Dementia

慈濟神經內科 核心教材

(台中神經內科 冷敏謙 20220524修訂)

教材使用參考

本修訂教材共五十九張投影片，茲標示投影片用途，供教師與學生運用：

- **黑字**抬頭：為過去國考測驗內容

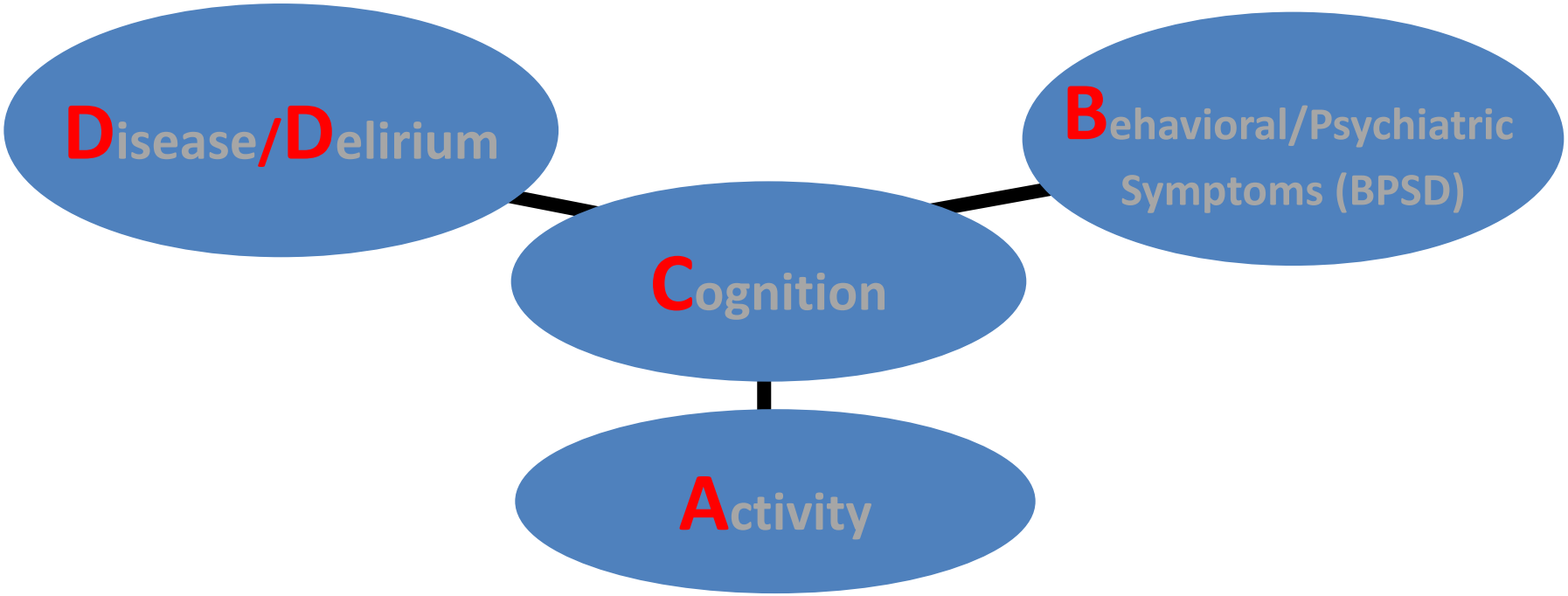
- 灰字抬頭：為臨床問診，衛教，測驗相關操作指引參考，內容多為中文，適合學生自行閱讀練習（P.7,10,21-23,25)共六張。

- 灰底抬頭：適合求知慾望強，想考高分的同學(P.43-46）共四張。

Outline

- Introduction – Definition/Diagnostic Criteria
  - Cardinal Cognitive Symptoms
  - Behavioral and Psychiatric of Dementia
- Disease Course and Epidemiology Report
- Diagnostic Repertoire – History, NE, and diagnostic tools
- Differential Diagnosis
- Specific topic I: Rapidly Progressive Dementia(RPD) (20220524新增)
- Therapeutic Strategies
- Specific topic II – Alzheimer's Disease (AD)
  - Vascular Cognitive Impairment (VCI)
  - Dementia with Lewy Bodies (DLB)

Definitions of Dementia



"A syndrome, usually of a chronic or progressive nature, in which there is deterioration in cognitive function beyond what might be expected from normal ageing." -WHO

Diagnostic Criteria of Dementia (1)
DSM-5 Criteria for Neurocognitive Disorders (NCD)

- Concerns of the individual/informant/clinician and evidence (standardized neuropsychological test or quantified clinical assessment) of substantial cognitive decline from a previous level of performance in ≥ 1 domain (s).
- The cognitive deficits are sufficient to*/don't & interfere with independence.
- Not exclusive in the context of delirium.
- The cognitive deficits are not primarily attributable to another mental disorder (e.g., major depressive disorder, schizophrenia).

*Major NCD: 2 SD below appropriate norm.

&Mild NCD: 1~2 SD below appropriate norm.

DSM-5 Cognitive Domains of NCD

- Complex attention
- Executive function
- Learning and memory
- Language
- Perceptual-motor function
- Social cognition

There are domain-specific cognitive tests for each domain.

Symptoms and Assessments for Specific Cognitive Domain

Cognitive domain	Symptoms or observations	Assessments
Complex attention	Multiple stimuli (TV, radio, conversation). Easy distraction. Difficulty in holding new information in mind. Longer thinking.	Sustained attention. Selective attention. Divided attention. Processing speed.
Executive function	Complex project. Effortful decision. Need to focus on one task at a time.	Planning. Feedback/error utilization. Decision making. Overridding habits/inhibition. Working memory. Mental/cognitive abilities.
Learning and memory	Repeats self in conversation. Require frequent reminders.	Immediate memory span. Recent memory. Semantic memory. Autobiographical memory. Implicit memory.
Language	Frequent use of general-use phrases, general pronounce, rather than names. Idiosyncratic word usage, grammatical error, low speech spontaneity, and utterances.	Expressive language. Grammar and syntax. Receptive language.
Perceptive-motor	Difficulties with previously-familiar activities (parking, carpentry, assembly, sewing, or knitting) and navigation. More confusion at dusk.	Visual perception. Visuoconstructional. Perceptual-motor. Praxis. Gnosis.
Social cognition	Behavior out of acceptable social range. Making decision without regard to safety.	Recognition of emotion. Theory in mind.

Diagnostic Criteria of Dementia (2)
NIAAA criteria (2011)

- Cognitive or behavioral impairment

A. Acquired and remember new things
B. Reasoning and handling complex task
C. Visuospatial ability
D. Language functions
E. Personality/behavior/comportment

- Cognitive decline is diagnosed in combination of Hx. + objective assessment
- ADL/decline from baseline/exclusion of delirium or major psychiatric disease

Update information:

1. **No hierarchy of cognitive domains**
2. **Issue on personality/behavior/comportment**
3. **Objective assessment as prerequisites**

Alzheimer's & Dementia 2011;7:263-269

Cardinal Cognitive Symptoms

A. Acquired and remember new things (≒ memory)

Missed appointment; repeat enquiry; forget scenarios of TV program.

B. Reasoning and handling complex task (≒ executive function)

Follow recipe; plan a trip; manage finance; calculation errors; dress; kitchen works.

C. Visuospatial ability (overlapping with perceptual-motor function)

Find cars in parking lot; find road; place items.

D. Language functions

Name family or friends, find words in conversations.

E. Personality/behavior/comportment (≒ social cognition)

Depressed mood; apathy; paranoia.

失智症十大警訊

Ten Warning Signs of AD*

1. Memory loss that affects job skills
2. Difficulty performing familiar tasks
3. Problems with language
4. Disorientation to time and place
5. Poor or decreased judgment
6. Problems with abstract thinking
7. Misplacing things
8. Changes in mood or behavior
9. Changes in personality
10. Loss of initiative

Used with the permission of the Alzheimer's Association.

1. 記憶衰退到影響日常生活
2. 無法勝任原本熟悉的事務
3. 說話表達出現問題
4. 喪失對時間、地點的概念
5. 判斷力變差、警覺性降低
6. 抽象思考出現困難
7. 東西擺放錯亂
8. 個性 (行為與情緒) 改變
9. 視覺與空間辨識困難
10. 社交畏縮

**: Recall DSM-5 and NIAAA guideline, cognitive domains section.*

American Academy of Neurology Guideline- Summary for Clinician

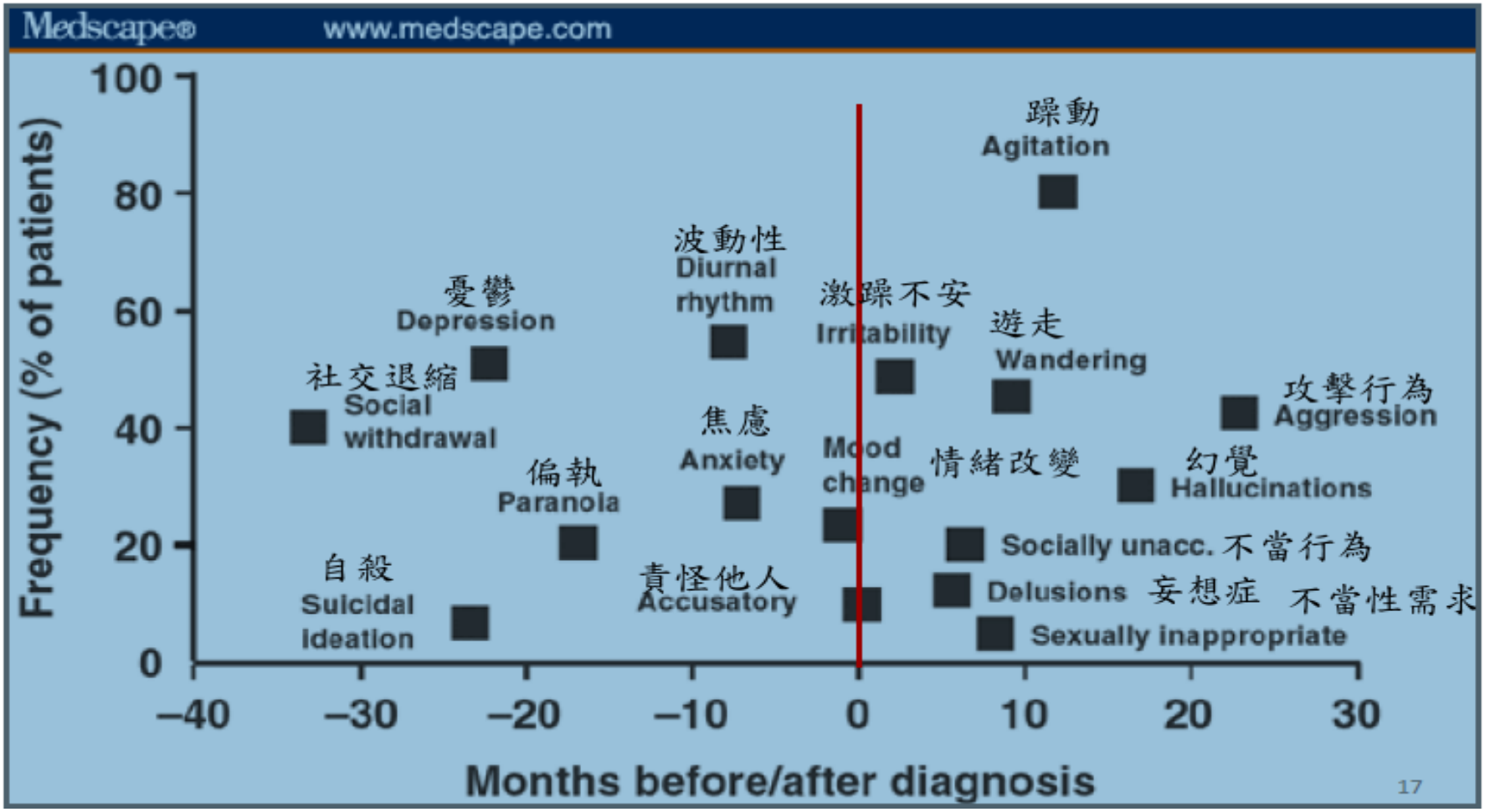
Common Behavioral and Psychiatric Symptoms of Dementia (BPSD)

TABLE 2-9 Most Common and Disruptive Behavioral and Psychiatric Symptoms of Dementia

Behavioral	Psychiatric
Wandering	Delusions
Physical aggression	Hallucinations
Restlessness	Anxiety
Agitation	Depression
Pacing	Sleep disturbances
Screaming	Misidentifications
Disinhibition and social inappropriateness	

Dementia Continuum Lifelong Learning in Neurology 13; 2007

BPSD Might Predate the Diagnosis



Evaluations of BPSD

TABLE 2-10 **General Principles for Investigating for Causes and Treating Behavioral Symptoms in Alzheimer's Disease**

- Exclude iatrogenic causes (primarily anticholinergic and pain medications).
- Exclude infections (frequently urinary or respiratory that might be regarded as minor in healthy older adults).
- Exclude other acute or chronic illnesses.
- Exclude potential causes for pain that may be difficult to diagnose and treat in the patient with severe dementia.
- Investigate for changes in patient's caregiver, living arrangements, or general routine.
- Identify and monitor target symptoms.
- Avoid drugs for treating behavioral abnormalities with anticholinergic side effects whenever possible.
- Start medications for treating behavioral problems "low" and go "slow." Too large a dose or rapid escalation will be very likely to cause adverse side effects in this population.
- When behavioral abnormalities are well controlled by a medication, reduce dose and withdraw medication as soon as possible.

