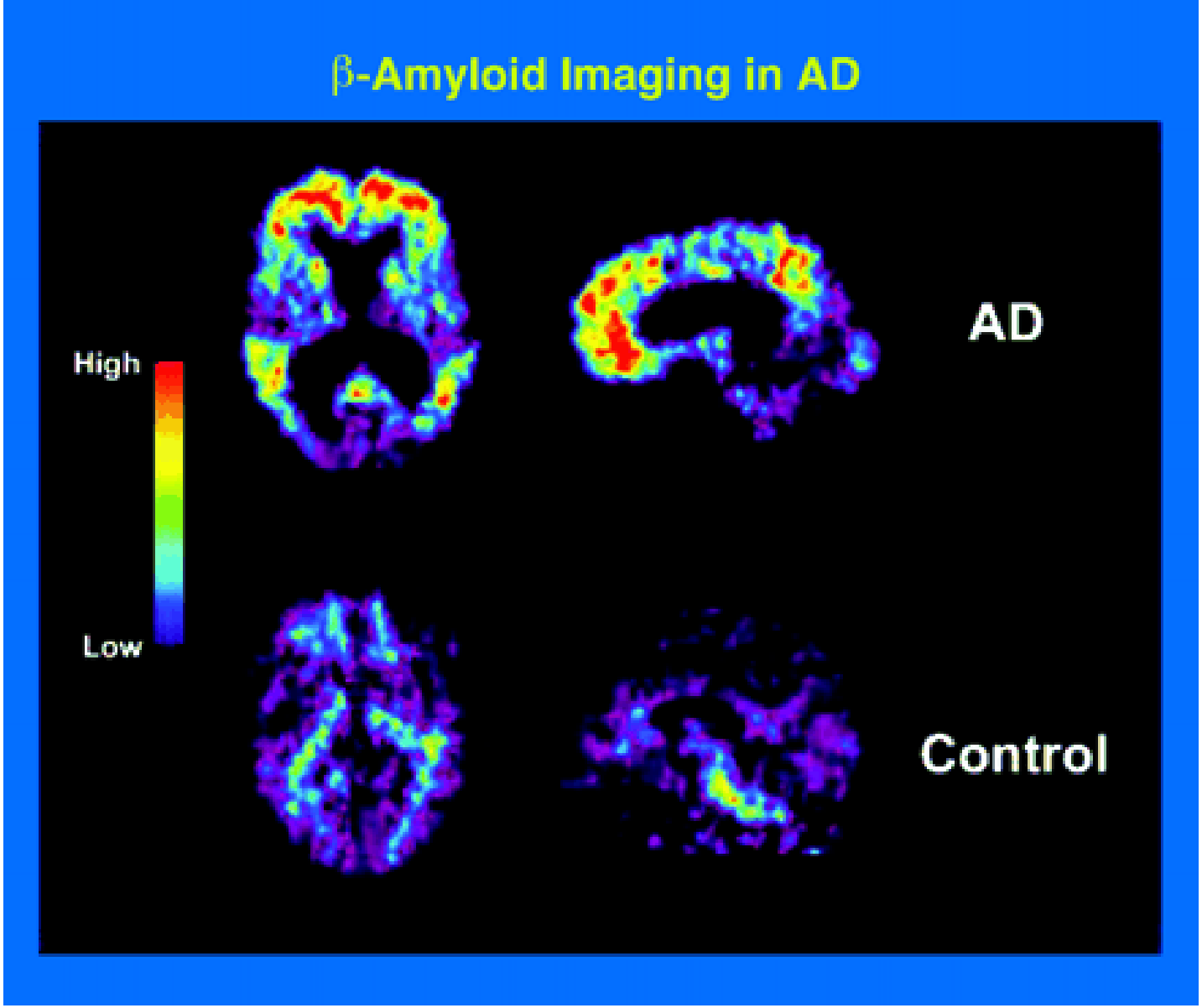


(Vinters, UCLA, From Cummings, 2003)



a: forms of extracellular BA protein deposits. **b**: neuritic plaques, tangles and neuropil threads. **c**: first traces of tangle material, **d**: the mature tangle fills the cell body, **e**: extraneuronal 'ghost', **f-m**: neurofibrillary tangles in different cell types of the hippocampus, **n**: tangle-bearing isocortical layer IIIab-pyramidal cell, **o**: ghost tangle in CA1. Silver technique. Braak and Braak.

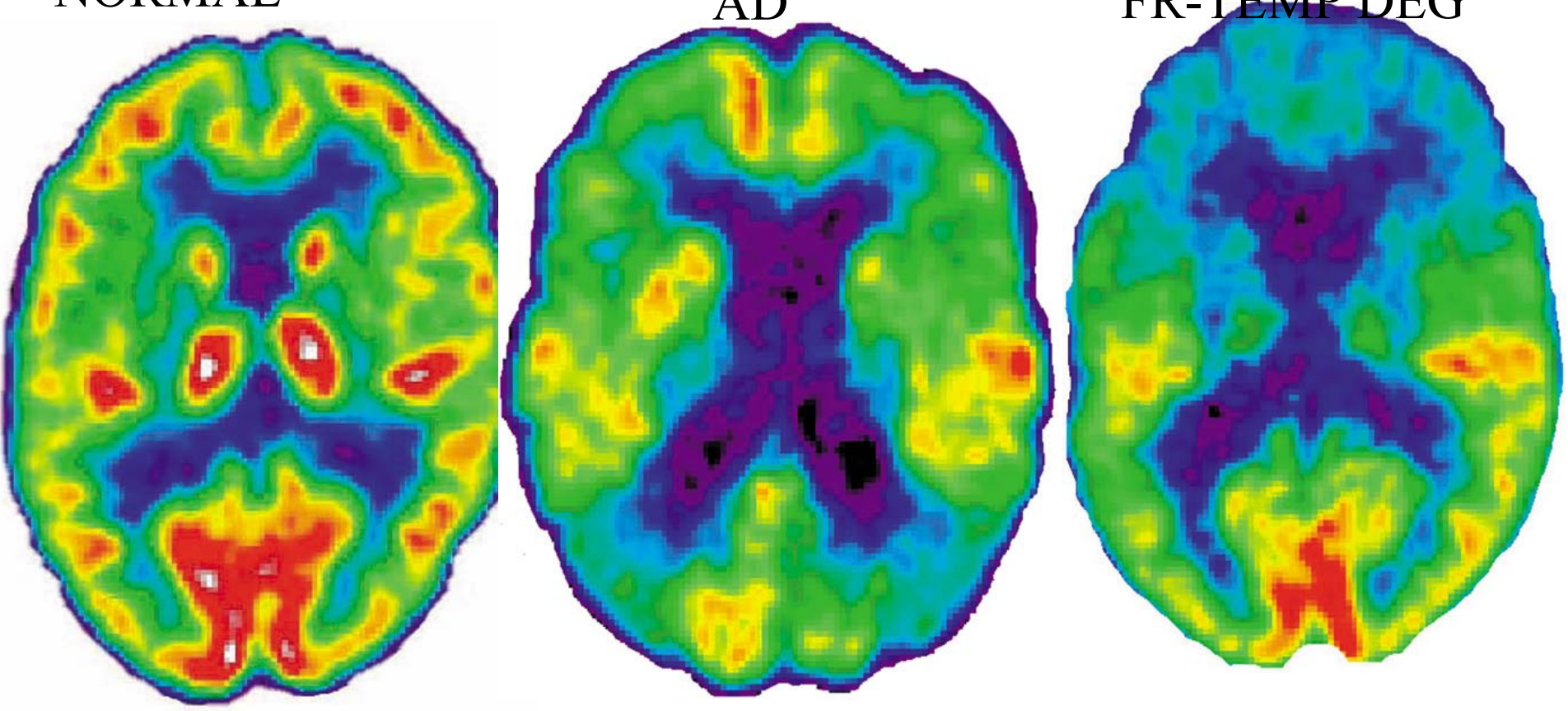

Neurotransmitter or marker
Somatostatin
? Glutamate
Paired helical
filaments (PHF)
Proteins include:
Tau
Phosphorylated
neurofibrillary protein
MAP-2
Other unknown peptides



PET study of amyloid ligand C11-BTA in an AD patient (upper panel) compared to a normal control subject (lower panel). Amyloid signal elevation is seen in the parietal and frontal lobes in the upper left (transverse view) and in the frontal lobe and posterior cingulate cortex (lateral view). The control scan shows no amyloid uptake. (W. E. Klunk and C. Mathis, University of Pittsburgh.)

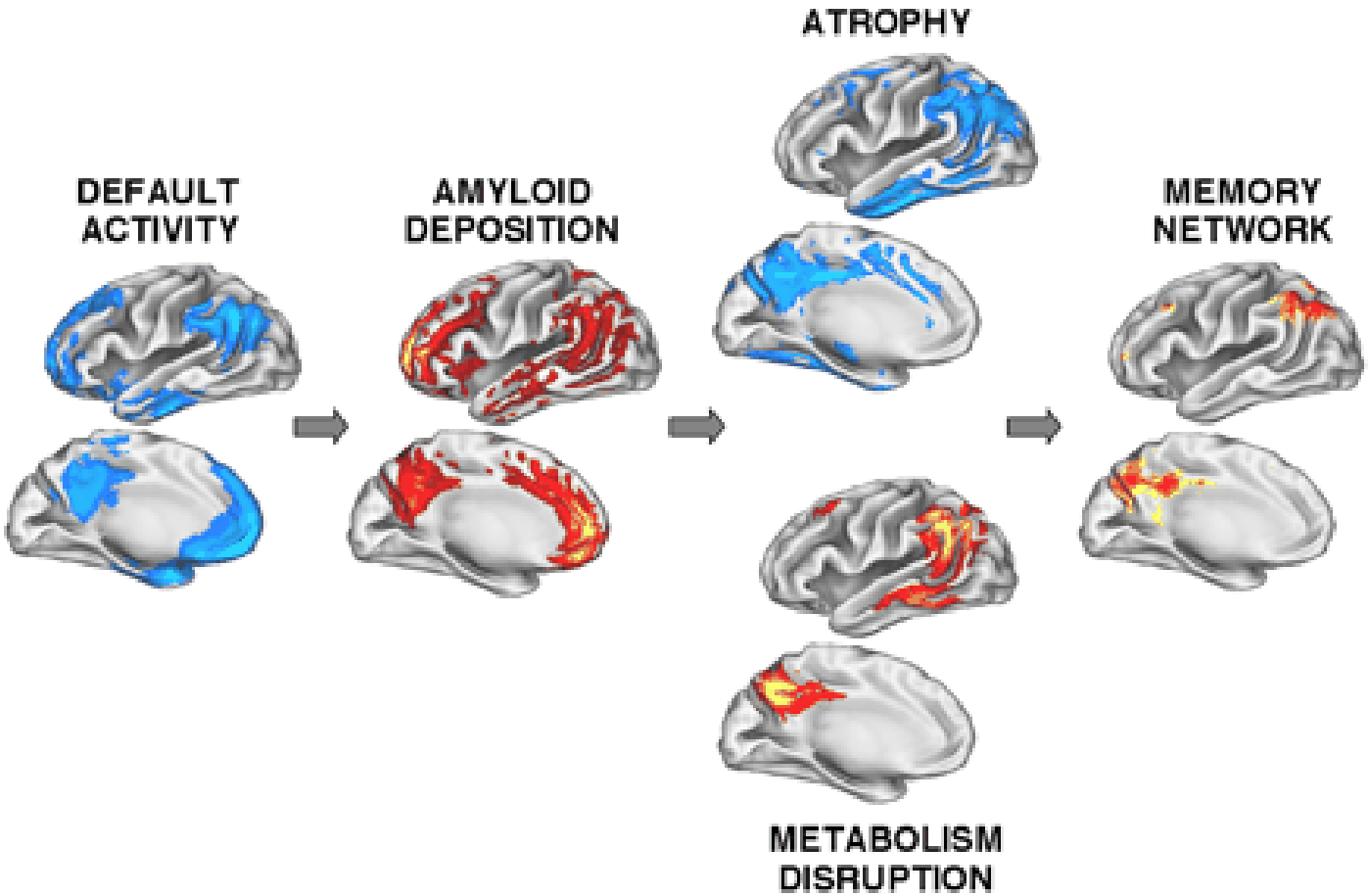
FRONTAL and PARIETAL HYPOMETABOLISM IN AD

NORMAL AD FR-TEMP DEG

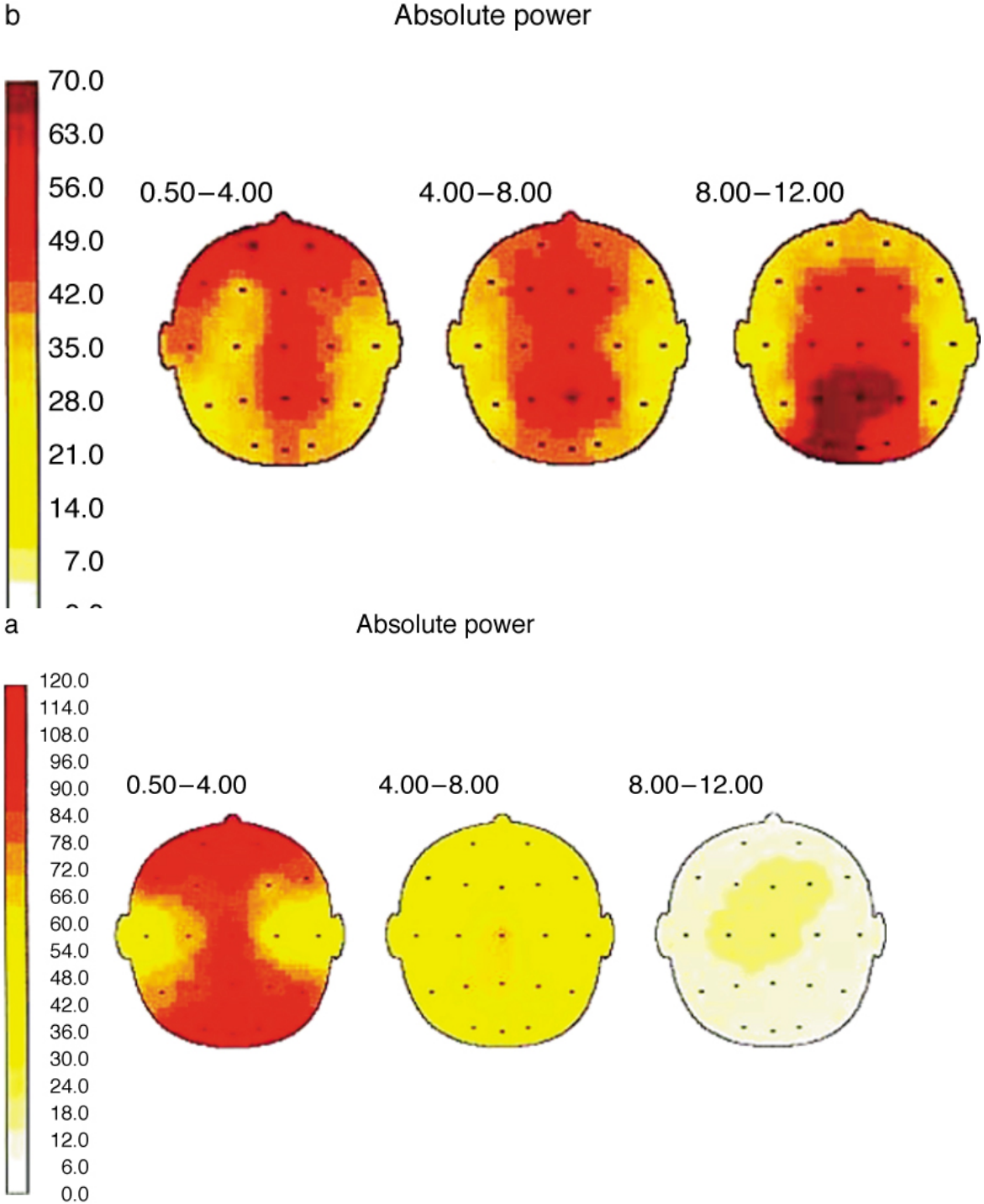


Fluorodeoxyglucose positron emission tomogram (FDG PET) of a normal elderly individual (left), patient with Alzheimer's disease (middle), and patient with frontotemporal lobar degeneration (right). Frontal involvement is seen in AD and frontal hypometabolism in frontotemporal lobar degeneration. (J Felix and A Toga, Laboratory of Neuroimaging, UCLA School of Medicine.)

Hypothetical relationships across molecular, structural, and functional measures



Each image represents the projection of original data onto the cortical surface of the left hemisphere. Three patterns emerge. First, regions showing default activity in young adults are highly similar to those showing amyloid deposition in older adults with AD, including both posterior cortical regions and anterior regions. Second, atrophy and metabolism disruption in AD prominently affect the posterior cortical regions also affected by amyloid deposition and less so the anterior regions. Third, the regions affected in AD and those active in default states in young adults overlap memory networks showing retrieval success effects during recognition in young adults (Buckner et al., 2005).



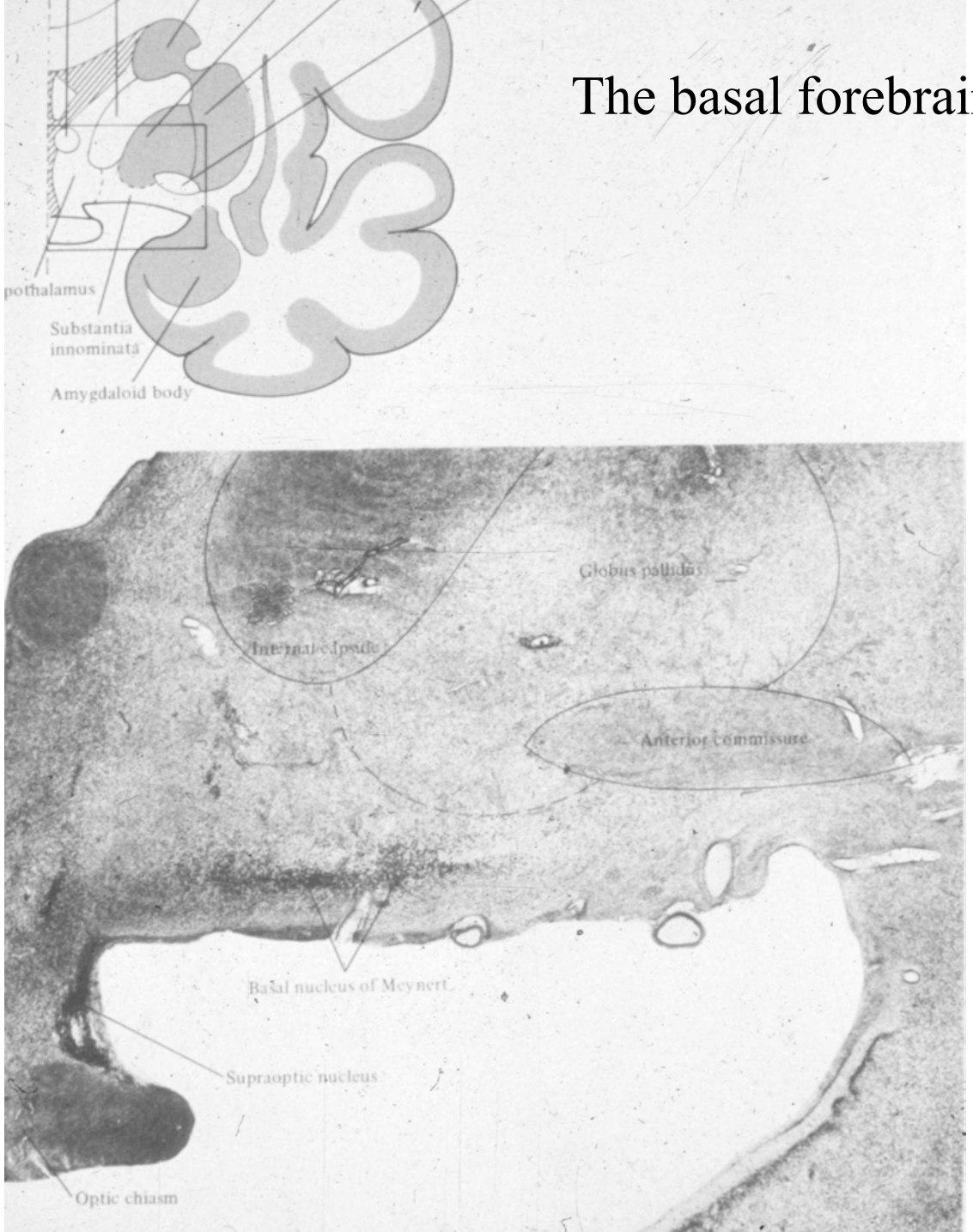
Quantitative EEG maps showing increased slow wave activity in psychotic patients (a) compared with nonpsychotic patients (b) with AD (Edwards-Lee et al., 2000).

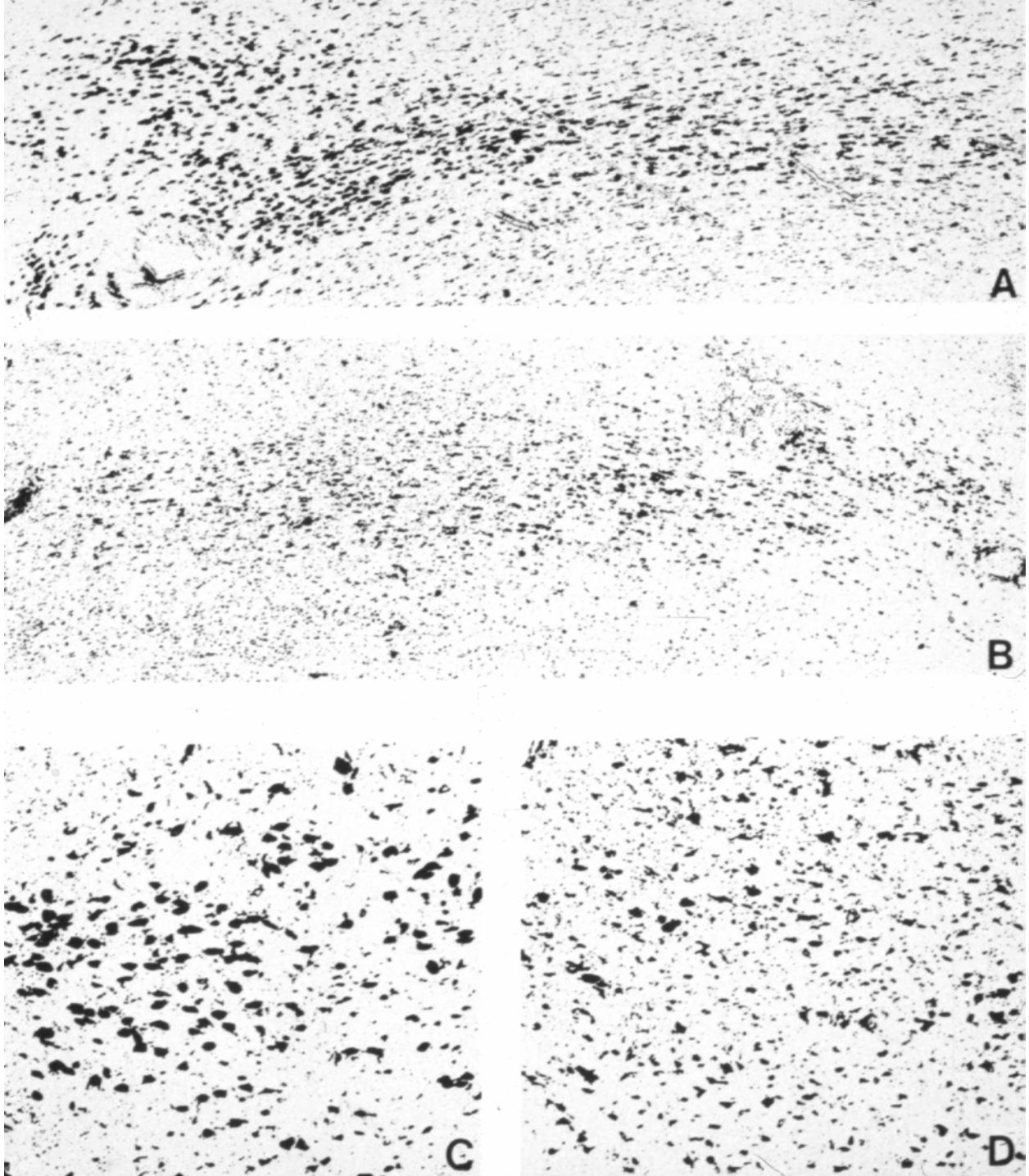
Quantitative Morphology of Alzheimer's Disease

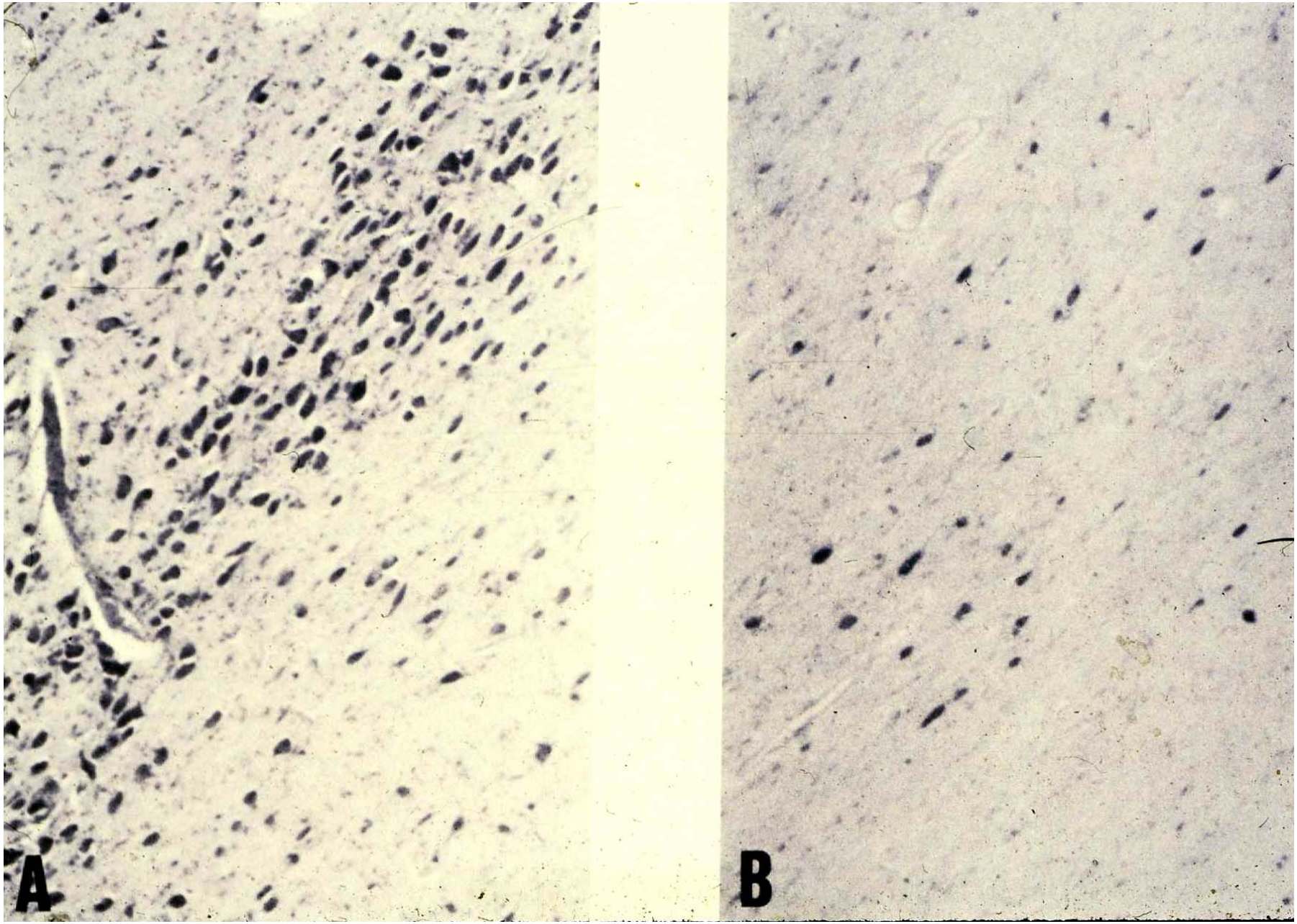
Type of Change	Reduction in Percent
Brain weight	7.5–18
Hemispheral volume	13–18
Ventricular volume	35–55
Weight cerebral cortex	
Inferior parietal	45–58
Temporal	20–45
Amygdala	47
Thickness of total cortex layers	10–35
Depth of temporal cortex[a]	50
Cross-sectional area (mm^2)[b]	
Temporal lobe	35–50
Frontal lobe	30
Insular cortex	25–28
Parietal lobe	21–28
Corpus callosum	30–39
Hippocampus	28
Amygdala	38
Caudate, thalamus	26
Putamen	14–22
Numbers of neurons (90μm)	
Midfrontal cortex	25–33
Precentral gyrus[a]	70
Superior temporal gyrus	22–40
Hippocampus	35–57
Occipital cortex[a]	45–50
Inferior parietal	41
Dendritic spines	
Frontal cortex	17
Temporal cortex	36
Synapses[c]	
Midfrontal cortex	34–47
Inferior parietal cortex	51–59
Superior temporal cortex	35–40
Astroglia, frontal cortex	+400
Subcortical nuclei, neuron loss	
Caudate nucleus[a]	12
Putamen[a]	3
Pallidum[a]	9
Subthalamic nucleus[a,d]	10–26
Anterior thalamus[a]	22
Mammillary body	20
Nucleus basalis of Meynert[a] (lit.)	58
	15/33–90
Locus ceruleus	30–85
Dorsal raphe nucleus	36–77
Substantia nigra, zona compacta	6–48
Pedunculopontine nucleus	29–34
Supraoptic nucleus	65
Dorsal vagal nucleus	44
Thalamic nuclei[d]	37–58

