Overview of Dementia & Delirium

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Disclosures

I have no financial conflicts of interest to disclose.

http://www.cliparthut.com/clip-arts/647/monopoly-man-647882.jpg

Objectives

- Your handout asks us to cover:
  1. Define dementia, describe dx criteria
  2. Define MCI, dx criteria, conversion to dementia / year
  3. Eval of pt with MCI or dementia
  4. Compare / contrast clinical pres, pathophys, dx eval, and treatment for AD, Lewy body dementia, FTD, NPH, and vascular dementia.
  5. Define delirium, describe dx criteria, management with pharm & non-pharm methods.

Review Articles I Will Provide

1. Burns A & S Iliffe. Alzheimer's disease. *BMJ* 2009; 338: b158: 467-471.
2. **Carson A & T Ryan. Managing acute behavioral disturbance in a neurology ward. *Pract Neurol* 2010; 10: 67-81. (READ CLOSELY)**
3. Ferman TJ & BF Boeve. Dementia with Lewy bodies. *Neurol Clin* 2007; 25: 741-761.
4. Galasko D. The diagnostic evaluation of a patient with dementia. *Continuum (Minneap Minn)* 2013; 19:397-410.
5. Graff-Radford NR. Normal pressure hydrocephalus. *Neurol Clin* 2007; 25: 809-832. **(With two-page Word abstract hitting the main points).**
6. **Petersen RC. Mild cognitive impairment. *NEJM* 2011; 364: 2227-2234 (with appendix on mental status tests). (READ CLOSELY)**
7. **Schneider L. Alzheimer's disease: pharmacologic treatment and treatment research. *Continuum (Minneap Minn)* 2013; 19:339-357. (Skim)**
8. Warren JD & MN Rossor. Frontotemporal dementia. BMJ 2013; 347:f4827. doi 10.1136/bmj.f4827

Our plan today

- Review dementia using a **syndromic** approach
- Identify distinguishing features of dementia syndromes

Four quibbles

A quibble is to Shakespeare what luminous vapours are to the traveller: he follows it at all adventures; it is sure to lead him out of his way and sure to engulf him in the mire.

(Samuel Johnson)

izquotes.com

http://izquotes.com/quotes-pictures/quote-a-quibble-is-to-shakespeare-what-luminous-vapours-are-to-the-traveller-he-follows-it-at-all-samuel-johnson-329612.jpg

Your assigned reading is pretty good. However….

- Mild cognitive impairment is usually NOT associated with “diminished independence…” (p. 38)

Petersen RC. NEJM 2011; 364: 2227-2234
Albert MS et al. Alzheimer’s & Dementia 2011; 7: 270-279

Your assigned reading is pretty good. However….

- "CSF biomarkers have no role in clinical diagnosis of AD…" (true)…"because of the absence of disease-modifying therapies…" (false) (p. 41)

- The reason not to send CSF is because:
  - Lab standards are still not uniform
  - Performance characteristics of tests (spec, sens, PPV, NPV) in *individuals* not yet precisely known.

McKhann GM et al. Alzheimer's & Dementia 2011; 7: 263-269
Tso J. Continuum (Minneap Minn) 2013; 19: 475-479

Your assigned reading is pretty good. However….

- The presence of motor & cognitive symptoms within 12 months is a handy mnemonic
- But NOT sufficient to distinguish dementia with Lewy bodies from Parkinson's disease dementia (p. 42)

Ferman TJ & BF Boeve. Neurol Clin 2007; 25: 741-761.

Your assigned reading is pretty good. However….

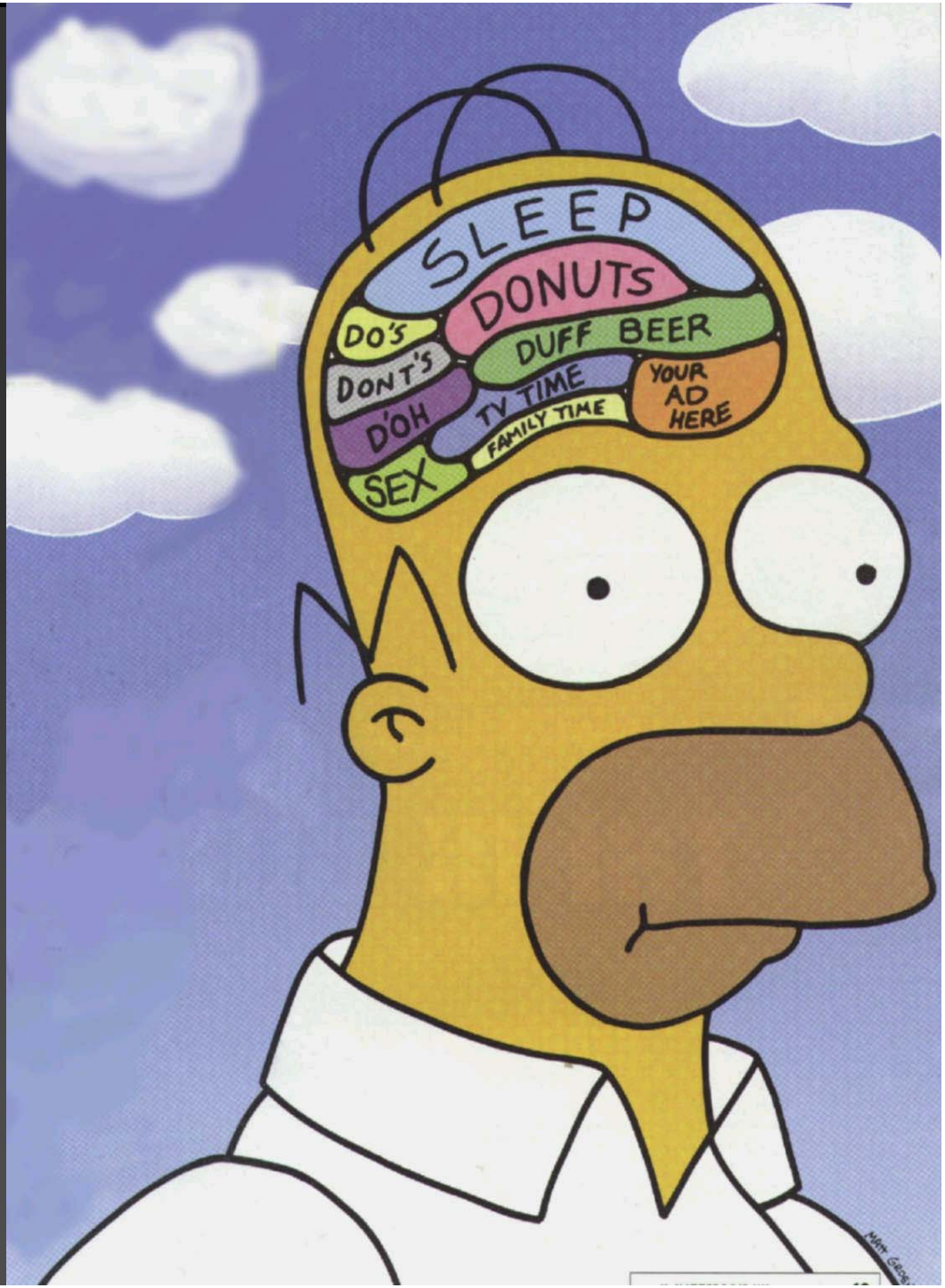
- Non-contrast CT or MRI are useful.
- If there is no contraindication, use a 21st century imaging test (MRI).*