Dementia Continuum Lifelong Learning in Neurology p.60; 13; 2007

Disease Course

- Median survival time: 8-10 yrs after initial symptoms, 3-5 yrs after diagnosis made. *J.Gen Intern Med 2004;19:1057-1063*
- In a cohort study recruiting 323 end-staged dementia patients (Mean age= 85.3 y/o, F/U period= 18 months):

-1/4: death within 6 months

-1/2: life expectancy= 478 days

- 40-50% morality in 6 months if fever or swallowing problems

- Most common Cx: 41.1% pneumonia, 52.6% fever, 85.8% swallowing problems *NEJM 2009;361:1529-38*

Disease Course

Among symptomatic demented patients

- Hippocampus atrophy ↓ 75 %
- Brain weight ↓ >5 %/yr
- CNS acetylcholine ↓ 50-67%
- CNS acetylcholine receptor number ↓ 80%

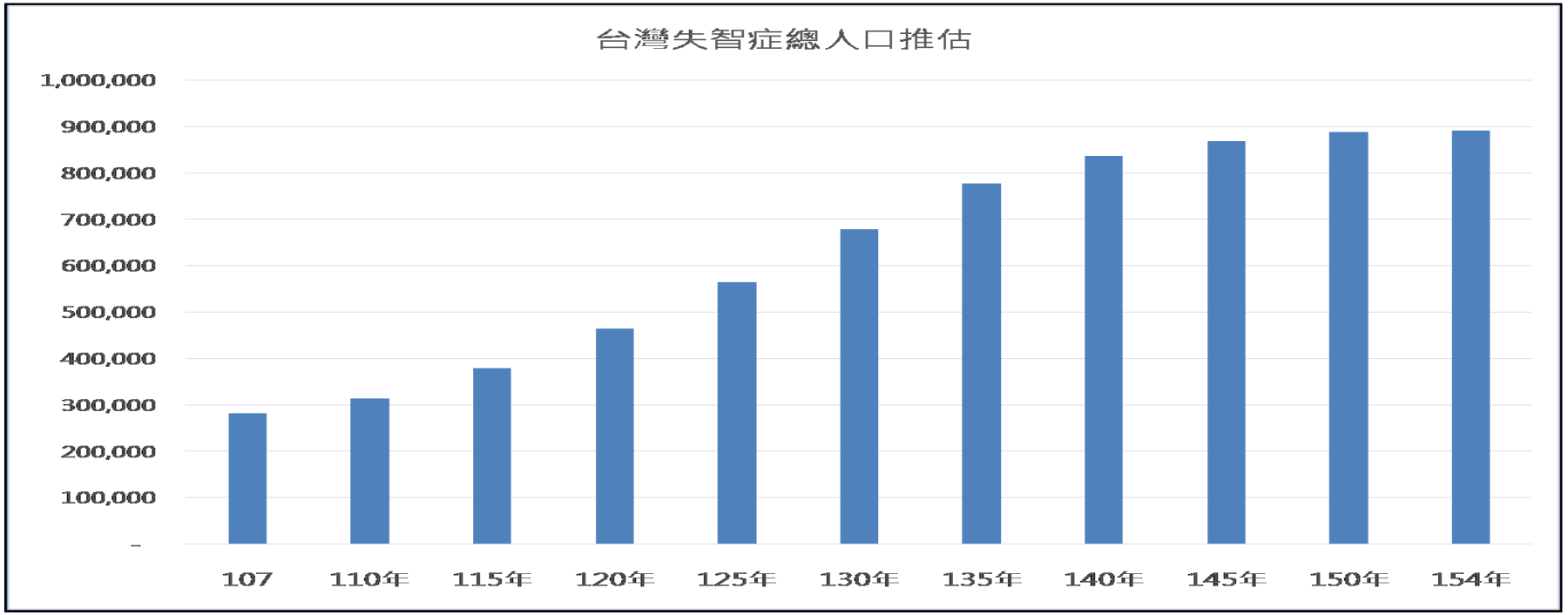
Rev Neurol 1999;155(supp 4)S33-37

Neurology 1984;34:939-944

Clin Neurol Neurosurg 2005; 107:165-173

Brain Res 1998;801:143-149

Epidemiology Reports in Taiwan (1)



表一：五歲分年齡層失智症盛行率

年齡(歲)	65~69	70~74	75~79	80~84	85~89	≧90
失智症盛行率(%)	3.40	3.46	7.19	13.03	21.92	36.88

http://www.tada2002.org.tw/About/IsntDementia

Epidemiology Reports in Taiwan (2)

機構別	入住人口數	65歲以上比率	失智症機構盛行率	推估人口數
安養機構	6,388	97%	26.8%	1,661
養護機構	30,288	88%	61.8%	16,472
護理之家	21,208	93%	64.5%	12,722
總計	57,884			30,855

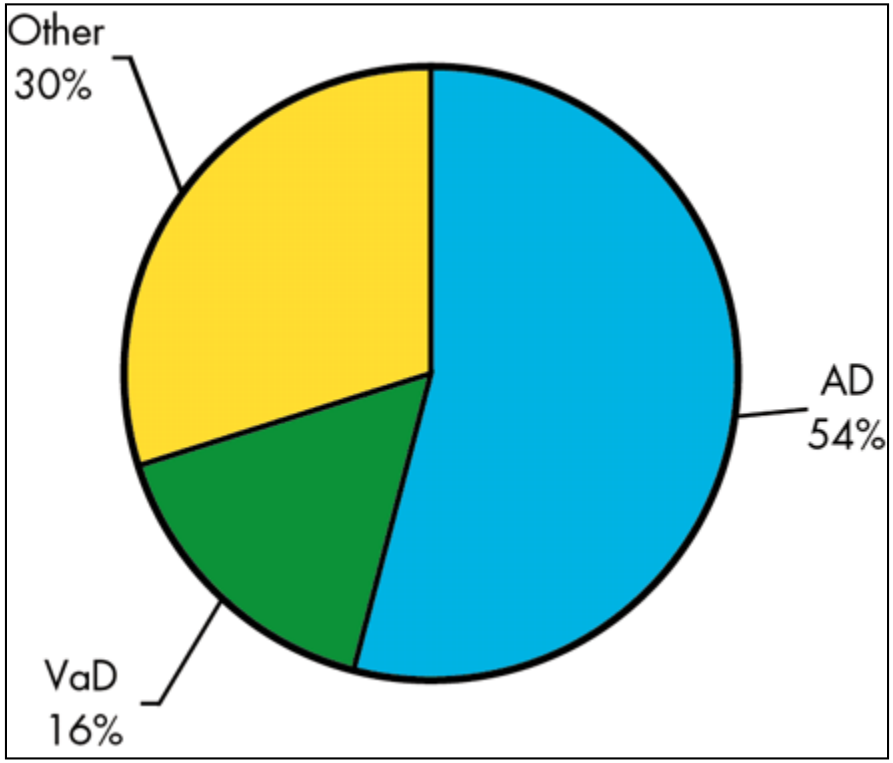
台灣失智症協會「台灣失智症機構照顧需求之調查-長期照護機構失智症患者之盛行率調查」研究共隨機抽樣60家安養護機構及護理之家，隨機抽樣1525位65歲以上老人，其中1308位完成二階段評估，共有631位老人診斷為失智症

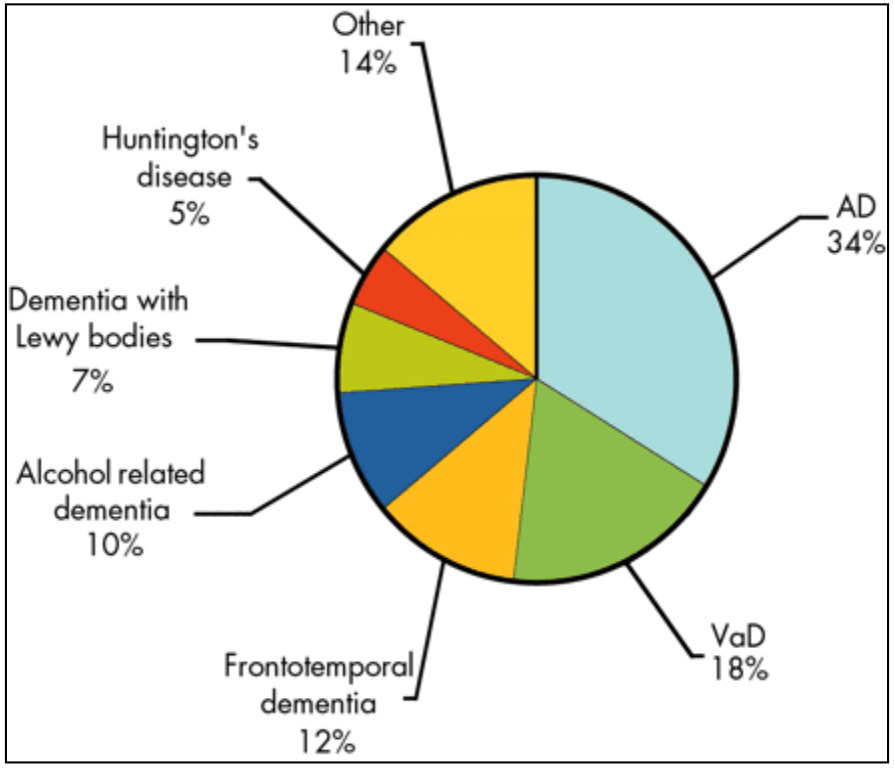
Chen TF et al., Neuroepidemiology. 2007;28(3):142-9

Epidemiology Reports in Taiwan (3)

失智相關之精神與行為障礙(behavioural and psychological symptoms of dementia)		
精神相關症狀	妄想(31-63%)	被偷妄想(27-56%)
		被害妄想(24-28%)
		忌妒妄想(3-17%)
		被遺棄妄想(2-9%)
	幻覺(21-26%)	視幻覺
		聽幻覺
	錯認(39%)	錯認不存在的人在屋子裡(22-23%)
		錯認現在住的房子不是自己的家(16%)
		錯認親人配偶是別人或偽裝者
		錯認電視上的內容是事實
		錯認鏡中的自己是別人
	情感症狀	憂鬱(17-50%)
		焦慮(35-76%)
行為障礙	睡眠障礙(26-61%)	
	重複行為	
	激躁行為(39-57%)	言語(70%)、行動(30%)
	遊走(26-45%)	
	病態收集(23-36%)	
	不當性需求(8-15%)	
	冷漠(42-47%)	Fuh, Acta Neurol Taiwan
	進食障礙(29-36%)	2006;15:154-160 66

Epidemiology Overview – Late vs. Young-onset dementia



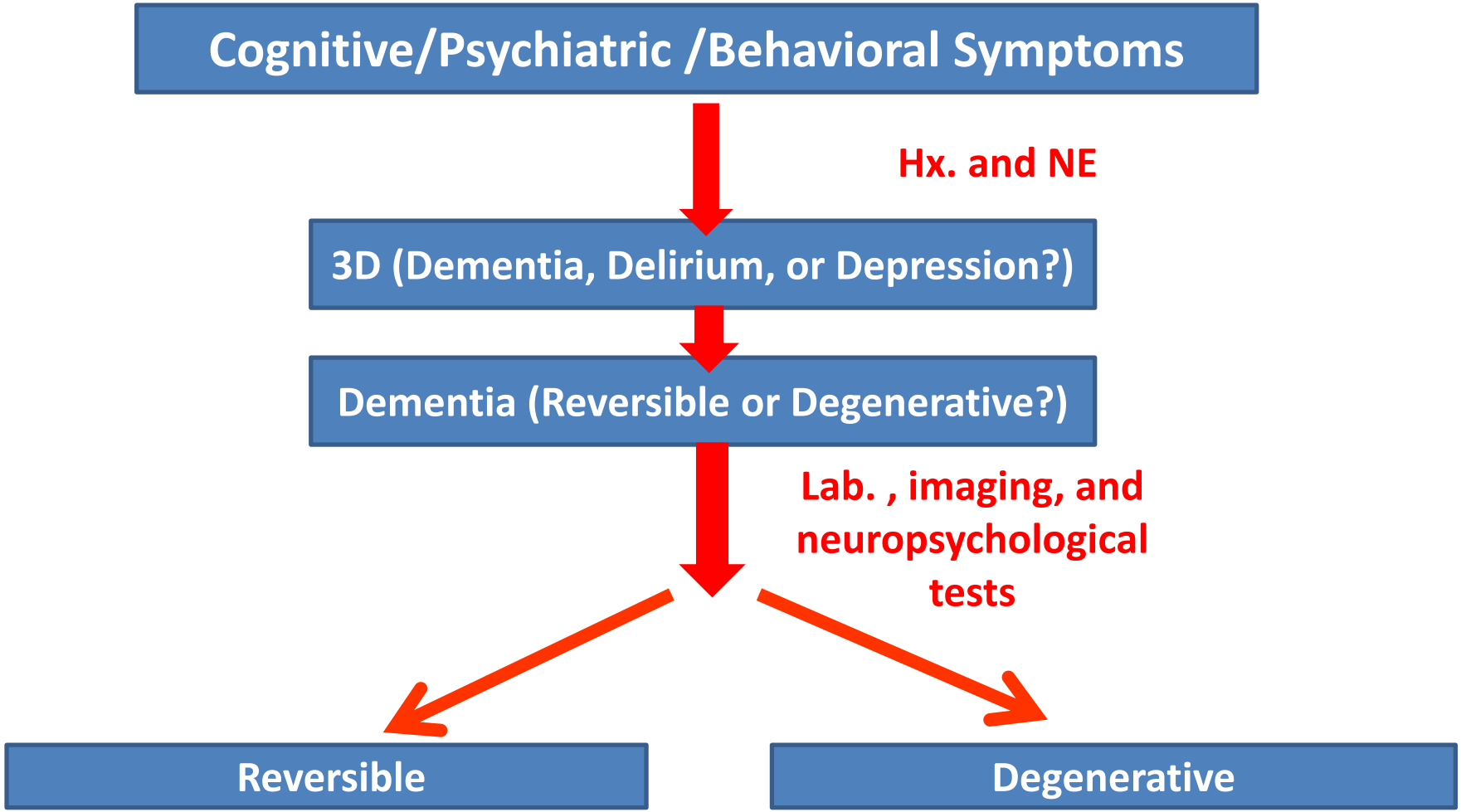


late onset (⩾ 65 years)

young onset (<65 years)

J Neurol Neurosurg Psychiatry 2005;76(Suppl V):v2–v7.