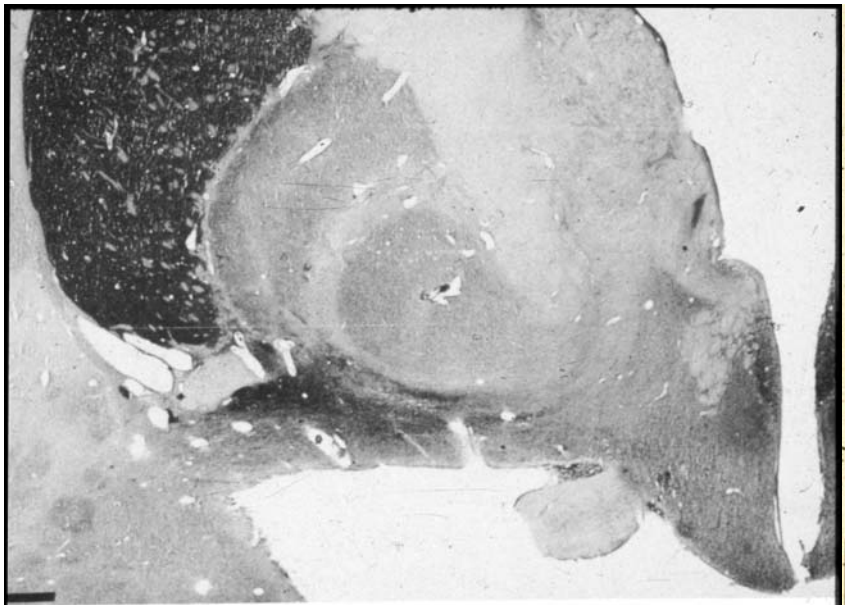
a: Jellinger, 1990; Mioyoshi and Sato, 1991; b : Manns et al., 1991; c: Masliah et al., 1991; d: Xuereb et al., 1991

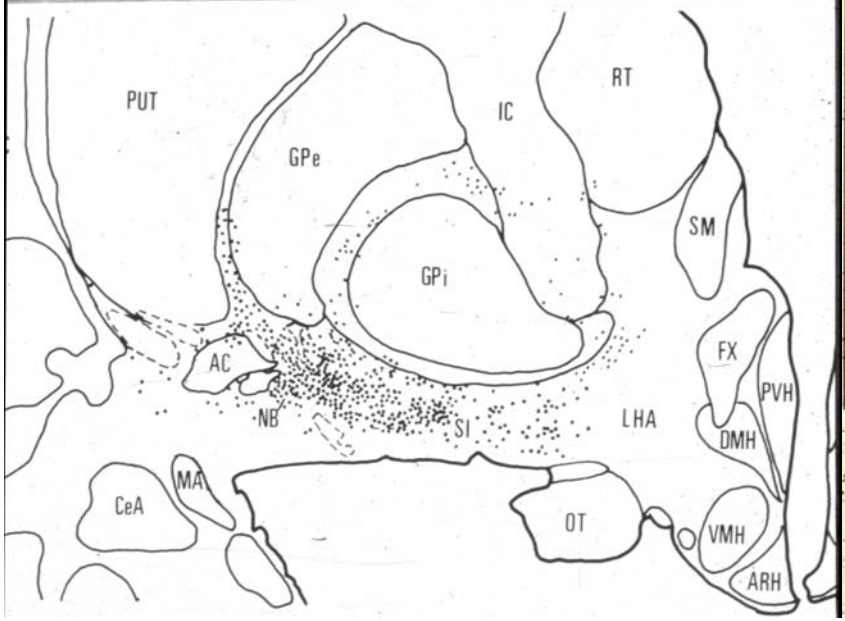
The basal forebrain cholinergic system




A
B
C
D


A
B




PUT
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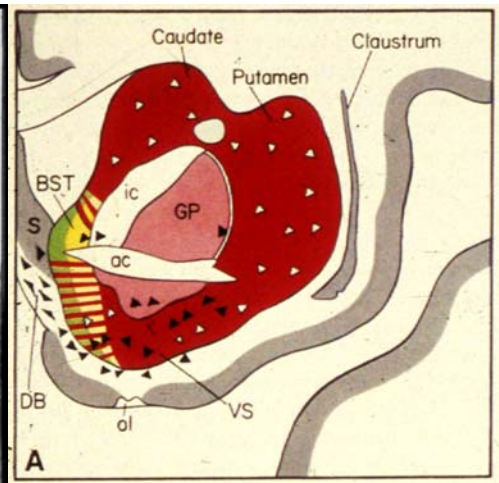
Caudate
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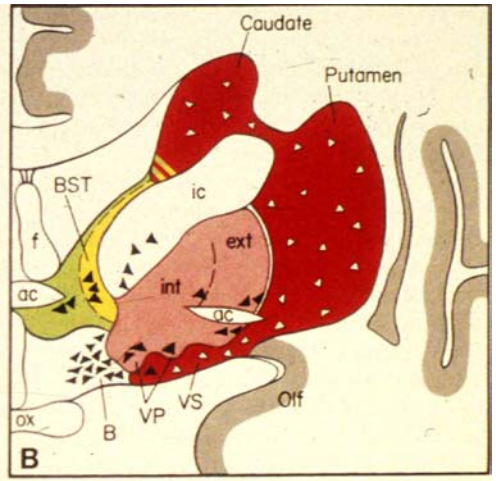
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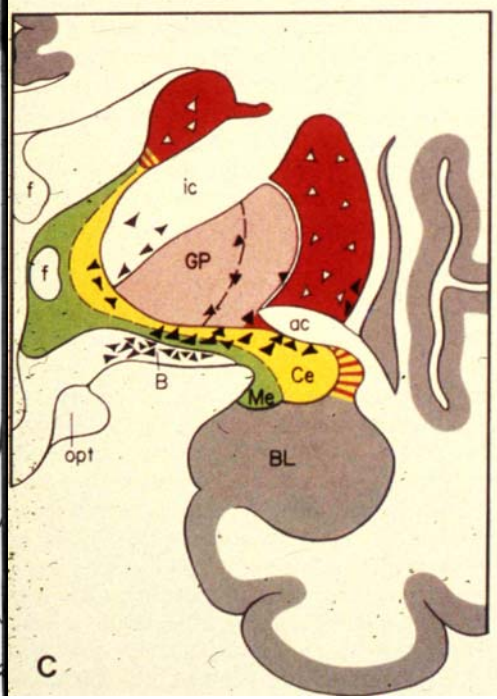
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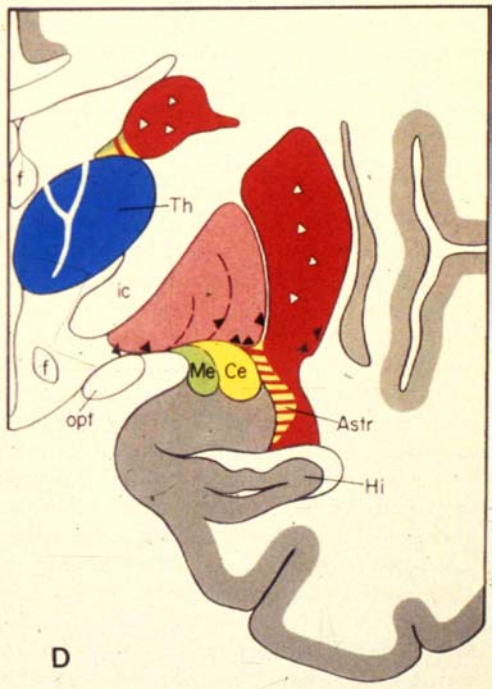
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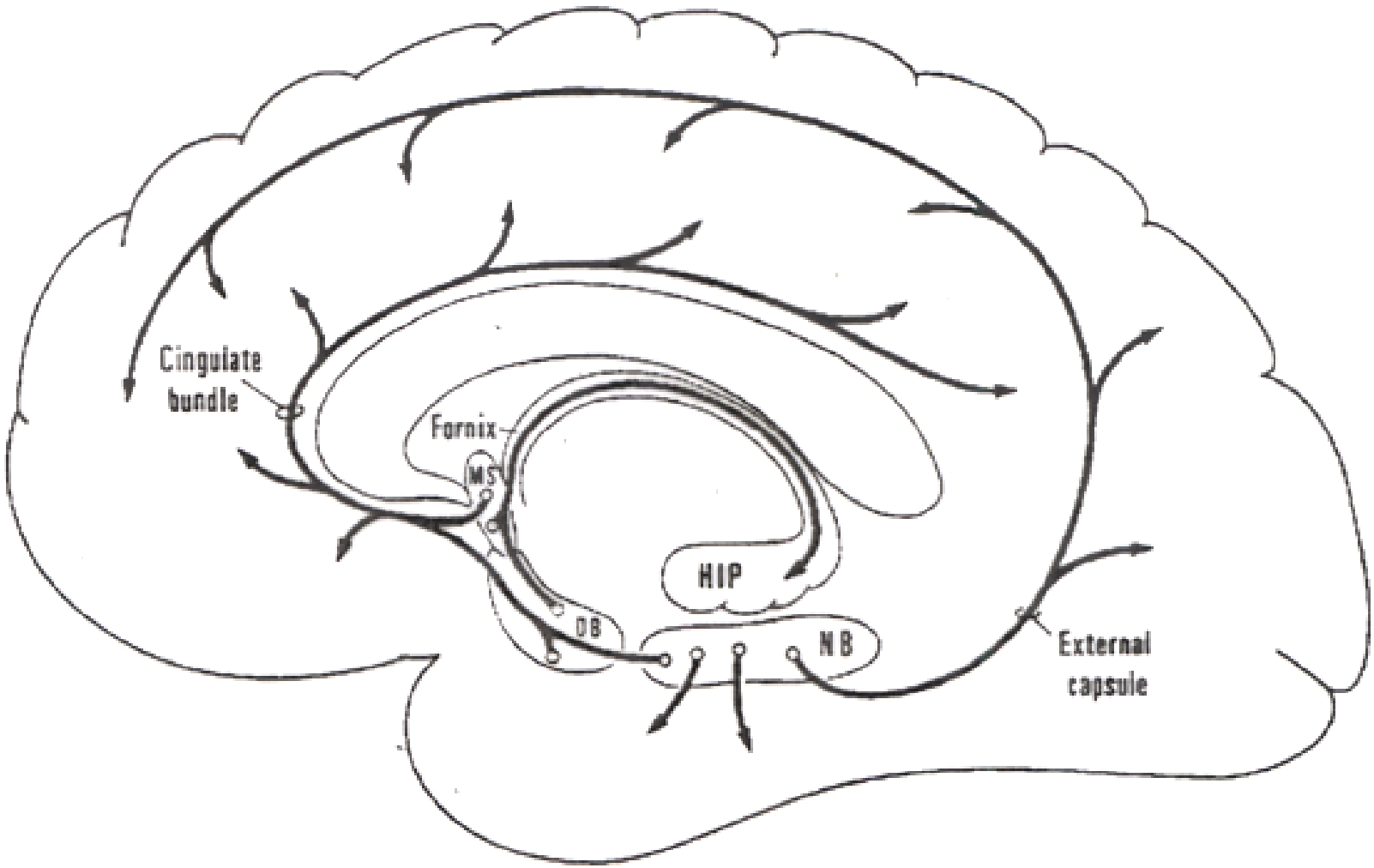
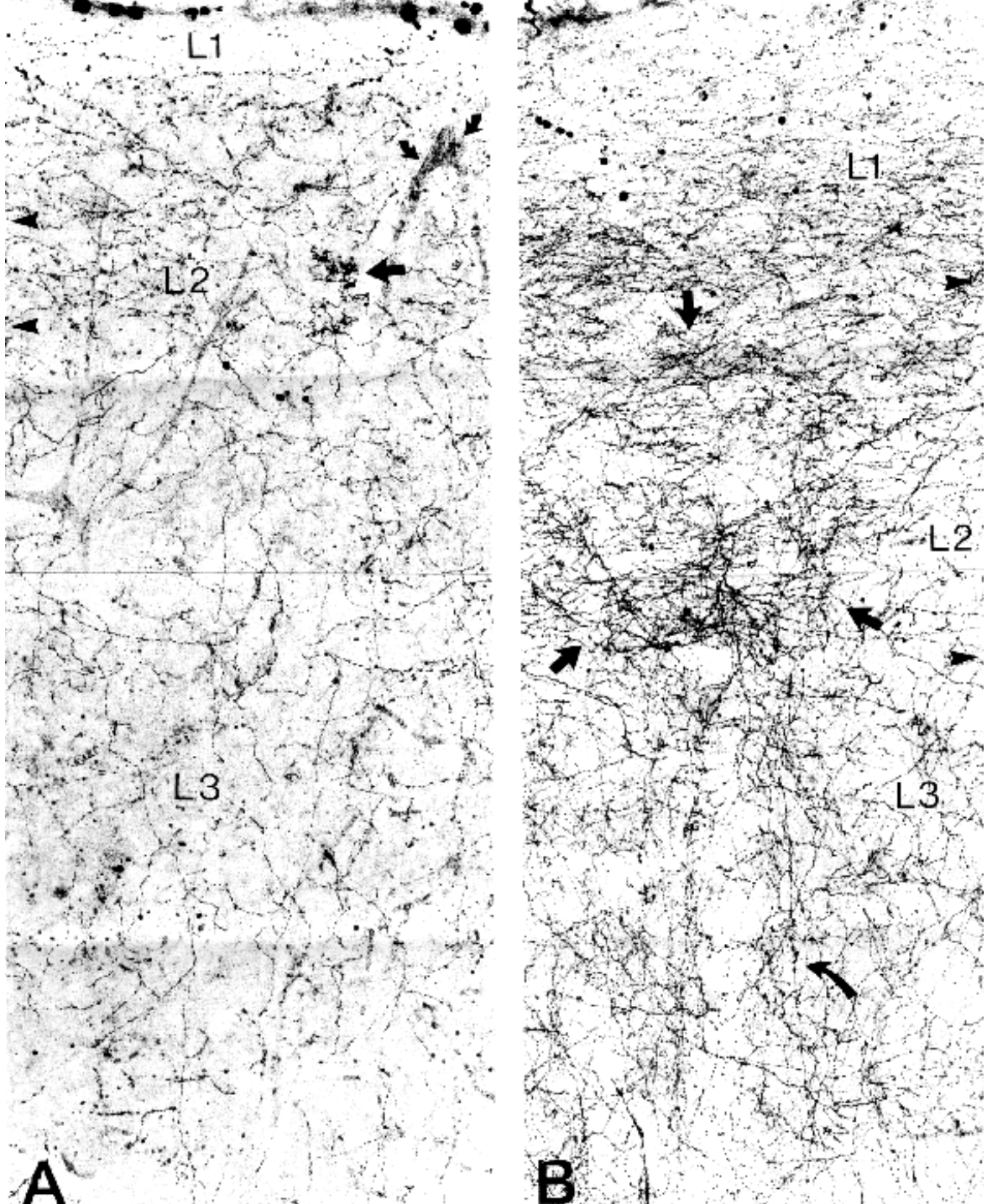
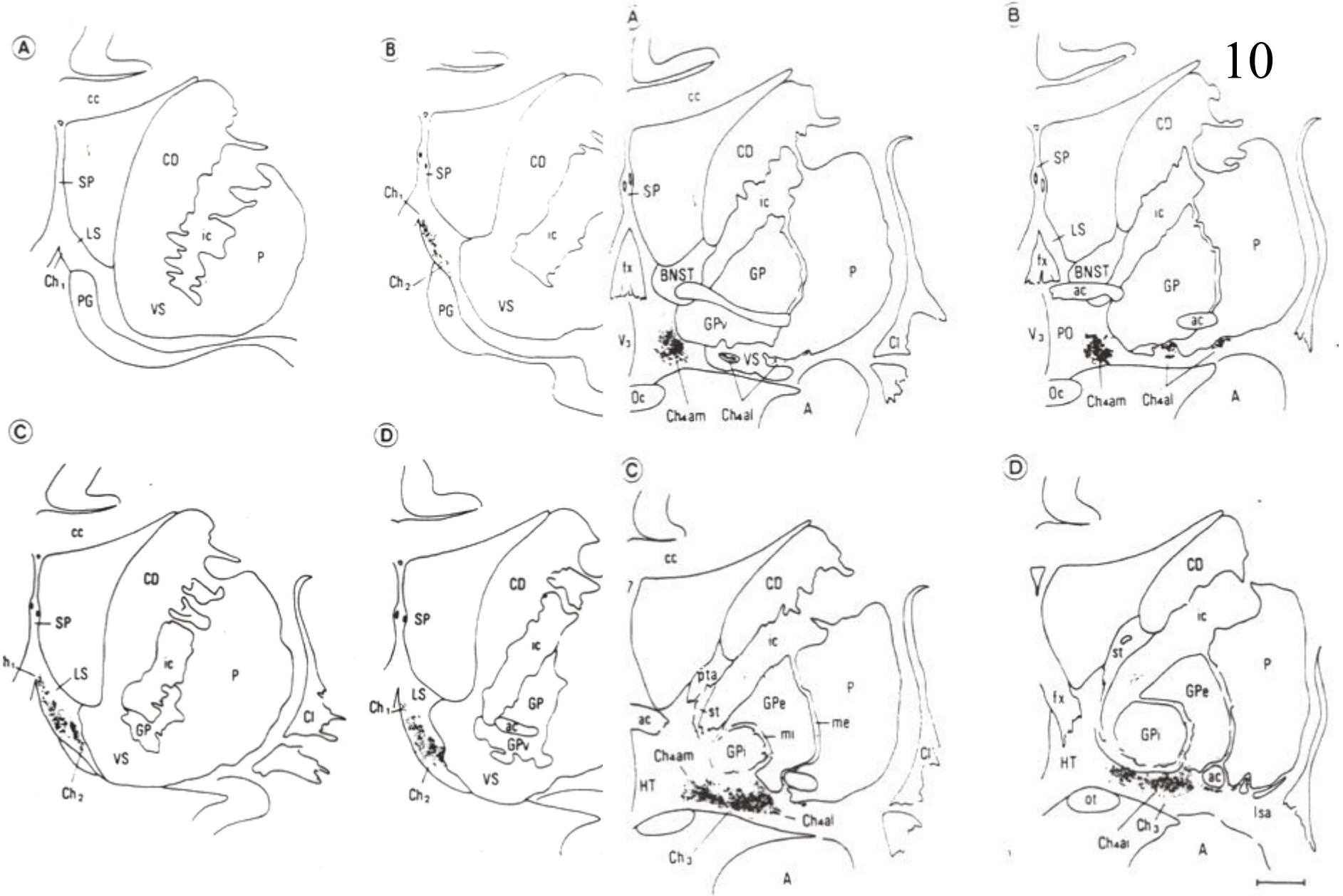
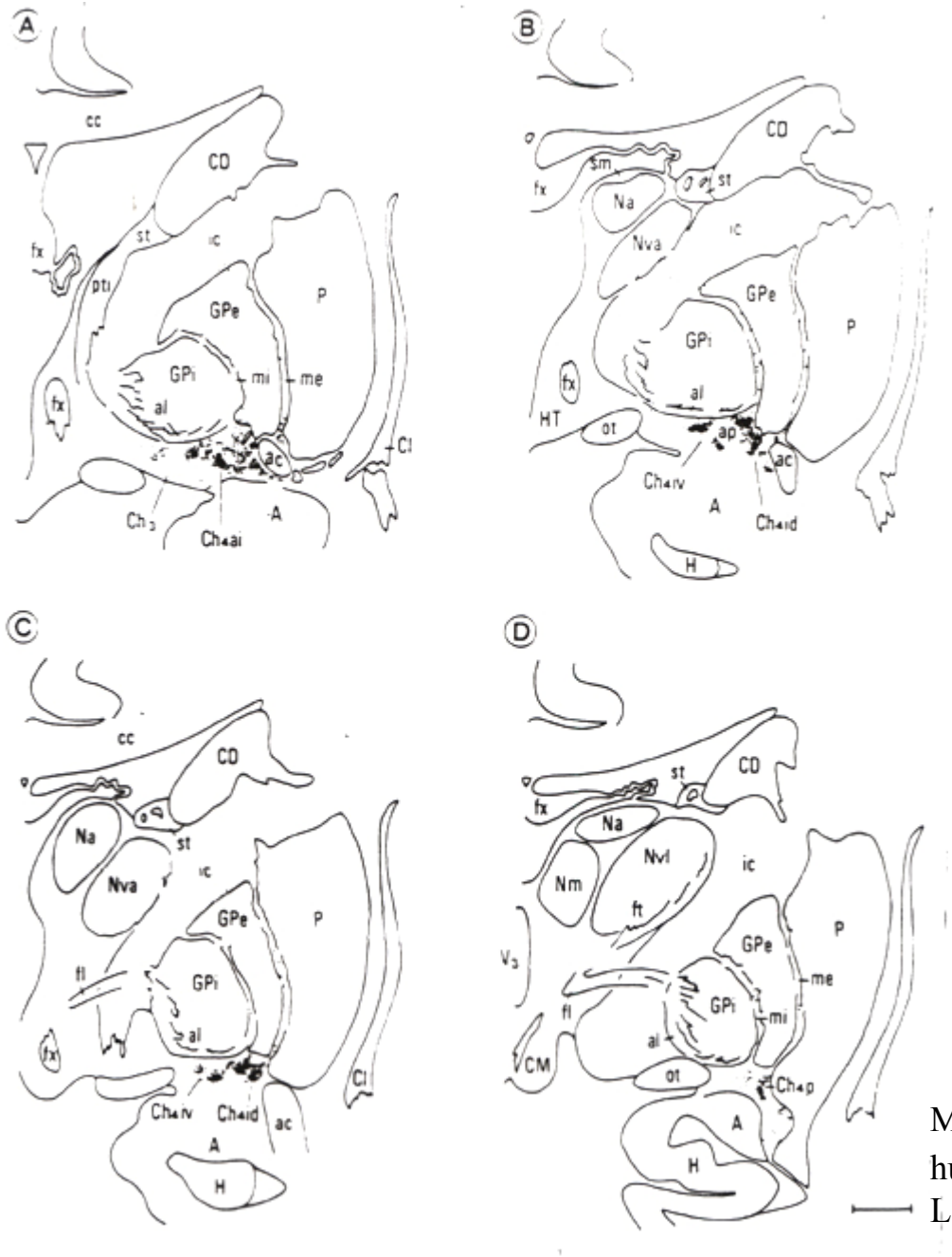


Summary of the major pathways for cholinergic innervation of the cortical mantle by the magnocellular basal complex (Saper, 1990).


L1
L2
L3
A
L1
L2
L3
B



Maps of rostro-caudal cholinergic neurons (stained with the antibodsy against choline acteyltransferase) in serial 40 um coronal sections of the basal forebrain in human. Ch1-Ch4 nomenclature according to Mesulam. From Lehericy et al. 1999



Maps of coronal sections in the human brain. ChAT staining. From Lehericy et al

Authors	Method	Total NB-Ch4	NB-Ch4a am	NB-Ch4a al	NB-Ch4i	NB-Ch4p
Whitehouse et al. (93)	Nissl		>75%			
Perry et al. (97)	Nissl		33%			
Tagliavini and Pilleri (113)	Nissl		47–76%[a]			
Arendt et al. (104)	Nissl	70%				
Wilcock et al. (102)	Nissl		50%			
Pearson et al. (94)	ChAT Immuno.	0 (n = 1)				
Nagai et al. (284)	ChAT Immuno.	>50%				
McGeer et al. (157)	ChAT Immuno.	50%[b]				
Mann et al. (112)	RNA stain		60%[a]			
Arendt et al (107)	Nissl	57%	46%	51%	63%	64%
Rogers et al. (285)	Nissl	Sig.				
Etienne et al. (95)	Nissl		73%		87%	
Rinne et al. (98)	Nissl		36%			
Doucette et al. (108)	Nissl		39%		53%	74%
Wilcock et al. (101)	Nissl		13%	52%	41%	57%
Mesulam and Geula (9)	Nissl, AChE histochem.	Sig.	25–54%			84%
Mufson et al. (106)	NGFr immuno.		35%	76%	62%	77%
Vogels et al. (114)	Nissl, all cells	20%	16%		18%	37%
Kobayashi et al. (116)	Nissl, AChE immuno.				53%, Sig.	
Iraizoz et al. (109)	Nissl		43%		25%	31%
Lehericy et al. (103)	ChAT immuno.	49%	47%	51%	47%	71%
Average of the loss reported by various studies		49%[c]	35%	57%	49%	62%
			48%			

Only studies that directly report on the status of the nucleus basalis-Ch4 complex (NB-Ch4) in AD are summarized in this table.

[a]The precise sector of NB-Ch4 studied is not mentioned by the authors. On the basis of descriptions in the methods, we assigned the sector shown.

[b]Percentages were calculated from the data presented in the tables of this report.

[c]The study by Pearson and Sofroniew, which reports no loss of NB-Ch4 neurons in AD was not included in the average because it was based on one case only.

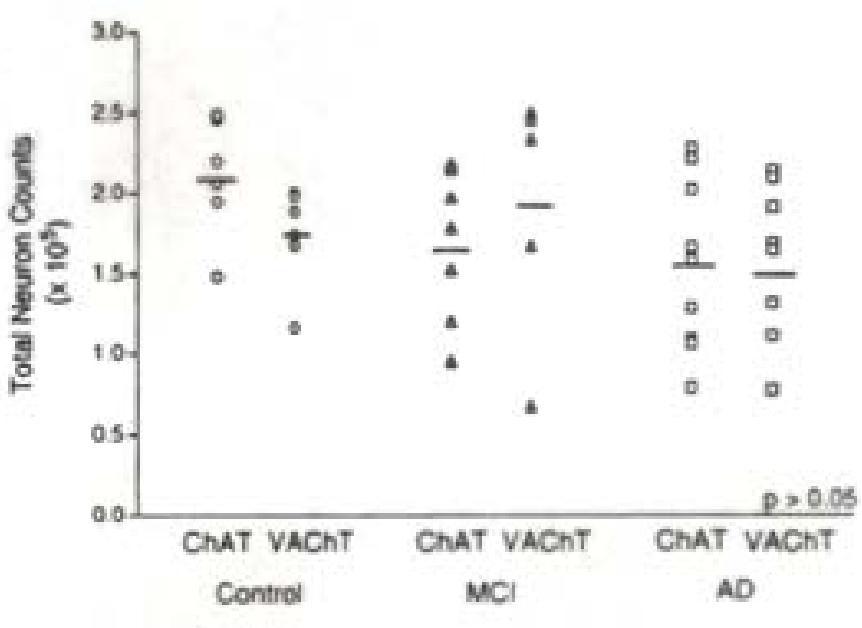
(Geula and Mesulam, 1994)

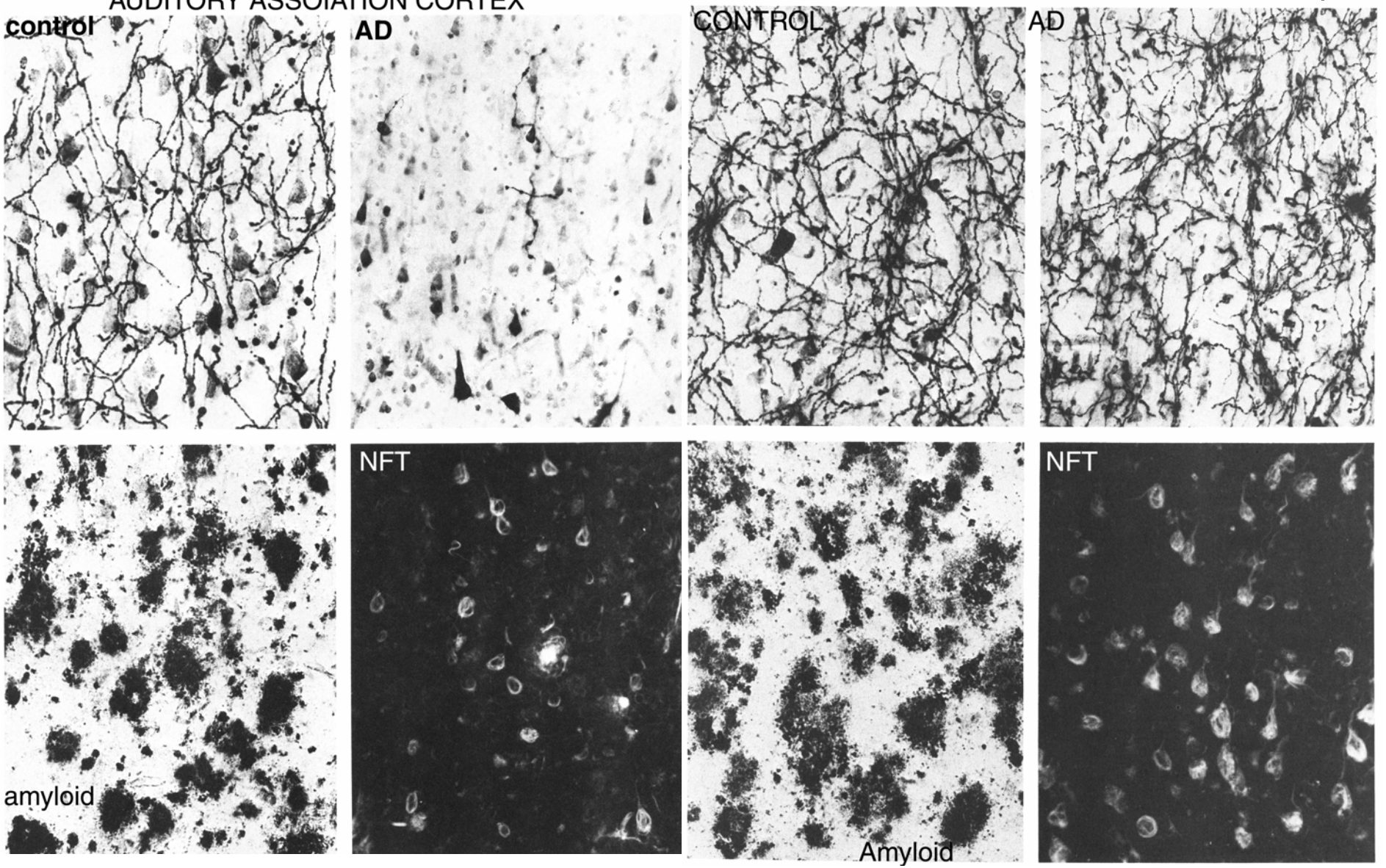
ChAT- and VAChT-Immunoreactive Neurons in the Nucleus Basalis of Meynert[1]

Cases	ChAT (mean ± standard deviation)	VAChT (mean ± standard deviation)
NCI	210,540 ± 15,240 (n = 6)	174,000 ± 12,773 (n = 6)
MCI	167,879 ± 17,903 (n = 7)	192,637 ± 34,737 (n = 5)
AD	155,565 ± 17,949 (n = 9)	149,423 ± 17,615 (n = 9)

[1]ChAT, choline acetyltransferase–immunoreactive neurons; VAChT, vesicular acetylcholine transporter–immunoreactive neurons; NCI, no cognitive impairment; MCI, mild cognitive impairment; AD, Alzheimer's disease.

t-test in the NCI group ($t = 1.84$, $P = 0.1$; Fig. 3). The calculated biological variation for the NCI group was approximately 17%.