- When checking B12, also check methylmalonic acid.†

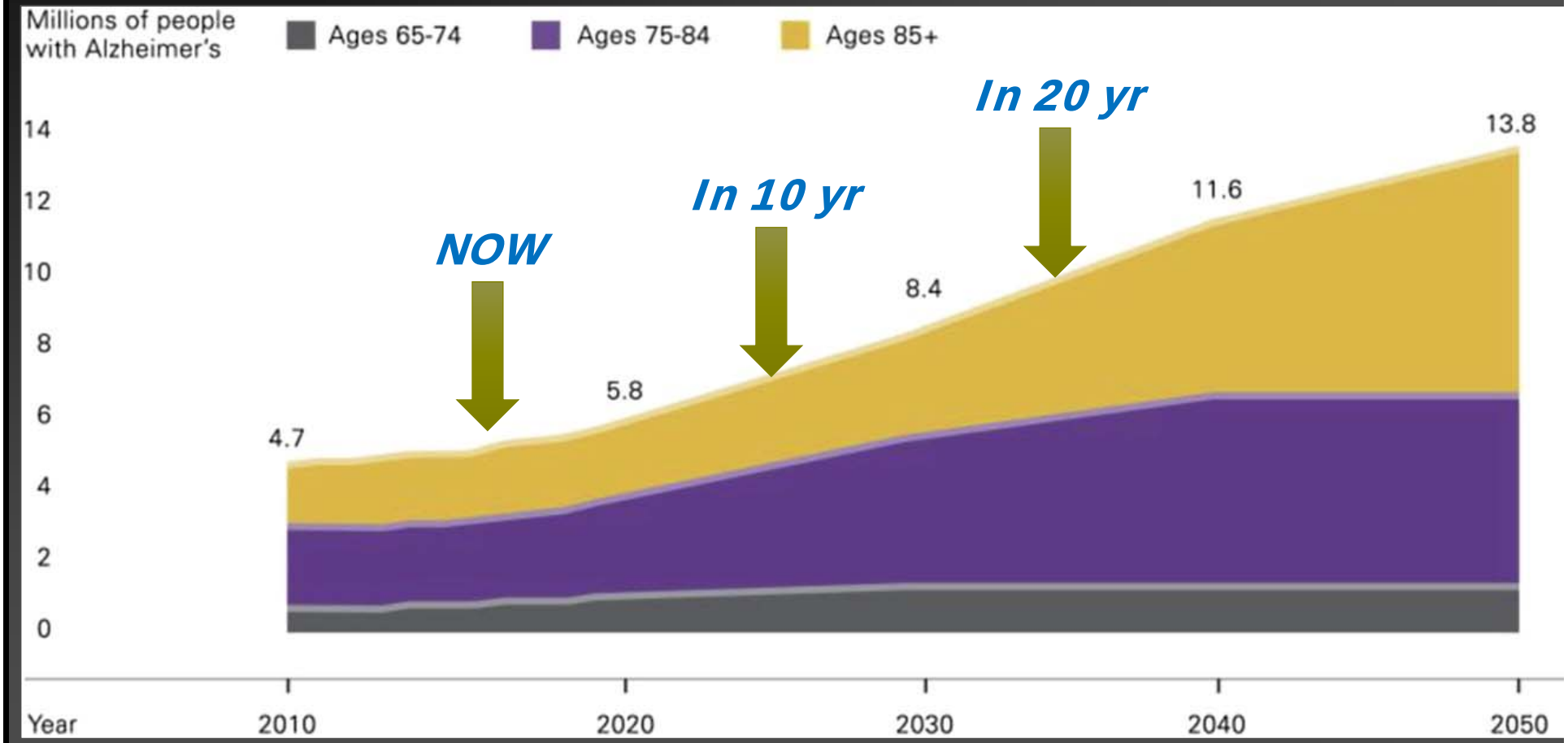
* Albert M et al. The Use of MRI and PET for Clinical Diagnosis of Dementia and Investigation of Cognitive Impairment: A Consensus report. Neuroimaging Work Group, Alzheimer's Association. Full text at : www.alz.org/national/documents/imaging_consensus_report.pdf

† Stabler SP. *NEJM* 2013; 368: 149-160.

Dementia


SLEEP
DONUTS
DO'S
DUFF BEER
DON'T'S
TV TIME
YOUR AD HERE
D'OH
FAMILY TIME
SEX

Number of People with AD is Increasing



Source: Alzheimer's Association

Alzheimer's & Dementia: The Journal of the Alzheimer's Association 2015 11, 332-384DOI: (10.1016/j.jalz.2015.02.003)

Alzheimer's treatment needs intensify role of primary doctors

Experts hope dementia prevention options become as routine as those for other common medical problems.

Victoria Stagg Elliott
AMNEWS STAFF

THE INCIDENCE OF ALZHEIMER'S disease is expected to more than triple in the coming decades. And new treatments and research into prevention will put primary care physicians on the front lines of dealing with the debilitating condition.

Much of the management and treatment of the disease has been largely in the realm of the specialist. But with the emergence in the past few years of modestly effective treatments for Alzheimer's that work primarily in the early stages, primary care physicians are already under increasing pressure to diagnose the disease early.

$31.9 billion
Cost to Medicare for Alzheimer's disease care in 2000

$49.3 billion
Expected cost to Medicare in 2010

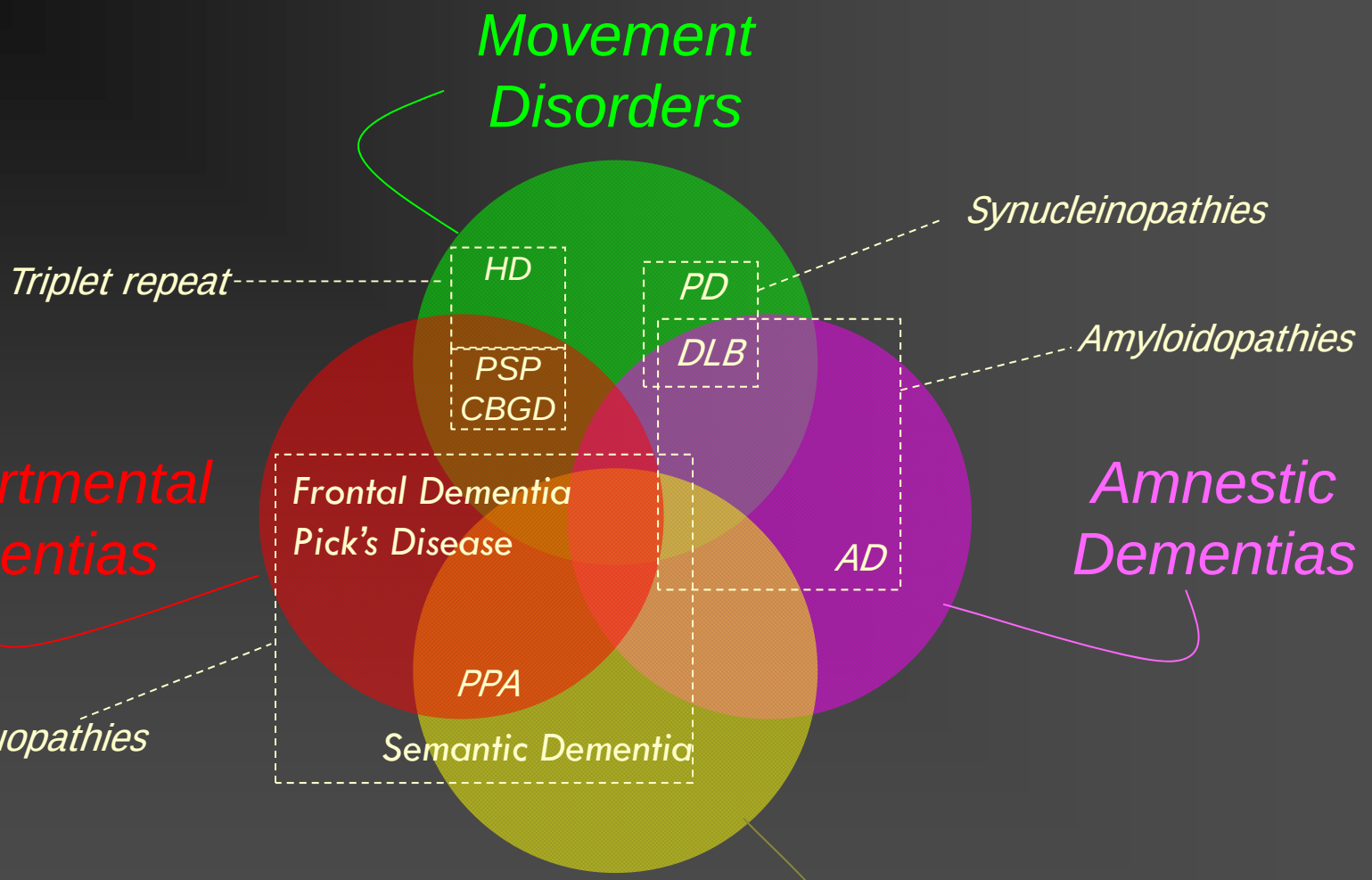
"The most urgent thing clinically is identifying people who, by the nature of the illness, won't present themselves for care," said Richard J. Ham, MD, director of the Center on Aging at West Virginia University in Morgantown. "Most people don't get diagnosed until they've had the disease for years."

Early detection remains extremely challenging. Diagnosis of mild cognitive impairment may indicate the patient eventually may develop full-blown Alzheimer's, but it also may not. Treatment efficacy remains modest if it works at all.