Clinical Flow Chart



History-taking under Cognitive-domain Oriented Strategies

A. Acquired and remember new things

會重複問同一件事情嗎? 聊天/電話中會不會馬上忘記剛剛講的事情?

B. Reasoning and handling complex task

工作順利嗎? 上司同事對他工作表現評價如何? 如果讓他獨力完成(工作), 你放心嗎?

C. Visuospatial ability

會迷路嗎? 開車技術如何? 大賣場回家要找停車處會有困難嗎?

D. Language functions

久未見面的親友, 名字會叫不出來? 要拿某個東西, 會不會叫不出名字? 講話有甚麼奇怪的地方嗎? 寫字呢? 多久沒看報紙了?

E. Personality/behavior/comportment

衛生習慣怎樣? 有沒有曾做出甚麼令你難堪或尷尬的舉動? 個人花錢或娛樂習慣有改變嗎? 會哭泣或談到不好的事情嗎?

History-taking under BPSD Oriented Strategies

- Use open question after developing rapport

  這段時間以來, 患者有沒有表現甚麼您覺得奇怪的地方?

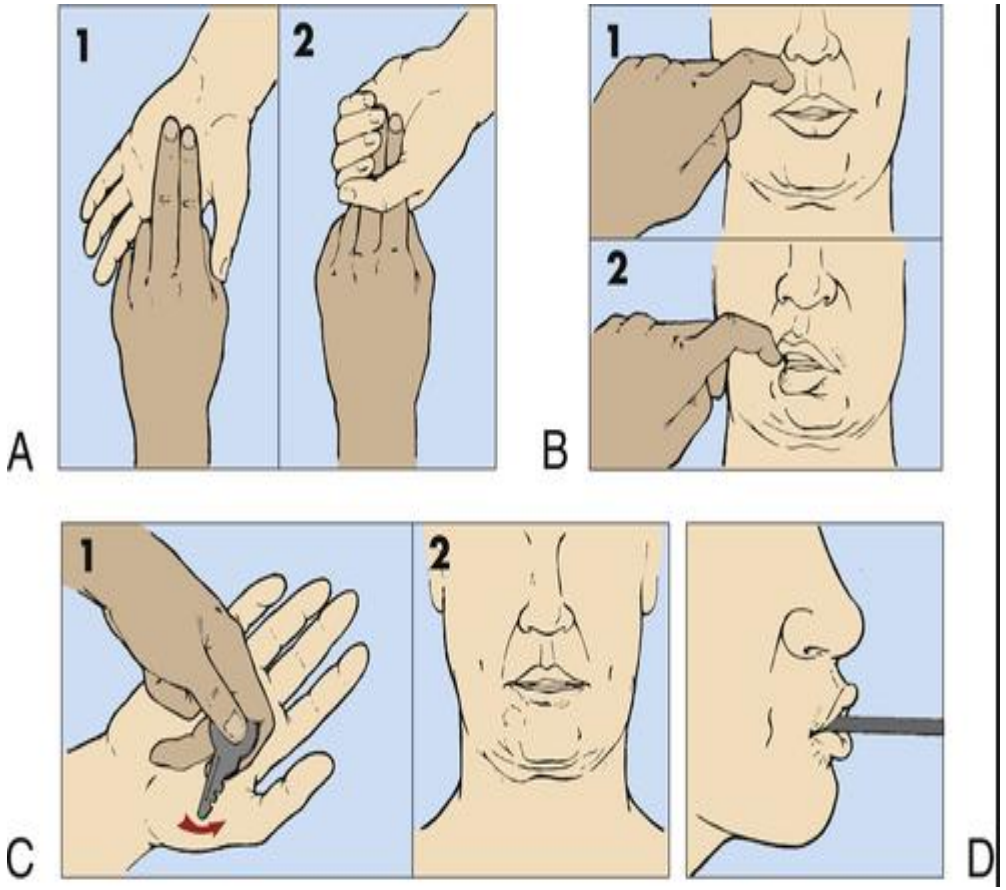
  例如說性格變化很大, 或著生活上習慣的改變 (或著疑神疑鬼, 或著很沮喪)?
- Wandering/Pacing 會漫無目的的遊走/反覆繞圈圈嗎?
- Aggression/Screaming會出手打人, 或說粗話, 或大吼大叫嗎?
- Restlessness/agitation會呈現不安, 不時搓手或衣服折角, 甚至很躁動?
- Disinhibition 有沒有甚麼嚴重的狀況, 是你叫他”不要這樣做”的?

History-taking under BPSD Oriented Strategies

- Delusion 長輩曾經有懷疑過有人要害她/丈夫外面找其他人/有人偷她錢/聲稱這不是我家/或家人不是家人?
- Hallucination 患者有沒有曾經看到您看不到的東西? 或有視覺/觸覺/味覺上的抱怨? (明明旁人就感受不到 , 可是患者卻說有)
- Anxiety 家人會常覺得長輩很"緊張兮兮" 或擔心被拋棄/擔心身體健康/擔心未來的生活變化?
- Depression 您有發現長輩比較少話, 足不出戶? 最近體重/睡眠/胃口怎麼樣? 會常想到"不好"的事情?
- Sleep disturbance 睡覺一直做夢? 隔天早上頭痛? 沒精神? 想睡又睡不著?
- Misidentification 會把你錯認為其他人嗎? (比如認為你是他兄弟, 或其他親友)

Neurological Signs Indicative Dementia –Primitive reflex

- A: Grasp reflex
- B:Snout reflex
- C: Palmomental reflex
- D: Suck reflex



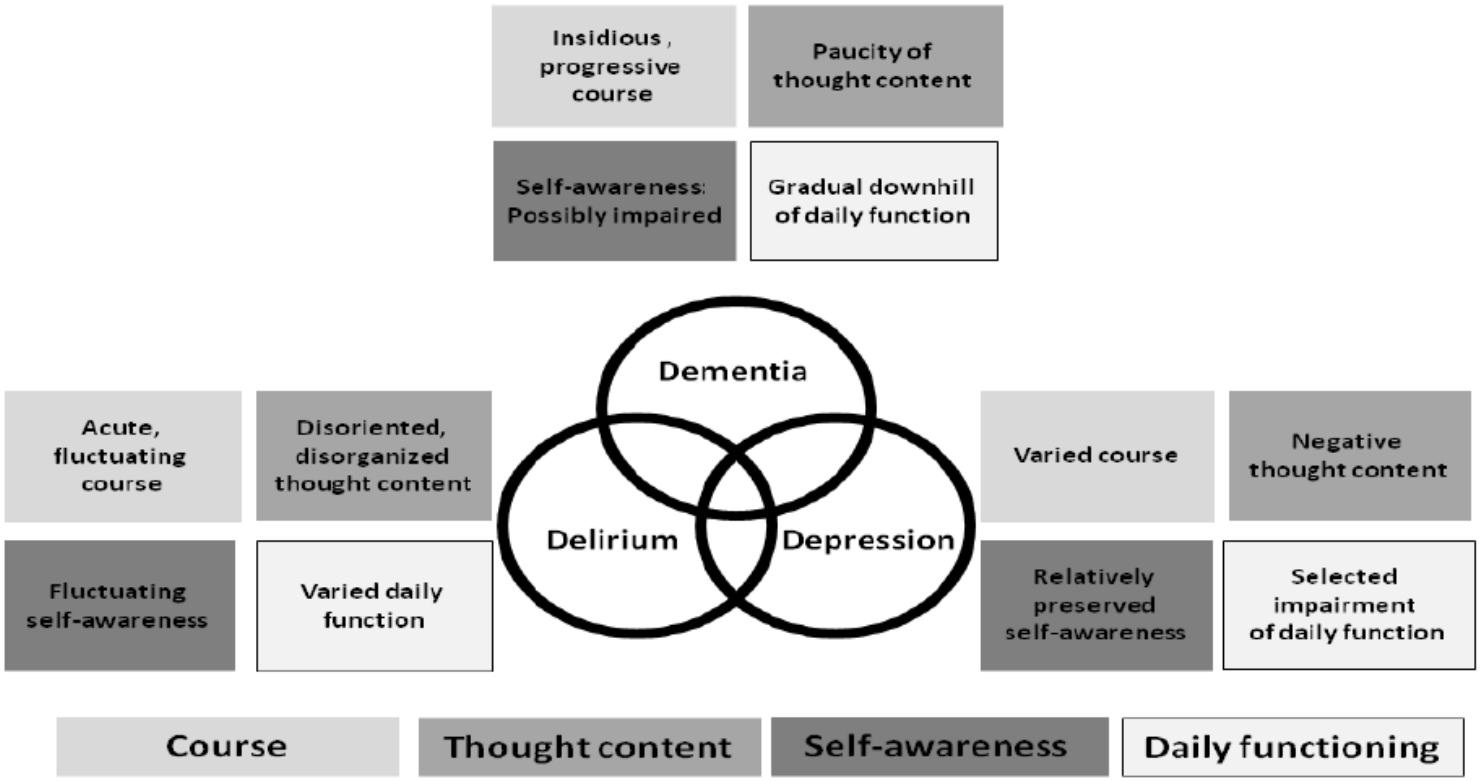
https://basicmedicalkey.com/alterations-in-cognitive-systems-cerebral-hemodynamics-and-motor-function/

Bedside Mental Status Examinations

Cognitive Domain	Test
Attention	Temporal orientation
	Forward digit span
	A vigilance
Language	Observation of spontaneous speech
	Yes/No question
	Verbal commands (token test)
	Verbatim repetition
	One-minute category fluency
	Naming to confrontation
Memory	Delayed recall of 3 words
	Serial word list learning
Visuospatial Function	Finger copy
	Finger constructions
	Clock draw
Executive Function	Luria 3 step-test
	Reverse digit span
	Imitation behavior

Disorders of Cognitive Function Continuum Lifelong Learning in Neurology p.130; 8; 2002

Comparisons among “3D”: Dementia, Depression, and Delirium



失智症- 臨床與生物標記並行的診斷結構 冷敏謙

Differential Diagnosis

- Primary Dementia: AD, FTD, CJD
- Dementia “Plus”: VCI, PDD, DLB, PSP, CBD
- Secondary Dementia ($\fallingdotseq$ reversible dementia) : Metabolic/Medication encephalopathy, space-occupying lesions, NPH, pseudodementia of depression, chronic meningitis, etc.

AD: Alzheimer’s disease, FTD: Frontotemporal lobar degeneration; CJD: Creutzfeldt-Jacob disease; VCI: Vascular Cognitive Impairment; PDD: Parkinson’s disease with Dementia; DLB Dementia with Lewy Bodies; PSP: Progressive Supranuclear Palsy; CBD: Corticobasal degeneration; NPH: Normal Pressure Hydrocephalus

Rapidly Progressive Dementia (RPD)

A term used for dementia progression within a period shorter than that in general* (e.g., months), including

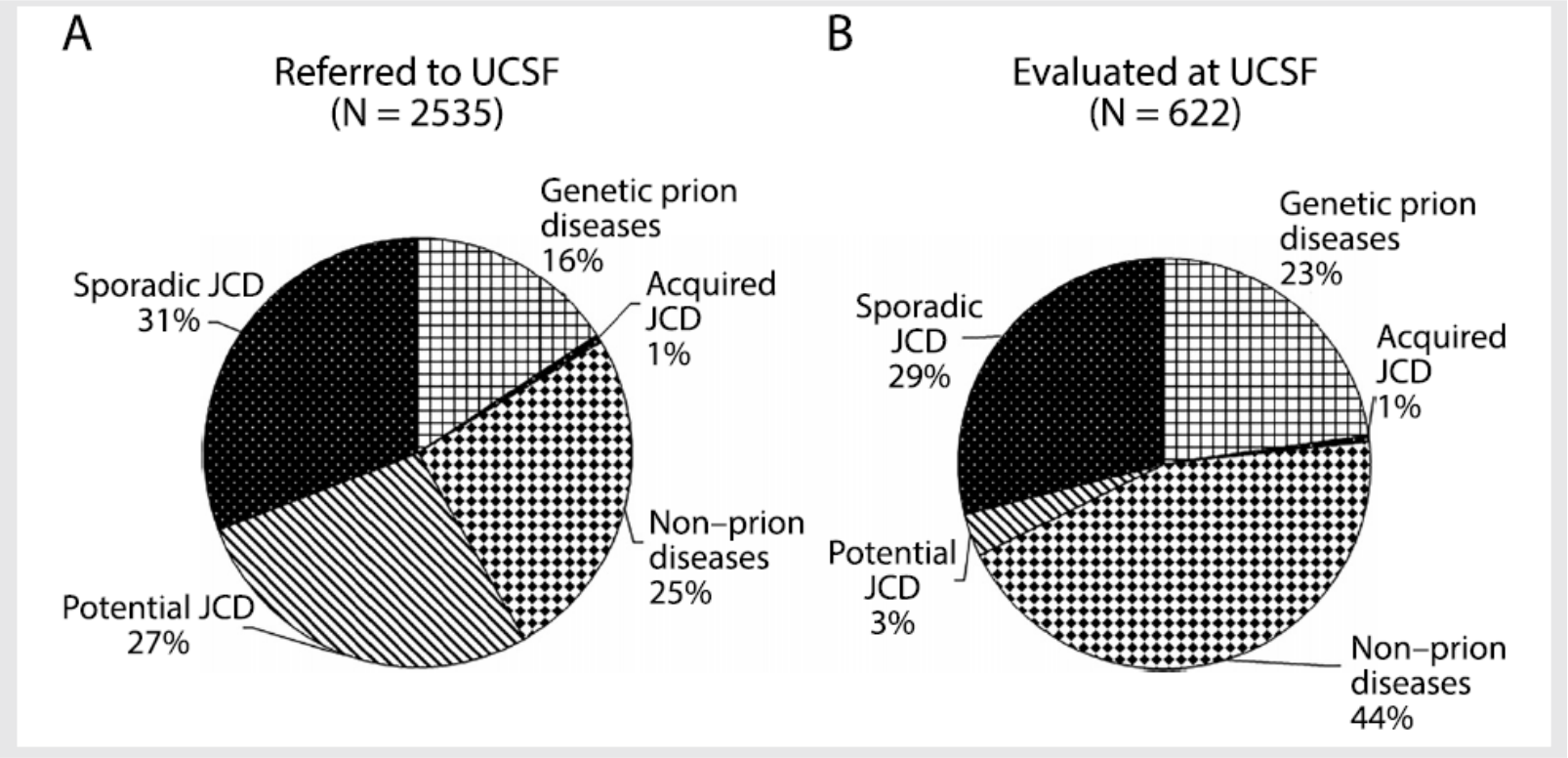
- Prion disease
- Inflammatory (immune- mediated and infectious) dz.
- Vascular dz.
- Metabolic dz.
- Neoplastic CNS dz.
- (Some) neurodegenerative diseases (but of atypical presentation)

Mostly "secondary dementia"

*Diverse operational definitions are proposed (e.g., onset-to-dementia/(death) ≤2 yrs, MMSE annual decline >6).