AChE-positive cholinergic fibers in layer III of the auditory assoc. cortex of a 71 year old normal person and of a 67-year old patient with AD. This region displays severe loss of cholinergic neurons, accompanied by a high density of plaques and tangles (NFT).

ACHE-positive cholinergic fibers in LIII of the cingulate cortex of a normal person and of a 67-year old patient with AD. The cingulate cortex shows a remarkable preservation of cholinergic fibres, however, this area contains high density of amyloid plaques and tangles. (Geula and Mesulam, 1994)

Cortical distribution of cholinergic deficit in AD

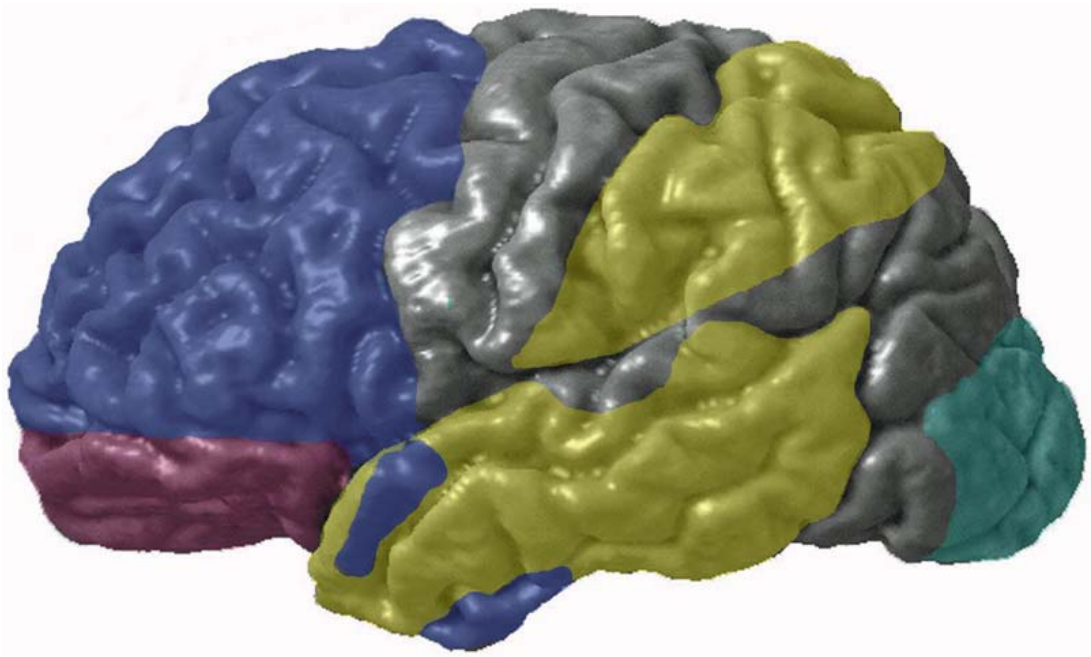
TABLE 2. *Loss of acetylcholinesterase-positive cortical cholinergic fibers in Alzheimer disease*[a]

Cortical area	Remaining fibers	% Loss
Areas displaying greater than 75% loss		
Temporal visual association (20)[b]	76 ± 72	85
Temporal visual association (21)	86 ± 56	82
Auditory association (22)	118 ± 81	78
Entorhinal cortex (28)	249 ± 107	76
Areas displaying 40–75% loss		
Insula	266 ± 100	67
Superior parietal association (7)	129 ± 70	66
Inferior parietal lobule (39-40)	175 ± 133	61
Temporal pole (38)	311 ± 56	58
Visual association (19)	133 ± 20	53
Prefrontal association (44)	230 ± 110	53
Prefrontal association (9)	216 ± 51	51
Subiculum	506 ± 69	48
Somatosensory association (5)	222 ± 42	47
Primary auditory (41-42)	282 ± 57	47
Posterior cingulate (23)	461 ± 142	44
Orbitofrontal cortex (11-12)	450 ± 47	43
CA1 sector of hippocampus	832 ± 29	41
Areas displaying less than 30% loss		
Primary visual (17)	257 ± 46	28
Premotor association (6)	361 ± 78	21
Anterior cingulate (32)	151 ± 9	19
Parolfactory area (25)	210 ± 166	19
Primary somatosensory (3,1,2)	480 ± 9	14
Primary motor (4)	522 ± 35	8
Anterior cingulate (24)	860 ± 43	4

[a]The data presented in this table are based on a study using three Alzheimer disease patients and three age-matched controls. See text, Endnote on Methods.

[b]Numbers in parenthesis refer to cortical areas according to Brodmann's classification.

Geula and Mesulam, 1994



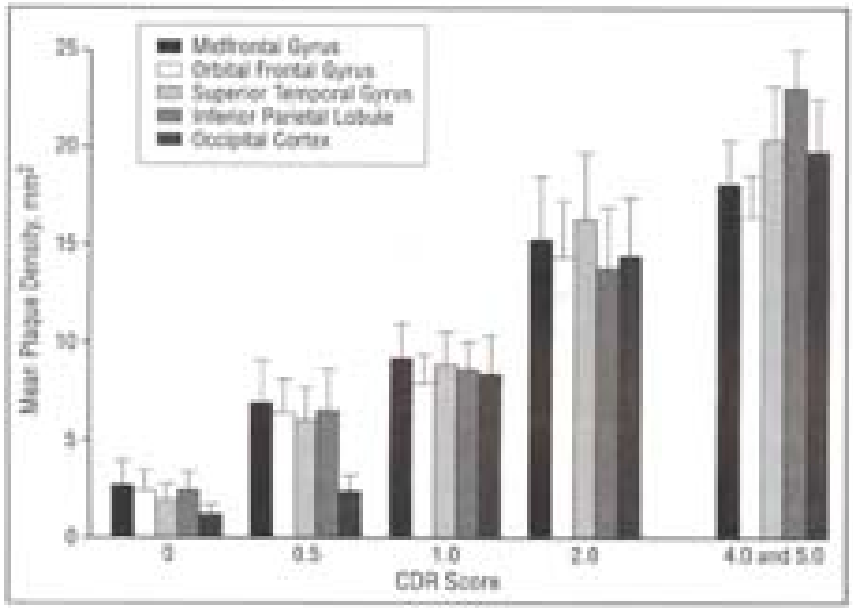
Cortical distribution of the cholinergic deficit in Alzheimer's disease. Gray areas have no consistent reduction of cholinergic markers; magenta indicates reduction of 40-50%; light blue, reduction of 50-60%; purple, reduction of 60-70%; and **yellow, reduction of 70-80%.** (J Felix, Laboratory of Neuroimaging, UCLA School of Medicine).

The Mount Sinai Study

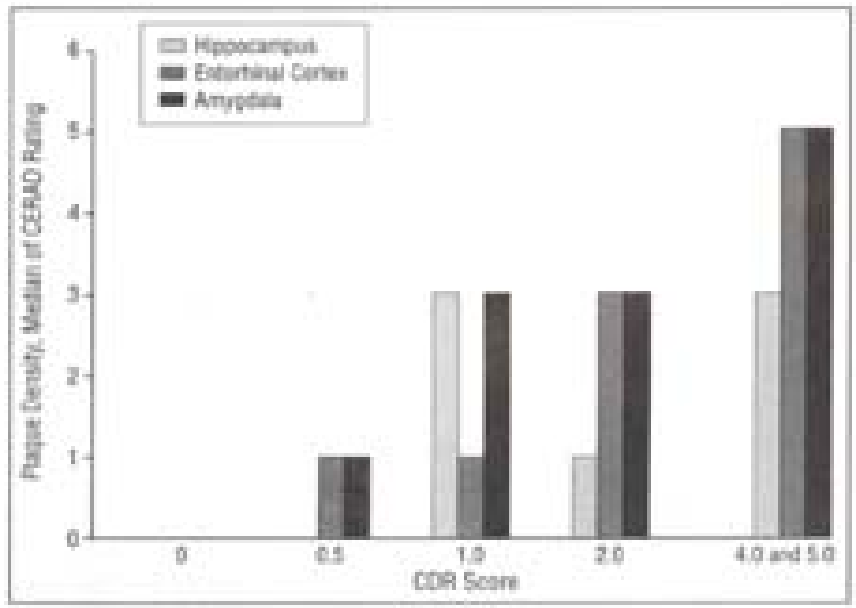
Table 1. Demographic Characteristics of the Sample*

	CDR Group					
	0.0	0.5	1.0	2.0	4.0 + 5.0	All
Sample size	18	11	22	15	15	**81**
Mean ± SD PMI, h	8.29 ± 5.96	5.59 ± 4.63	4.79 ± 3.97	6.09 ± 6.04	5.84 ± 7.39	6.17 ± 5.07
Age, y						
Mean ± SD (range)	83.8 ± 9.9 (64-99)	85.8 ± 8.3 (69-94)	82.9 ± 8.2 (74-103)	89.1 ± 5.7 (74-97)	85.4 ± 10.3 (62-103)	86.7 ± 8.9 (62-103)
Male	82.3	77.5	88.0	83.7	69.0	81.6
Female	84.1	87.7	89.7	90.4	89.0	88.1
Sex, No.						
Male	3	2	6	3	3	**17**
Female	15	9	16	12	12	**64**

*CDR indicates Clinical Dementia Rating Scale: PMI, postmortem interval. CDR group 0.0 indicates cognitively intact; 0.5, questionable dementia; 1.0, mildly impaired; 2.0, moderately impaired; and 4.0 and 5.0, severely demented.

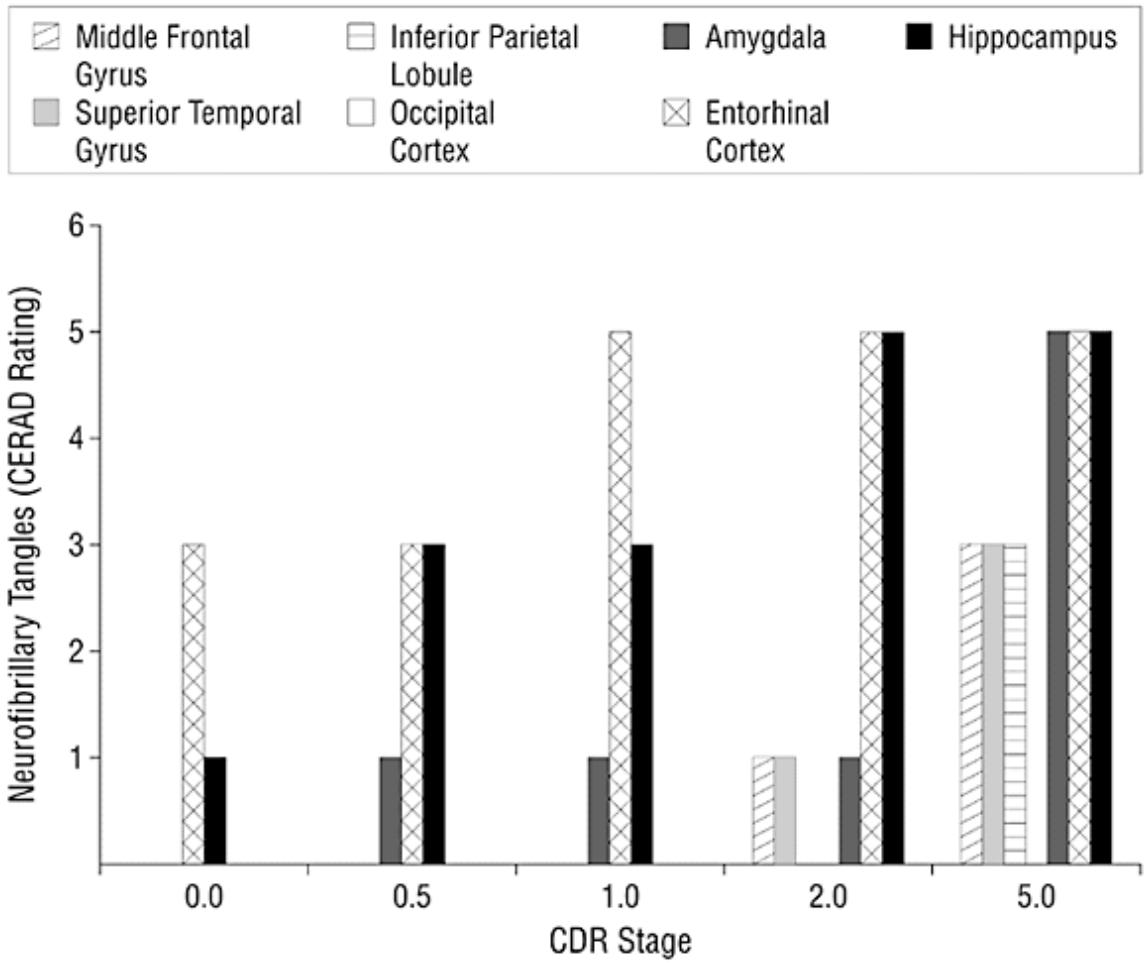


Mean density of neuritic plaques in 5 neocortical regions as a function of dementia severity. (Haroutunian et al., 1998)



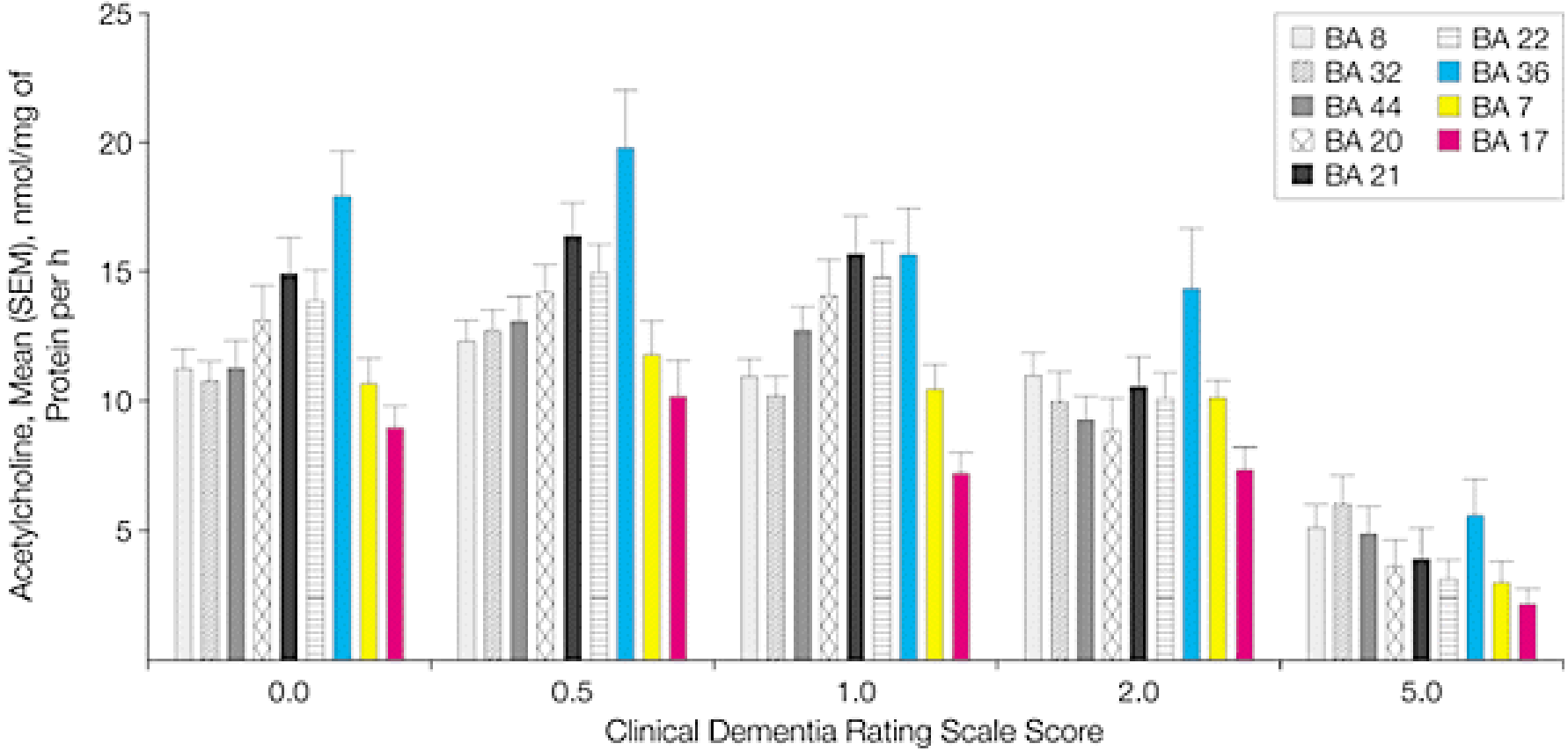
Median of ratings of neuritic plaque density using the neuropathological battery of the CERAD. 0=absent; 1=sparse; 3= moderate and 5=severe in the hippocampus, entorhinal cortex and amygdala.

Neurofibrillary tangles. THE MOUNT SINAI STUDY



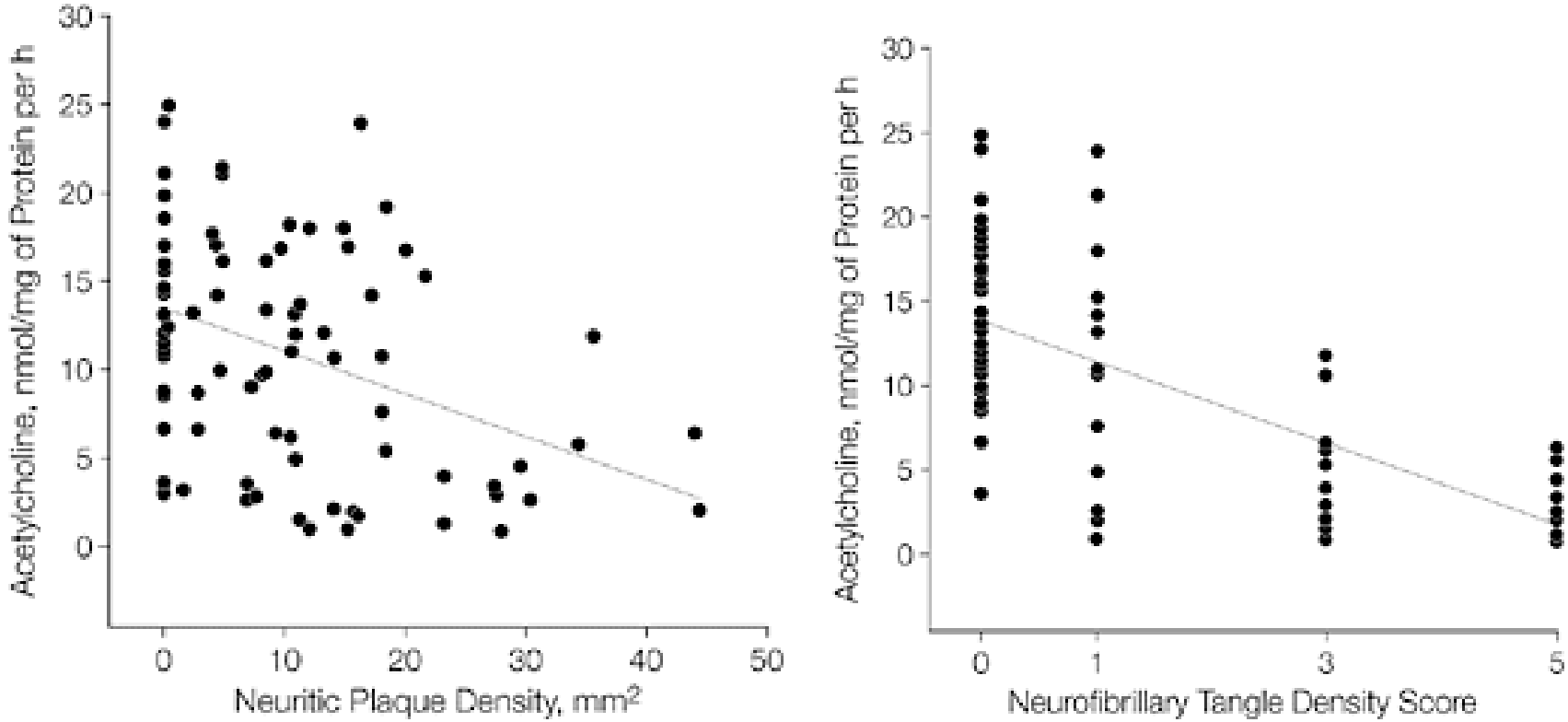
Density of neurofibrillary tangles in four neocortical regions and in the entorhinal cortex, hippocampus and amygdala in non-demented (CDR score 0), questionable (CDR= 0.5), moderately (CDR=2) and demented (CDR=5) subjects. The y axis represents the median of Consortium to Establish a Registry for Alzheimer's Disease (CERAD) neurofibrillary ratings (0 indicates none; 1 sparse; 3=moderate and 5=severe). (Haraoutuniqan et al., 1999)

CHOLINERGIC DEFICIT IN THE CORTEX



Activity of ChAT in 9 cortical regions as a function of dementia severity. Relative to the group without dementia (CDR score=0), the activity of ChAT was significantly reduced ($p<0.001$ for all) in the CDR 5.0 group only. BA indicates Brodmann area. (Davis et al., 1999)

CORRELATION OF CHAT ACTIVITY WITH PLAQUES AND TANGLES



Correlation of ChAT activity in the superior temporal gyrus (Brodmann area 22) with neuirtic plaque density (left chart) and neurofIbriallary tangle density (right chart) for the entire cohort. (Davis et al., 1999)

SUMMARY OF RELATIONSHIPS BETWEEN NEUROPATHOLOGICAL, CHOLINERGIC CHANGES AND DEMENTIA

PATHOLOGY	CORRELATION TO DEMENTIA
Loss of synapses in the cortex	Highly significant+
Increased number of plaques in the cortex/(CDR score=5)	Significant *
Increased number of tangles in the cortex/CDR5 score=5)	Significant*
Loss of cholinergic innervation/density of cortical plaques	Significant*
Cortical ChAT/cortical tangles (CDR=5)	Significant*
Loss of BFC neurons/cortical plaques	Modest
Loss of BFC neurons/cortical tangles	Non significant

+ Terry, Masliah; * Mount Sinai Study

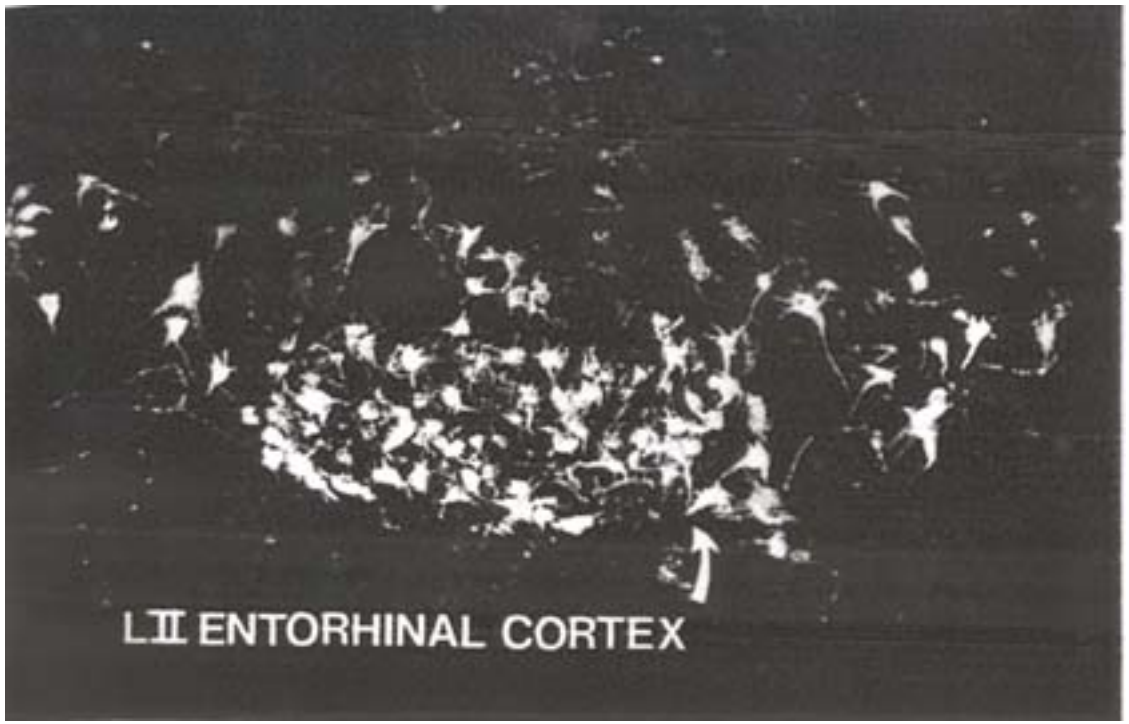
Neuronal Loss in Hippocampus in Aging and Alzheimer's Disease

Region	Age Range	Percent	Cell loss	Reference
Total hippocampus	47/89	27	(Over age 50)	Ball et al., 1977[a]
Subiculum	19/77	29		Shefer (1977)[a]
H1–H3	21/91	19–25	Pyramidal cells	M. Dam (1979)[a]
		15	Granule cells	
Subiculum	69/95	14	(Over age 70)	Anderson et al., 1984[a]
Sector H 1	15/96	3.5	Per decade	Miller et al., 1984[a]
		29	(Over age 15)	
	10/97	6.2	Per decade after age 50	Mann et al., 1985[a]
CA1–4	49/77	0	Total pyramidal cells	Brown & Cassell, 1980[a]
	4/98	3.8	Per decade	Mann et al., 1986[a]
CA4		25	(Over age 65)	
CA1–4	6/87	0	(All sections)	Davies et al., 1992
For comparison: Neuronal loss in Alzheimer's disease				
Total hippocampus	47			Ball, 1977[a]
Subiculum	39			Doebler et al., 1987[a]
Sector H1	22			Ince et al., 1991
Sector H1	28			
subiculum	44			Davies et al., 1992
CA1	41			
Prosubiculum	39			
Presubiculum	19			
CA3	17			

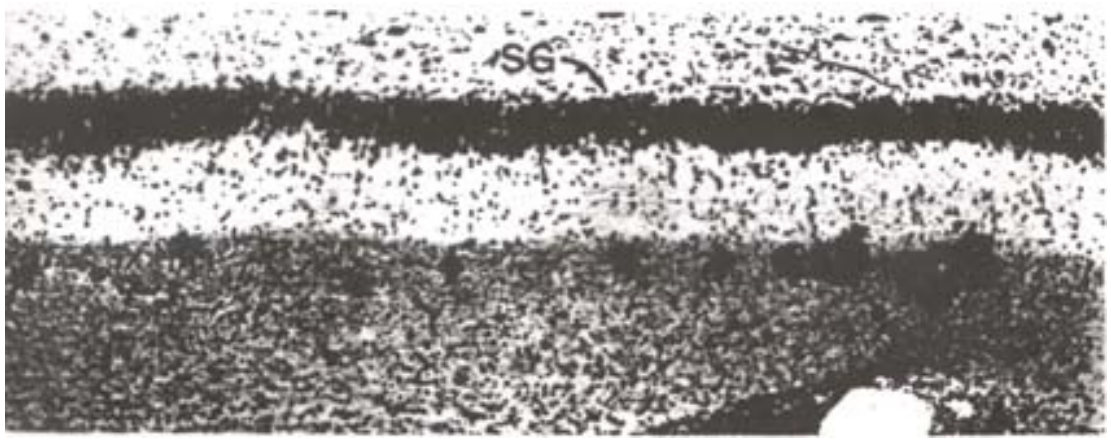
[a] For refs. see Jellinger (1989).