"The issue that the researcher and the clinician face is trying to figure out if somebody, especially over the age of 65 or 70, is experiencing cognitive impairment because of depression, heart disease or medications they take, or are they on the way to dementia," said Steven DeKosky, MD,

Continued on next page

Dementia in a Single Slide

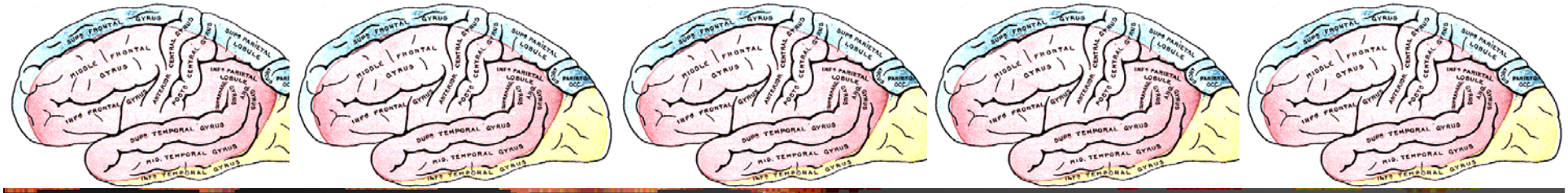


Relkin NR & GL Caporaso. Degenerative diseases. In: Rizzo M & PJ Eslinger (eds). Principles and Practice of Behavioral Neurology and Neuropsychology. Philadelphia: Saunders, 2004, pp. 477-513

Features of Dementia

- Usually gradual in onset & progression
  - Exception: vascular dementia
- Affects at least 2 cognitive domains
  - Memory *often* but not always involved
- Represents a *decline from a premorbid ability*
- Affects ADLs
- No better explanation

Galasko D. Continuum (Minneap Minn) 2013; 19: 397-410



Elements of Diagnosis in Any Cognitive Complaint

Diagnosis =

Tests of major cognitive domains

+

Tempo of evolution of symptoms

+

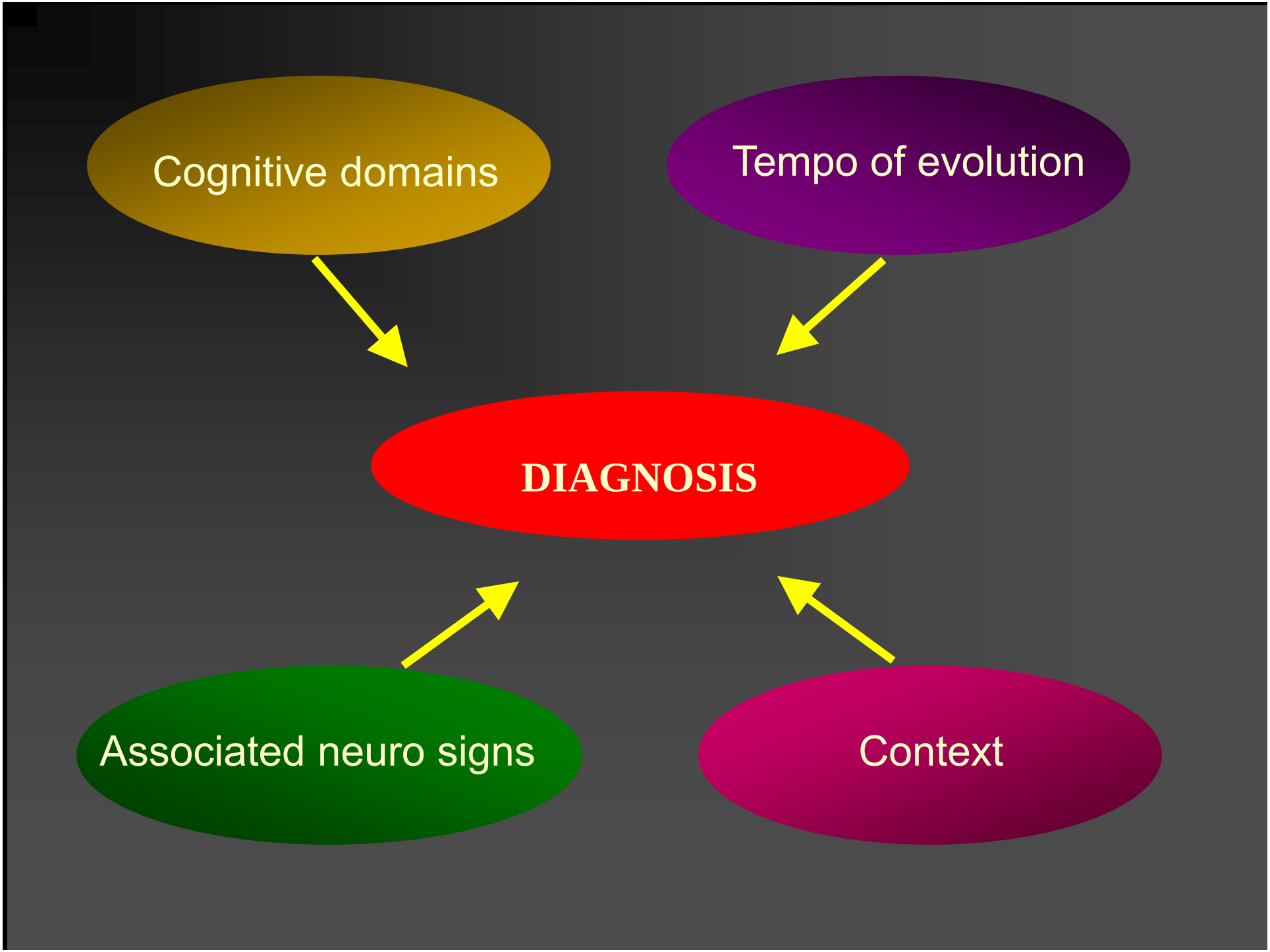
Associated neurologic signs

+

Context (other diseases, etc.)

Diagnosis =

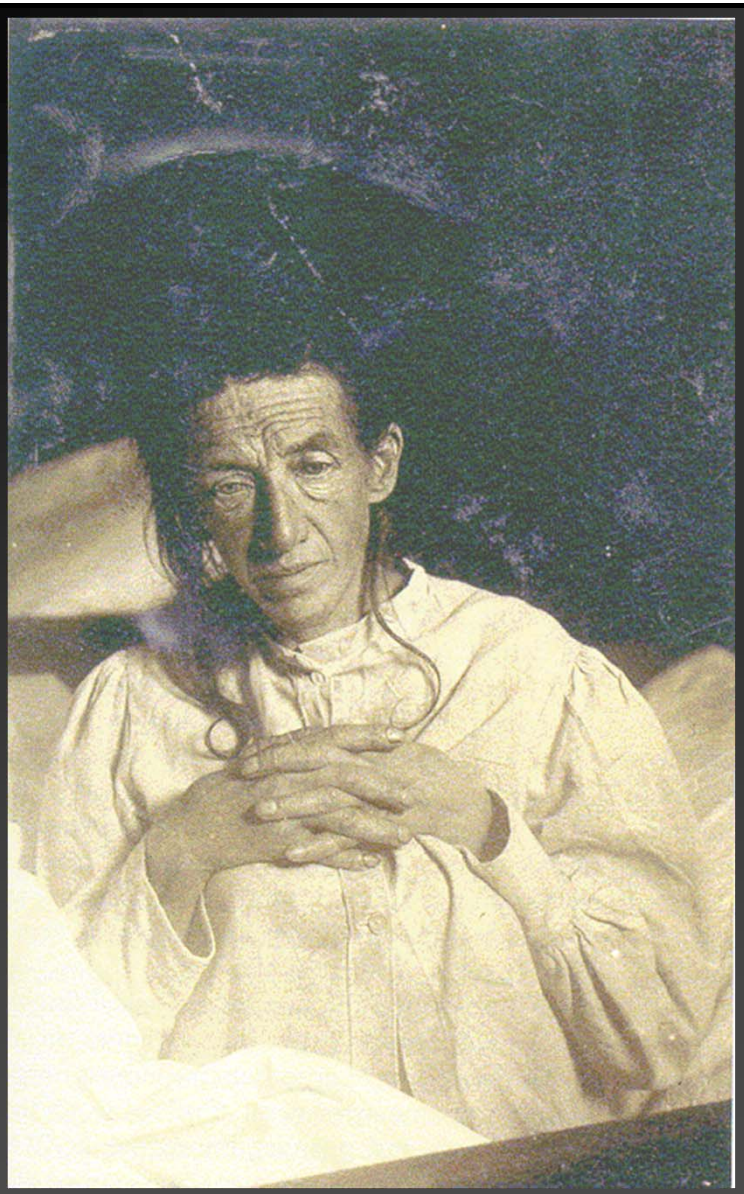
- Tests of major cognitive domains
  - Frontal, perisylvian, visuospatial, praxis, mood, Ψ
- Tempo of evolution of symptoms
  - Gradually progressive, stepwise, fluctuating, chronic, subacute, acute, or combination
- Associated neurological signs
  - Focal signs, parkinsonism, neuropathy, myopathy
- Context (e.g., other diseases)
  - Vascular disease elsewhere, infectious diseases, liver disease, lung disease