Nat Rev Neurol (2022). https://doi.org/10.1038/s41582-022-00659-0

Prion and Non-prion Disease in RPD



Continuum (Minneap Minn) 2016; 22(2): 510-537

Comparisons between Creutzfeldt–Jakob Disease (CJD) Subtypes

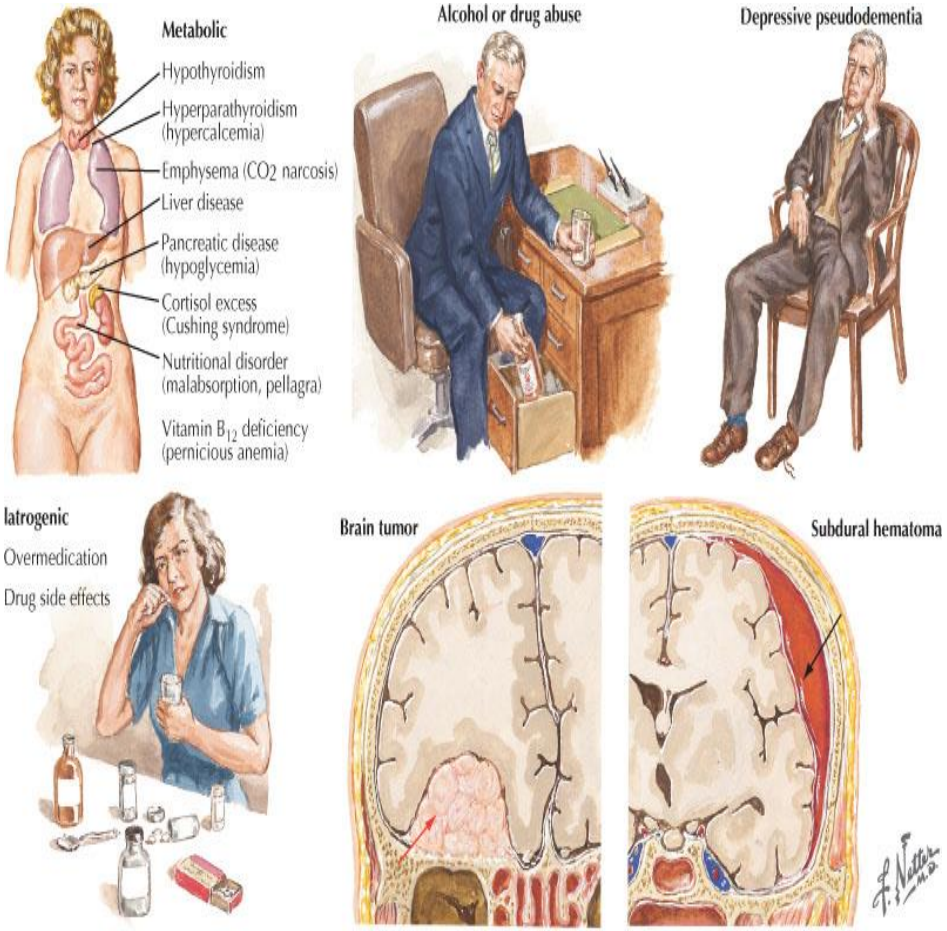
	Variant CJD	*Typical sporadic CJD (MM1)*
Clinical features[a,b]		
Mean age at death	29 years	65 years
Median duration of illness	14 months	4 months
Neurological signs	*Presentation*: affective or psychotic disorder, persistent pain, sensory symptoms, sometimes gait ataxia or dysarthria	*Presentation*: cognitive impairment, ataxia, mental, and visual signs
	Later stage: ataxia, dementia	*Later stage*: myoclonus, ataxia, and pyramidal signs
General diagnostic test[a]		
Thalamic MRI high signal	Pulvinar 90%	Caudate/putamen 60%
EEG	'Typical' 0%	'Typical' 80%
PrP^{Sc} detection in tonsil biopsy	Positive	Negative
Neuropathological features[b,c]		
Cerebral and cerebellar cortex	Multiple florid plaques in H&E sections, numerous small clusters of plaques in PrP stained sections, amorphous pericellular and perivascular PrP accumulation	Widespread fine spongiform degeneration, astrogliosis, neuronal loss; punctate PrP immunoreactivity; 'brush stroke' pattern in cerebellar molecular layer
Caudate nucleus and putamen	Severe spongiform change, perineuronal and axonal PrP accumulation	Fine spongiform degeneration and astrogliosis; punctate PrP immunoreactivity
Posterior thalamic nuclei and midbrain	Marked astrocytosis and neuronal loss	Fine spongiform degeneration and astrogliosis; punctate PrP immunoreactivity; substantia nigra not affected
Brainstem and spinal cord	Reticular and perineuronal PrP accumulation in gray matter	No spongiform degeneration and PrP immunoreactivity
Molecular features of PrP^{Sc}		
129 Polymorphism	MM	MM
Gel mobility (type)	19 kDa (type 2)	21 kDa (type 1)
N-terminal PK cleavage site	Residue 97	Residue 82

[a]Will RG and Ward HJ (2004) Clinical features of variant Creutzfeldt–Jakob disease. *Current Topics in Microbiology and Immunology* 284: 121–132.
[b]Gambetti P, et al. (2003)Sporadic and familial CJD: Classification and characterisation. *British Medical Bulletin* 66: 213–239.
[c]Ironside JW and Head MW (2004) Neuropathology and molecular biology of variant Creutzfeldt–Jakob disease *Current Topics in Microbiology and Immunology* 284: 133–159.
Source EEG, Electroencephalogram.

Encyclopedia of Movement Disorders (pp.315-320)

Reversible Etiologies of Dementia

- Medication encephalopathy
- Pseudodementia of depression
- Normal pressure hydrocephalus
- Hypothyroidism
- Vitamin B12/folic acid deficiency
- Resectable intracranial tumors
- Subdural hematomas
- Chronic meningitis



Classes of Medications Impairing Cognition

Classes of Medications	Examples
● Cholinergic antagonist	● Baclofen/Mephenoxalone
● Sedatives/hypnotics	● Lorazepam/Zolpidem
● Narcotics	● Tramadol/Morphine
● Antihistamine	● Cyproheptadine/Diphenhydramine
● Dopaminergic antagonist	● Metoclopramide/Proclorperazine/Haloperidol

失智症- 臨床與生物標記並行的診斷結構 涂敏謙

Diagnostic Tools

- Biochemistry:

  - Serology: CBC, Cr/LFT/(ammonia*), cortisol/fT4, folic acid/Vit B12, (HIV/heavy metal/drugs panel*), and RPR

  - CSF*

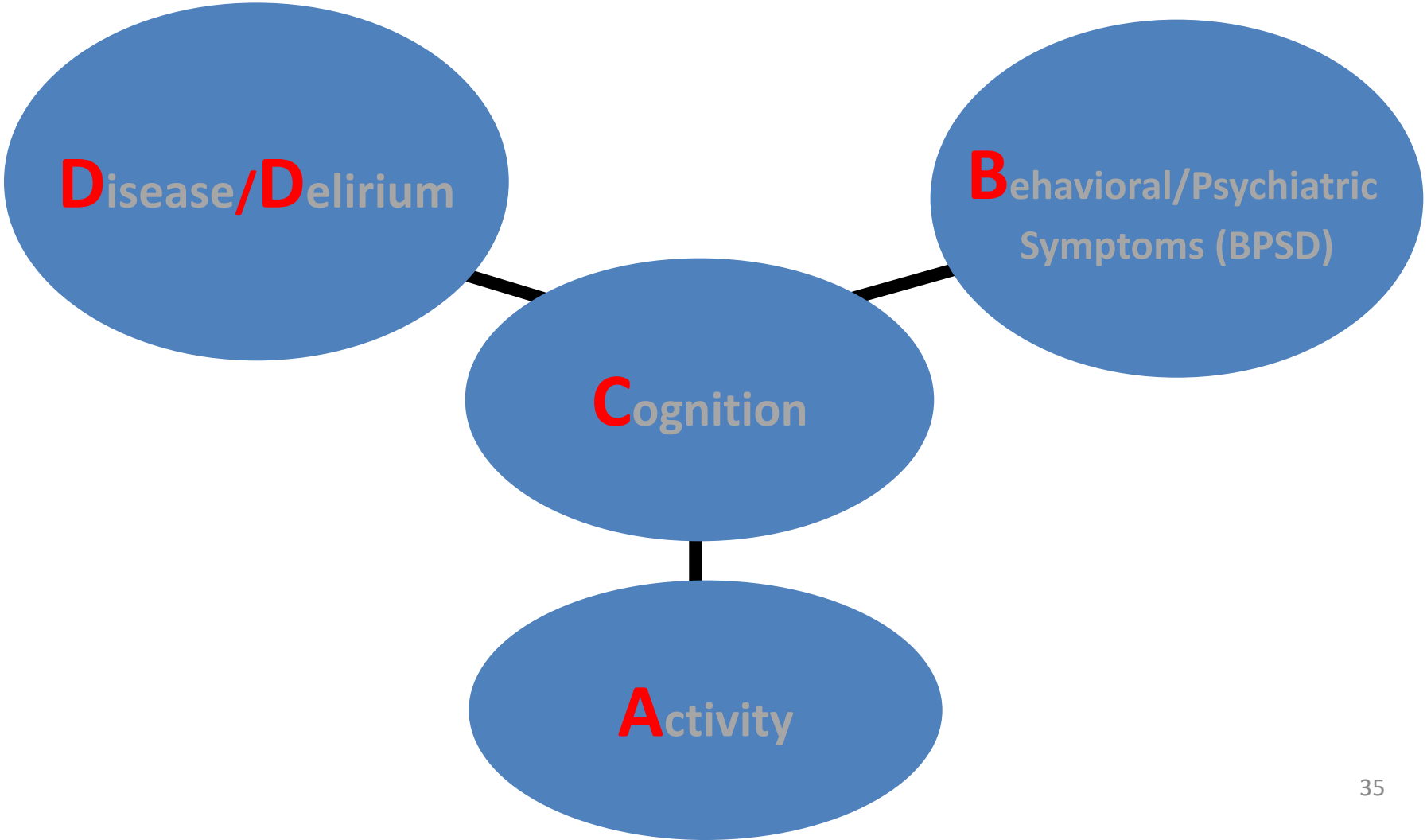
- Structural neuroimaging: CT, MRI
- Neuropsychological tests
- Functional neuroimaging*: SPECT, PET
- Electrophysiology*: EEG *: based on clinician's judgment

Dementia Continuum Lifelong Learning in Neurology p.51; 13; 2007

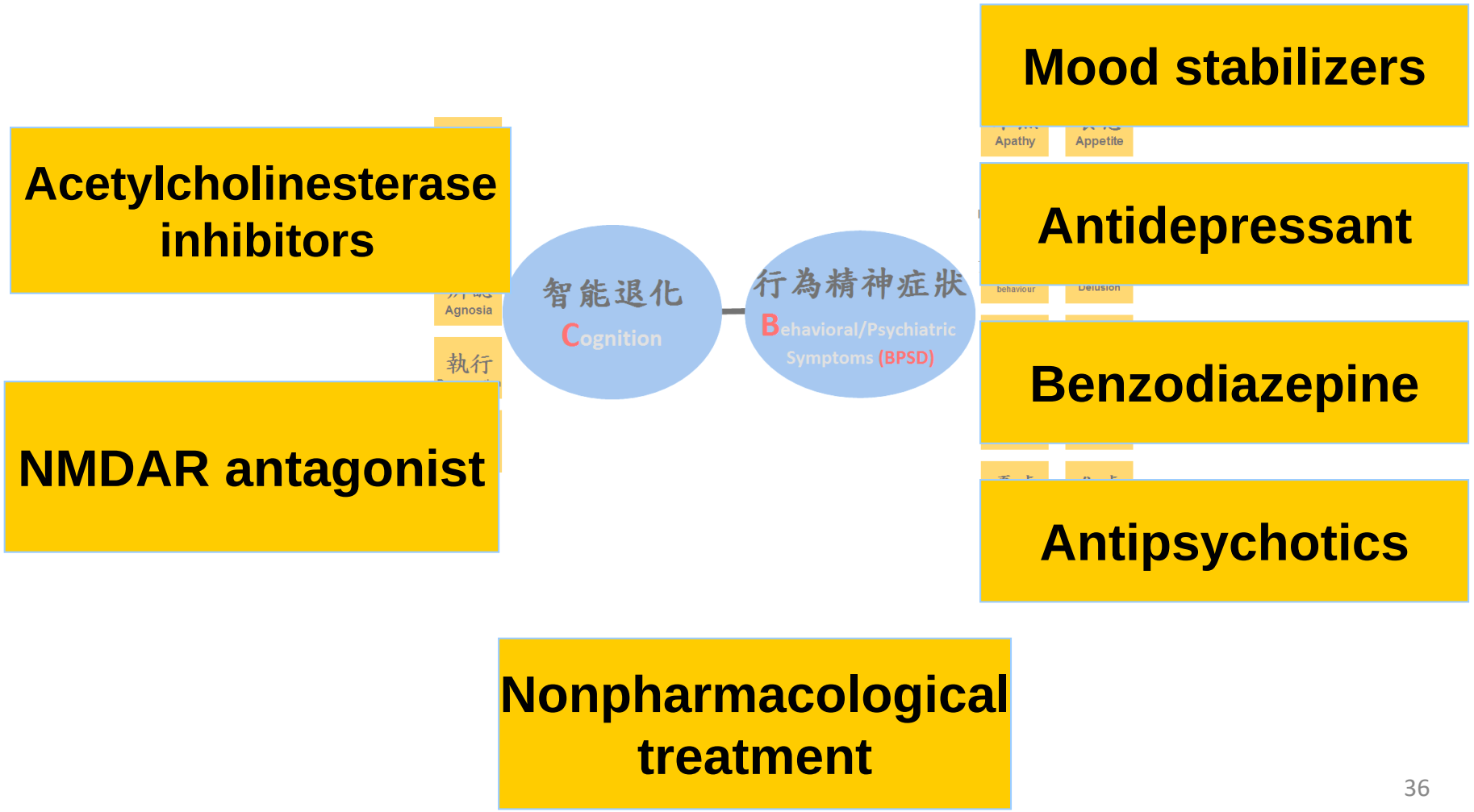
Therapeutic Strategies- General Principle