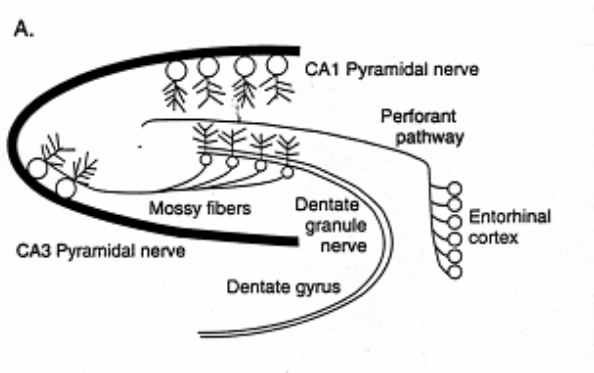
TANGLES AND ALZ-50-IR IN THE HIPPOCAMPUS

A



B



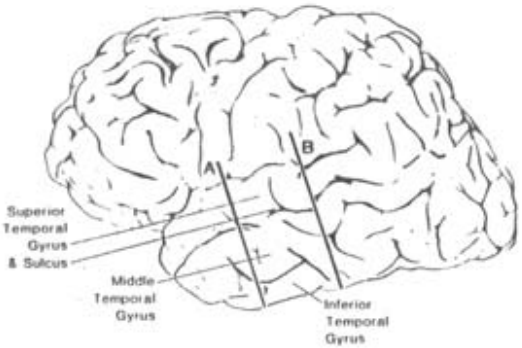


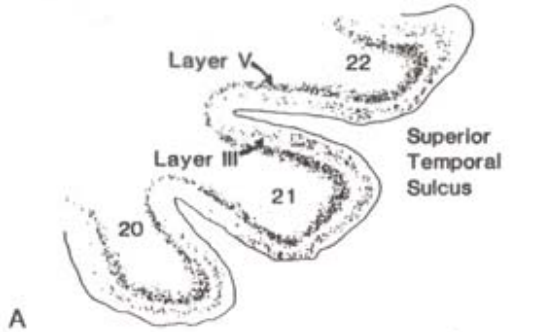
A. Thioflavin S-stained neurofibriallary tangles in layer II of the entorhinal cortex in AD. These neurons give rise to major component of the perforant pathway that links the cortex with the dentate gyrus.

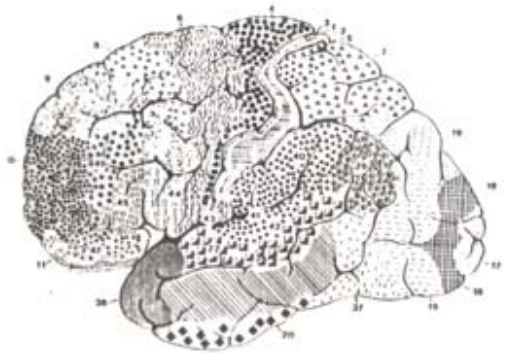
B: Alz-50 terminal immunoreactivity in the outer two thirds of the molecular layer of the dentate gyrus in an area that would correspond to the terminal zone of the perforant pathway. This pattern of immunoreactivity suggests that the AD antigen recognized by Alz-50 is located in the terminals of LII entorhinal neurons. The granule cells of the dentate gyrus (SG) have been stained with thonin.

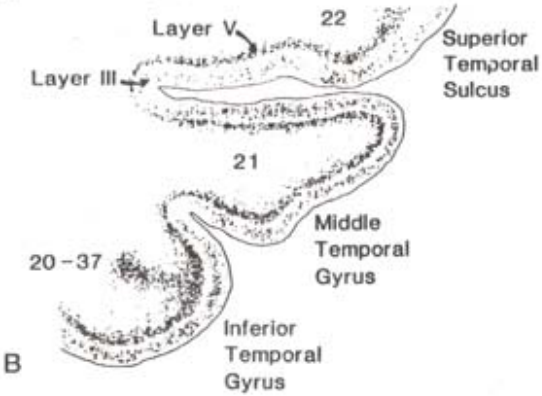
(G. van Hoesen)

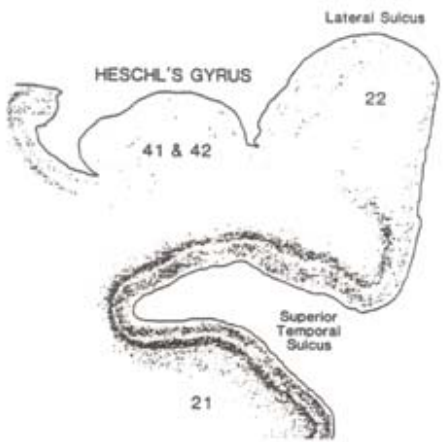
Distribution of NFTs in the auditory cortex from a case of AD





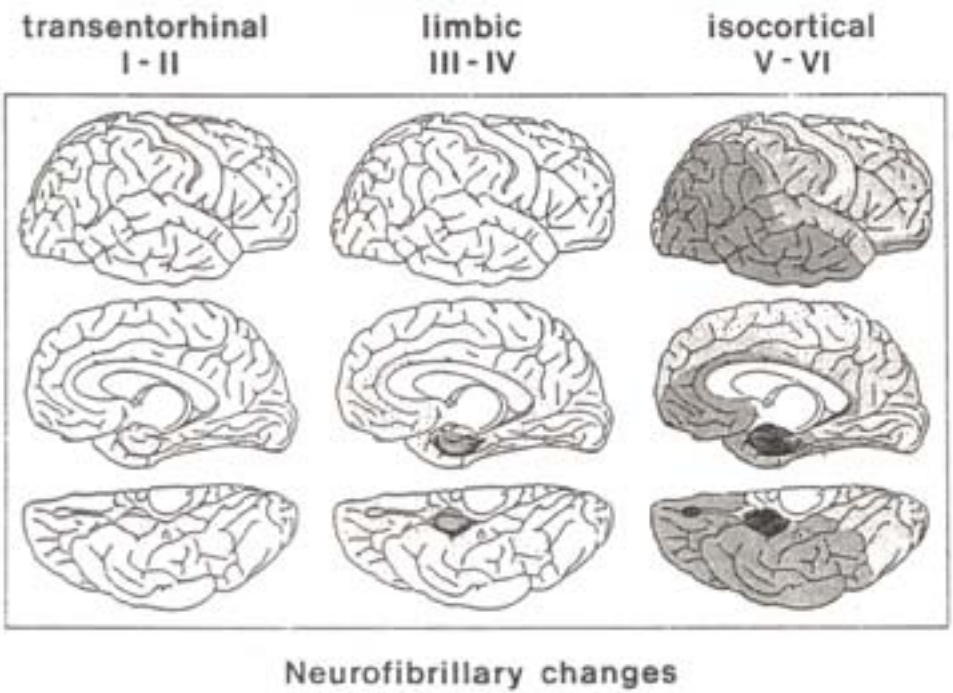




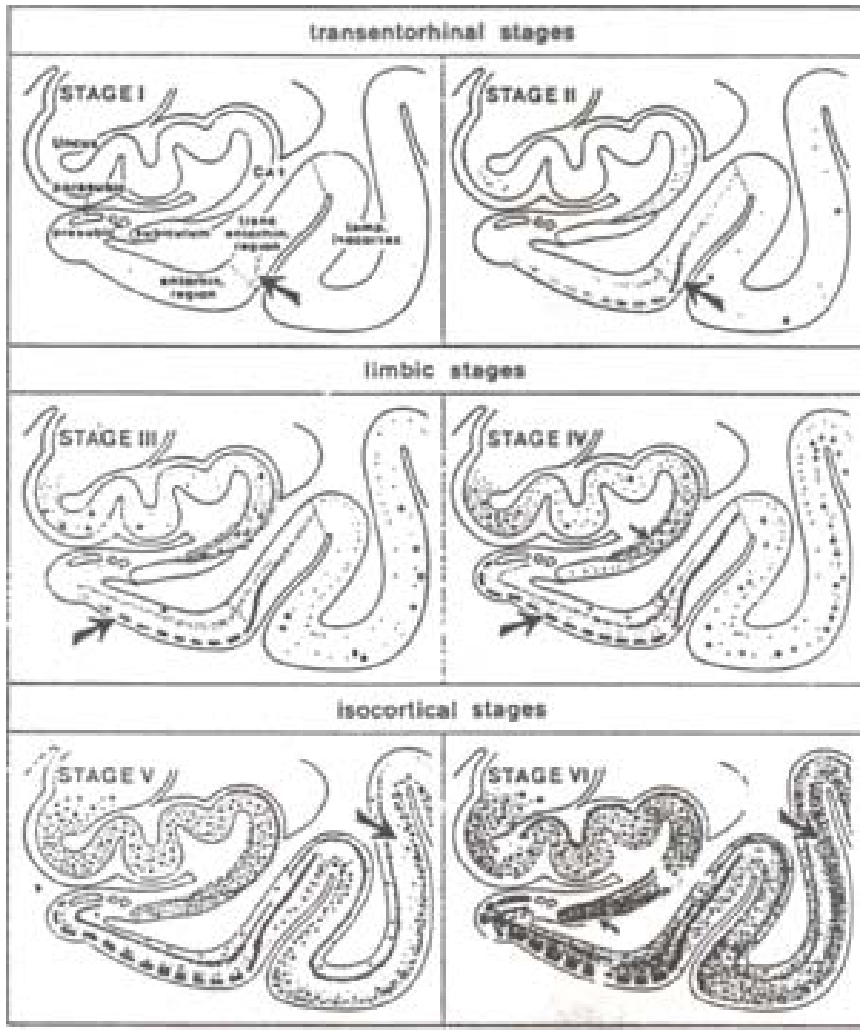


Note the primary auditory coretx (Brodmann's area 41 and 42 is largely spared. The dorsal and lateral parts of area 22, the sensory association cortex, are also relatively spared. More distal auditory association areas in the upper bank of the superior temporal sulcus contain extensive pathology (Mesulam)

Development of neurofibrillary tangles and neuropil threads from transentorhinal to isocortical stages

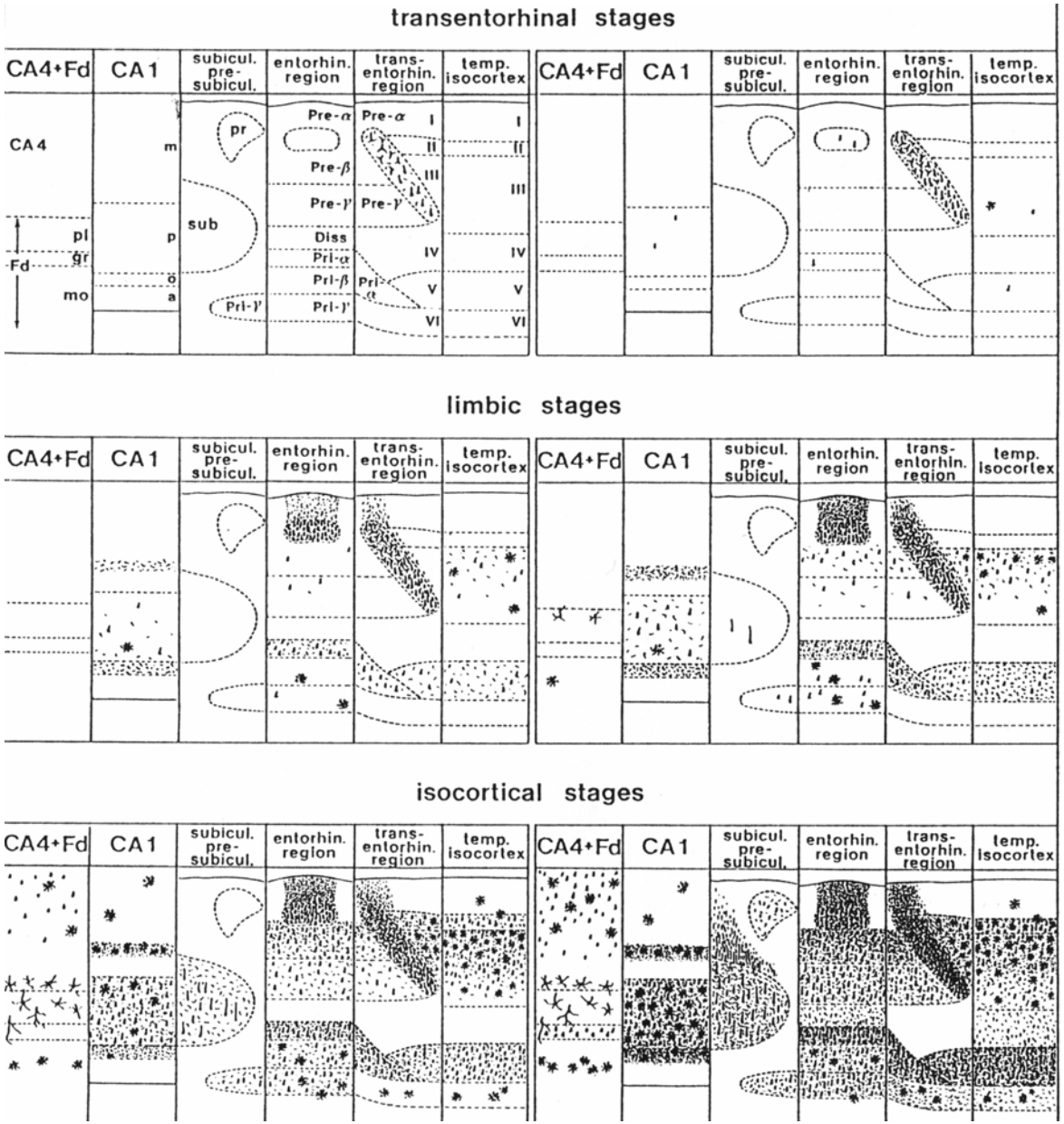


Increasing density of shading indicates increasing severity of the pathological changes. (Braak and Brrak, 1994)



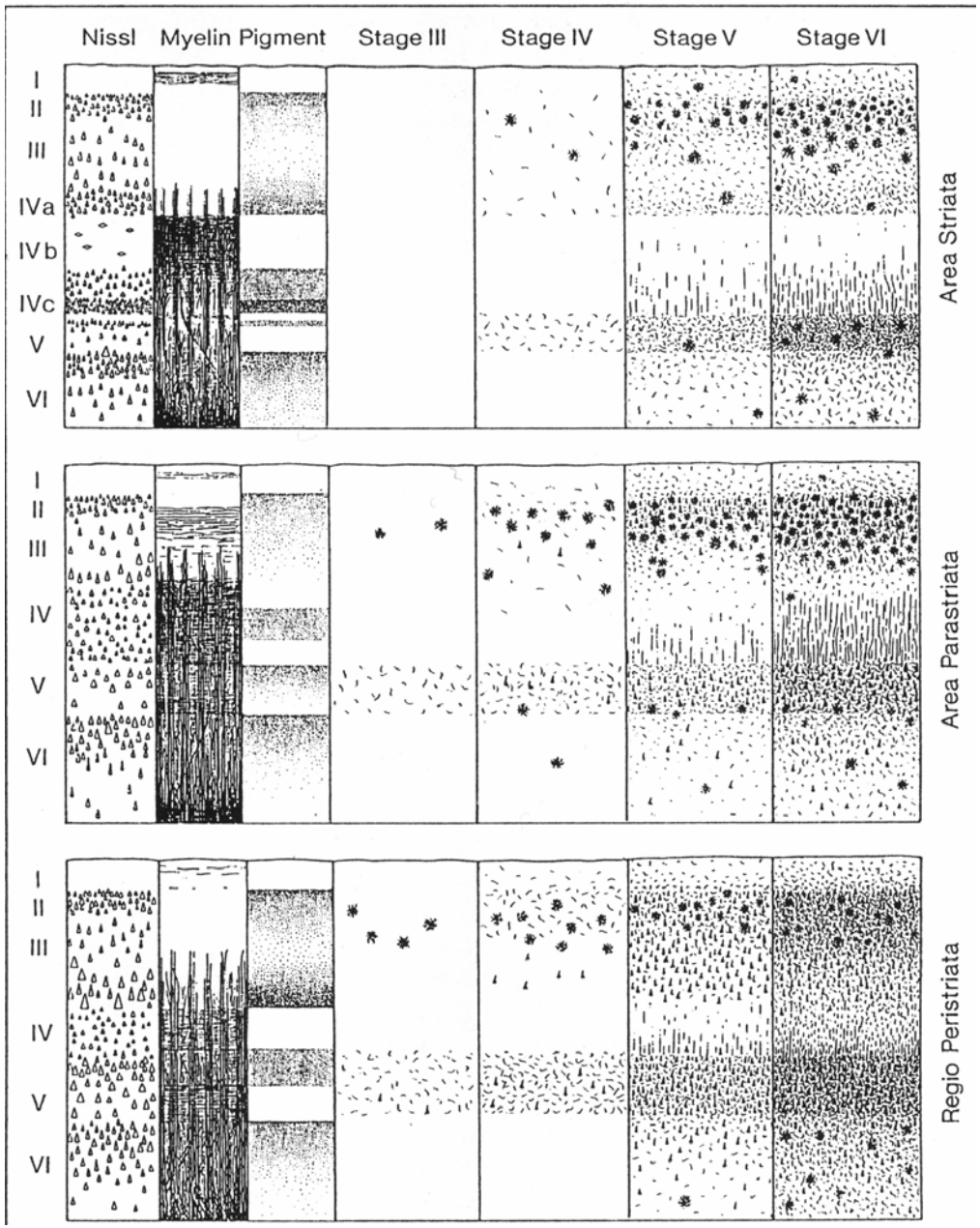
Neuropathological staging of AD-related changes in the anteromedial portion of the temporal lobe, (Braak and Braak, 1994).

Neurofib. changes seen in anteromedial portions of the temporal lobe



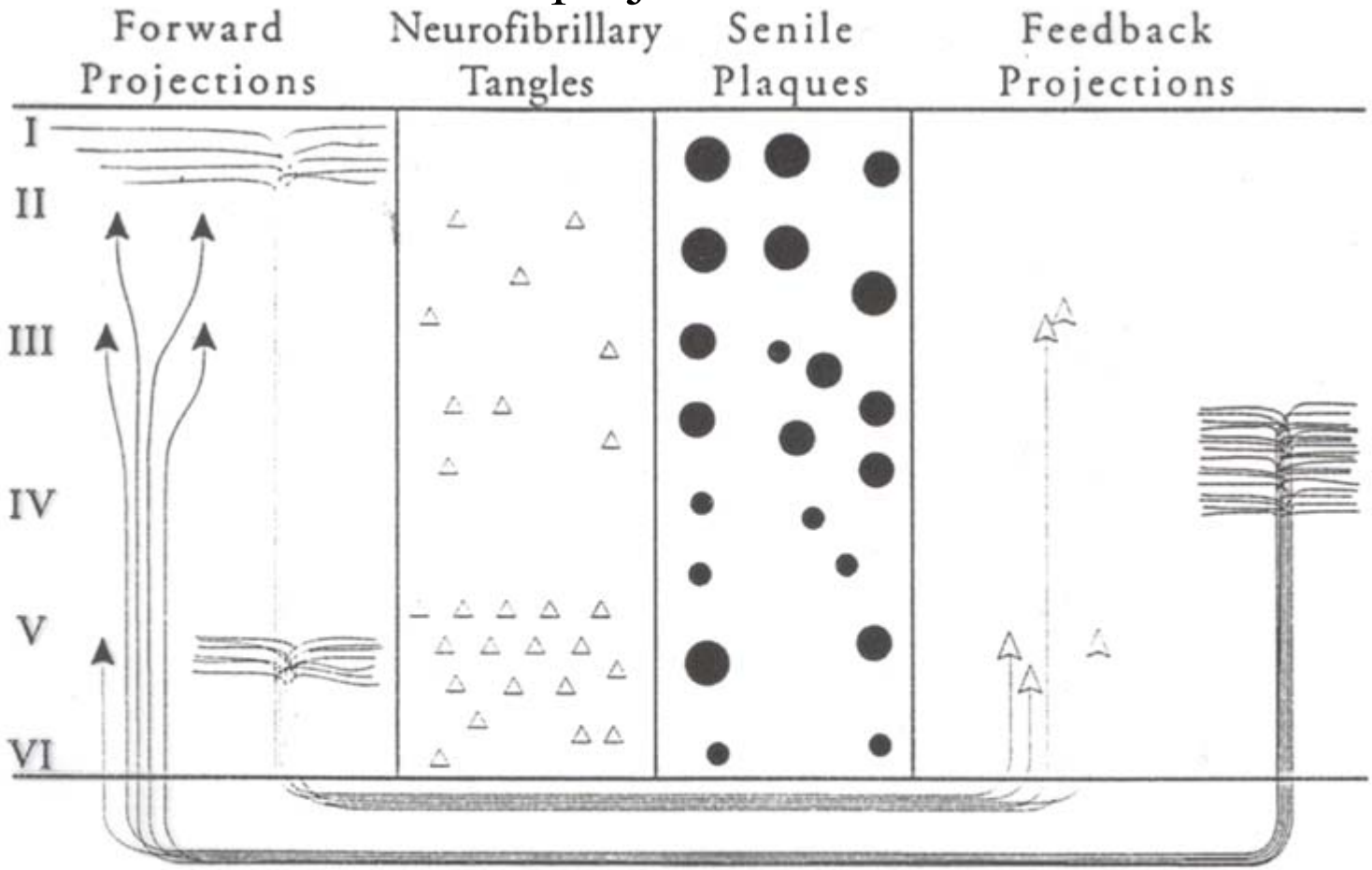
Summary development of changes from stage I to stage VI of AD. Fd=fascia dentata; gr=granula, mo=molecular layer. CA1: m=molecular; p=pyramidal; o=oriens; a=alveus. (Braak and Braak, 1994)

Neurofibrillary changes seen in the occipital cortex



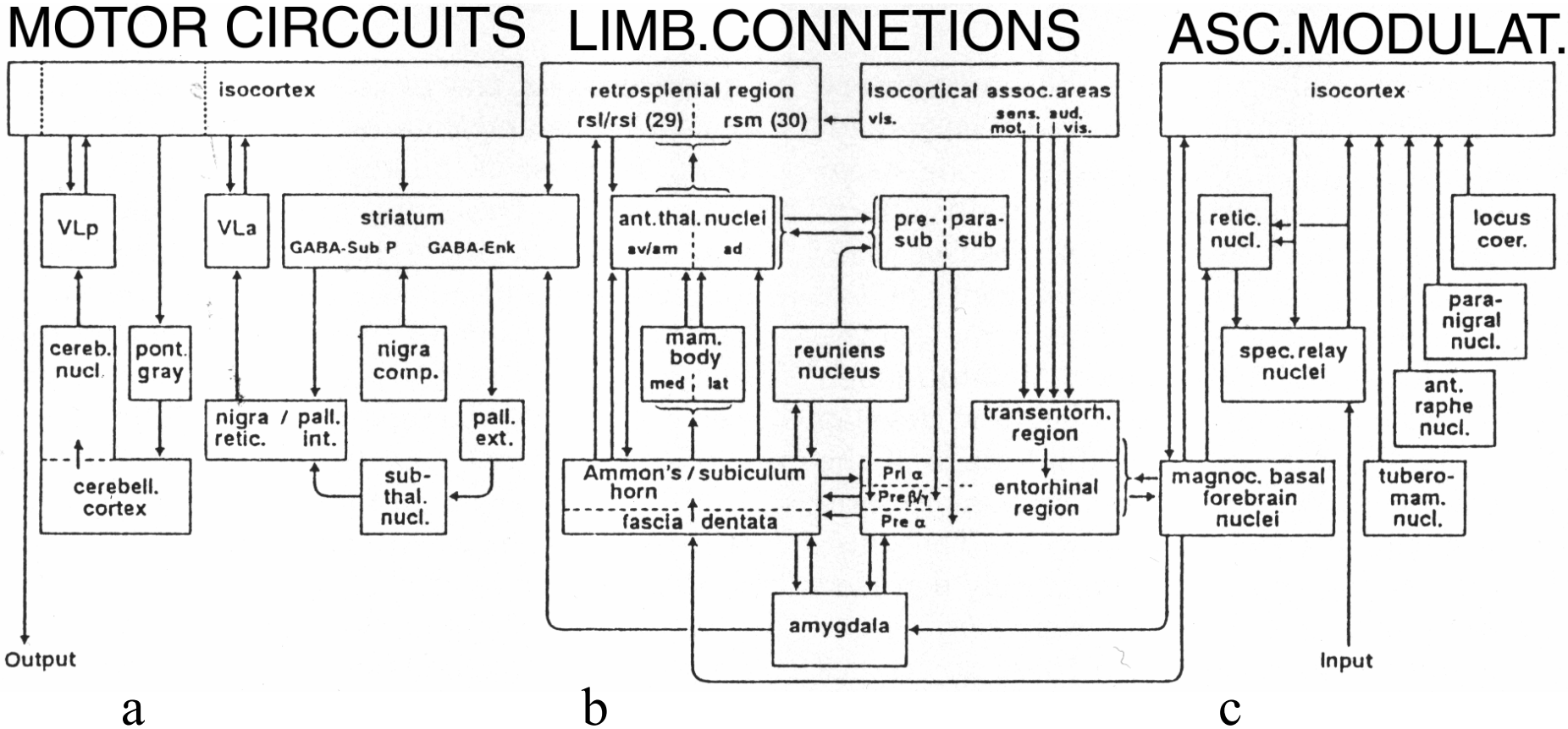
Summary diagram of neurofibrillary changes seen in the occipital cortex in stages III-VI of AD. Left, various architectonic schemes to show the laminar pattern in the striate (core), parastriate (belt) and the peristriata association cortex (Braak and Braak, 1994