Cognitive domains
Tempo of evolution
DIAGNOSIS
Associated neuro signs
Context


Key Syndromes

Primary Amnestic Syndromes

- Alzheimer's Disease
- Mild Cognitive Impairment



Auguste D., ca. 1902

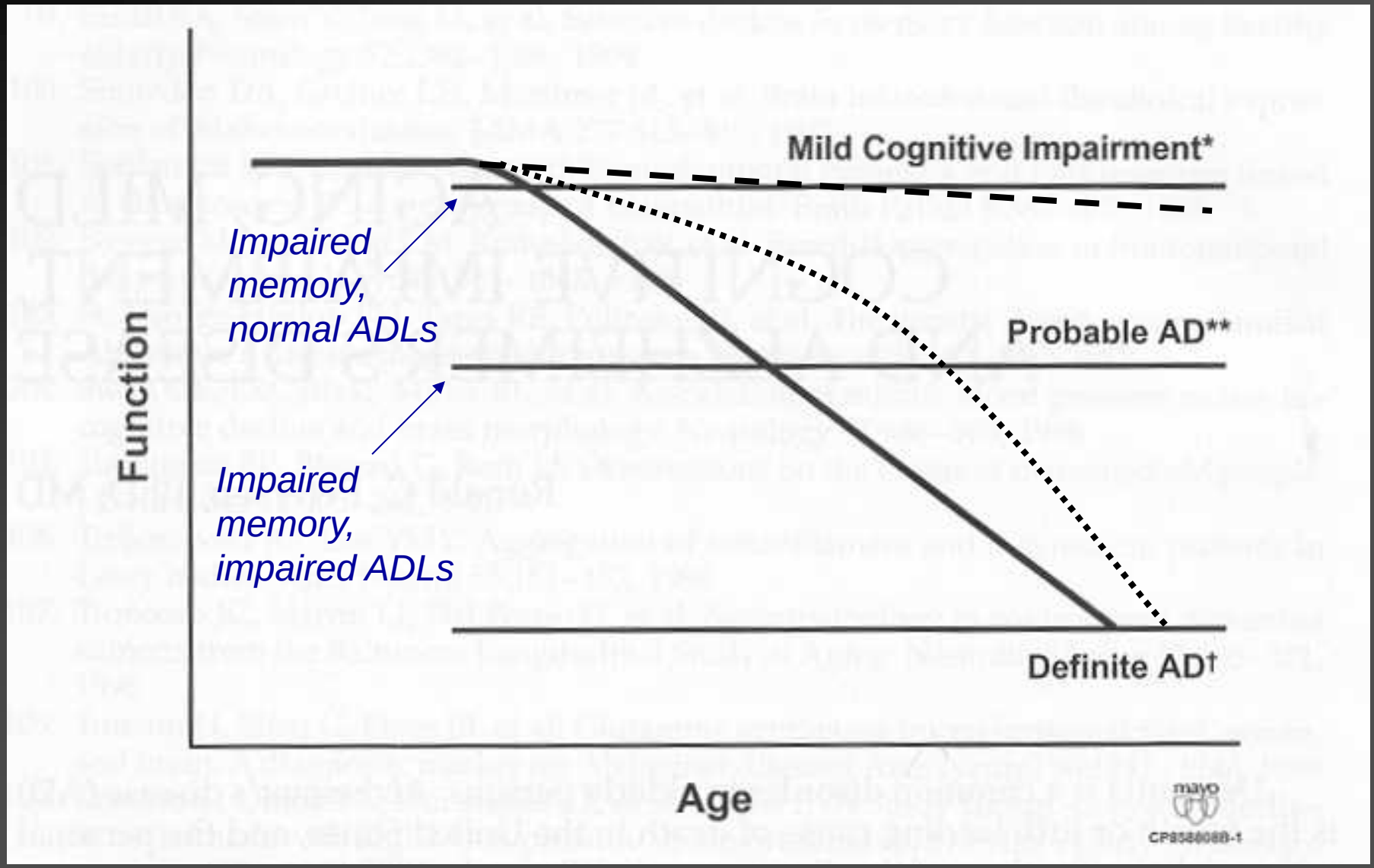
Alois Alzheimer, ca. 1907

Maurer K et al. Lancet 1997; 349: 1546-1549

Key Concept

Significant declines in cognitive function do not represent normal aging.

Multiple refs. E.G., *Brain & Cog* 2006;60:146.



Adapted from Petersen, 2002

Alzheimer's Disease

- DOMAINS
  - Memory invariably involved
  - Apraxia, amnesia, aphasia, agnosia, neglect
- TEMPO
  - Gradually progressive
- ASSOCIATED FINDINGS
  - Paratonia
- CONTEXT
  - Usually otherwise healthy

Neurology 1984;34:939.
DSM IV 1994

Key Concepts of AD

- Age is the single greatest risk factor
- Acetylcholine is the main transmitter affected
  - Glutamate, NE, 5-HT, & others are affected
- Apo-E status increases risk
- Role of insulin-like growth factors unclear
- Aβ-42 is increased in brain but *low* in CSF
- Tau is increased in CSF
- PET CT and β-amyloid CT may soon be approved for general use

→ ***Do <u>not</u> send these labs*** ←

Treatment of AD

- The 3 FDA-approved cholinesterase inhibitors are equal in efficacy for AD.
  - EXCEPTION: Exelon appears better for Parkinson's disease dementia.
  - TIP: avoid oral Exelon, favor Exelon patch.
    - Oral has more diarrhea, nausea.
- Begin with cholinesterase inhibitor therapy, add memantine for mid- to late-stage dz once cholinesterase inhibitor dose is stable.

Treatment of AD

- Cholinesterase inhibitors slow decline *even in late stage AD*.
- "Lack of efficacy" in late stage disease is not a reason to d/c.
- Possible reasons to d/c in late stage dz:
  - Side effects (nausea, diarrhea)
  - Ethical: what are we prolonging?
- Additional possible benefit in late stage dz: psychiatric sx (depression, anxiety, agitation)

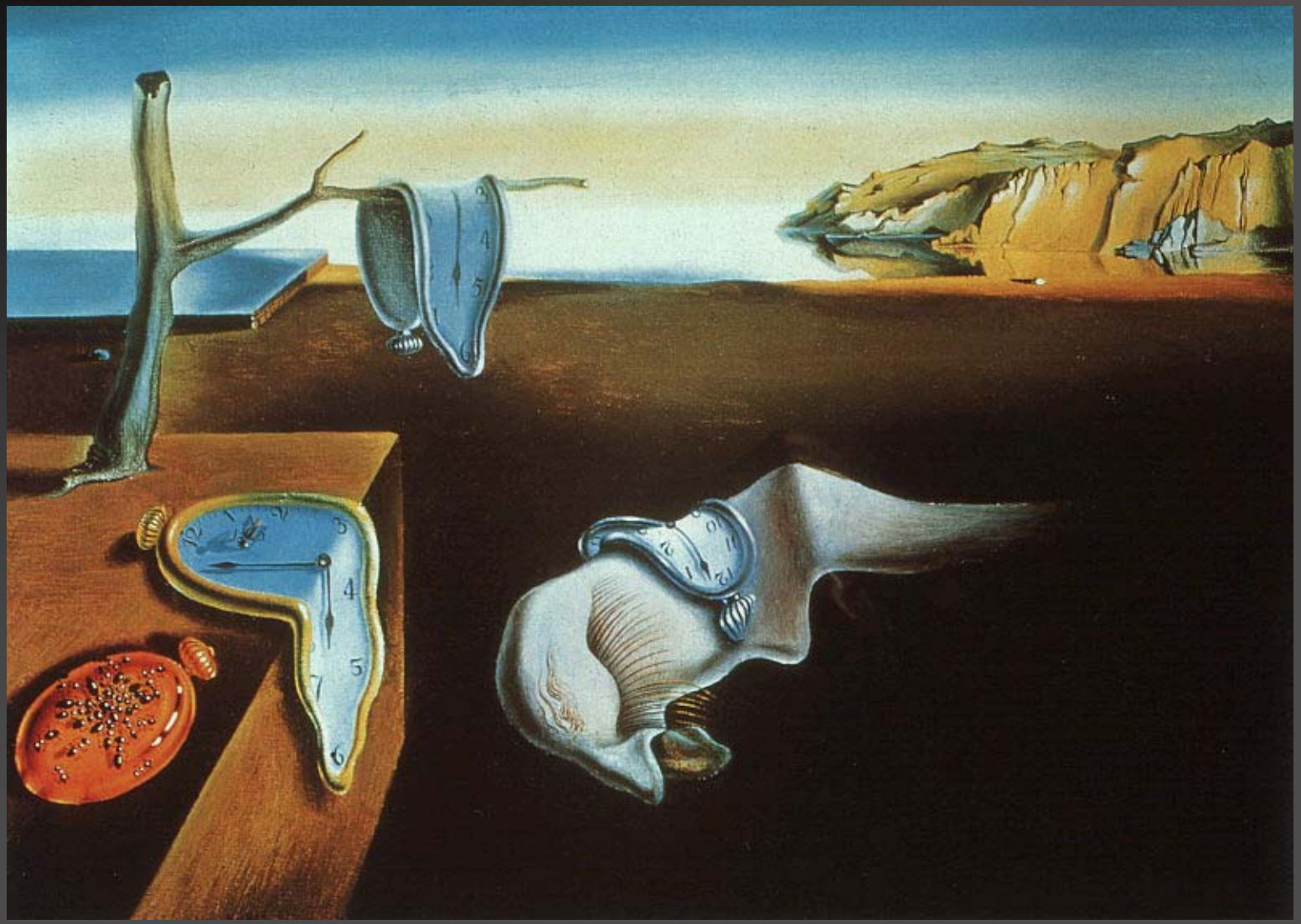
Feldman et al., Neurology 2001;57:613-620.
Lockhart IA et al. Dement Geriatr Cogn Dis Extra. 2011; 1: 212-227.
Kaduszkiewicz H et al. BMJ 2005; 331: 321-327