- Diagnosis documentation
- Control confounding systemic disease/medication
- Patient and family consultation
- Pharmacological treatment
  - Cognition
  - Psychiatric symptoms
  - Behavior
  - Functional performances
  - Caregivers' burden
- Non-pharmacological treatment

Algorithm of Management (D->C->B->A)



Symptoms-targeted Therapeutic Strategies



Pharmacological Treatment

- AchEI:

  Donepezil: Mild to severe AD *, (DLB)

  Rivastigmine: Mild to moderate AD, PDD#, (DLB)

  Galantamine: Mild to moderate AD, (DLB)
- Memantine: Moderate to severe AD
- Antidepressants/BZD/antipsychotics/Mood stabilizers/AchEI: BPSD

* preserved mobilization capacity is mandatory # only capsule formulation permitted

() based onto mixed but positive results and clinical observations.

AchEI: Acetylcholinesterase inhibitors; PDD: Parkinson's disease with Dementia; DLB Dementia with Lewy Bodies

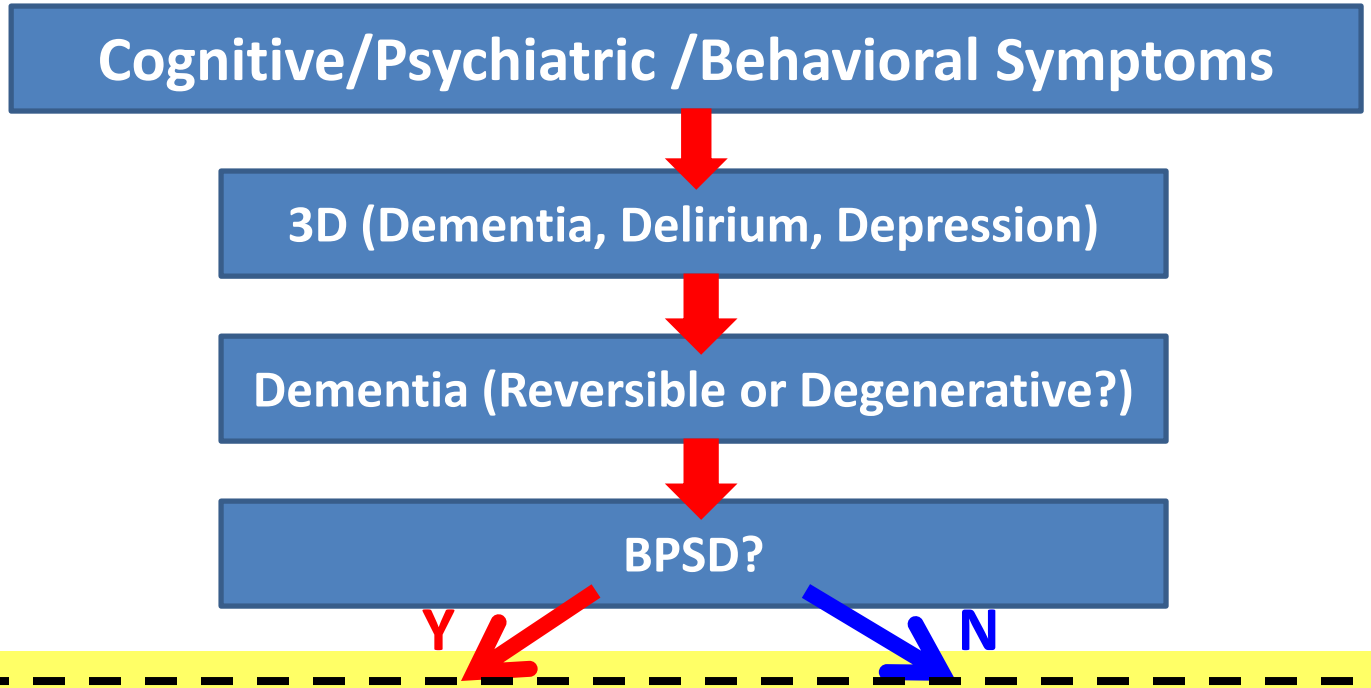
Non-pharmacological Therapy

STRATEGIES TO IMPROVE FUNCTIONAL PERFORMANCE AND REDUCE PROBLEM BEHAVIORS

Strategy	Strength Of Evidence
To improve functional performance	
– Behavior modification, scheduled toileting, prompted voiding to reduce urinary incontinence	Strong
– Graded assistance, practice and positive reinforcement to increase functional independence	Good
– Low lighting levels, music and simulated nature sounds to improve eating behaviors	Weak
– Intensive multi-modality group training may improve activities of daily living	Weak
To reduce problem behaviors	
– Music, particularly during meals and bathing	Good
– Walking or other forms of light exercise	Good
– Simulated presence therapy, such as use of videotapes of family	Weak
– Massage	Weak
– Comprehensive psychosocial care programs	Weak
– Pet therapy	Weak
– Utilizing commands issued at the patient's comprehension level	Weak
– Bright light, white noise	Weak
– Cognitive remediation	Weak

American Academy of Neurology Guideline- Summary for Clinician

Flow Chart: From Evaluation to Treatment



Nonpharmacological Tx.

Antipsychotic
Antidepressants
BZD
Mood stabilizers
AchEI

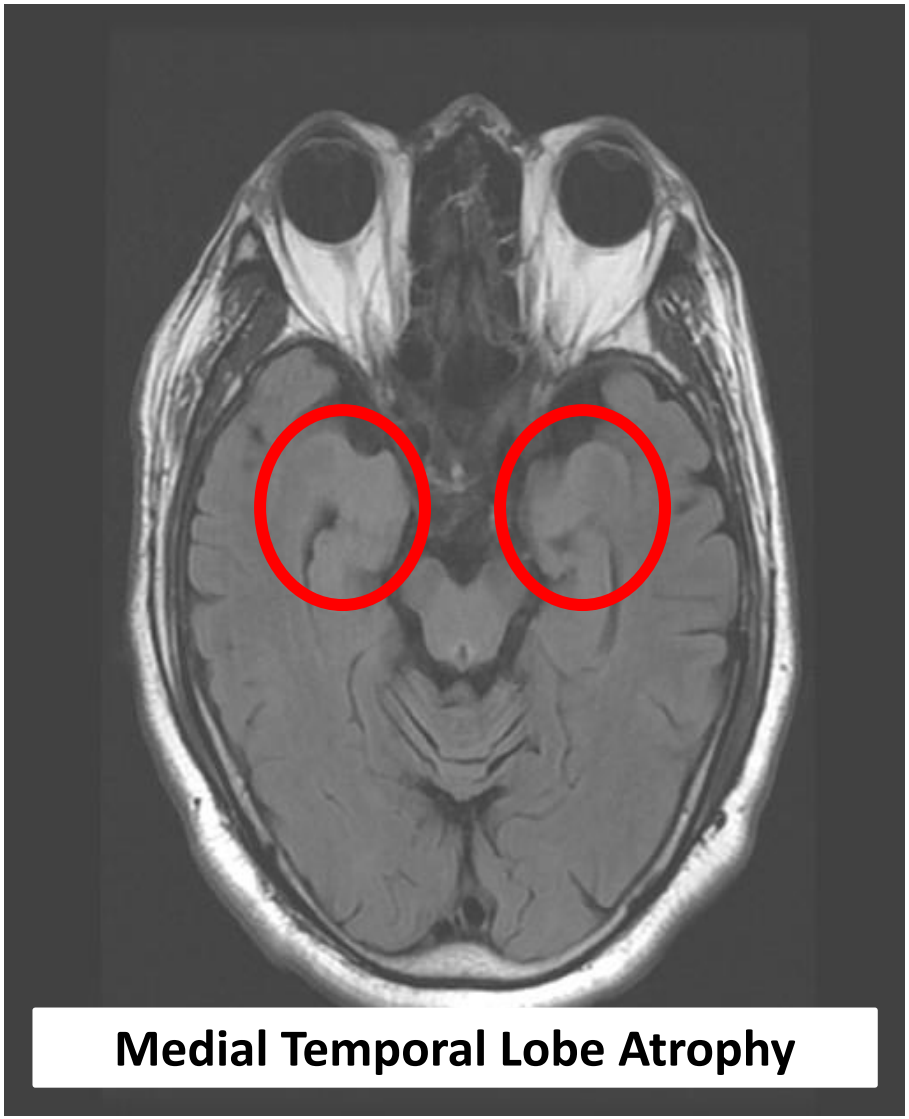
Degenerative :
AD: AchEI/Memantine
DLB/PDD: AchEI (Rivastigmine)
VCI: CVA preventions
Reversible: Correction of underlying

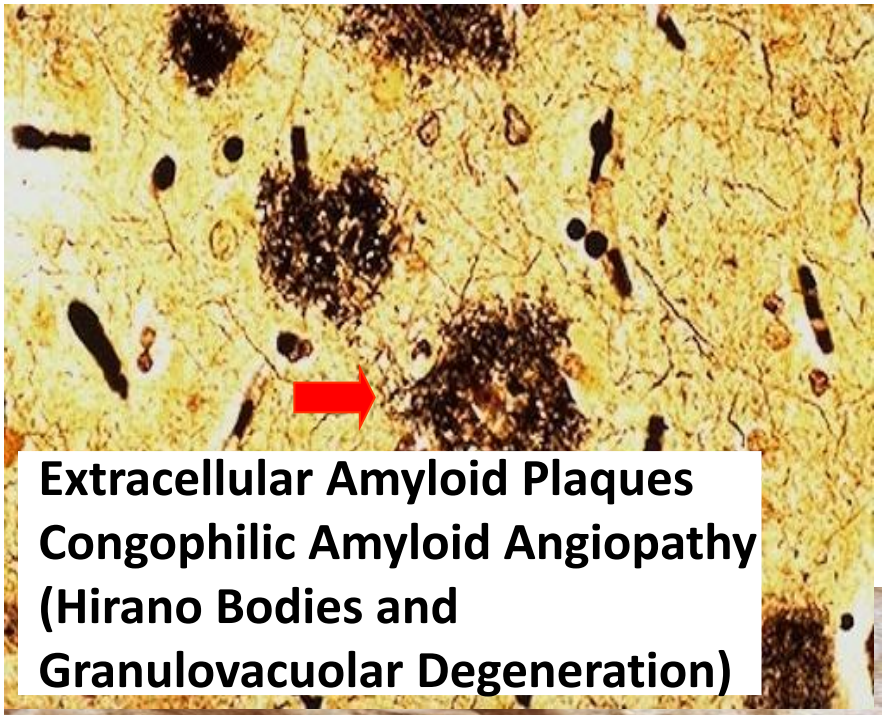
Pharmacological Tx. : "D->C->B->A rule"

Alzheimer's Disease (AD)

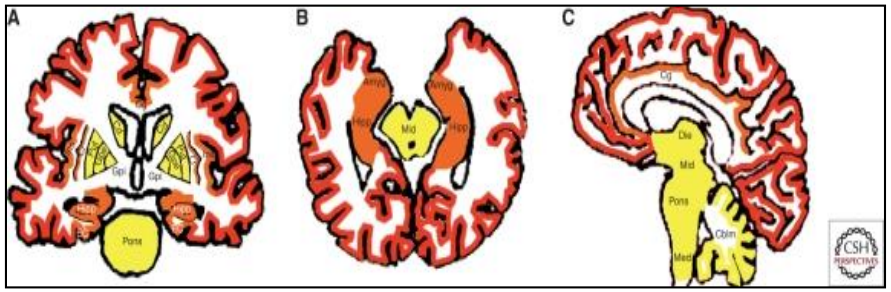
- Classical phenotypes: Amnestic (60%) and nonamnestic presentations
- Increasing prevalence with age D/D early vs. late onset by 65's
- Medial temporal lobe + other neocortex atrophy