Correlation between the distribution of NFT/SP and cortico-cortical projections

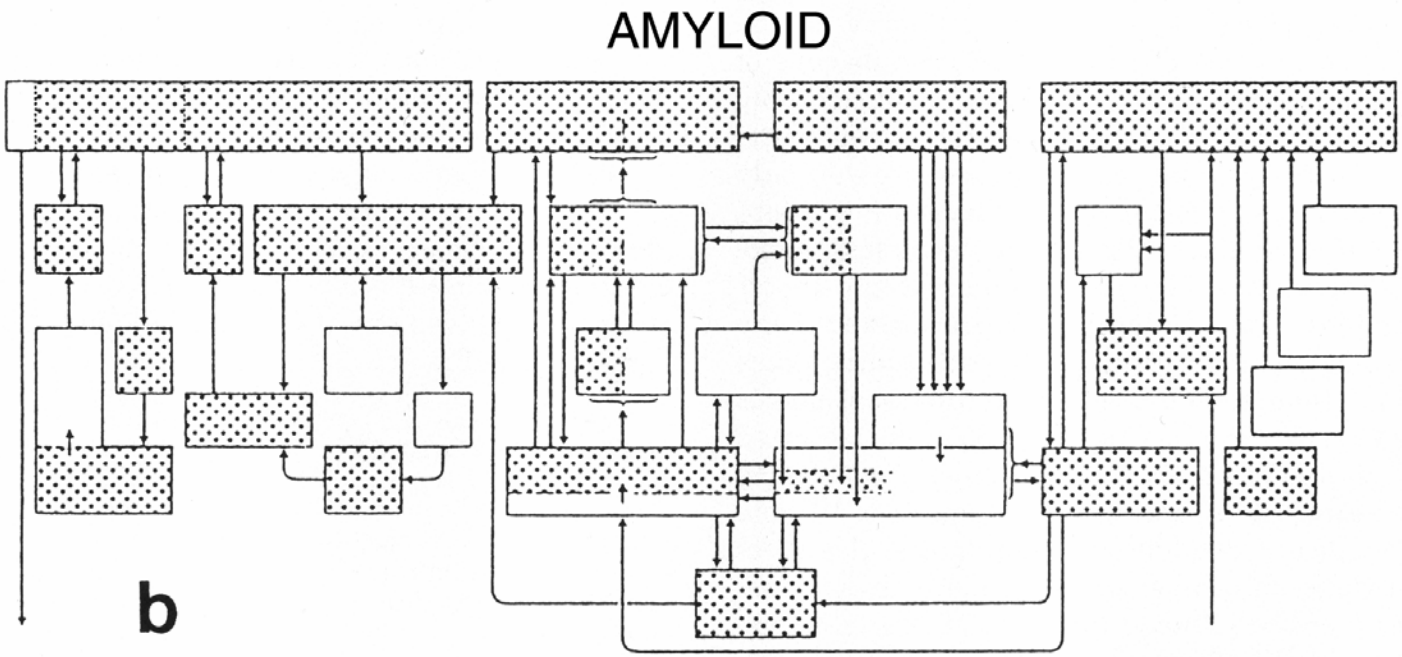


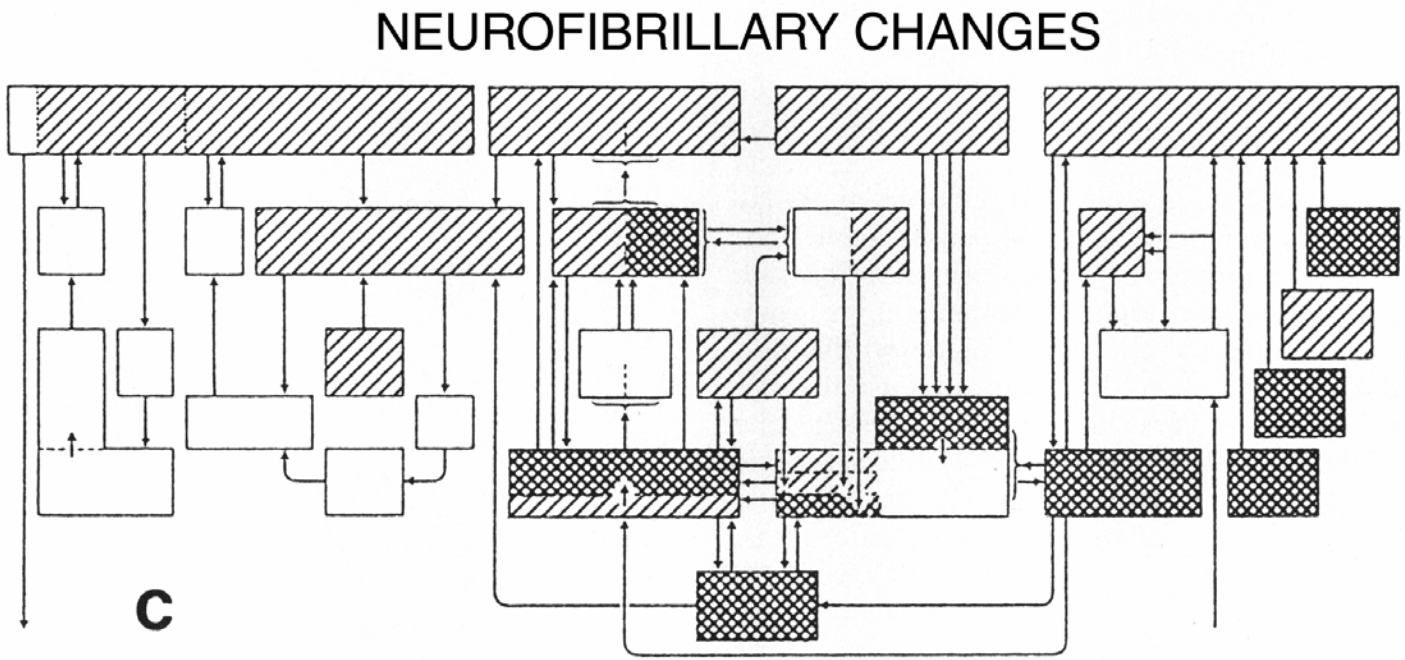
Correlation between the distribution of NFT and SP and the distribution of corticocortical projections. Neurofibrillary tangles are located in the same layers where the neurons of origin of forward and feedback corticocortical projections are found. They tend to be more numerous in the deep layers, suggesting a stronger correlation with feedback projections. Senile plaques are observed in higher densities in the zone of the termination of forward projection (layer IV and the lower two-thirds of layer III).

Hof and Morrison, 1994



Simplified diagrams of connections between the isocortex and subcortical ‘centers’ of the motor cortex (a); connections between imortant centers of the ‘limbic’ system (b) and diagram of connections between the isocortex and ascending subcortical modulatory centers (Braak and Braak, 1994).





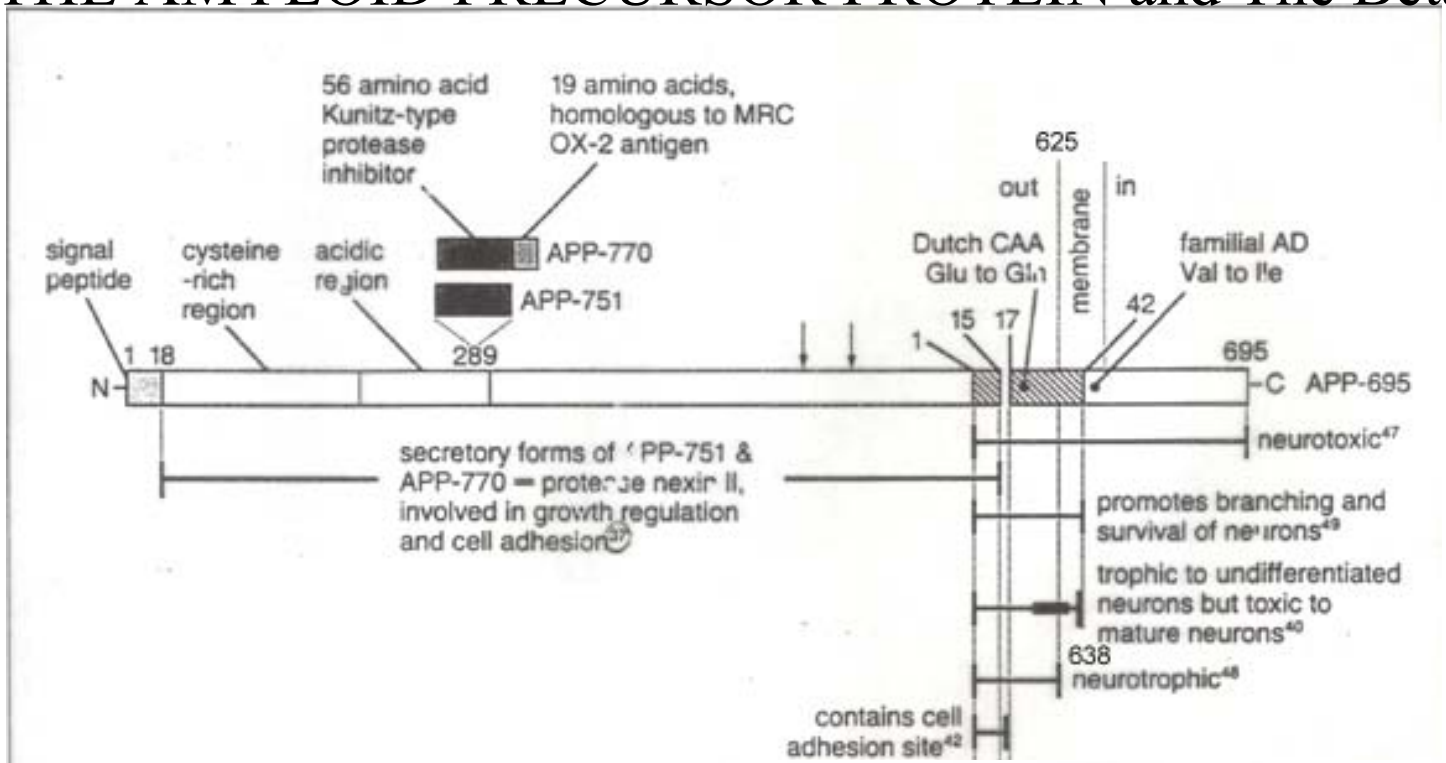
Predilection sites for amyloid deposits (b) and neurofibrillary changes. Compare with Plate 28 for identification of boxes. (Braak and Braak, 1994).

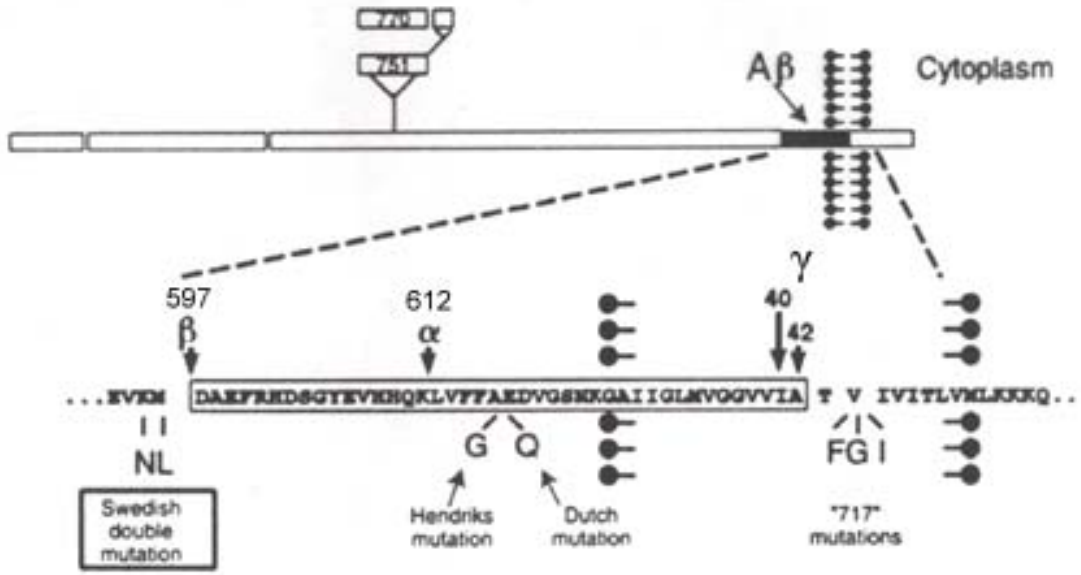
GENETIC DEFECTS IN AD AND DOWN SYNDROME

Gene defect	Chromosome	Age of onset	effect
Down syndrome	21	20	More AB1-42; more AB1-40
APP670/671 mut.	21	50s	Potentiation of Bsecretase, more AB1-40
APP692 mut.	21	50s	Inhibition of alfa secretase, more AB1-42
APP716 mut.	21	50s	Alteration of site of gamma-secretase cut, more AB1-42
APP717 mut.	21	50s	Alteration of site of gamma secretase cut
apoE4 polymorp.	19	60s and older	AB plaques and vascular deposits, risk factor, sporadic AD
PS1 mutation	14	40s and 50s	Subtle alteration of APP processing, more AB42
PS2 mutation	1	50s	Subtle alteration of APP processing, more AB42
Alfa2-macroglobulin (mutation or polymorphism)	12		The presence of the 'good' gene prevent the formation of insoluble AB fibrils, mutation predispose individuals to sporadic AD

THE AMYLOID PRECURSOR PROTEIN and The Beta Amyloid

A



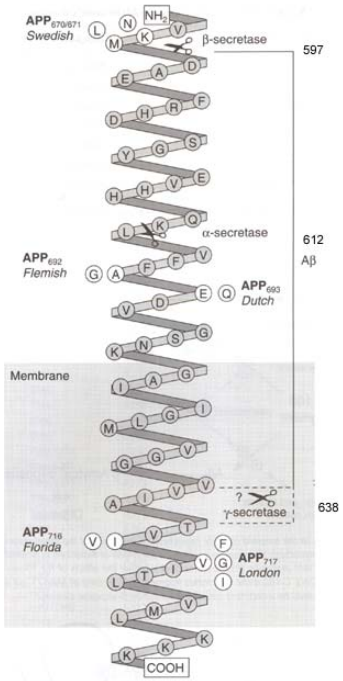


A: Domain structure and functional map of APP showing location of the BA4 region (shaded). The APP-770 transcipt includes a Kunitz protease inhibitor-motif (from Hardy).

B: Schematic showing the BA domain, residing partially in the transmembrane, partially extracellularly. Note the alfa and Beta-secretase cleavage sites and the positions of APP mutations linked to familial AD. Cleavage at residues 40 and 42 is thought to be the result of the gamma-secretase (from D. Price).

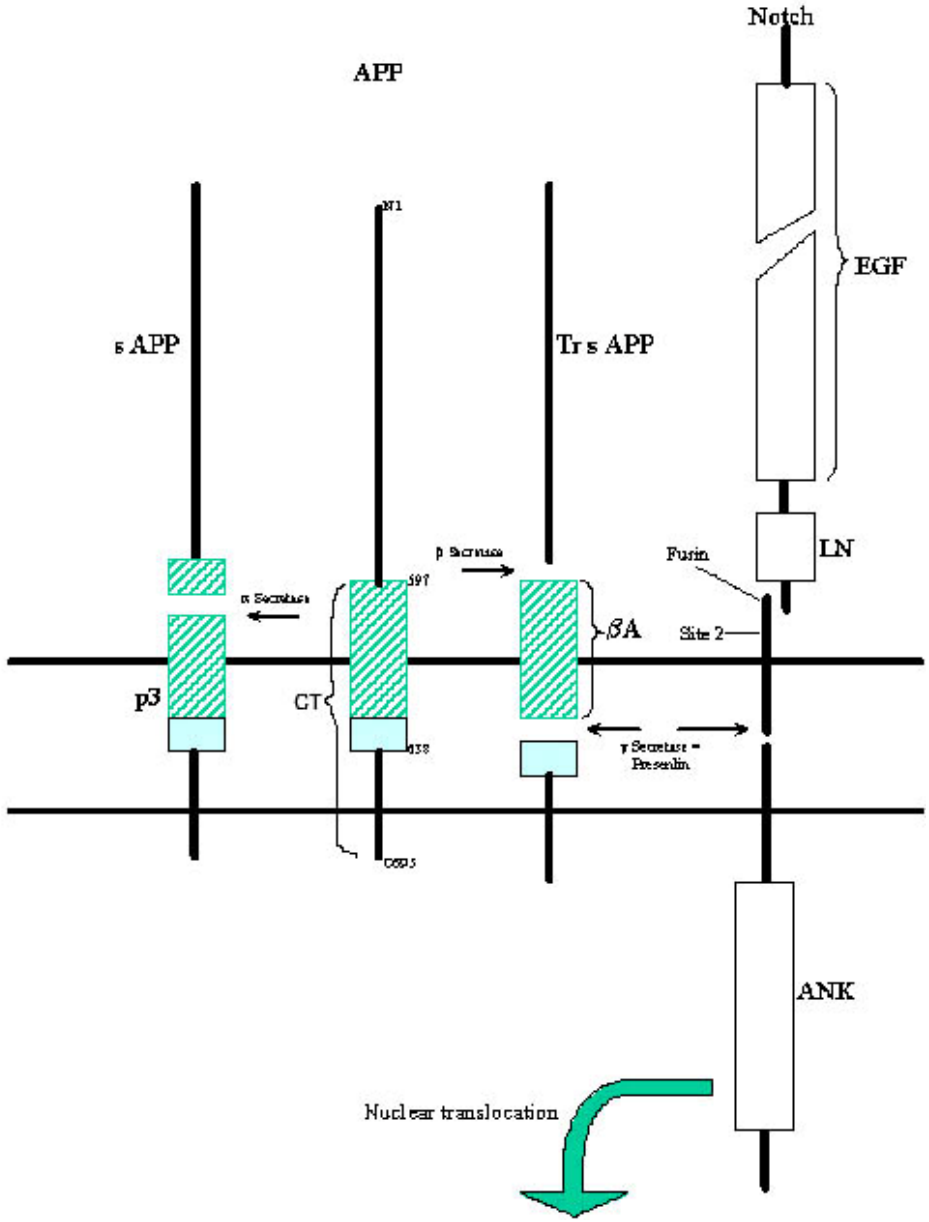
APP and its cleavage sites by alfa, beta and gamma secretases

A



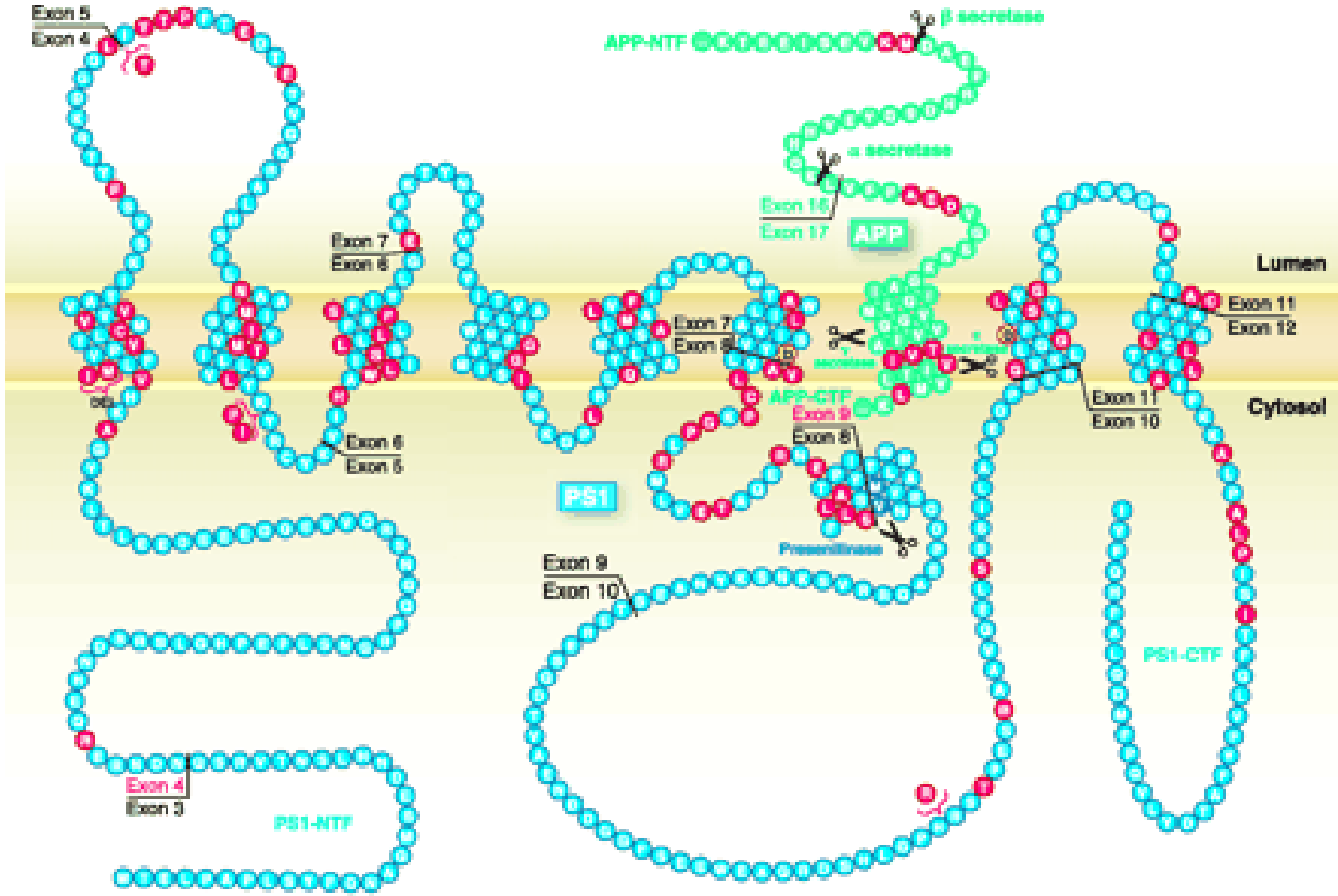
Cell membrane

B



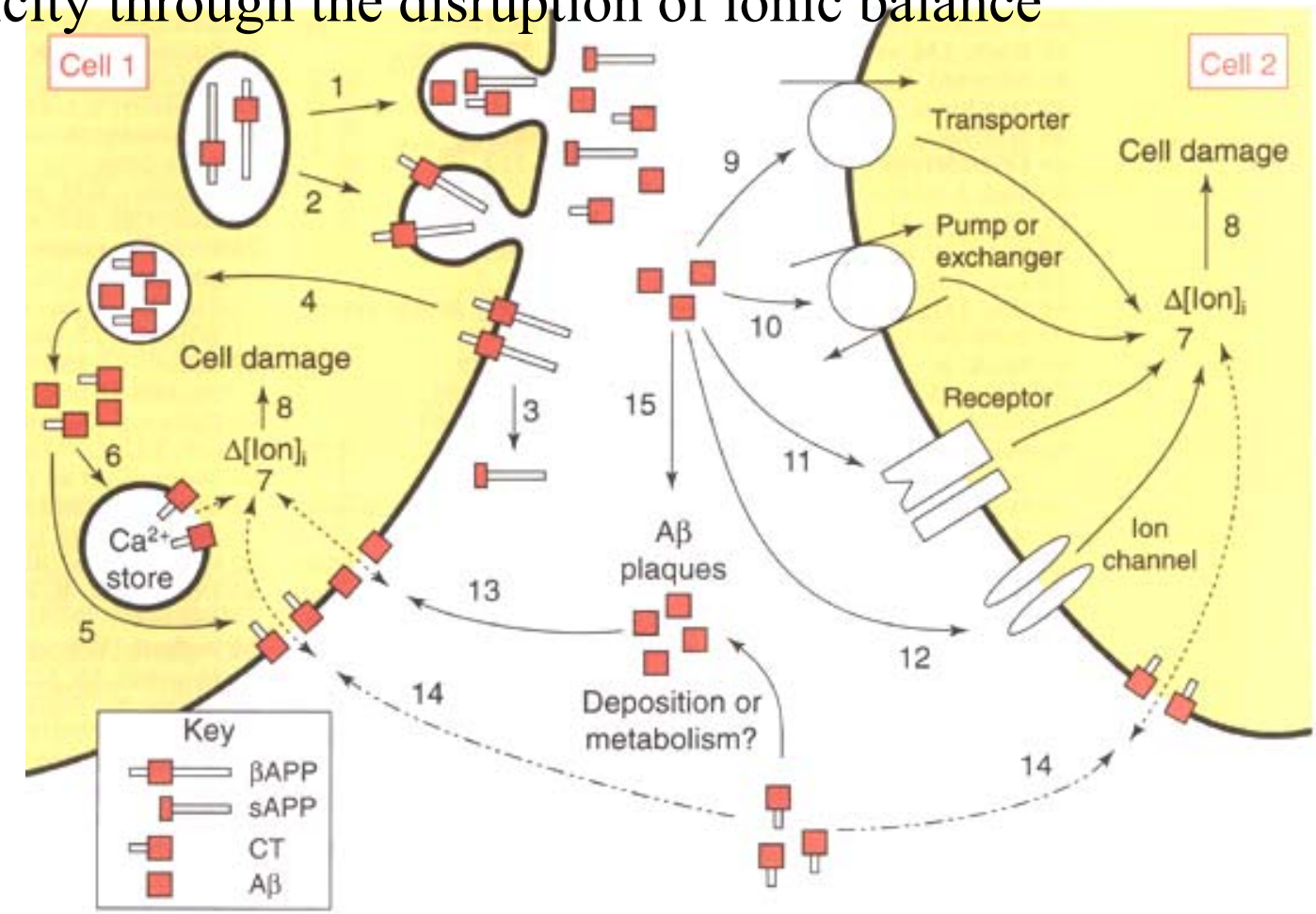
A: APP mutation helix. The relationships between mutatio and the cleavage sites are indicated. Gray area: membrane (Hardy). **B**: Schematic drawing showing the cleavage sites alfa, Beta and gamma-secretase and the resulting fragments left side shows the APP, the right the Notch proteolytic processing. sAPP= soluble APP, CT= C-terminus fragment sAPP=truncated sAPP; p3=fragment. ANK, LN, EGF = dif Notch domains

Putative intramembranous processing of APP at the proposed active site of the gamma-secretase/PS1 aspartyl protease



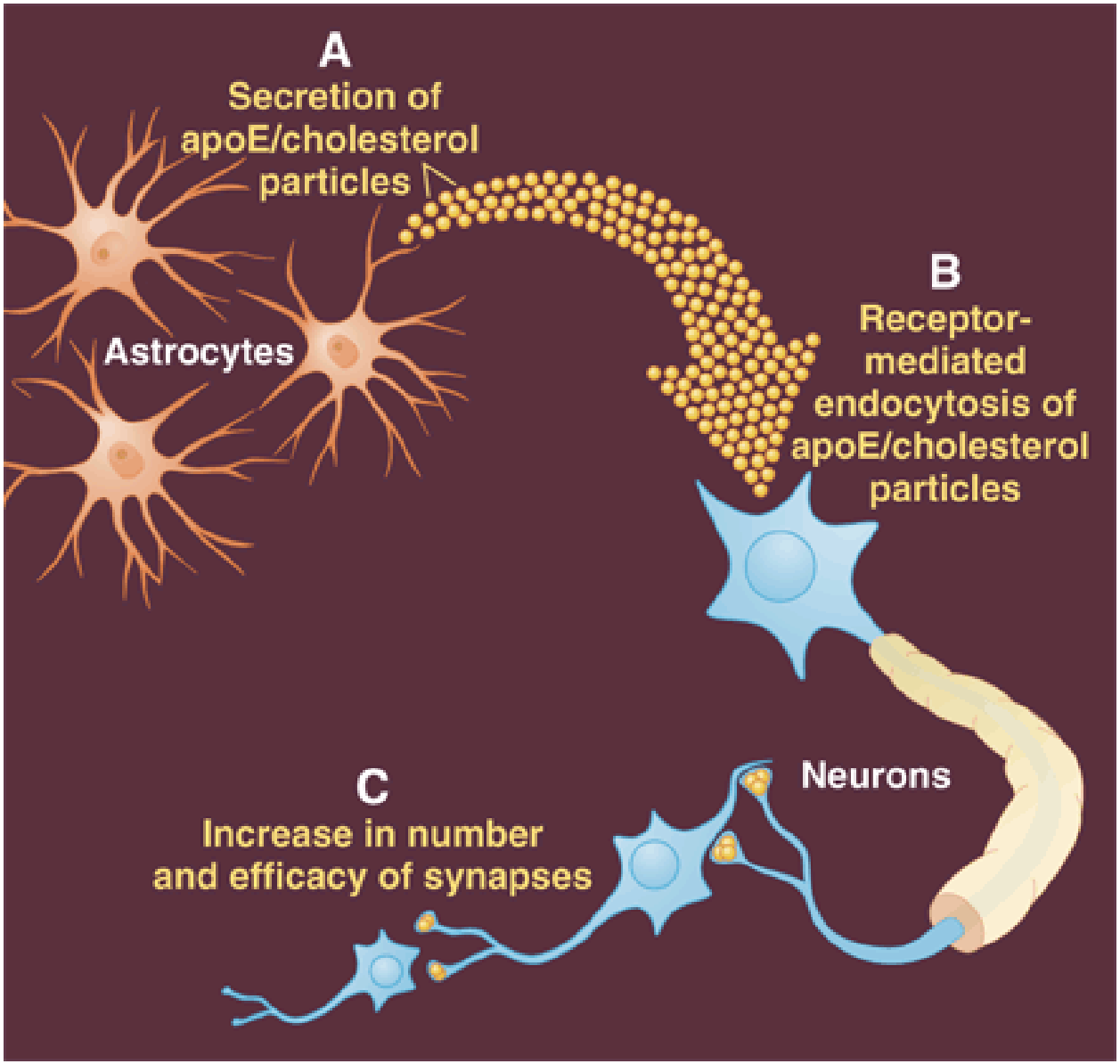
Shown is the entire amino acid sequence of PS1 (blue circles) and a portion of the COOH-terminal sequence of APP (green circles). Mutations in each molecule known to cause familial AD are depicted in red. The principal sites at which the beta, alfa, gamma and epsilon protease cleavages of APP occur are indicated by small scissors (89-91). The two amino acid residues between which the principal endoproteolytic cleavage of PS1 by a presenilinase takes place are shown in dark blue. The two intramembranous aspartate residues in PS1 that may represent the active site of *gamma -secretase are highlighted in yellow (*Hardy-Selkoe, 2002)

Hypothetical scheme to show the APP-metabolite-induced toxicity through the disruption of ionic balance



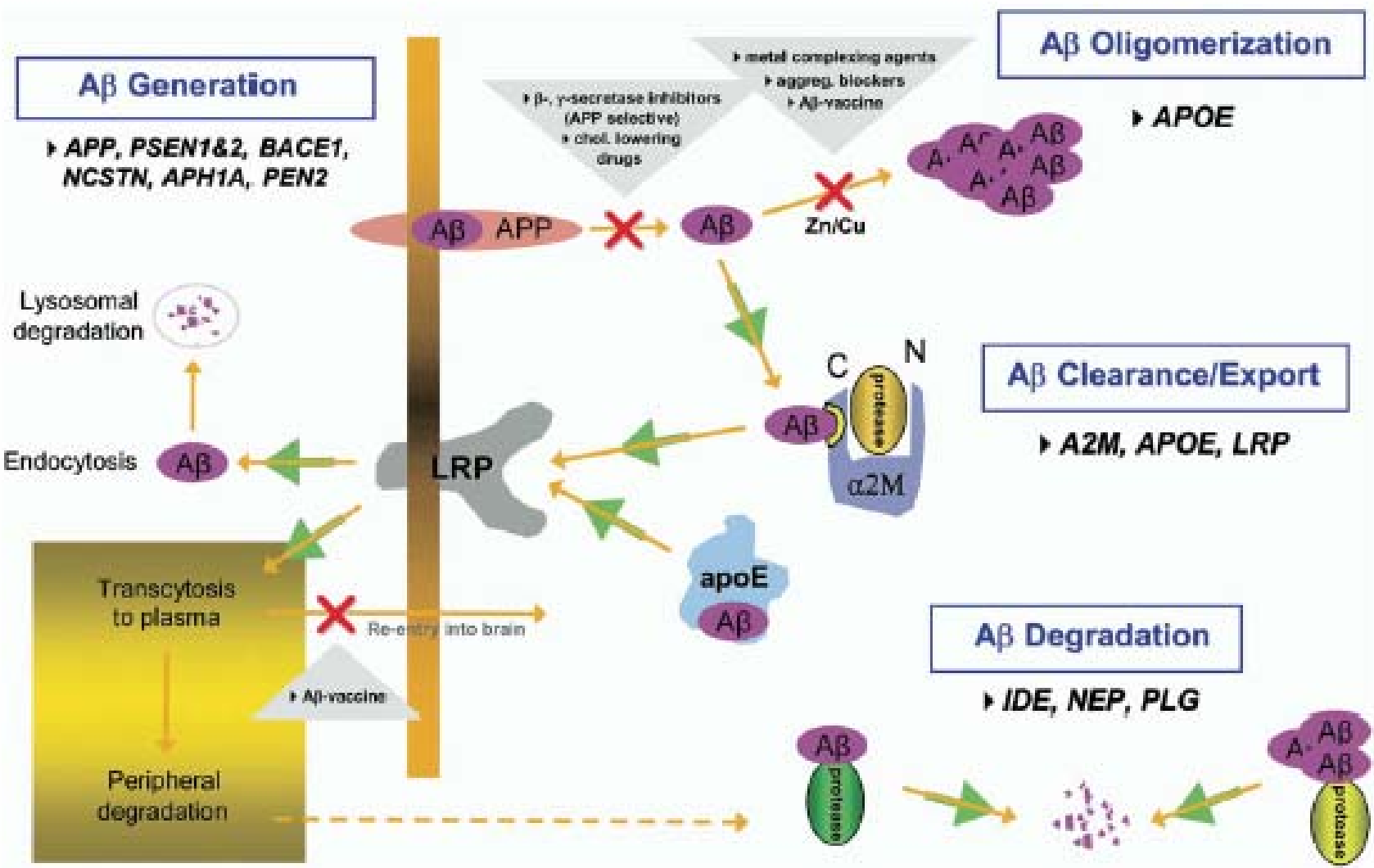
APP is processed through the Golgi apparatus and is either (1) metabolized to sAPP, CT and BA fragments and released from the cell or (2) transported to and incorporated into the membrane as full-length APP. (3) APP might be cleaved to release sAPP or (4) might be transported to the endosomes or lysosomes. Intracellular CT fragments and BA might (5) form ion channels in the cell membrane or (6) puncture holes in Ca2+ stores. Both actions could result in ionic imbalance and cell damage (7-8), leading to cell death through apoptosis or necrosis. BA fragments released from the cell could modulate surrounding transportes (10), ionic pump or exchangers (11), receptors (12) ion channels (13) and form de novo ion channels (14). (Fraser et al).