Future Treatment of AD

- Immunotherapy is in phase 3 clinical trials*, †
- Genetic tx of Apo-E is in phase 1-2 trials ‡
- Pre-symptomatic detection is a focus of intense work§
- Prevention is the target of a $100 M clinical trial £, ¥
- See www.banneralz.org/ for more info

* Agadjanyan MG et al. *Alz & Dem* 2015; 11: 1246-1259
† Wisniewski T & F Goñi. *Neuron* 2015; 85: 1162-1176
‡ Liu C-C et al. *Nat Rev Neurol* 2013; 9: 106-118
§ Sperling RA et al. *Alz & Dem* 2011; 7: 280-292
£ Tariot PN et al. *Alz & Dem* 2014; 10(4): supplement P247
¥ Reiman EM et al. *J Alzheimers Dis* 2011: 26 (suppl 3): 321-329

Mild Cognitive Impairment (MCI)



Salvador Dali,
Persistence of Memory
Oil on canvas, 1931

Mild Cognitive Impairment (MCI) Amnestic Type: Clinical Definition

- DOMAIN
  - Memory *only*
  - Memory impairment corroborated by friends/family
  - Intact ADLs
- TEMPO
  - Gradual onset, variable decline
  - Conversion to AD: ~ 16 – 20% per year
- ASSOCIATED FINDINGS
  - Otherwise normal
- CONTEXT
  - Otherwise healthy

Petersen R. *Mild Cognitive Impairment.* New York: Oxford, 2003

Mild Cognitive Impairment (MCI) Amnestic Type: Research Definition

- Subjective memory impairment corroborated by other informants
- Performance on objective memory tests > 1.5 SD below norms for age & education
- Intact ADLs
- Otherwise normal cognitive function

Albert MS et al. *Alz & Dem* 2011; 7: 270-279

Amnestic MCI: Key Points

- Increased risk of AD
  - Conversion rate to AD 16-20% per year
  - 1-2 % per year for healthy elderly
- Is all MCI just early AD?
  - Maybe yes, maybe no
  - Seems safe to assume that not all MCI is the same
  - Some MCI patients appear stable over many years

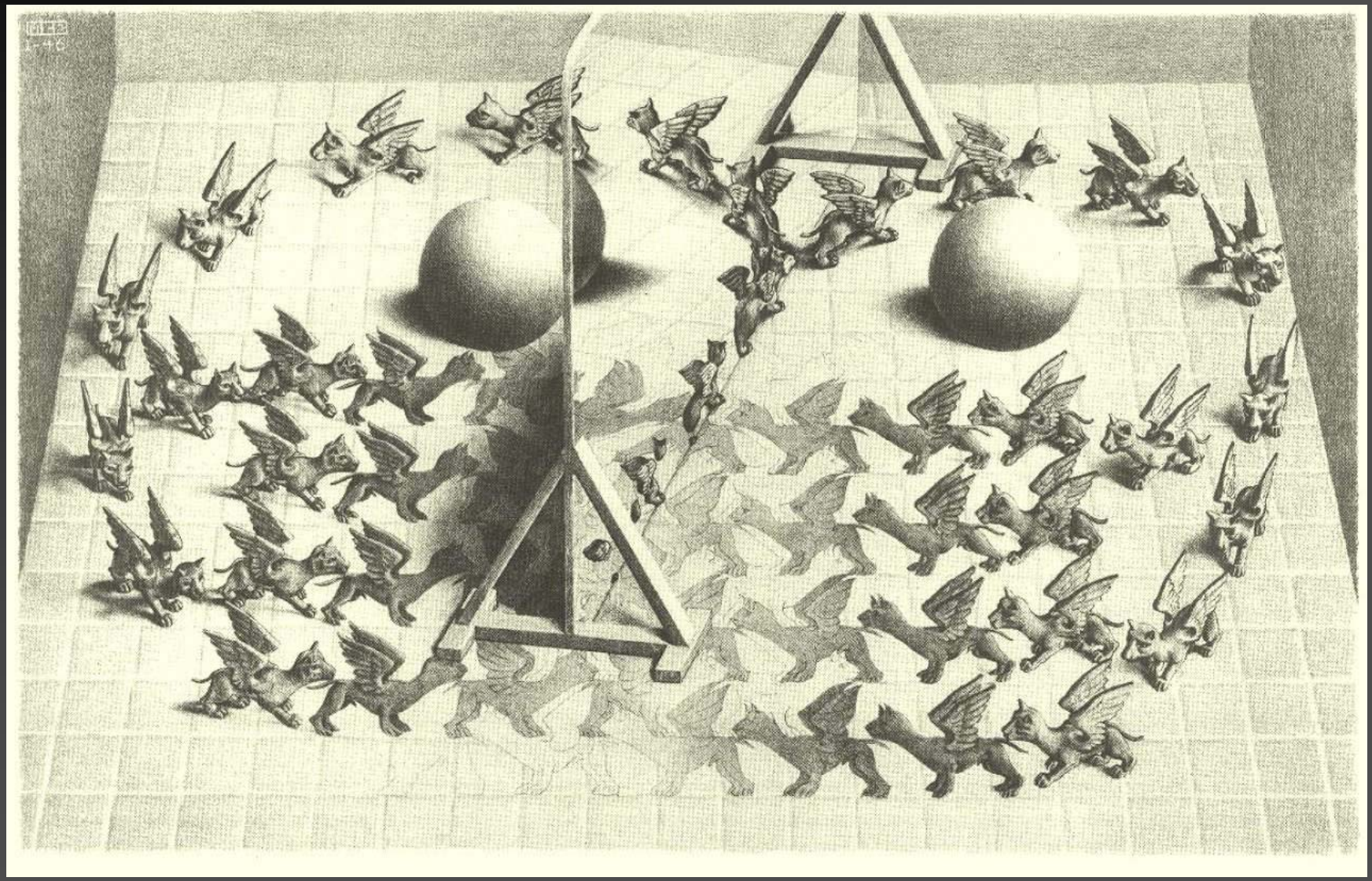
Petersen R. *NEJM* 2011; 364: 2227-2234

Amnestic MCI: Treatment

- Optimal tx not known
- "Vitamin E & Donepezil for Treatment of MCI"*
  - Vitamin E showed no benefit
  - Aricept slowed progression to AD only during the first 12 months of therapy
- Many questions remain
  - Are all subjects with MCI the same?
  - Is 3 years sufficient follow up?
  - Subgroup analyses suggest higher benefit for some subjects – there seem to be subtypes of MCI (likely true pre-AD MCI derives most benefit)
- Should we still use donepezil in MCI????