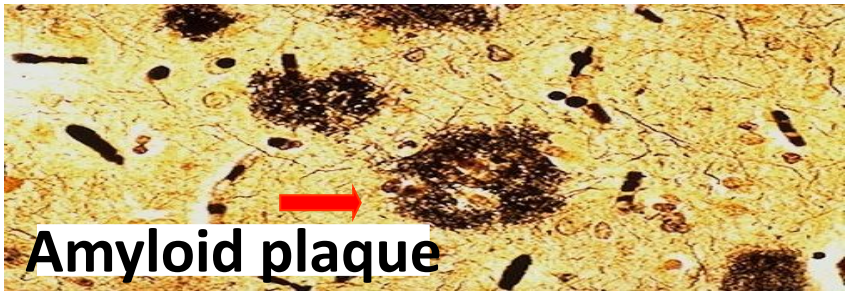
Pathology of AD

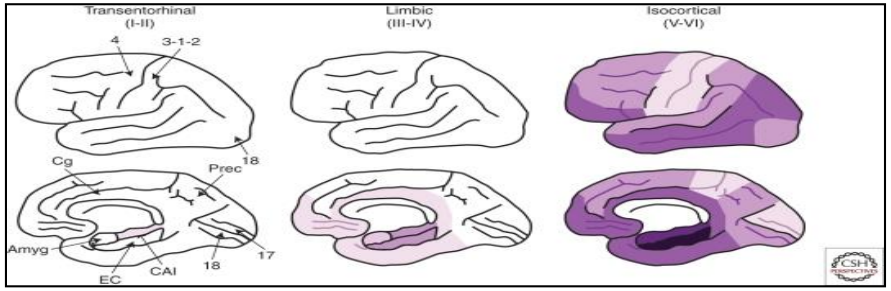


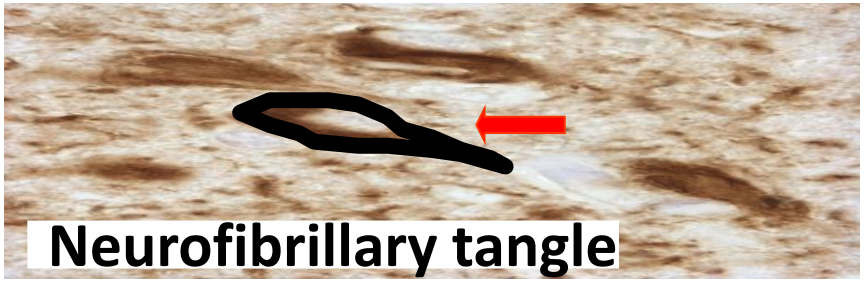


Pathogenesis: Pathology Viewpoints







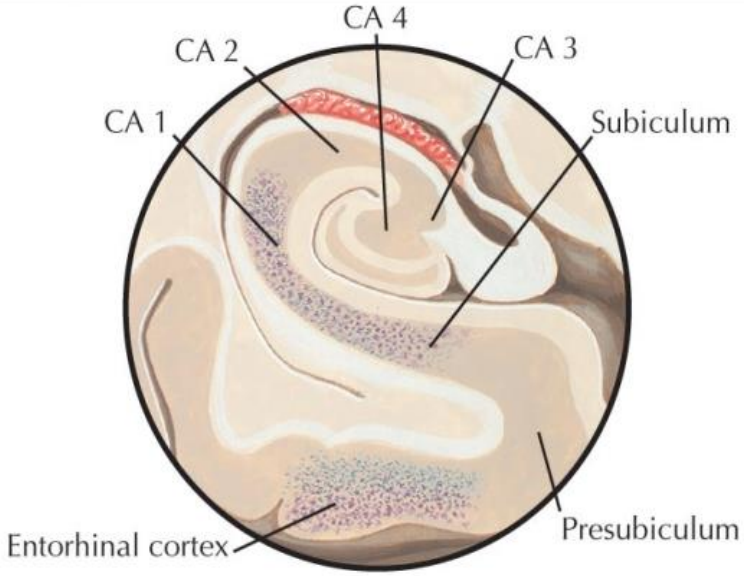


Amyloid plaque (Upper row): Isocortex (basal then association areas of F-T-O regions)-> Allocortex (hippocampus)-> subcortical-> brainstem and cerebellum.

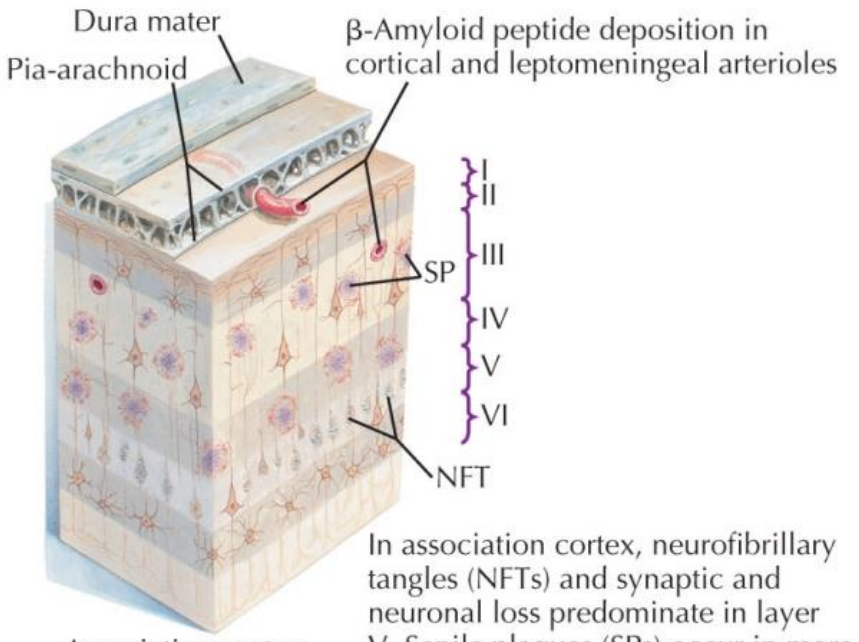
Neurofibrillary tangle (Lower row): Allocortex (entorhinal/perihinal cortex)-> hippocampus->Isocortex (association cortex/neocortex).

Cold Spring Harb Perspect Med. 2011 Sep; 1(1): a006189

Pathogenesis: Pathology Viewpoints

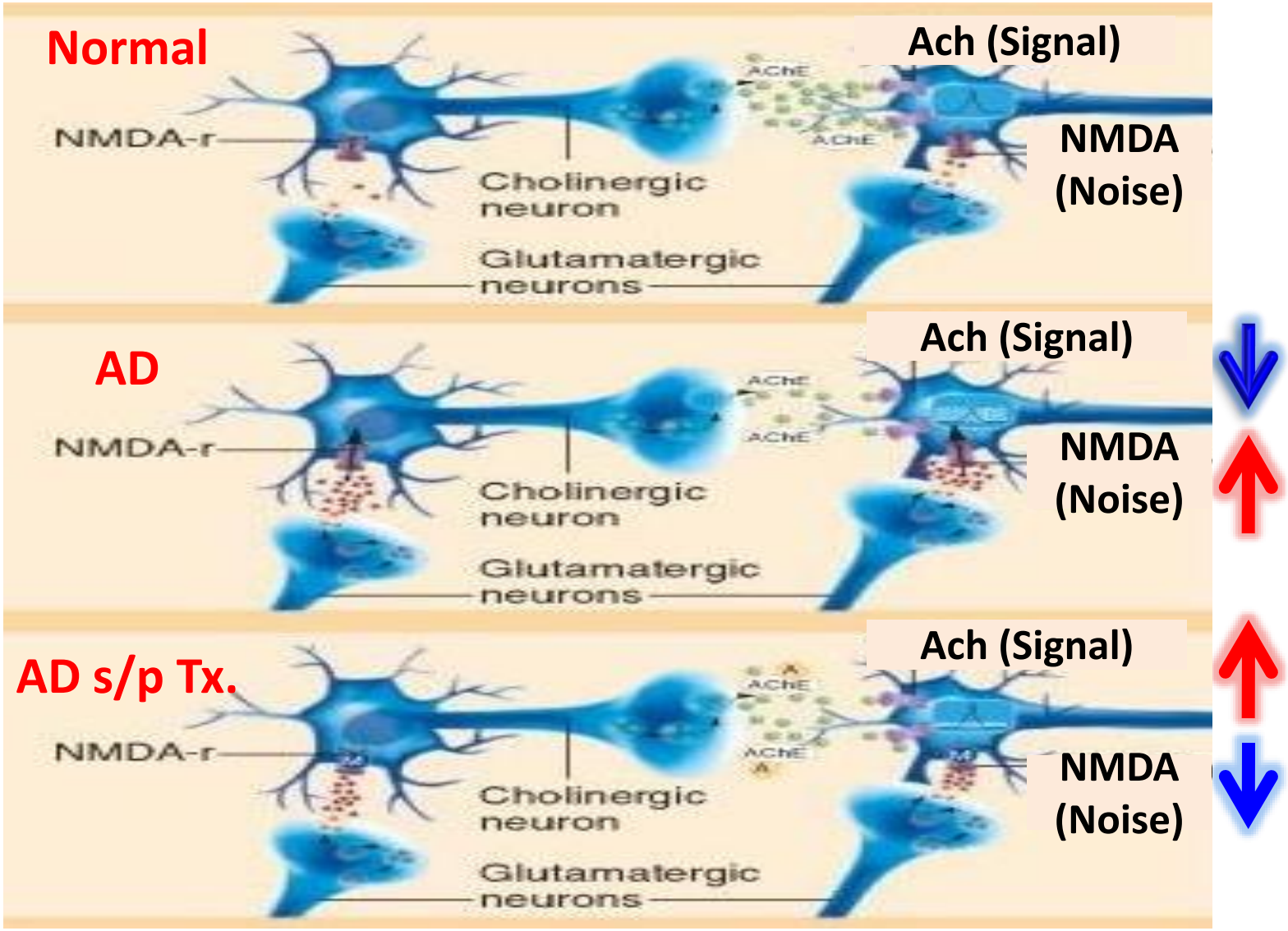


In hippocampus, neurofibrillary tangles, neuronal loss, and senile plaques primarily located in layer CA1, subiculum, and entorhinal cortex

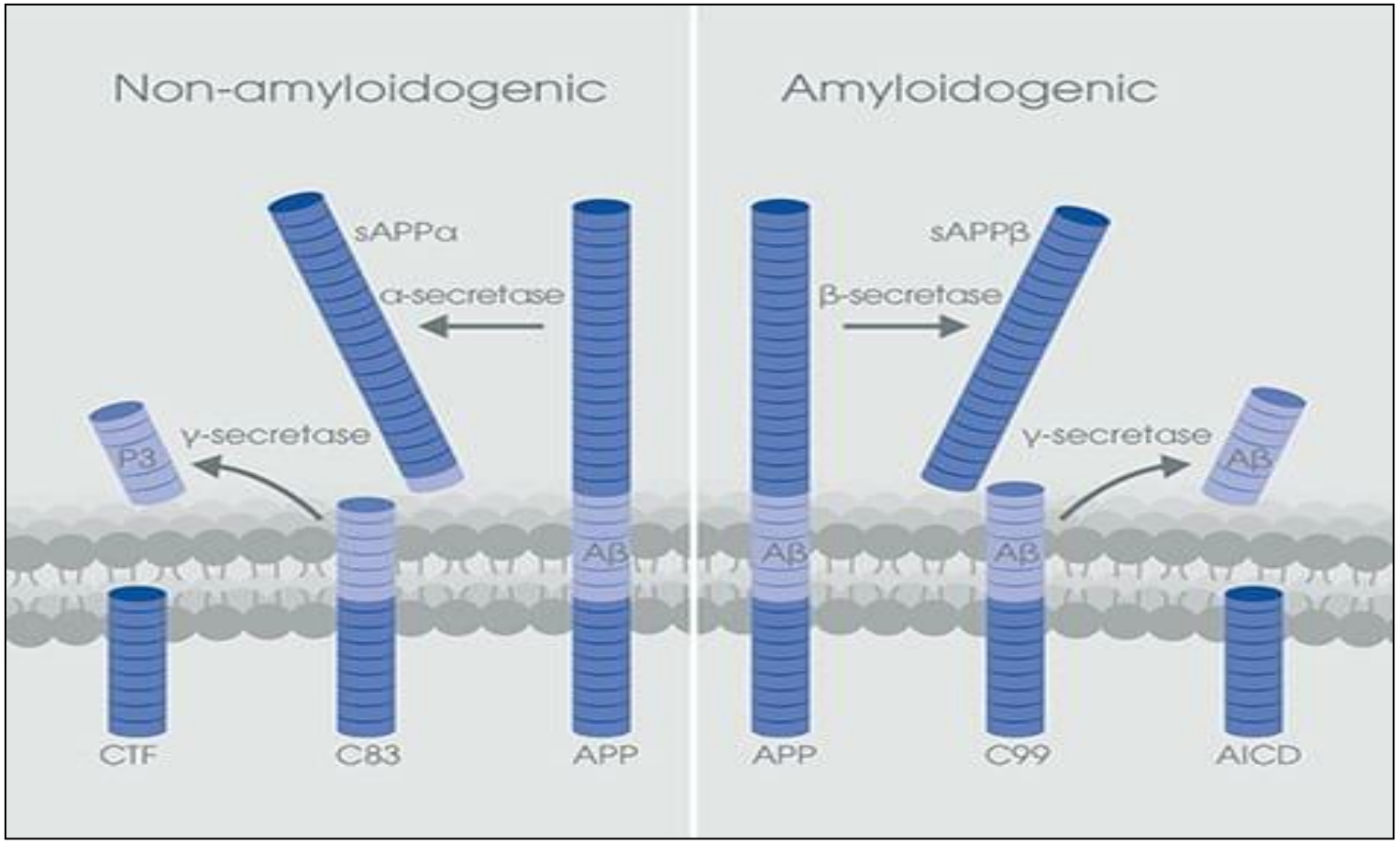


In association cortex, neurofibrillary tangles (NFTs) and synaptic and neuronal loss predominate in layer V. Senile plaques (SPs) occur in more superficial layers.