The apoE/cholesterol metabolism story



cholesterol secreted by astrocytes bound to large lipoprotein particles containing **apoE**. These particles are internalized by neurons, leading increased cholesterol within neuronal membranes. Cholesterol is needed to activate signaling pathway that triggers synaptogenesis –either an apoE receptor pathway or another signaling pathway such as the sonic hedgehog, Wnt cascades. Alternatively, a sufficient amount of cholesterol itself might be needed to support the structural demands of synaptogenesis (Science, 294,1296, 2001).

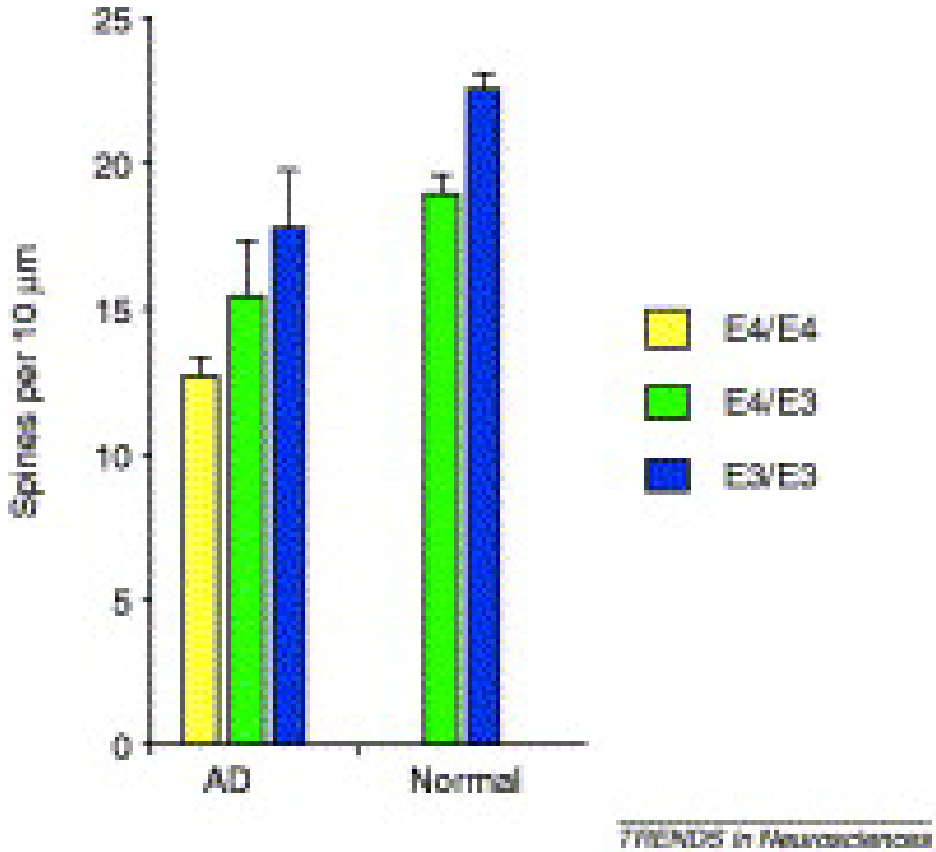
Genes influencing beta-amyloid life cycle with some therapeutic interventions



(Tanzi and Bertram, 2005)

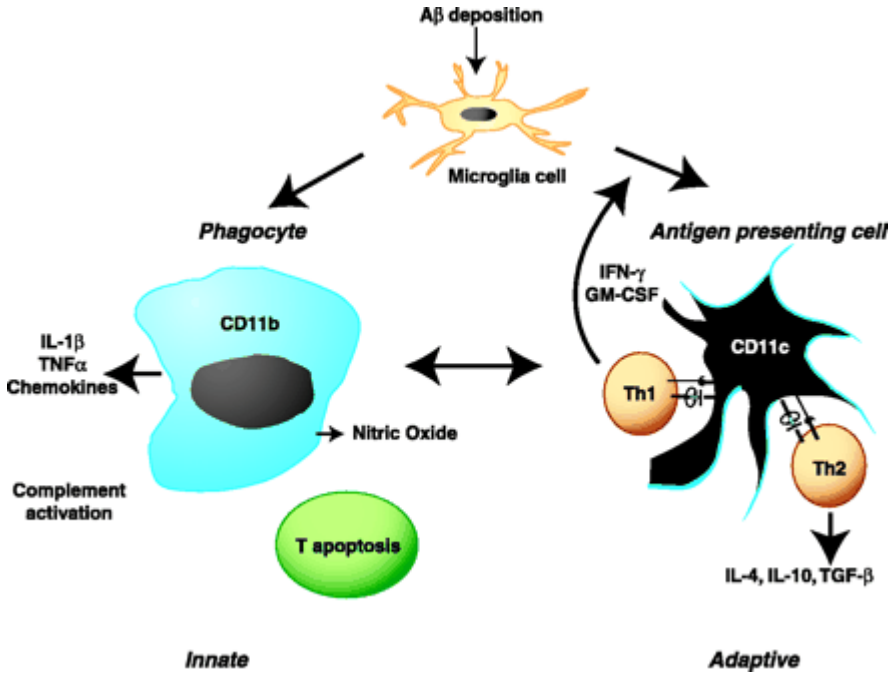
Green arrows indicate steps in the pathway that might be potentiated as a means for preventing accumulation of cerebral BA, while red crosses indicate potential inhibition points

ApoE alleles modulate normal and pathological aging



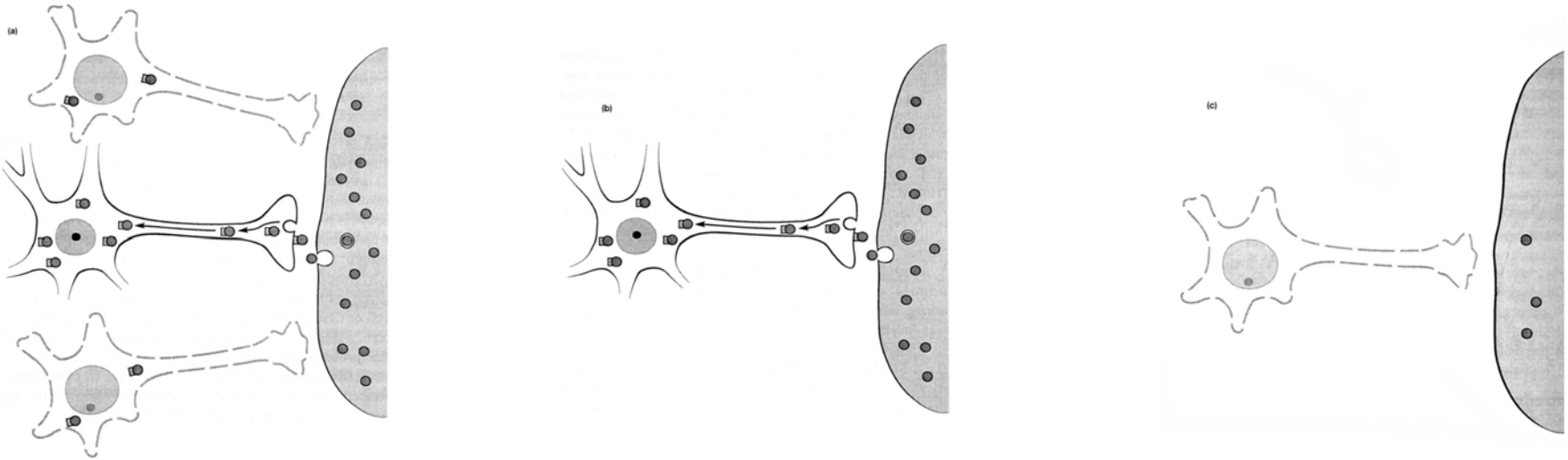
In healthy, non-demented elederly brains, ApoE4 carriers (E4/E3) have 16% fewer dendritic spines in hippocampal dentate granule neurons than ApoE3 homozygotes (E3/E3). In AD, the effect of ApoE4 shows an allelle-dose response: E4/E4 carriers display a 28% reduction in spine density. This effect might originate in midlife because tarnsgenic Apo4 mice at 1 year of age have fewer dendritic spines than weanlings (Ji et al., 2003)

Microglia activation and inflammatory molecules in Alzheimer's diseases



Microglia are bone marrow–derived cells that acquire ramified morphology in the intact CNS. In response to Aß deposition in AD, microglial cells are activated and differentiate into phagocytic cells (CD11b+) (**left**), which induce a proinflammatory environment and secrete IL-1ß, TNF- , NO, free radicals, chemokines, and activate complement. The NO secreted by CD11b+ cells may enhance T cell apoptosis in the CNS. A second pathway for microglial cells is to differentiate into antigen presenting cell [APCs] (**right**), which are induced in the presence of GM-CSF and/or IFN- secreted by microglia, astrocytes, or other immune cells (T cells, macrophages) that infiltrate the CNS. As a result, microglia cells differentiate to dendritic-like cells that then may function as APCs for both TH1 and TH2 cells. These cells also may migrate from the CNS to secondary lymph nodes and induce T cell activation. In AD, this pathway could suppress the toxic innate immune response and can be enhanced by TH2 immunization (Monsonego and Weiner, 2003).

TROPHIC FACTORS



Hipp. pyramidal n: BDNF, NGF, IGF, bFGF

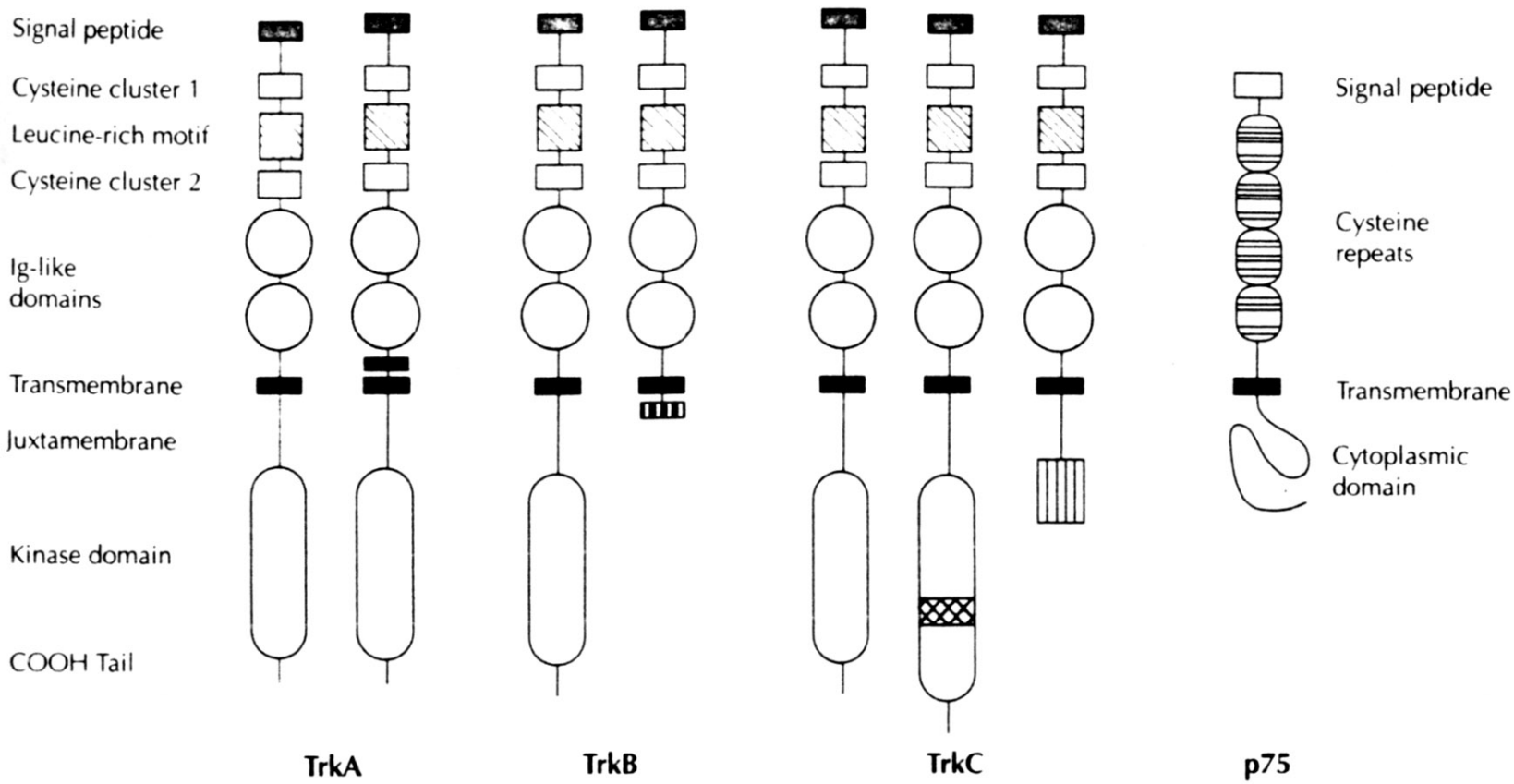
BFC: NGF, BDNF,

Striatal medium sized spiny: NGF, BDNF

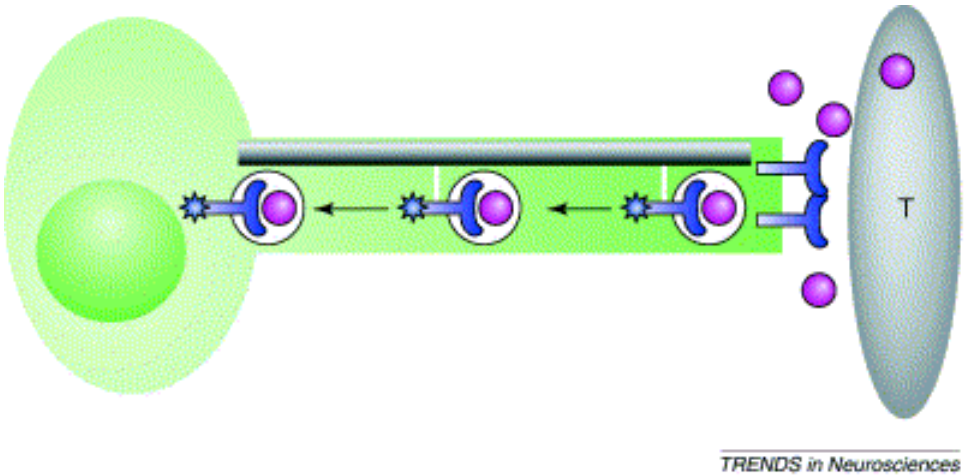
SN dopaminergic n: GDNF, BDNF

Motor neurons: IGF1, BDNF

Composition of receptors for various trophic factors

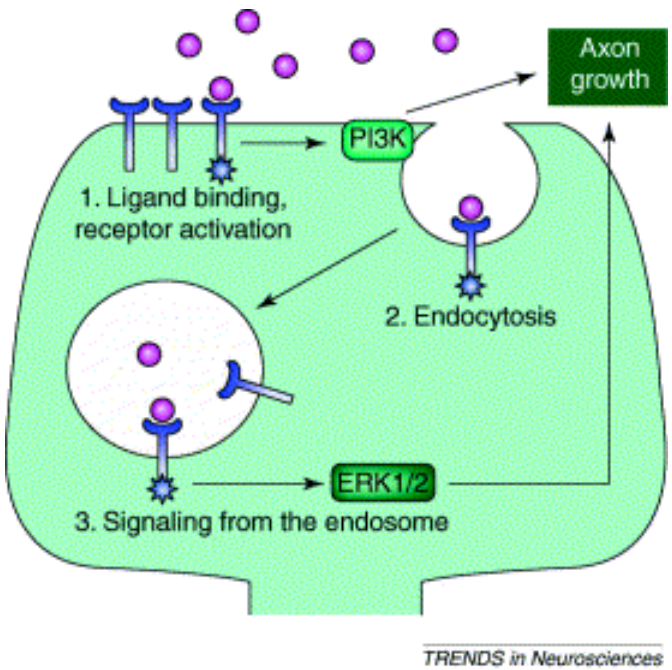


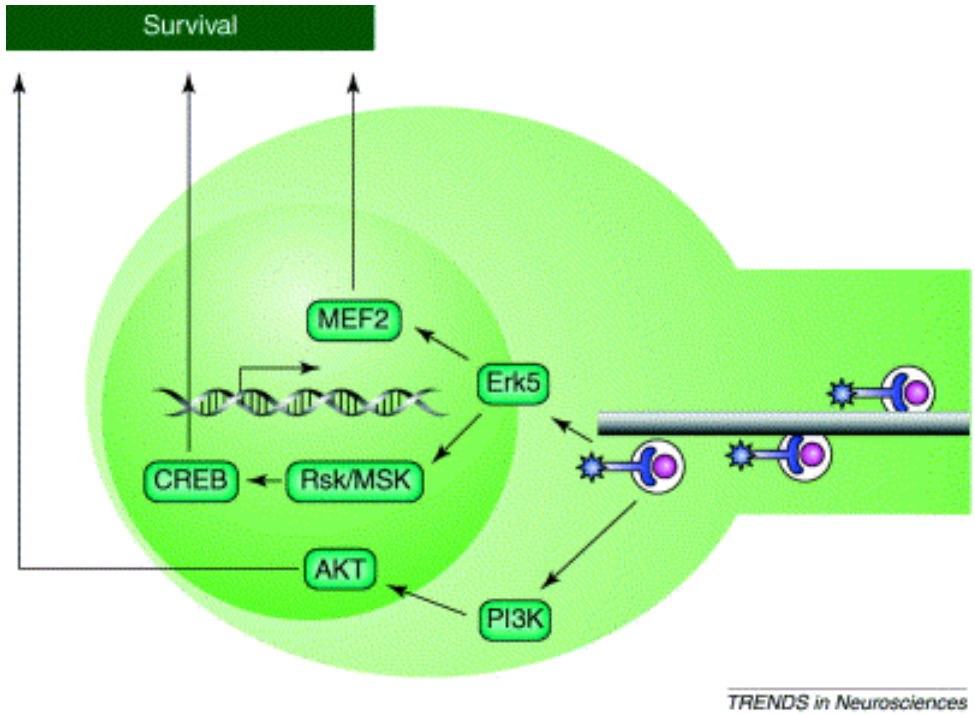
SIGNALING BY TROPHIC FACTORS



Signaling endosomes mediate a retrograde neurotrophic signal. Neurotrophins (purple spheres) released by target tissues (T) bind to and activate Trks (blue) at the nerve terminal. Activated Trks (starred) undergo endocytosis to form signaling endosomes (white circles). Dynein (white bars) transports Trk-containing signaling endosomes retrogradely along microtubules to the cell body. Activated Trks initiate signaling throughout the transport process, both in the axons and at the cell body.

SIGNALING AT THE AXON AND THE CELL BODY

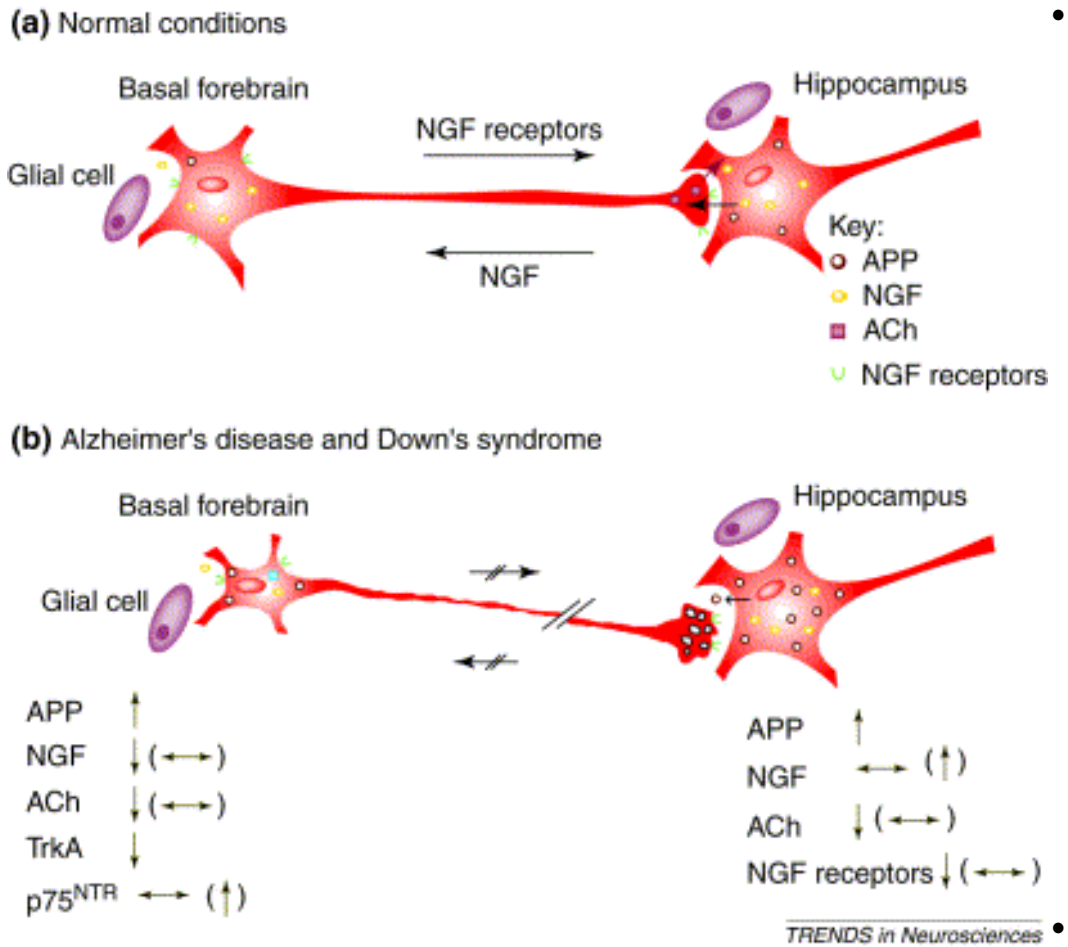




Local signaling within the axon. Neurotrophin (purple spheres) binds to Trks (blue) at the nerve terminal. Local activation of the PI3 kinase cascade promotes both axon outgrowth and receptor endocytosis. Activated endosomal Trks within the terminal and axon might be primarily responsible for activating the Erk1/2 pathway, which also contributes to axon growth.