* Petersen R et al. *NEJM* 2005; 352: 2379-2388
Cooper C et al. *Br J Psychiatry* 2013; 203: 255-264

Other Dementias



M. C. Escher, “The Magic Mirror”
Lithograph, 1946

Other Dementias

- Vascular
- Parkinson's plus
  - Dementia with Lewy bodies
  - PSP
  - CBD
- Frontal
- NPH

Multi-infarct dementia

- No formal diagnostic criteria[1]
- DOMAINS
  - Multiple domains (and may look like AD)
- TEMPO
  - Gradual; step-wise hx not always clear
- ASSOCIATED FINDINGS
  - Supported by MRI findings
  - Often multiple abnormalities on elemental exam
  - Hachinski ischemic index score (?)
- CONTEXT
  - Vascular risk factors
- ***Treatment of modifiable risk factors***

[1]See Chui et al., *Arch Neurol* 2000;57:191-196

Parkinson's Plus Syndromes

- Dementia with Lewy bodies (DLB)
- Progressive supranuclear palsy (PSP)
- Corticobasal degeneration (CBD)
- ~~Multiple system atrophy (MSA)~~

Parkinson's Plus Syndromes

- Common to all syndromes:
  - DOMAINS
    - All associated with apraxia, amnesia, bradyphrenia.
  - TEMPO
    - Gradual
    - Progression often atypical for PD (rapid, fluctuating, etc.).
  - ASSOCIATED FINDINGS
    - Parkinsonism w/o sustained improvement on Sinemet.
  - CONTEXT
    - ~~Cognitive & motor impairments evolve *within 12 months* of each other.~~
    - No better explanation (e.g., multi-infarct).

Lopez et al., *Neurol* 1999;53:1292-1299

Parkinson's Plus Syndromes

- Common to all syndromes:
  - Cholinergic deficit → cholinesterase inhibitor therapy is appropriate
  - Unknown if memantine may benefit
  - Trial of carbidopa / levodopa may or may not be of benefit, and benefit may not be sustained
  - Antipsychotic medications may be needed for aggression, hallucinations
    - Quetiapine usually least offensive

Ferman TJ & BF Boeve. *Neurol Clin* 2007; 25: 741-761

Lopez et al., *Neurol* 1999;53:1292-1299

Parkinson's Plus Syndromes

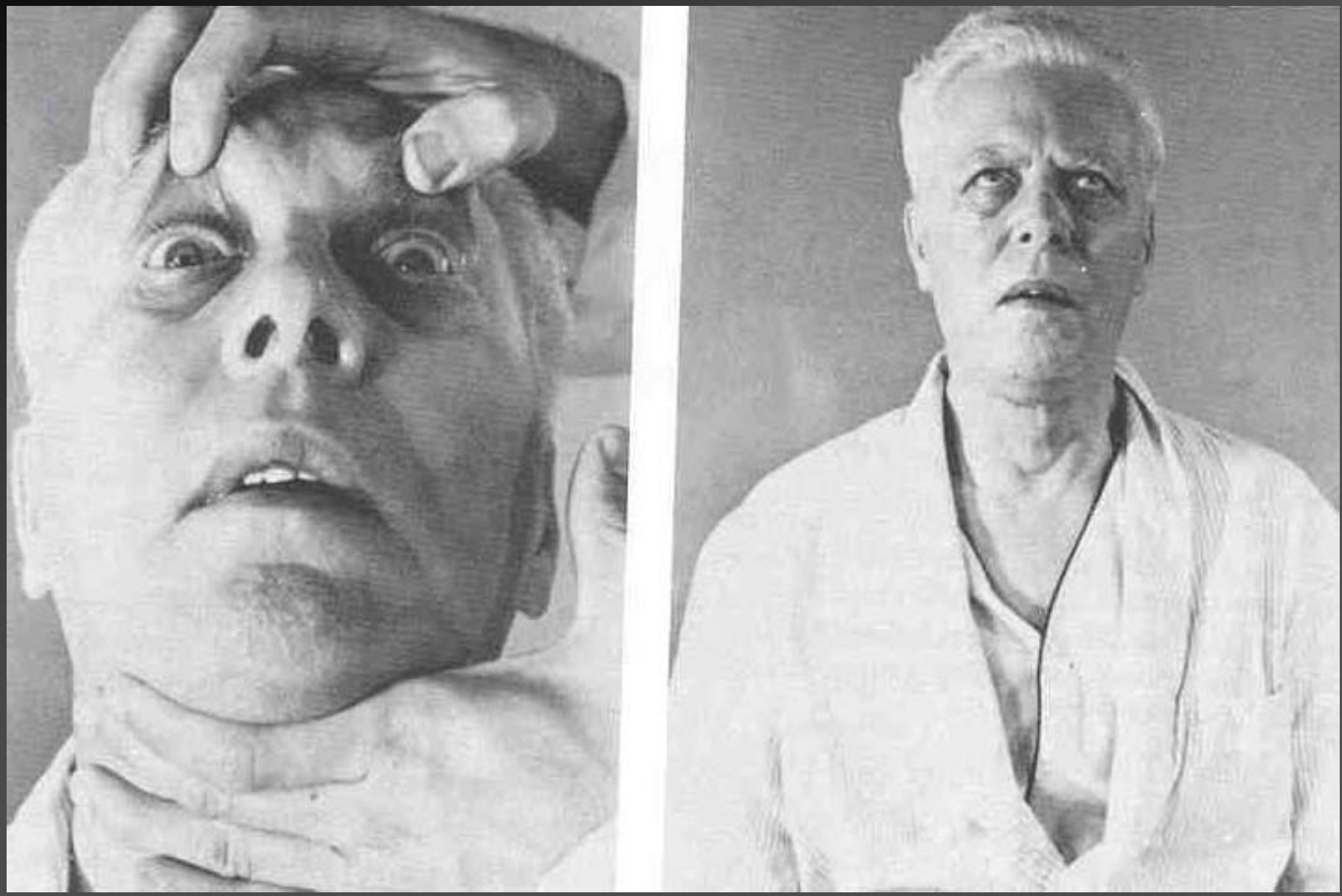
- Dementia with Lewy Bodies (DLB; ~~DLBD~~)
  - DOMAINS
    - Amnesia with motor findings
  - TEMPO
    - Gradual, *fluctuating cognition* (dramatic)
  - ASSOCIATED FINDINGS
    - *Parkinsonism*
    - *Visual hallucinations*
  - CONTEXT
    - Sensitivity to neuroleptics
    - Hallucinations other than visual
    - Early falls
    - Depression
    - REM sleep behavior disorder

McKeith et al., *Neurol* 2000;54:1050-1058
Lopez et al., *Arch Neurol* 2002;59:43-46

Parkinson's Plus Syndromes

- Progressive Supranuclear Palsy (PSP)
  - DOMAINS
    - Apraxia, amnesia
  - TEMPO
    - Gradual
  - ASSOCIATED FINDINGS
    - *Supranuclear vertical gaze palsy*
    - *Early postural instability*
    - *Axial rigidity*
  - CONTEXT
    - Otherwise healthy

Litvan et al., *Neurol* 1996;47:1-9



Parkinson's Plus Syndromes

- Corticobasal(ganglionic) Degeneration CB(G)D
  - DOMAINS
    - Alien limb/"useless arm" = *severe, **asymmetric** apraxia & rigidity*
    - Cortical sensory loss
  - TEMPO
    - Gradual
  - ASSOCIATED FINDINGS
    - Stimulus-sensitive myoclonus
    - Frontal release signs
  - CONTEXT
    - Otherwise healthy

Riley & Lang, *Adv Neurol* 2000;82:29-34

Dufoil, 1885

Frontal Dementias

Frontal & Frontotemporal Dementias

- Frontal dementia (behavioral variant)
- Semantic dementia
- Primary progressive aphasia (PPA)

Frontal/Frontotemporal Dementia

- DOMAINS
  - Early personality change OR (AND?)
  - Early language impairment
  - [Apraxia, executive dysfunction, vigilance errors, perseveration/impersistence, concrete thought, anosognosia]
- TEMPO
  - Gradual onset, decline of variable rapidity
- ASSOCIATED FINDINGS
  - Frontal release signs
- CONTEXT
  - Often younger (~ 50's)

Warren JD & MN Rossor *BMJ* 2013; 347:f4827. doi 10.1136/bmj.f4827

Working Group on Frontotemporal Dementia and Pick's Disease, *Arch Neurol* 2001

Normal Pressure Hydrocephalus

NPH

- DOMAINS
  - Difficulty walking
  - Urinary incontinence
  - Memory problems *but no cortical signs* (aphasia, apraxia, agnosia)
- TEMPO
  - Gradual onset, decline of variable rapidity
- ASSOCIATED FINDINGS
  - “Magnetic gait”
- CONTEXT
  - Prior SAH or CNS dz more consistent with NPH

Graff-Radford NR. Normal pressure hydrocephalus. Neurol Clin 2007; 25: 809-832.
Finney GR. Normal pressure hydrocephalus. Int Rvw Neurobiol 2009; 84: 263-281.