Pathogenesis: Neurotransmitter Viewpoints



Pathology: Protein Synthesis Viewpoints



www.abcam.com/neuroscience/

Pathogenesis: Genetic Viewpoints

Late-onset AD/Susceptibility gene

- APOE ε4 : Chr 19q; lipid transporter protein

  - Effect predominantly on age-of-onset

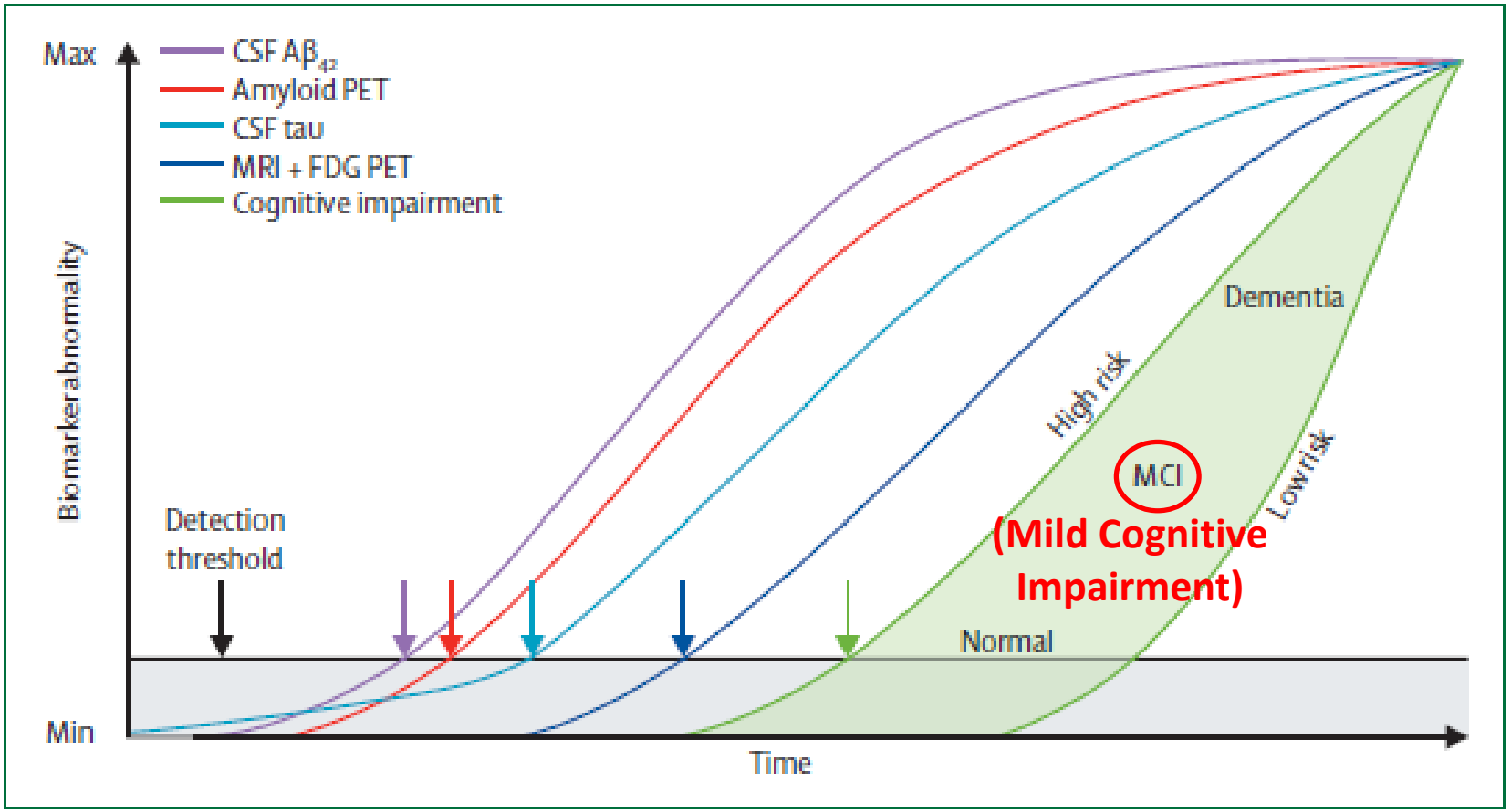
  - Homozygous: increased risk of developing AD at 85 y/o

  - Improper as "routine" diagnostic tool or risk assessment

Early-onset/Familial AD: (<1~5% of overall AD)

- Amyloid precursor protein (APP): Chr 21q: β-amyloid protein
- Presenilin 1 (PS-1): Chr 14q: ϒ-secretase
- PS-2: Chr 1q: ϒ-secretase

Hypothetical temporality of AD biomarkers



Lancet Neurol. 2013 Feb;12(2):207-16.

NIAAA Criteria of AD

ELSEVIER

Alzheimer's & Dementia 7 (2011) 263–269

Alzheimer's & Dementia

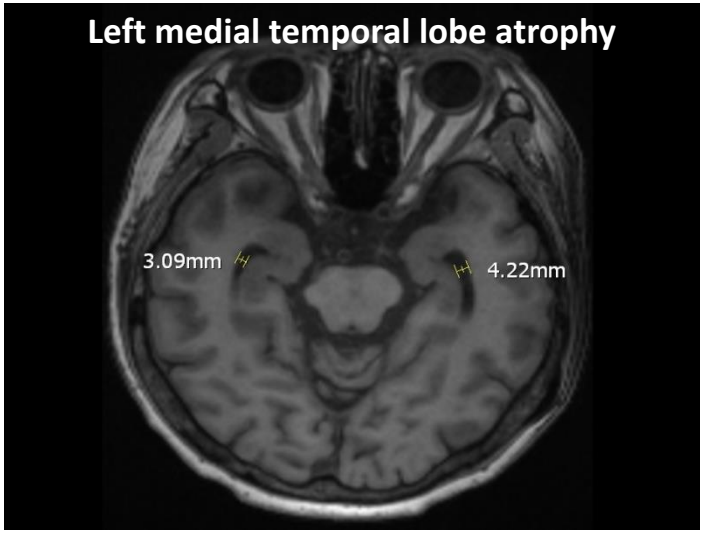
The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease

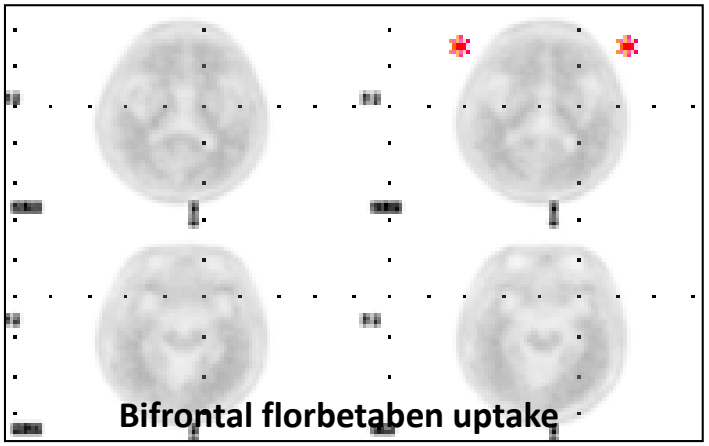
Guy M. McKhann[a,b,*], David S. Knopman[c], Howard Chertkow[d,e], Bradley T. Hyman[f], Clifford R. Jack, Jr.[g], Claudia H. Kawas[h,i,j], William E. Klunk[k], Walter J. Koroshetz[l], Jennifer J. Manly[m,n,o], Richard Mayeux[m,n,o], Richard C. Mohs[p], John C. Morris[q], Martin N. Rossor[r], Philip Scheltens[s], Maria C. Carrillo[t], Bill Thies[t], Sandra Weintraub[u,v], Creighton H. Phelps[w]

- Reasons of revising NINCDS-ADRDA criteria
- Core clinical criteria for "all-cause dementia"
- Core clinical criteria for "AD"

Current Confirmed Biomarkers in NIAAA criteria

- MRI: medial temporal lobe atrophy (through visual/parametric/volume assessment)
- PET: amyloid plaque deposition (e.g., Florbetaben and Pittsburgh compound B)
- CSF: Aβ42 level: inverse correlation with total Aβ load in the brain; tau level positive correlation with the number of neocortical neurofibrillary tangles. Phosphorylated tau may increase diagnostic specificity.





Incorporation of Biomarkers into Criteria of AD

AD dementia criteria incorporating biomarkers

Diagnostic category	Biomarker probability of AD etiology	Aβ (PET or CSF)	Neuronal injury (CSF tau, FDG-PET, structural MRI)
1 Probable AD dementia			
Clinical Criteria	Uninformative	Unavailable, conflicting, or indeterminate	Unavailable, conflicting, or indeterminate
Pathophysiological Process	Intermediate	Unavailable or indeterminate	Positive
	Intermediate	Positive	Unavailable or indeterminate
	High	Positive	Positive
2 Possible AD dementia (atypical clinical presentation)			
Clinical Criteria	Uninformative	Unavailable, conflicting, or indeterminate	Unavailable, conflicting, or indeterminate
Pathophysiological Process	High but does not rule out second etiology	Positive	Positive
3 Dementia-unlikely due to AD	Lowest	Negative	Negative

Abbreviations: AD, Alzheimer's disease; Aβ, amyloid-beta; PET, positron emission tomography; CSF, cerebrospinal fluid; FDG, ^{18}fluorodeoxyglucose; MRI, magnetic resonance imaging.

Modified Table 1, *Alzheimer's & Dementia 2011(7):263-269*

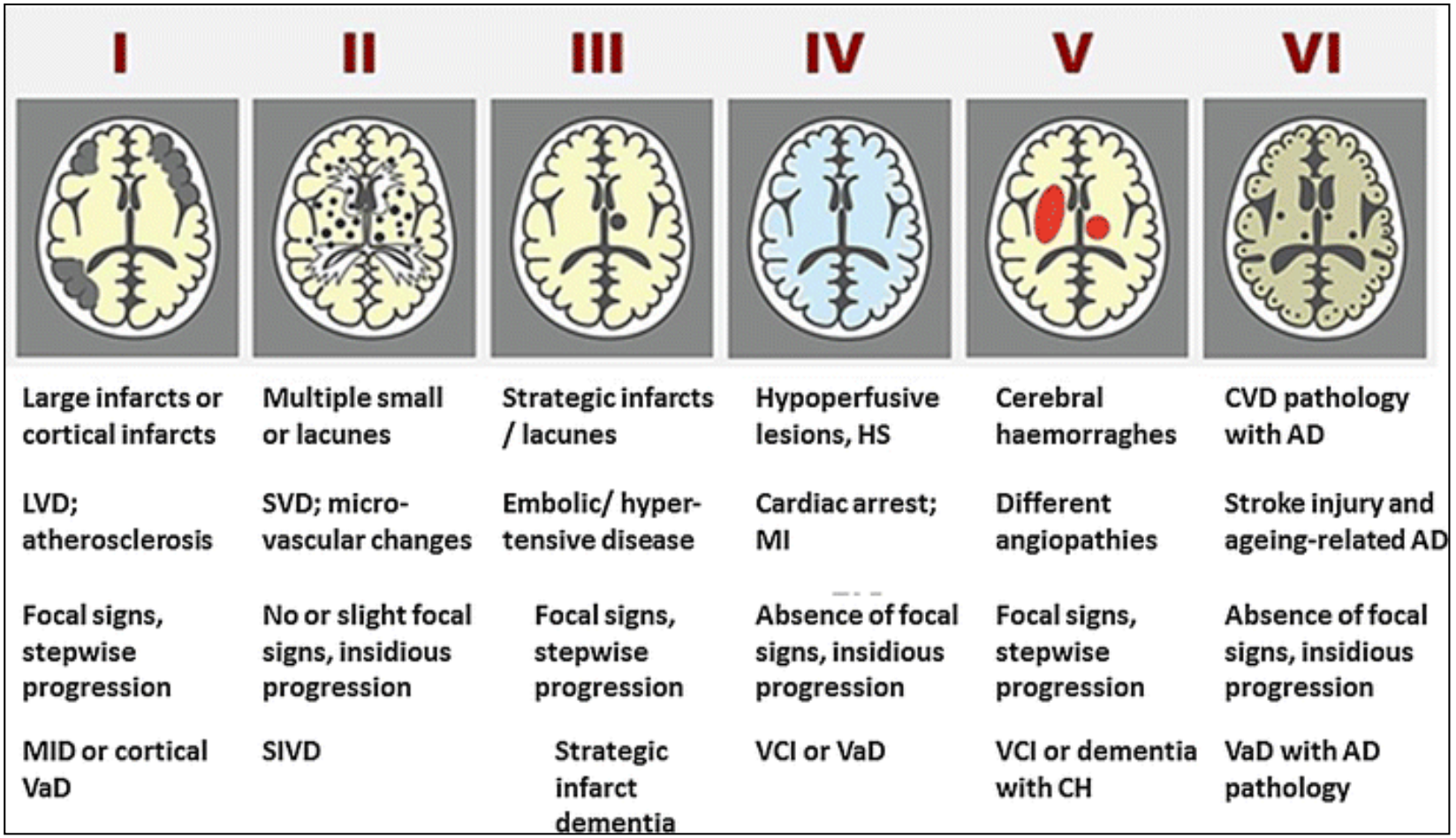
Vascular cognitive impairment (VCI)

- Classical phenotypes: early gait problems, impaired bladder/bowel control, and cognitive decline

- Close temporal relationship (< 3 months) with stroke might (but not always) be clarified.

- Diffuse cerebral vascular damages or strategic infarcts (angular gyrus, thalamus, basal forebrain, or PCA or ACA territories).

Pathology of VCI



Acta Neuropathologica May 2016, Volume 131, Issue 5, pp 659–685

NINDS-AIREN Diagnostic Criteria of VCI

NINDS–AIREN criteria for probable vascular dementia

The criteria for the clinical diagnosis of probable vascular dementia include all of the following:
Dementia
Defined by cognitive decline from a previously higher level of functioning and manifested by impairment of memory and of two or more cognitive domains (orientation, attention, language, visuospatial functions, executive functions, motor control, and praxis), preferably established by clinical examination and documented by neuropsychological testing; deficits should be severe enough to interfere with activities of daily living not due to physical effects of stroke alone.
Exclusion criteria: Cases with disturbance of consciousness, delirium, psychosis, severe aphasia, or major sensorimotor impairment precluding neuropsychological testing. Also excluded are systemic disorders or other brain diseases (such as AD) that in and of themselves could account for deficits in memory and cognition.
Cerebrovascular disease
Defined by the presence of focal signs on neurologic examination, such as hemiparesis, lower facial weakness, Babinski sign, sensory deficit, hemianopia, and dysarthria consistent with stroke (with or without history of stroke), and evidence of relevant CVD by brain imaging (CT or MRI) including multiple large vessel infarcts or a single strategically placed infarct (angular gyrus, thalamus, basal forebrain, or PCA or ACA territories), as well as multiple basal ganglia and white matter lacunes, or extensive periventricular white matter lesions, or combinations thereof.
A relationship between the above two disorders
Manifested or inferred by the presence of one or more of the following:
(a) Onset of dementia within three months following a recognized stroke;
(b) Abrupt deterioration in cognitive functions; or fluctuating, stepwise progression of cognitive deficits.