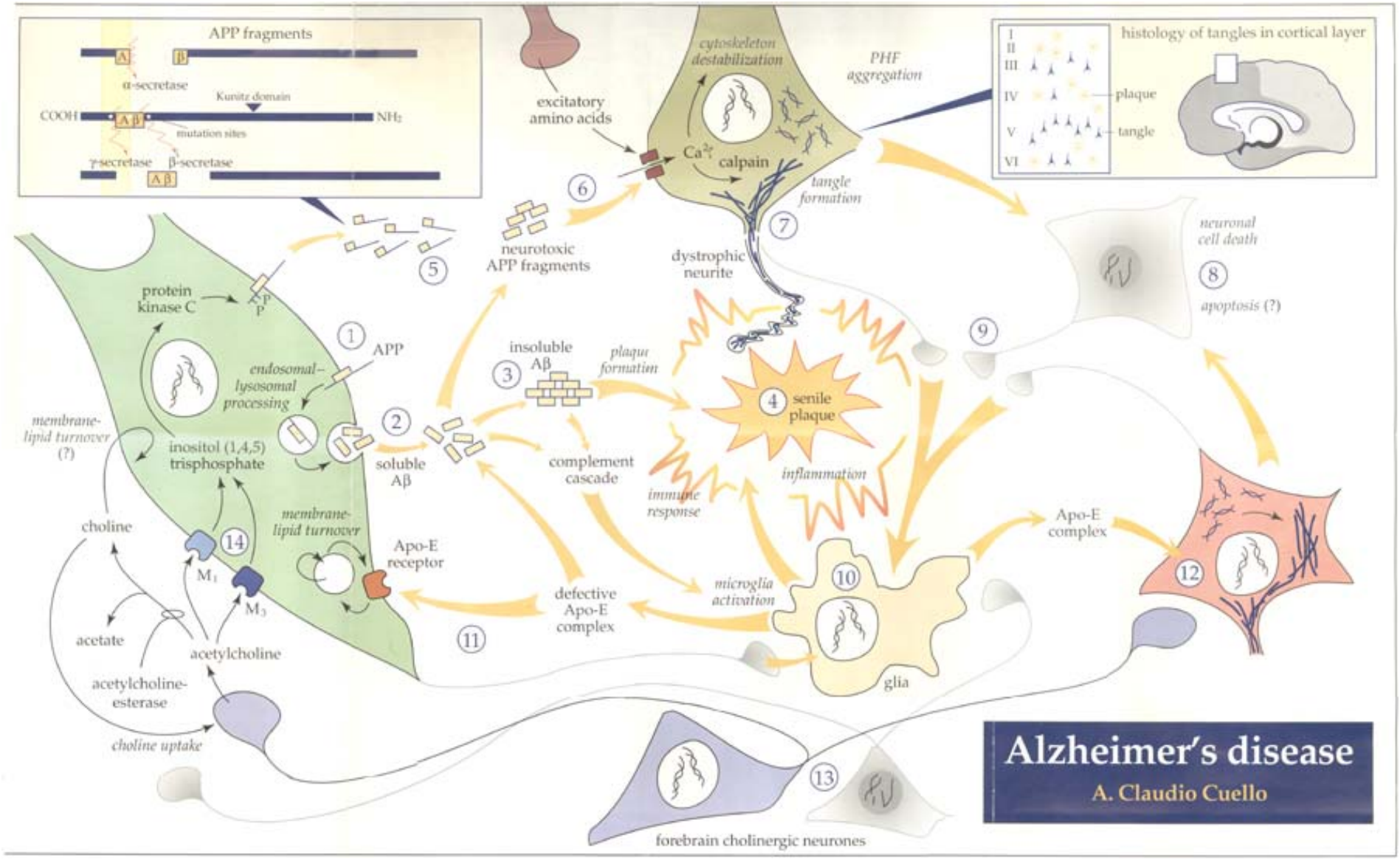
Signaling at the cell body. As retrogradely transported Trk-containing endosomes reach the cell body, they activate at least two signaling pathways, both of which promote survival. Activation of PI3 kinase (PI3K) prevents apoptosis through stimulation of the anti-apoptotic kinase AKT. Trk-mediated Erk5 activation at the cell body results in activation of the transcription factors CREB (via activation of the intermediate kinase Rsk/MSK) and MEF2 to support survival (Heersen and Segal, 2002)

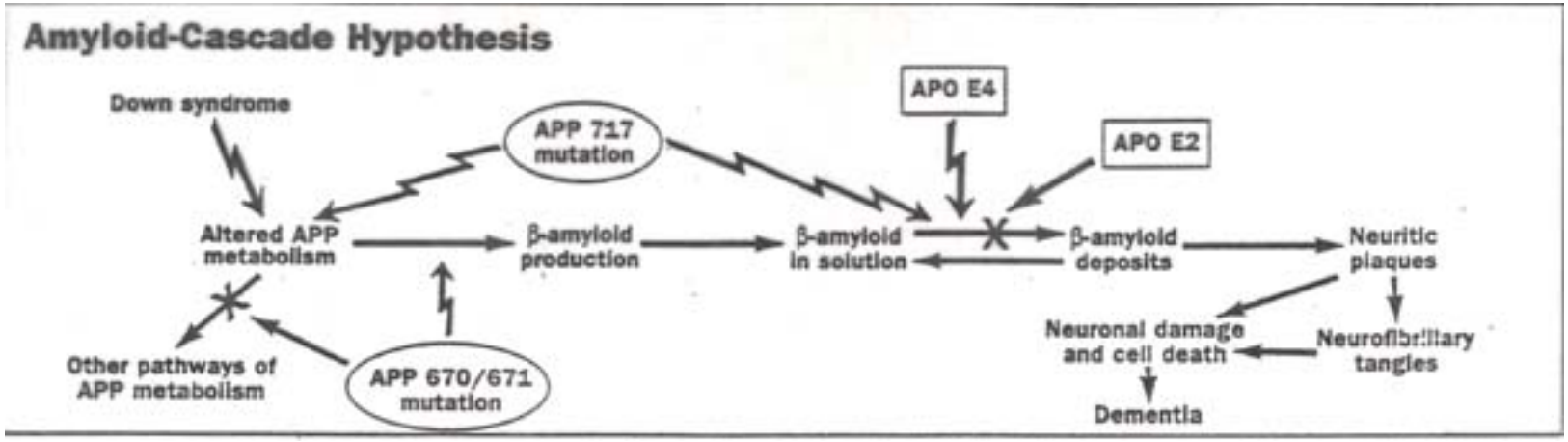
NGF, TrkA, p75 in normal condition (a) and in AD (b)



- In cholinergic neurons of the BF in individuals with AD, ChAT immunoreactivity, cell size and number, and NGF and TrkA levels are decreased. In the hippocampus of individuals with AD, ChAT levels and ACh-mediated signaling are reduced but NGF levels are increased or unchanged. In the hippocampus and BF of individuals with AD, APP expression and A aggregate levels are increased, whereas secreted (trophic) sAPPs are decreased. There are also degenerating terminals in the hippocampus. These altered levels indicate that NGF retrograde transport or NGF binding to trkA receptors, or both, are reduced in the individuals with AD, which results in inappropriate trophic support of the cholinergic system during degenerative disease
- A: amyloid ; ACh, acetylcholine; AD, Alzheimer's disease; APP, amyloid precursor protein; ChAT, choline acetyl transferase; DS, Down's syndrome; NGF, nerve growth factor; sAPP, soluble APP; TrkA, tyrosine receptor kinase A.
(Isacson et al., 2002)

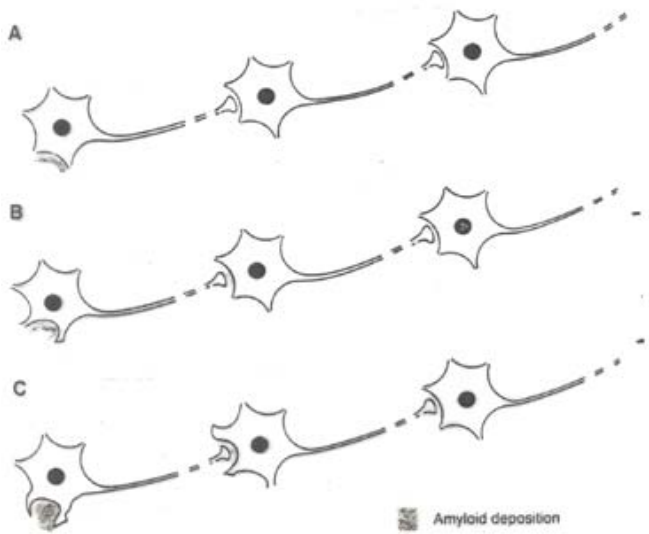
MECHANISM OF NEURODEGENERATION IN AD: A SUMMARY



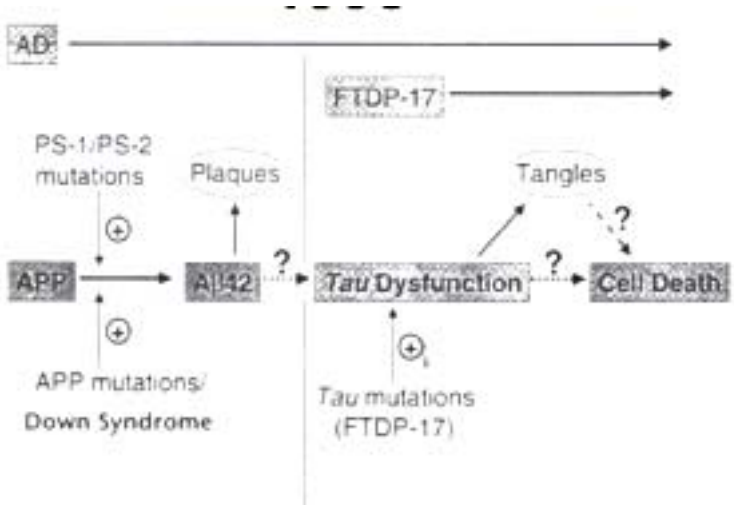


1992

In the amyloid-cascade hypothesis, the deposition of B-amyloid protein in brain parenchyma is the pivotal event. B-amyloid deposition can be triggered by mutations in the gene encoding the APP or by binding to apoE4. B-amyloid deposition then leads to the formation of neuritic plaques, NFts and nerve cell death (Hardy, 1992).

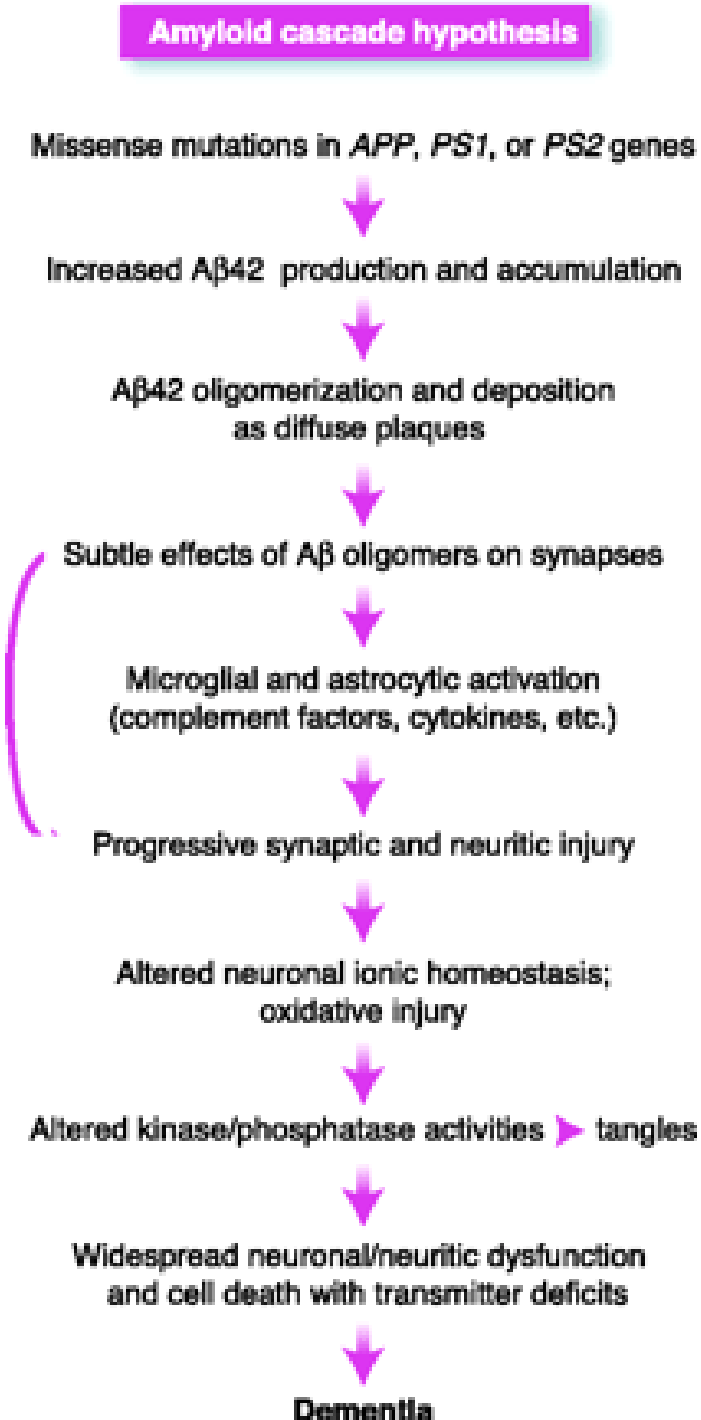


A possible mechanism fro the spread of focal B-amyloid deposition in AD (Hardy, 1992)



1998

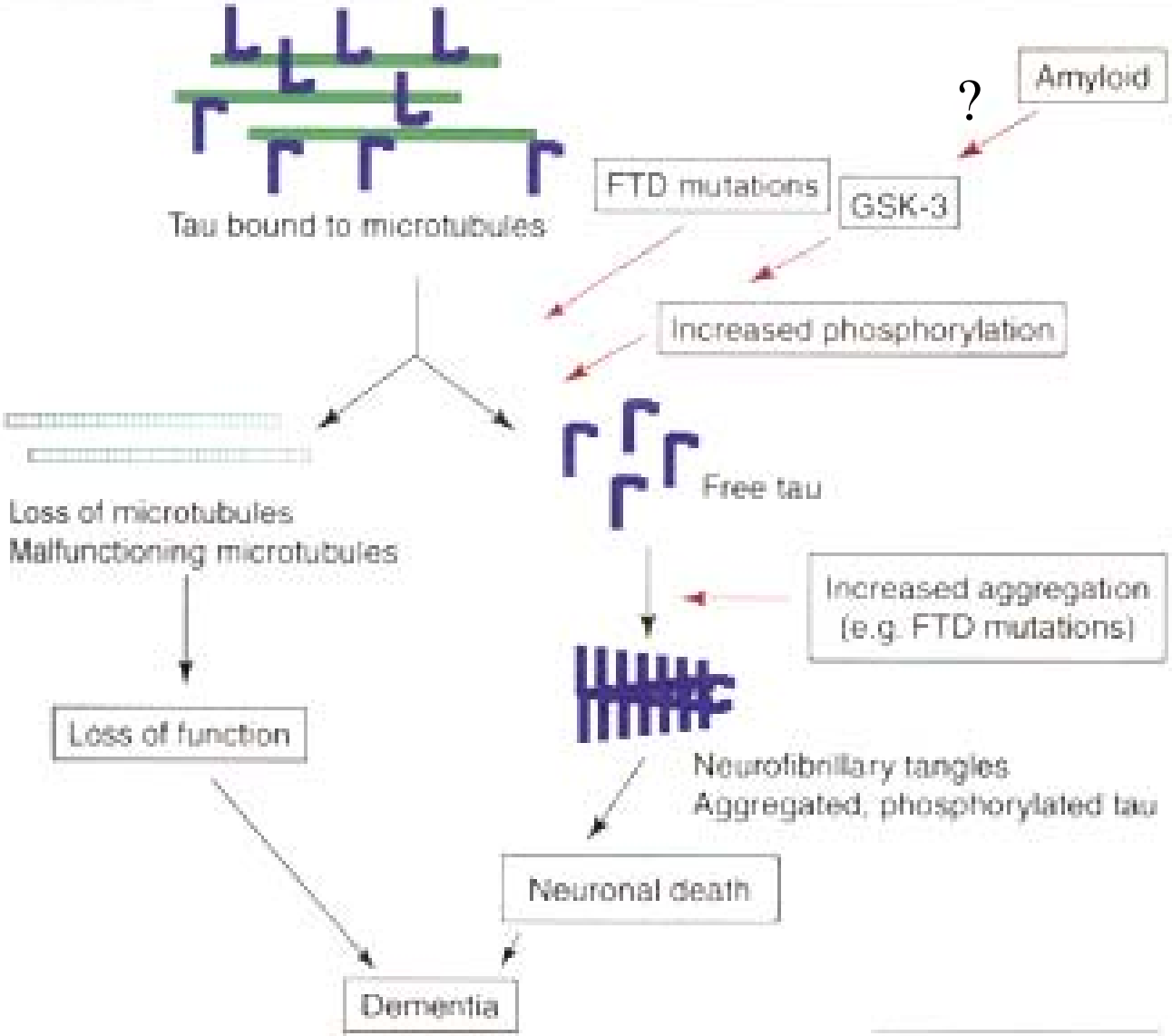
The relationships between BA and tau and between AD and FTDP-17 (front-temporal dementia). The link between BA42 overproduction and tau dysfunction is presently uncertain and represented by a ? mark. In addition, it is unclear whether tau dysfunction leads directly to cell death or if the formation of NFTs are a necessary intermediate (Hardy, 1998).



2002

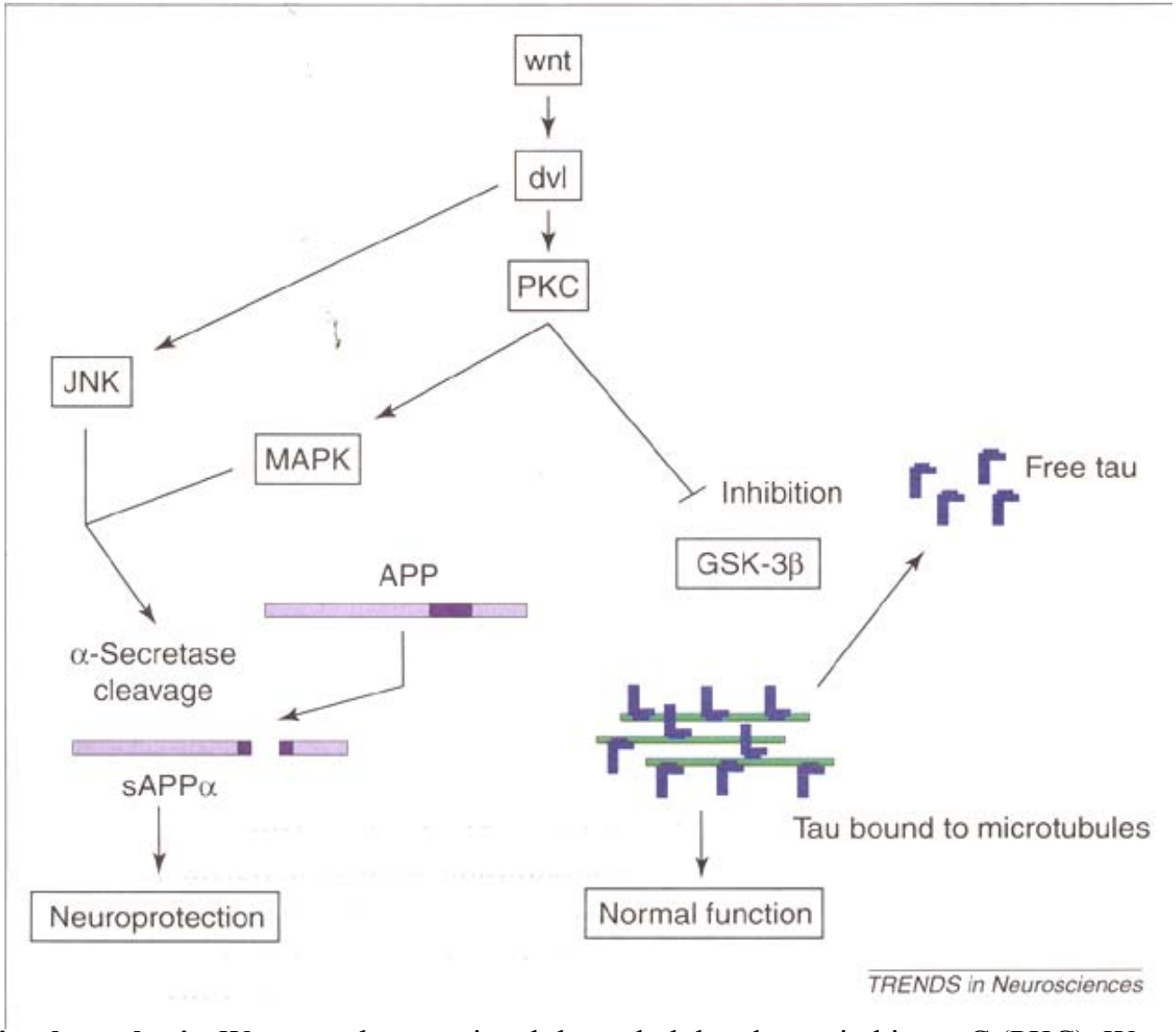
The curved violet arrow indicates that AB oligomers may directly injure the synapses and neurites of neurons, in addition to activating microglia and astrocytes.

POSSIBLE RELATIONSHIP BETWEEN AMYLOID AND TAU PATHOLOGY

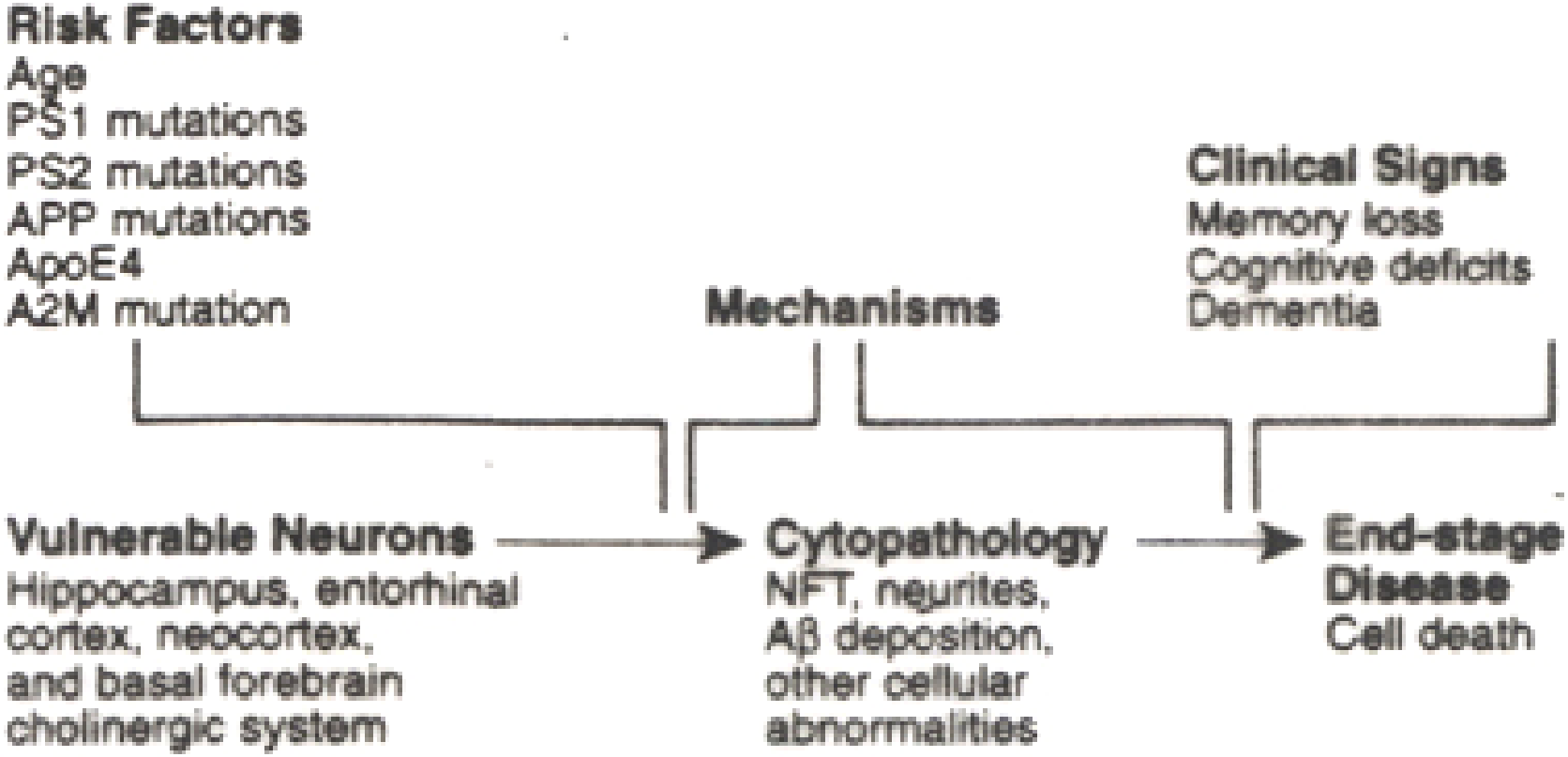


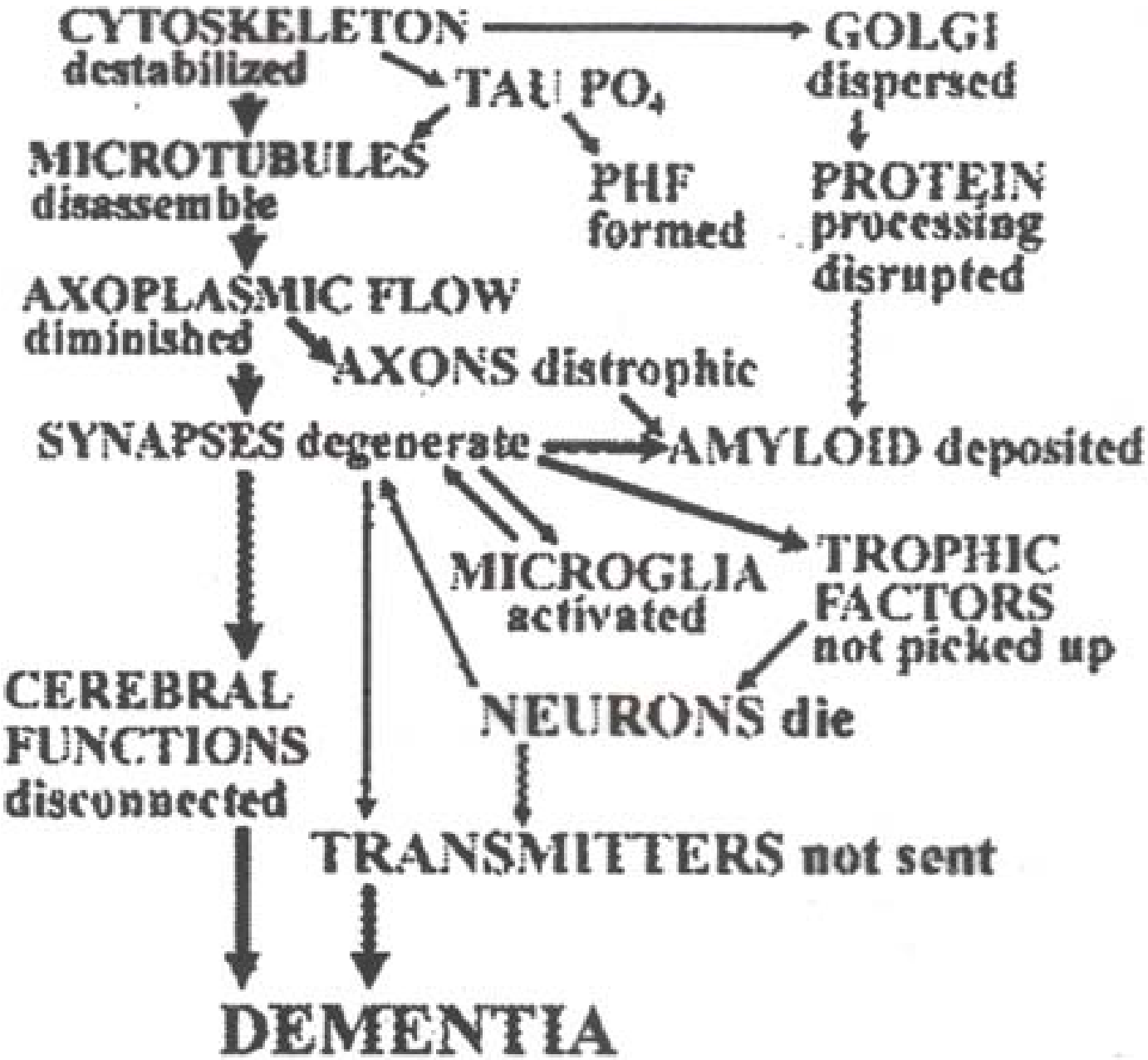
The tau and tangle hypothesis. Tau binding to microtubules is disrupted by phosphorylation, directly by mutations that alter isoform expression. Decreased tau binding to microtubules might result in increased free tau which, under the appropriate conditions will self-aggregate to form insoluble paired helical filaments. ? Mark indicates the putative role of **amyloid induced increased GSK-3 (glycogen synthethase kinase**) activity that leads to increased tau phosphorylation (From Mudher and Lovestone, 2002)

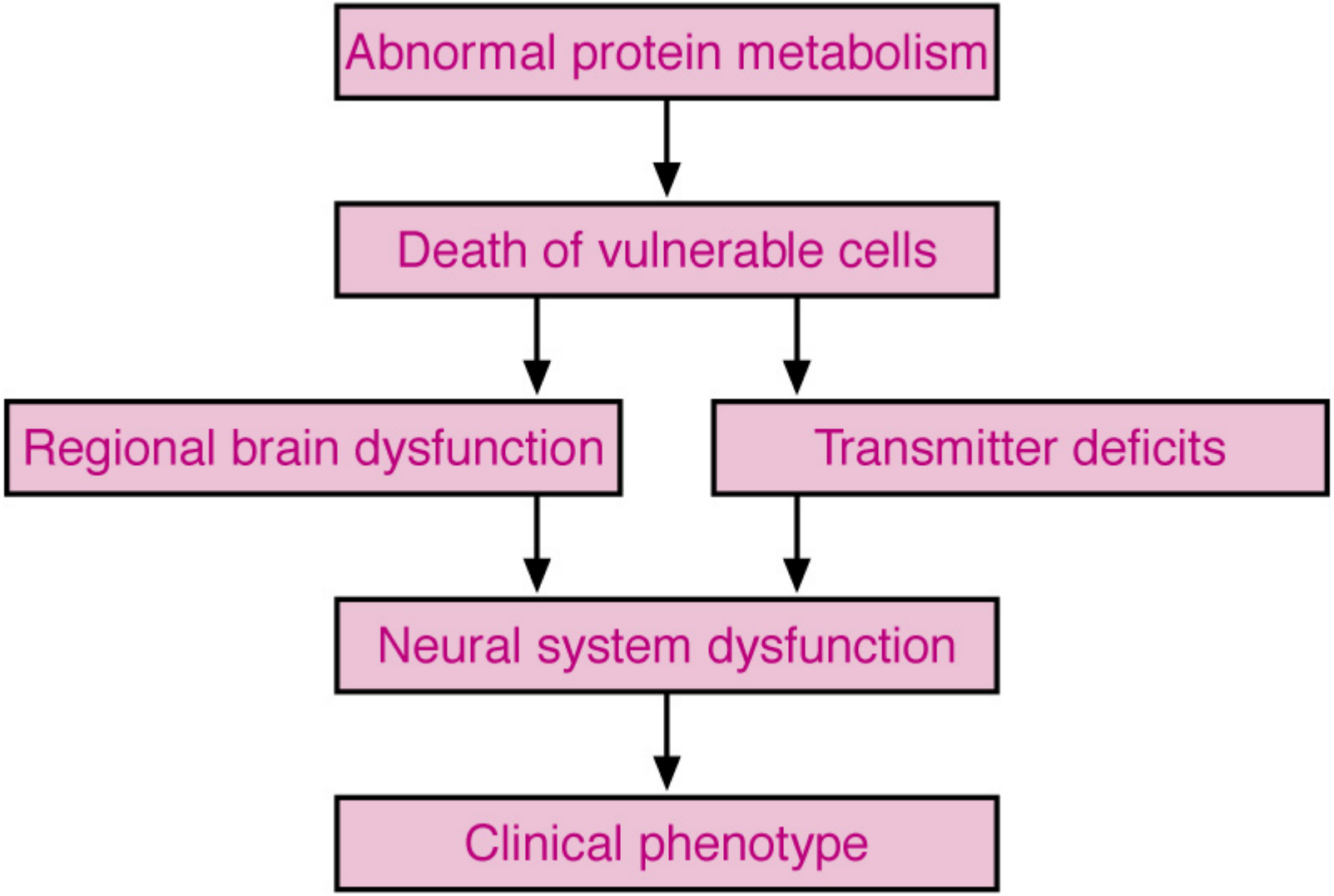
POSSIBLE RELATIONSHIP BETWEEN AMYLOID AND TAU PATHOLOGY



The wnt signalling hypothesis. Wnt transduces a signal through dvl and protein kinase C (PKC). Wnt and dvl increase secreted sAPP and inhibit glycogen synthase kinase 3 (GSK-3B) phosphorylation of tau. Both processes might be normal. Loss of wnt signal would result in decreased sAPP, increased tau phosphorylation and both pathological hallmarks (plaques and tangles) of AD. JNK, c-Jun N-terminal kinase; MAPK, mitogen-activated protein kinase (Mudher and Lovestone, 2002)


Risk Factors
Age
PS1 mutations
PS2 mutations
APP mutations
ApoE4
A2M mutation
Clinical Signs
Memory loss
Cognitive deficits
Dementia
Mechanisms
Vulnerable Neurons
Hippocampus, entorhinal cortex, neocortex, and basal forebrain cholinergic system
Cytopathology
NFT, neurites, Aβ deposition, other cellular abnormalities
End-stage Disease
Cell death

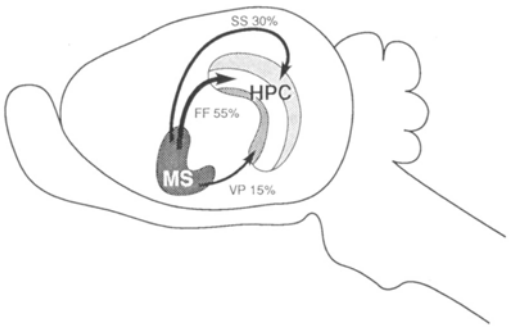

CYTOSKELETON
destabilized
TAU PO4
GOLGI
dispersed
MICROTUBULES
disassemble
PHF
formed
PROTEIN
processing
disrupted
AXOPLASMIC FLOW
diminished
AXONS distrophic
SYNAPSES degenerate
AMYLOID deposited
MICROGLIA
activated
TROPHIC
FACTORS
not picked up
CEREBRAL
FUNCTIONS
disconnected
NEURONS die
TRANSMITTERS not sent
DEMENTIA



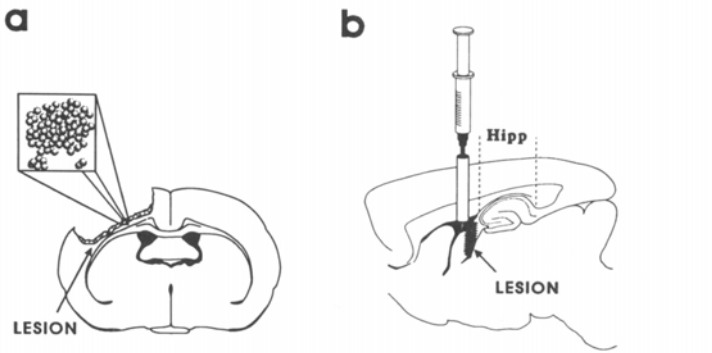
Hierarchical model of behavior applied to dementia disorders. Changes in protein metabolism lead to cell death and transmitter deficits in neural systems that produce clinical phenotypes and lead to social and occupational disability (from Cummings, 2004).