The New England
Journal of Medicine

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Volume 273 JULY 15, 1965 Number 3

SYMPTOMATIC OCCULT HYDROCEPHALUS WITH "NORMAL" CEREBROSPINAL-FLUID PRESSURE*

A Treatable Syndrome

R. D. ADAMS, M.D.,† C. M. FISHER, M.D.,‡ S. HAKIM, M.D.,§ R. G. OJEMANN, M.D.,¶ AND W. H. SWEET, M.D.‖

BOSTON, MASSACHUSETTS, AND BOGOTÁ, COLOMBIA

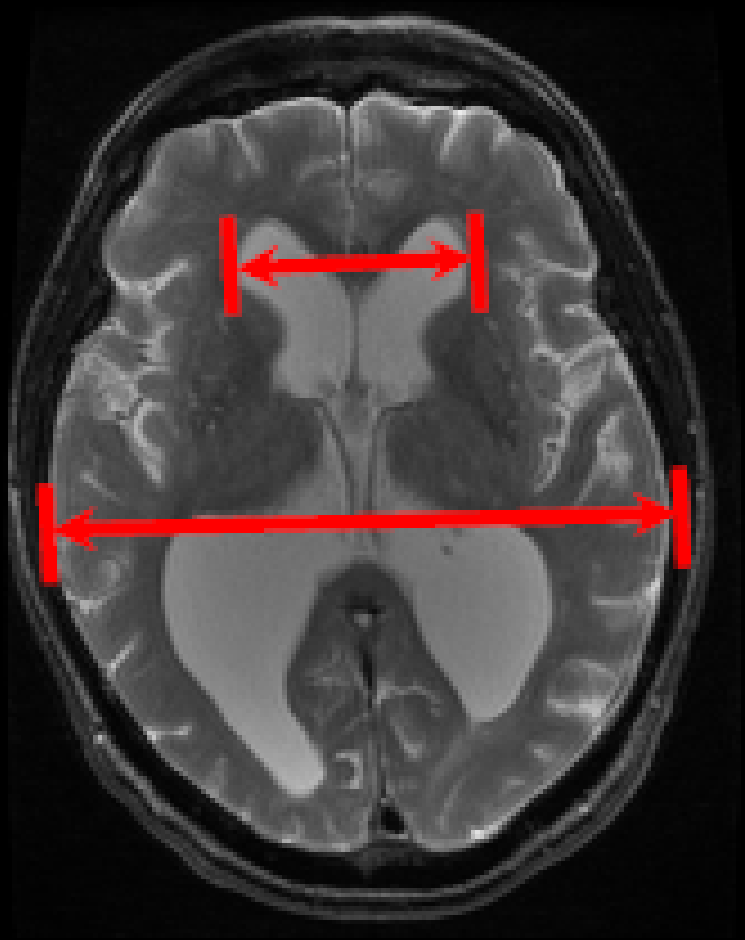
- Single LP in each of 3 patients.
- One patient later found to have obstructive 3rd ventricular lesion

Tips on NPH

Graff-Radford, Neurologic Clinics 2007:25:809-832; see the 2 page handout I promised.

- HISTORY
  - Pts with dementia > 2 years are less likely to respond to surgery.
  - If gait disorder began before or concurrently with dementia, improvement with surgery is more likely.
- TESTING
  - Evans index & callosal angle helpful.
  - Large volume LP: 30-50 cc.
  - Poor sensitivity (~25%) but good positive predictive value.
  - Look for improvement of gait immediately after LP.

Evan's index

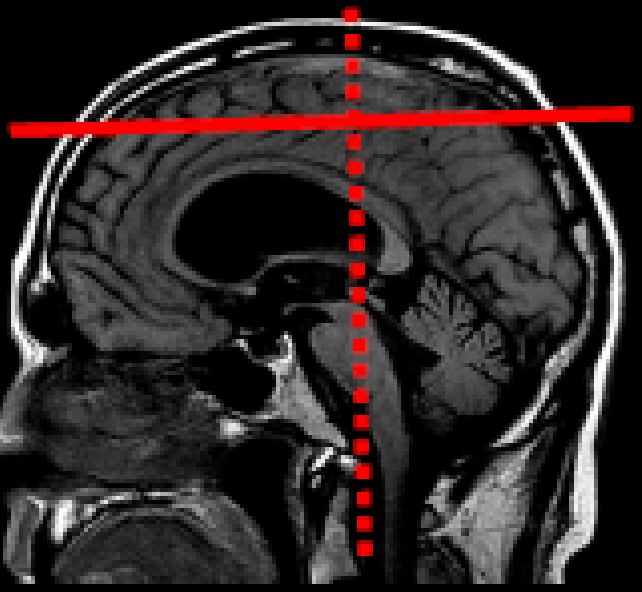


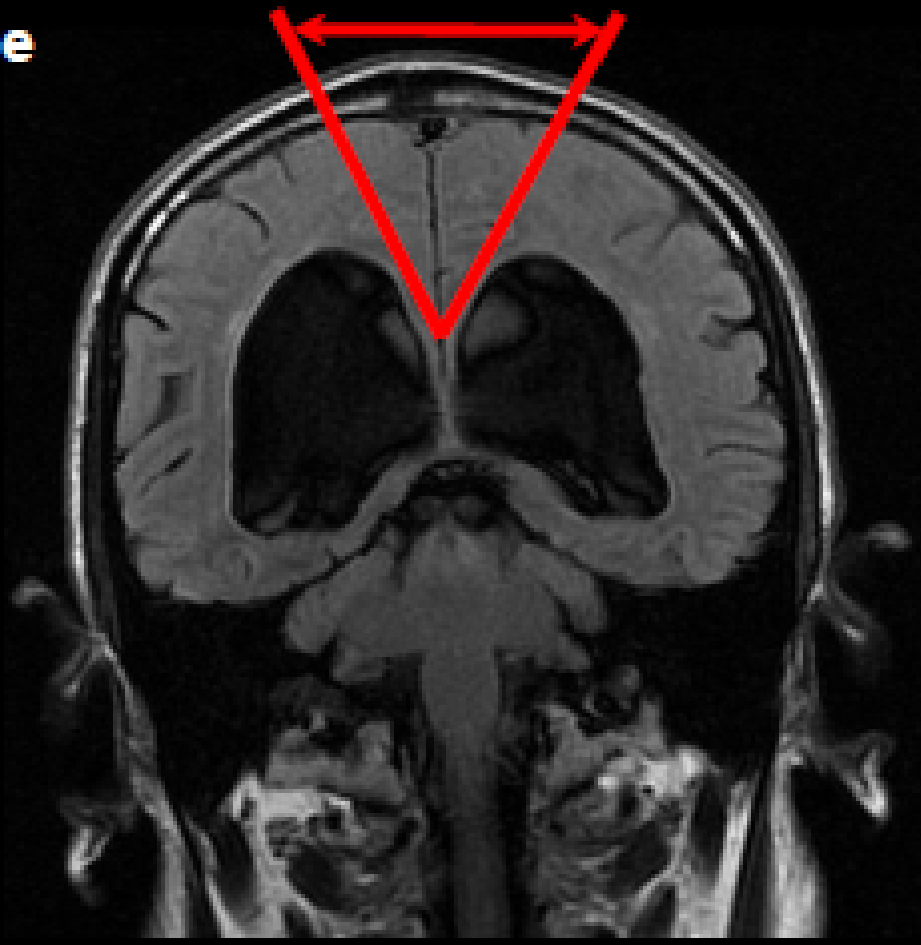
- Ratio of maximum width of frontal horns to maximum transverse inner diameter of the skull
- Frequently used by neurosurgeons
- High sensitivity, low specificity (large in both atrophy and hydrocephalus)
- No direct correlation between Evans Index and response to shunting