AD: Alzheimer disease; CVD: cerebrovascular disease; CT: computed tomography; MRI: magnetic resonance imaging.

A Useful Score to D/D AD from VCI

Hachinski ischemic score

Feature	Value
Abrupt onset	2
Stepwise deterioration	1
Fluctuating course	2
Nocturnal confusion	1
Preservation of personality	1
Depression	1
Somatic complaints	1
Emotional incontinence	1
Hypertension	1
History of stroke	2
Associated atherosclerosis	1
Focal neurologic symptoms	2
Focal neurologic signs	2

A high score (≥7) suggests vascular dementia, while a low score (≤4) suggests Alzheimer disease.

UpToDate®

Dementia with Lewy bodies (DLB)

- 3rd (or 2nd) leading cause of cognitive decline in late-life
- Incidence: 1/1,000/year general population
- A spectrum with similar pathology with PDD (and AD)
- Classical presentations: Fluctuation of cognitive and motor performances and vivid visual hallucinosis.

J Neurol Neurosurg Psychiatry 2010;81:742-746

Pathology of DLB

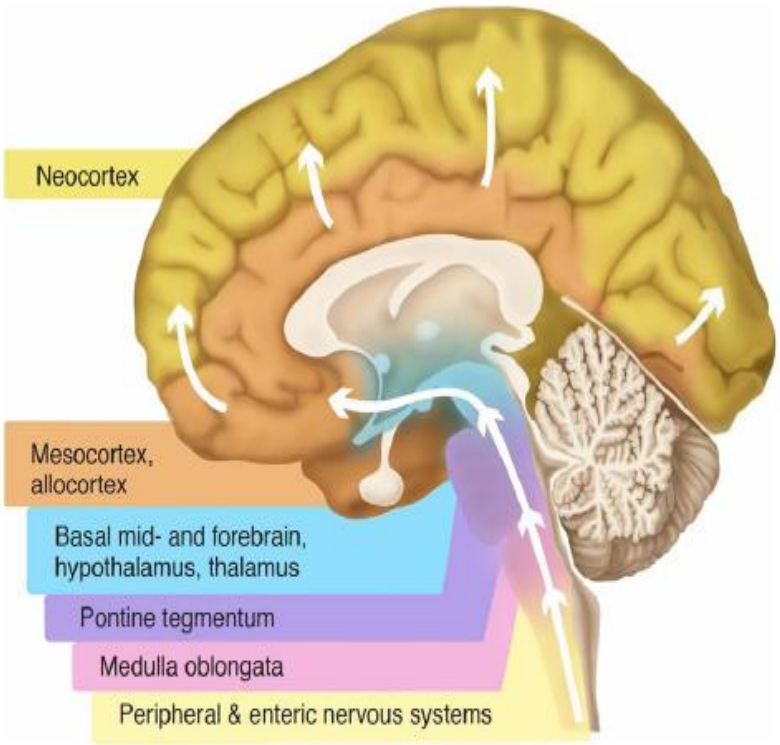
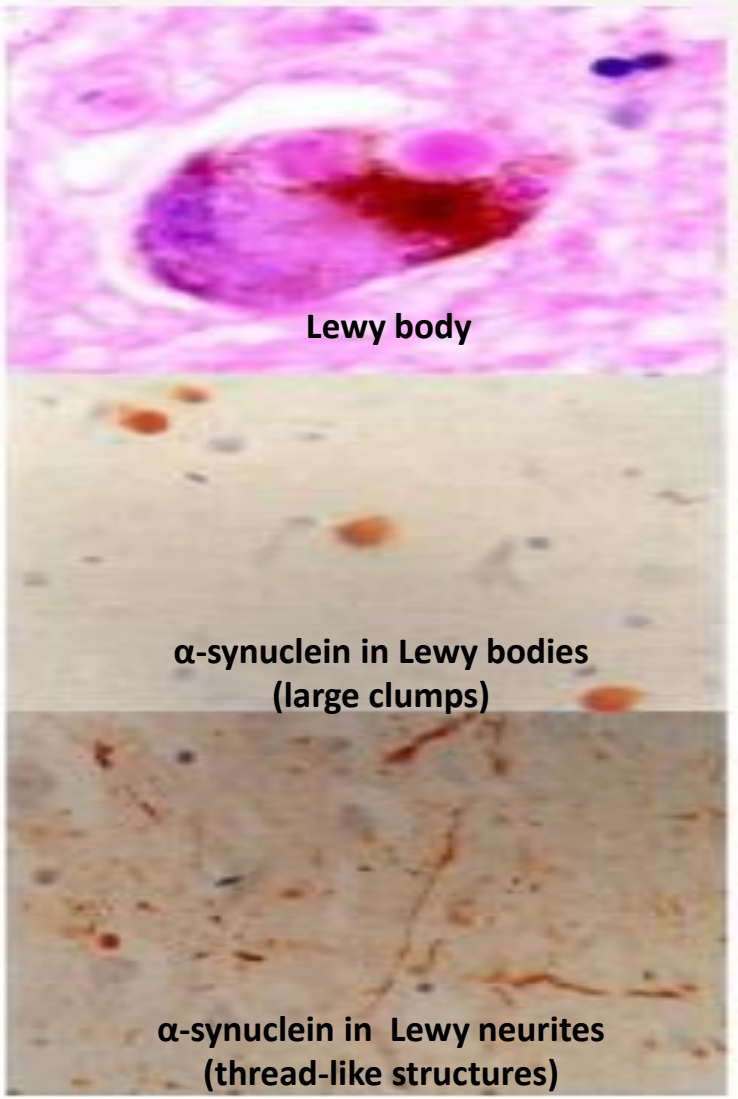


Figure 4 Progression of Lewy body pathology. Schematic diagram of the pattern of alpha-synuclein deposition as hypothesised by Braak and colleagues [32]. Deposition is first seen in the peripheral autonomic nervous system, including the enteric nervous system. This is then followed by deposition in the brainstem, ascending to the limbic system and, finally, the neocortex. Illustration from [88], available under creative commons license.



Alzheimer's Research & Therapy 2014, 6:46

Diagnostic Criteria of DLB

Clinical and radiologic features of dementia with Lewy bodies (DLB)

	Frequency in DLB (percent)*
Central feature (essential for the diagnosis)•	
Progressive cognitive decline, dementia	100
Core features (two features essential for diagnosis of probable DLB, one for possible DLB)•	
Fluctuating cognition	60-80
Recurrent well-formed, detailed visual hallucinations	50-75
Spontaneous features of parkinsonism	80-90
Suggestive features (one suggestive feature with one core feature may diagnose probable DLB, one or more suggestive features may diagnose possible DLB)•	
REM sleep disorder	85
Severe neuroleptic sensitivity	30-50
Low dopamine transporter uptake in basal ganglia on SPECT or PET	
Supportive features (common features with undetermined diagnostic specificity)•	
Repeated falls	33
Syncope or transient loss of consciousness	
Severe autonomic dysfunction	
Hallucinations in other modalities	20
Systematized delusions	55-75
Depression	30-40
Relative preservation of medial temporal lobe on MRI or CT	
Generalized low uptake on SPECT or PET perfusion imaging with reduced occipital activity	
Abnormal (low uptake) MIBG myocardial scintigraphy	
Prominent slow wave activity and temporal lobe transient sharp waves on EEG	
Conflicting features (features which make DLB less likely)•	
Cerebrovascular disease evidenced by focal neurologic signs or neuroimaging	
Other physical illness or brain disorder which is consistent with some or all of clinical features	
First appearance of parkinsonism at late stage (severe) dementia	
Temporal sequence (feature which distinguishes DLB from Parkinson disease dementia)•	
Dementia should occur before or concurrently with onset of parkinsonism	

* References for frequency provided in text.
• Consensus criteria of the third report of the DLB consortium. McKeith IG, Dickson DW, Lowe J, et al. Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. Neurology 2005; 65:1863.

Comparisons by Dementia Subtypes

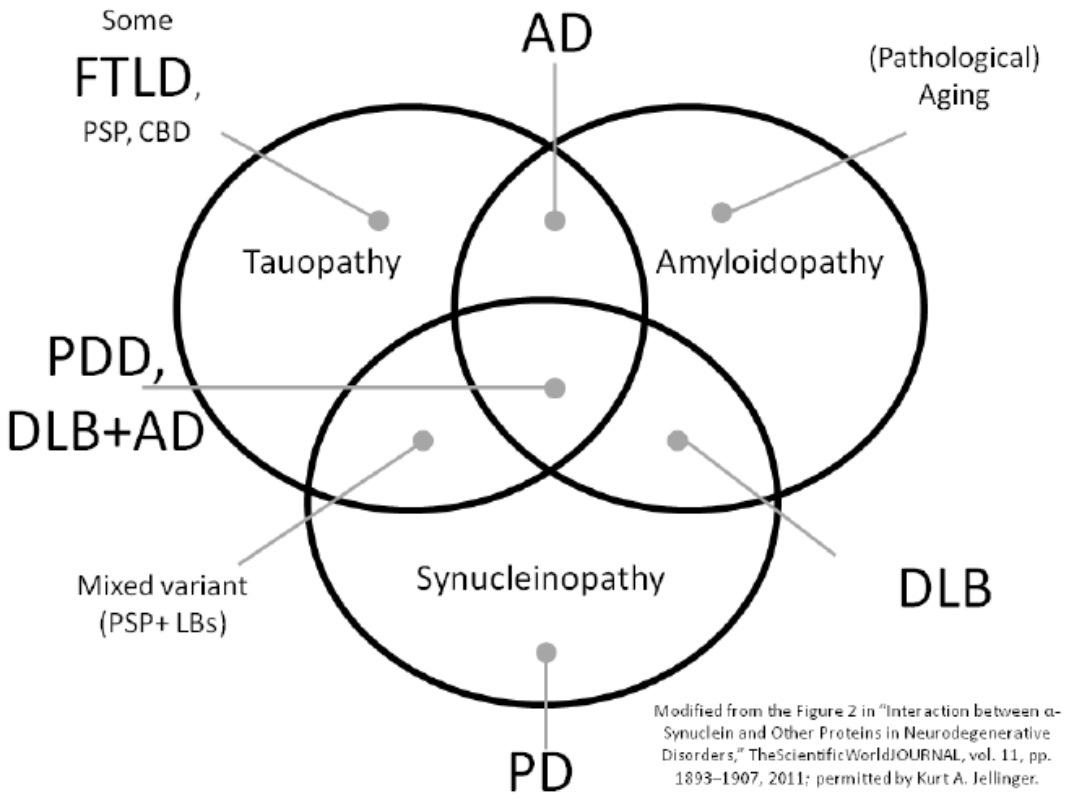
Dementia		Clinical Features	Biomarkers			Treatment
Category	Subtypes		Biochemical	Cognitive§	Imaging	
Primary	AD	● Amnestic ● Non-amnestic	● CSF Aβ42↓tau↑	● Memory ● Other cognitive domains	● MRI: MTL atrophy ● PET/CT: Aβ deposition ● SPECT/CT: T-P-O↓	● AchEI ● Memantine
	DLB	Dementia + ● Fluctuating cognition ● Recurrent visual hallucination ● Spontaneous parkinsonism	(Undetermined)	● Attention ● Visuospatial ● Executive function	● MRI: Aging brain with relatively preserved MTL ● SPECT/CT: BG↓O↓	● AchEI ● L-dopa
	FTLD	● Speech disturbance, or ● Behavior/personality changes, or both		● Language ● Social Cognition	● MRI: F-T atrophy	● Symptomatic treatment
Secondary	VCI	Cognitive complaints +/- ● Early gait problems/falls ● Early incontinence		● Executive function ● Attention	● Single-/Multi-infarcts ● Macro-/Micro-hemorrhage ● WMHs ● Vasculopathy	● CVA risk reduction ● AChEI (?) ● Memantine (?)

§Cognitive profiles in each dementia subtypes are those domains that are classically affected, yet not strictly confined to.
The most-validated treatment for AD is (i) AChEIs including donepezil, rivastigmine, and galantamine, and (ii) memantine as a N-Methyl-D-aspartate receptor antagonist. Benefits of AChEIs and memantine in DLB and VCI cases are less concretized. AChEIs: Acetylcholinesterase inhibitors; AD: Alzheimer's disease; BG: Basal Ganglia; CVA: Cerebrovascular Accident; DLB: Dementia with Lewy bodies; FTLD: Frontotemporal Lobar Degeneration; F: Frontal; MRI: Magnetic Resonance Imaging; MTL: Medial Temporal Lobe; O:Occipital; P: Parietal; Positron Emission Tomography/ Computed Tomography; PET/CT; Single Photon Emission Computed Tomography/Computed Tomography, SPECT/CT; T: Temporal; VCI: Vascular Cognitive Impairment; WMHs: White Matter Hyperintensities.

《表四》失智症臨床特徵、生物標記、暨對應藥物治療整理

失智症- 臨床與生物標記並行的診斷結構 涂敏謙

Comparisons by Proteinopathies



《圖三》常見神經退化性疾病與病理機轉

AD: 阿茲海默症；**CBD** :皮質基底核退化；**DLB**: 路易士體失智症；**FTLD**: 額顳葉失智症；

PD: 帕金森病；**PDD**:帕金森合併失智症；**PSP**:進行性核上麻痺症；**LBs**:路易士體。

失智症- 臨床與生物標記並行的診斷結構 冷敏謙

Modified figure from TheScientificWorldJOURNAL 11, 1893-1907; 2011, permitted by the authors