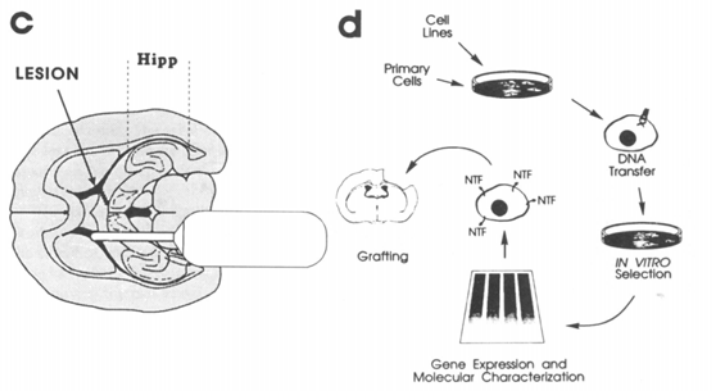
MODELS OF AD

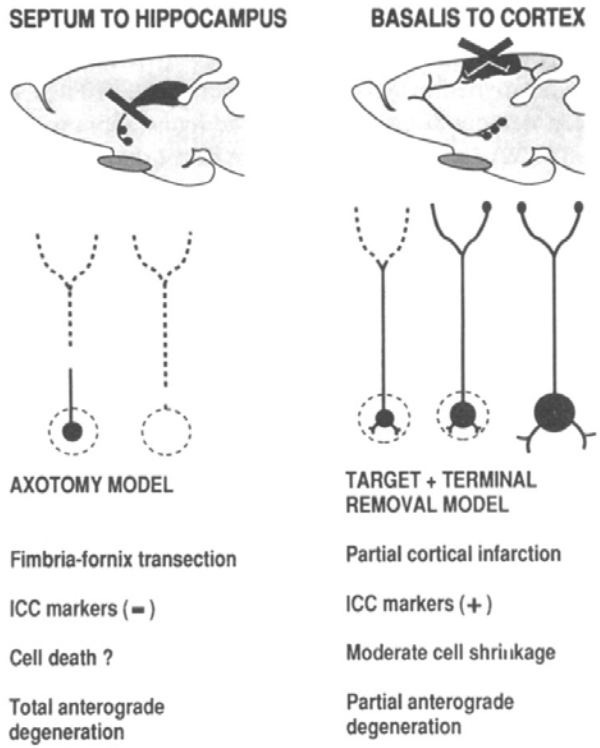
EXPERIMENTAL AD MODELS USING TROPHIC FACTORS



Septohippocampal cholinergic pathway







Effect of axotomy or target removal on the survival of BF cholinergic neurons (Gage)

Methods to deliver trophic factors (Cuello)

MOUSE MODELS of ALZHEIMERS DISEASE

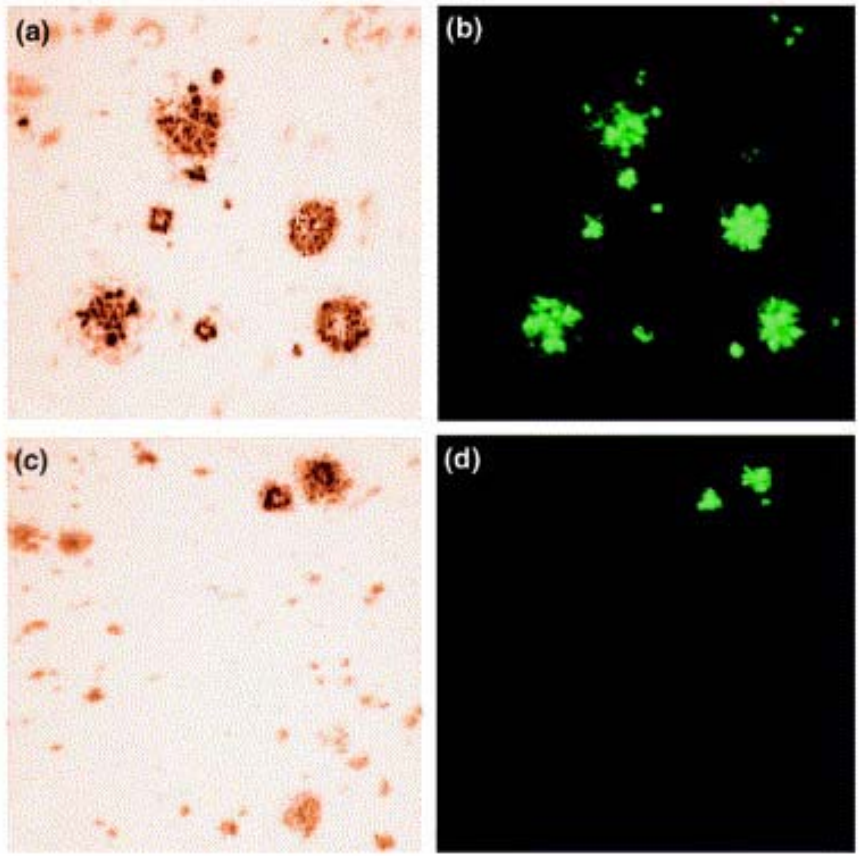
PDAPP: First mutant APP transgenic model with robust plaque pathology. Mice express a human *APP* cDNA with the Indiana mutation (APPV717F). Plaque pathology begins between 6–9 months in hemizygous PDAPP mice. There is synapse loss but no overt cell loss and no NFT pathology is observed. This model has been used widely in vaccination therapy strategies.

Tg2576: Mice express mutant APPSWE under control of the hamster prion promoter. Plaque pathology is observed from 9 months of age. These mice have cognitive deficits but no cell loss or NFT pathology. It is one of the most widely used transgenic models.

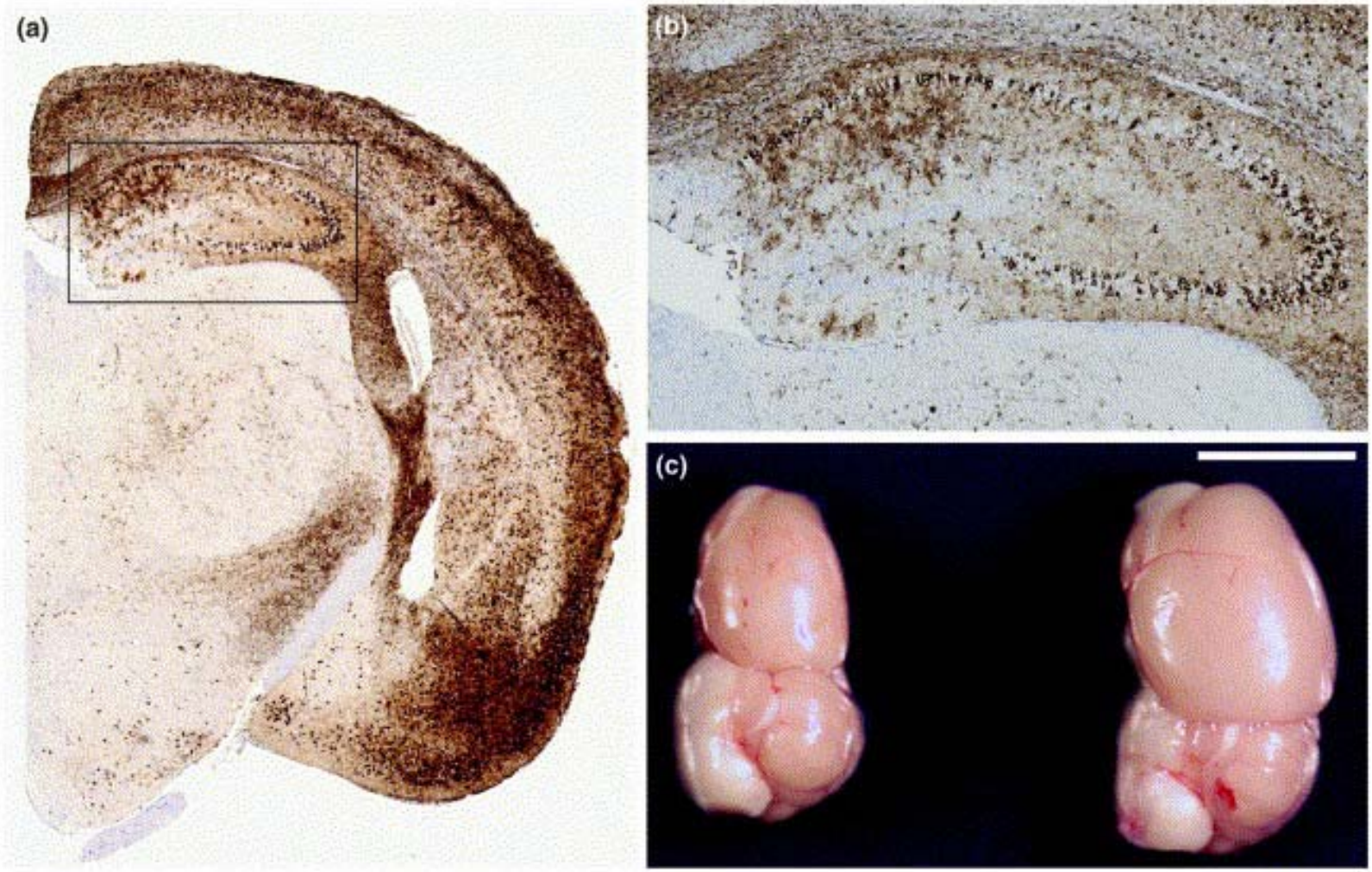
rTg4510: Inducible *MAPT* transgenic mice using the TET-off system. Abnormal MAPT pathology occurs from one month of age. Mice have progressive NFT pathology and severe cell loss. Cognitive deficits are evident from 2.5 months of age. Turning off the transgene improves cognitive performance but NFT pathology worsens.

PSEN1M146V or PSEN1M146L (lines 6.2 and 8.9, respectively): These models were the first demonstration *in vivo* that mutant *PSEN1* selectively elevates Aβ42. No overt plaque pathology is observed .

3×TgAD: Triple transgenic model expressing mutant APPSWE, MAPTP301L on a PSEN1M146V 'knock-in' background (PSEN1-KI). Mice develop plaques from 6 months and MAPT pathology from the time they are 12 months old, strengthening the hypothesis that APP or Aβ can directly influence neurofibrillary pathology.

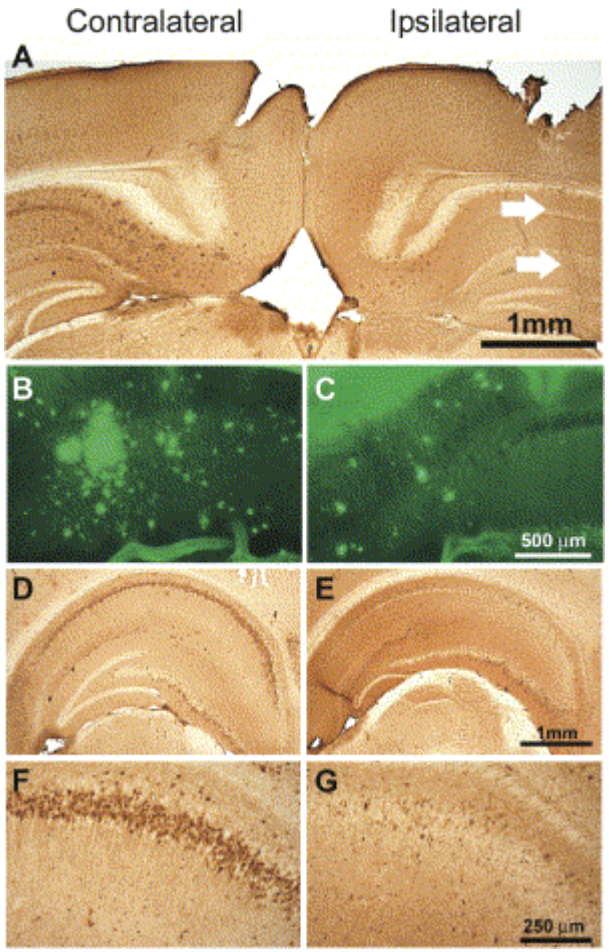


Mutant *PSEN1* accelerates amyloid deposition in mutant APP (Tg2576) mice. Representative sections from the entorhinal cortex of 17-month-old aged-matched PSAPP mice, expressing **(a)** mutant *PSEN1* and **(b)** mutant *APP* transgenes, and Tg2576 transgenic mice expressing **(c,d)** mutant *APP*, immunostained with a (a,c) pan- Aβ antibody or stained with (b,d) Thio-S Tg2576 mice develop plaque pathology from 9-12 months of age. (McGowan et al.,2006)



Neurofibrillary pathology is associated with neuronal loss and brain atrophy in mutant MAPT transgenic mice (rTg4510). At 9 months of age there is widespread neurofibrillary pathology in many forebrain structures, including the cortex, hippocampus, striatum and hypothalamus. These sections were immunostained with the MAPT antibody, Ab39, which specifically labels mature NFT, and were counterstained with hematoxylin. rTg4510 mice have significant forebrain atrophy compared with non-transgenic age-matched control littermates, as shown in **(c)**, and have significant decreases in whole brain weight from an early age (McGowan et al., in press).

Intrahippocampal administartion of Anti-BA antibodies clears both intracellular and extracellular BA aggregates and tau pathology, provided that intervention occurs early in the disease course



The anti-A monoclonal antibody, 1560, was administered via intra-hippocampal injections into 12-month-old hemizygous 3xTg-AD
mice.
(A) Low-magnification view of the hippocampus/neocortex the contralateral (uninjected) and ipsilateral (injected) sides. Arrows on the right side denote the cannula track. Note the reduction in the number of A immunoreactive deposits in the ipsilateral side of injection.

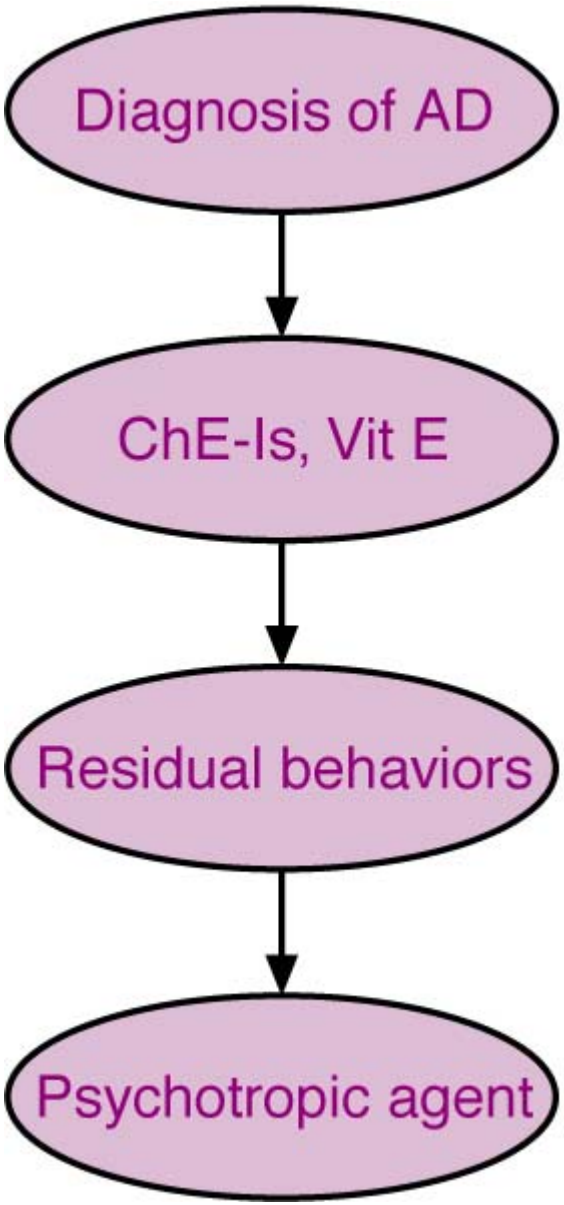
Oddo et al., 2004

Potential Treatments for Alzheimer's Disease

Type	Examples	Action	FDA Status
Cholinesterase Inhibitors	Tacrine, donepezil, besipirdine, ENA-713, eptastigmine, metrifonate, physostigmine	Inhibit enzyme that breaks down acetylcholine	Tacrine and donepezil approved; several others in Phase III
Cholinergic Agonists	ABT-418, AF102B, arecoline, nicotine, RS-86, SB 202026, xanomeline	Artificially stimulate acetylcholine receptors	Several in Phase III
Calcium Channel Blockers	Nimodipine, sabeluzole	Maintain cellular calcium levels	Several in Phase III
Anti-Inflammatory Drugs	Aspirin, colchicine, hydroxychloroquine, ibuprofen, indomethacin, prednisone	Counteract inflammatory responses	Approved for other conditions
Estrogen	Estradiol	Promotes cell metabolism and survival	Approved for other conditions
Anti-Oxidants	Vitamin E, vitamin C, selegiline	Protect neurons from oxidative damage	Some approved for other conditions; some in Phase III
Ampakines	CX-516	Enhance response of neuronal receptors	Clinical trials to begin soon
Neuropeptides	TRH, neuropeptide Y, somatostatin	Support memory and neuronal communication	Not yet in clinical trials
Trophic Factors	NGF, GM1, BDNF	Help neurons grow and survive	Not yet in clinical trials

Potential Treatments of AD (cont.)

Kv1.1	Potassium channel disinactivators
Gamma-secretase inhibitor, LY411575	
Passive immunization with α-AB mAB	in PDAPP mouse model reverses memory deficits
Vaccination with AB peptide	APP+PS1 transgenic mouse
Statins (Simvastin)	Lower LDL, increases HDL
B-secretase inhibitor	

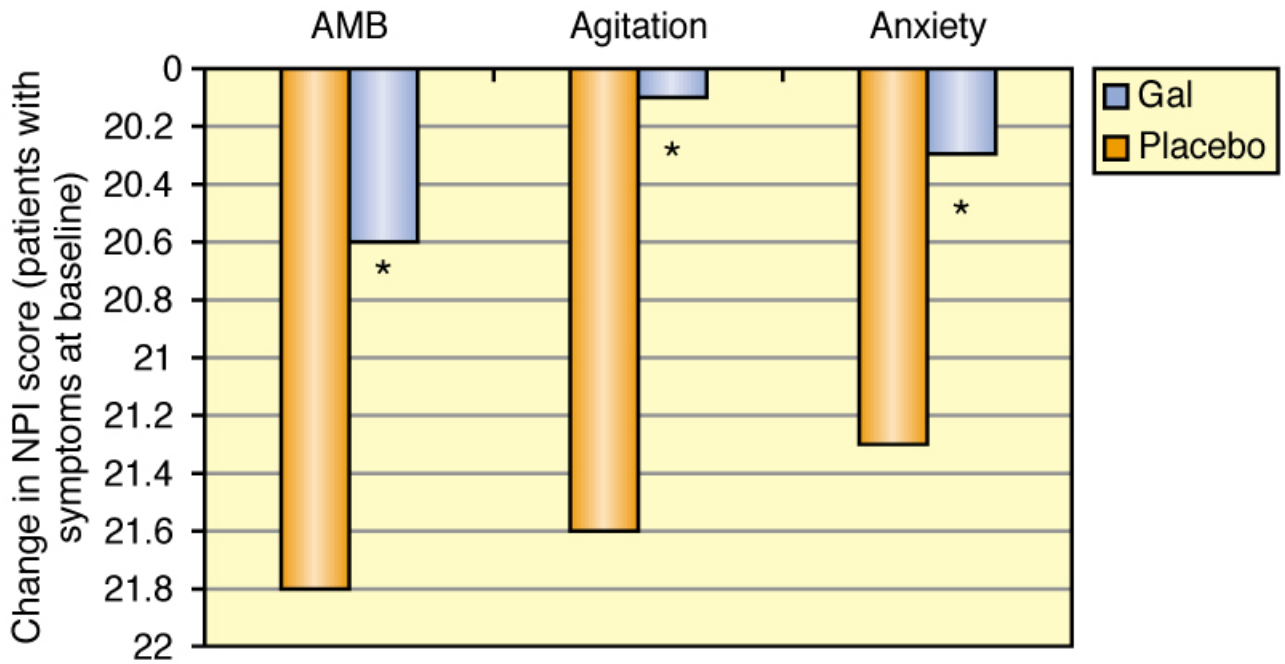


Treatment algorithm for pharmacologic management of patients with Alzheimer's disease (Cummings, 2004)

Cholinesterase inhibitors (ChE-Is,): tacrine, donepezil, galantamine, rivastigmine

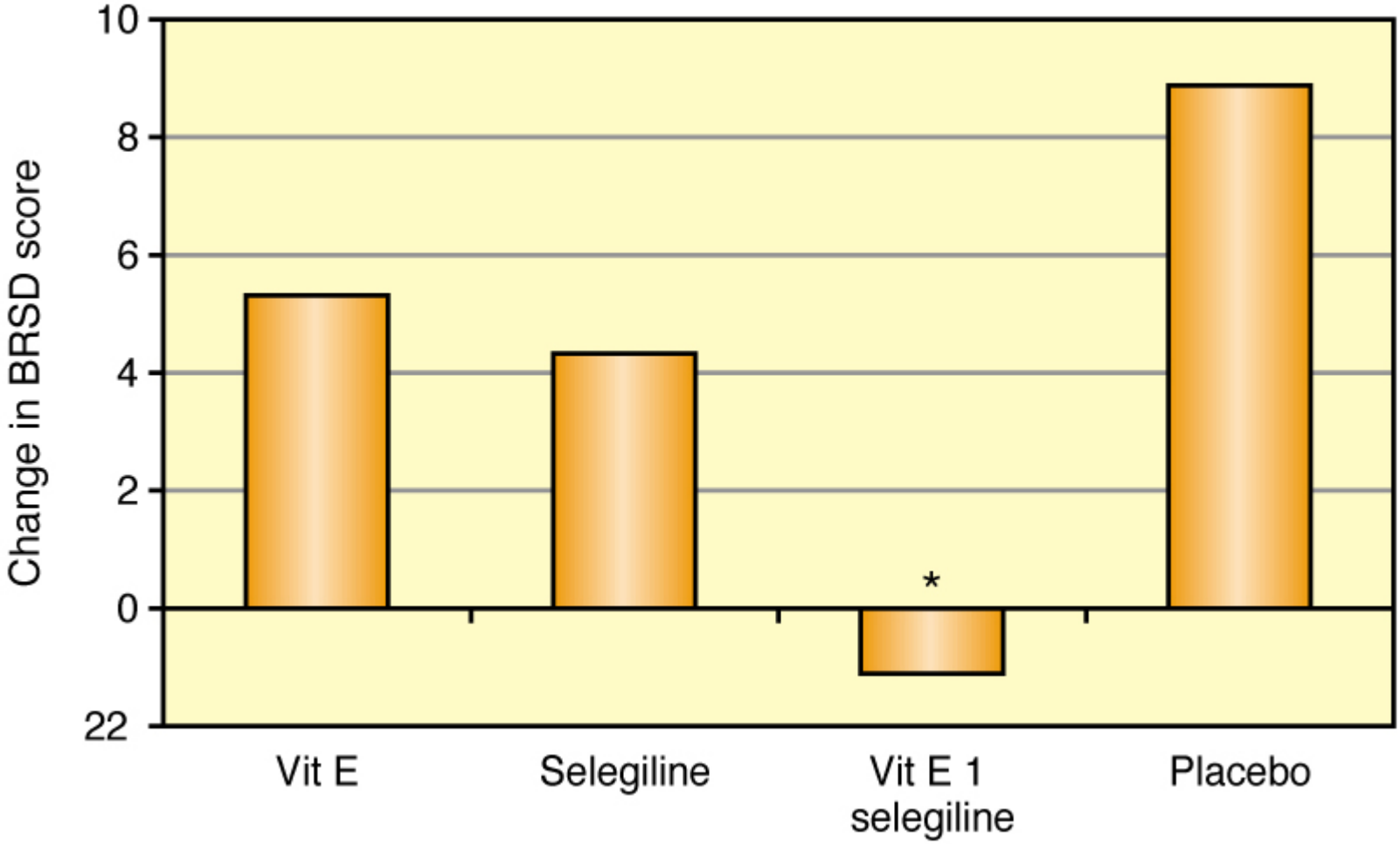
Psychosis is treated with atypical antipsychotics (olanzapine, risperidone), 5HT reauptake inhibitors, conventiona neuroleptics (haloperidol); anticonvulsans; benzodiazepines; psychostimulants

Cholinesterase inhibitor: galantamine



Galantamine reduced depression, anxiety, and agitation in patients exhibiting these symptoms (Cumings, 2004)

Neuroprotective treatment: Vit E and selegiline (MAO B inhibitor)



Score changes on the Behavior Rating Scale for Dementia (BRSD) following treatment with vitamin E, selegiline, vitamin E plus selegiline, or placebo (Tariot et al., 1995).