Courtesy Bruce L. Miller, MD "Dementia Update" February 16, 2012

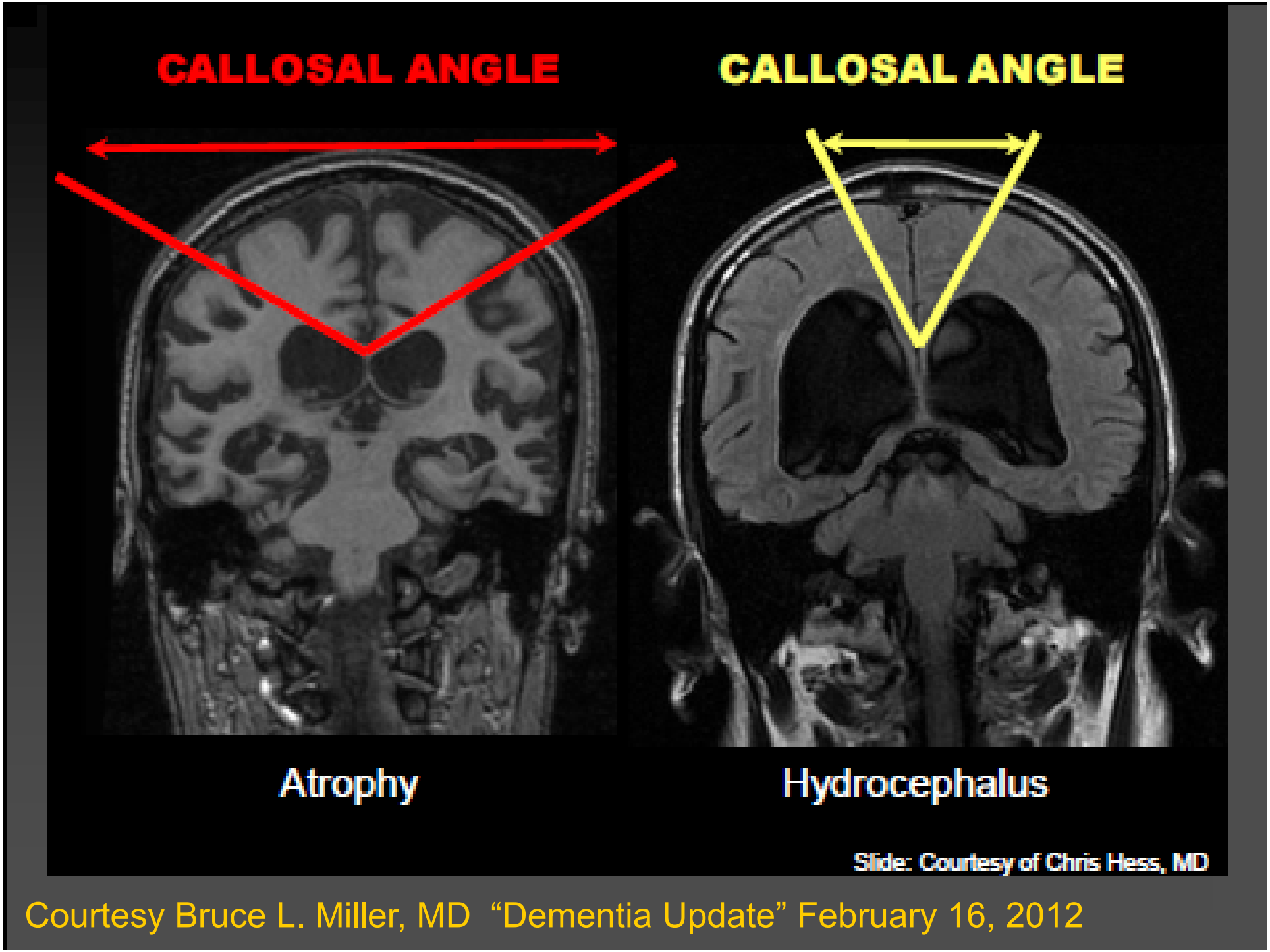
Hydrocephalus: Callosal Angle

- Measured on coronal images at the level of the posterior commissure
- Coronal images should be perpendicular to AC-PC line





Courtesy Bruce L. Miller, MD "Dementia Update" February 16, 2012



Courtesy Bruce L. Miller, MD "Dementia Update" February 16, 2012

Delirium

R. Magritte, “God’s Salon”
Oil on canvas, 1948

Key Points

1. Delirium is an *acute, fluctuating* alteration in mental status characterized by altered level of *consciousness*, fluctuating *attention*, and globally clouded *cognition*.
2. Risk increases with age, presence of dementia, polypharmacy, severity of illness, and metabolic derangement.
3. Delirium increases risk of death.
4. Delirium increases is costly and increases length of hospital stay.
5. The best treatment for delirium is prevention, and directed interventions can prevent delirium.
6. Other treatments exist, but prevention is key.

Key Points

- Delirium is most commonly a *medical* condition
  - You don’t have to be a neurologist or psychiatrist to diagnose or manage it.
  - You *do* have to be a meticulous internist.

Epidemiology

- 20-50% older patients (esp. postoperatively)
- 70-90% of patients in ICU
- 80% of patients at end of life
- Community prevalence: < 1-2%

- Mortality 25-75% (***comparable to MI or sepsis***)
- One-year mortality: 35-40%

- Up to 20% of 12.5 M patients > 65 years
- Cost ≈ $2,500/pt ($6.9 billion) per year

DHHS 2004 CMS Statistics (pub. #03445)
Inouye, Clin Geriatr Med 199;14:745-764
Pisani et al, Clin Chest Med 2003;24:727-737
Casarett & Inouye, Ann Intern Med 2001;135:32-40

Definitions

- Synonyms:
  - Acute confusional state (psychiatry)
  - Encephalopathy (neurology)

- Delirium is a *syndrome* not a diagnosis
  - It has an underlying cause
  - Dementia is ***not*** the cause (but can contribute)
  - Your job is to find & correct the cause

Clinical Features

- Acute
  - May occur gradually (hours to a few days)
  - Not weeks or months
  - Reliable informants often needed
- Fluctuating
  - Symptoms wax and wane over 24 hours
  - Often worse at night (“sundowning”)
  - Commonly with lucid intervals

Compiled from Inouye 2006; Lipowski, 1990; Maldonado, 2008

Clinical Features

- Perceptual disturbances are common
  - Illusions or hallucinations in ≈ 30% of pts
- Psychomotor disturbances
  - Hyperactive, hypoactive, or both
- Altered sleep-wake cycle

Risk Factors

Table 2. Predisposing Factors for Delirium.

Demographic characteristics
Age of 65 years or older
Male sex
Cognitive status
Dementia
Cognitive impairment
History of delirium
Depression
Functional status
Functional dependence
Immobility
Low level of activity
History of falls
Sensory impairment
Visual impairment
Hearing impairment
Decreased oral intake
Dehydration
Malnutrition
Drugs
Treatment with multiple psychoactive drugs
Treatment with many drugs
Alcohol abuse
Coexisting medical conditions
Severe illness
Multiple coexisting conditions
Chronic renal or hepatic disease
History of stroke
Neurologic disease
Metabolic derangements
Fracture or trauma
Terminal illness
Infection with human immunodeficiency virus

Inouye SK. N Engl J Med 2006;354:1157-1165.

Precipitating Factors

Table 3. Precipitating Factors or Insults That Can Contribute to Delirium.

- Drugs
  - Sedative hypnotics
  - Narcotics
  - Anticholinergic drugs
  - Treatment with multiple drugs
  - Alcohol or drug withdrawal
- Primary neurologic diseases
  - Stroke, particularly nondominant hemispheric
  - Intracranial bleeding
  - Meningitis or encephalitis
- Intercurrent illnesses
  - Infections
  - Iatrogenic complications
  - Severe acute illness
  - Hypoxia
  - Shock
  - Fever or hypothermia
  - Anemia
  - Dehydration
  - Poor nutritional status
  - Low serum albumin level
  - Metabolic derangements (e.g., electrolyte, glucose, ac
- Surgery
  - Orthopedic surgery
  - Cardiac surgery
  - Prolonged cardiopulmonary bypass
  - Noncardiac surgery
- Environmental
  - Admission to an intensive care unit
  - Use of physical restraints
  - Use of bladder catheter
  - Use of multiple procedures
  - Pain
  - Emotional stress
- Prolonged sleep deprivation

Inouye SK. N Engl J Med 2006;354:1157-1165.

Treatment

1. **PREVENTION**
2. **PREVENTION**
3. **PREVENTION**

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A MULTICOMPONENT INTERVENTION TO PREVENT DELIRIUM IN HOSPITALIZED OLDER PATIENTS

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Preventing Delirium

1. Orientation & therapeutic activities
2. Early mobilization
3. Minimize psychoactive drugs
    a. Orientating stimuli
    b. Normal sleep-wake cycles
4. Adaptive equipment
    a. Glasses, hearing aids
5. Early intervention for volume depletion

Preventing Delirium*

- In addition to the above…

6. Optimize oxygen delivery to brain
7. Monitor fluid & electrolyte balance
8. Pain management
9. *Attend to bowel & bladder function*

**Marcantonio et al. J Am Geriatr Soc 2001;49:516-22*

Treating Delirium

- Acute stabilization
  - Airway
  - Hydration/volume status
  - Close nursing supervision (ICU?)
  - Positioning (prevent decubiti)
  - DVT prophylaxis

Treating Delirium

- Environmental cues
  - Calendars, clocks, familiar home objects
  - Reorienting by staff
- Limit staff & room changes
- Allow for uninterrupted sleep at night
  - Coordinate VS measures, meds, etc.
- Low noise, low light at night
- Up and about during the day

Pharmacologic Treatments

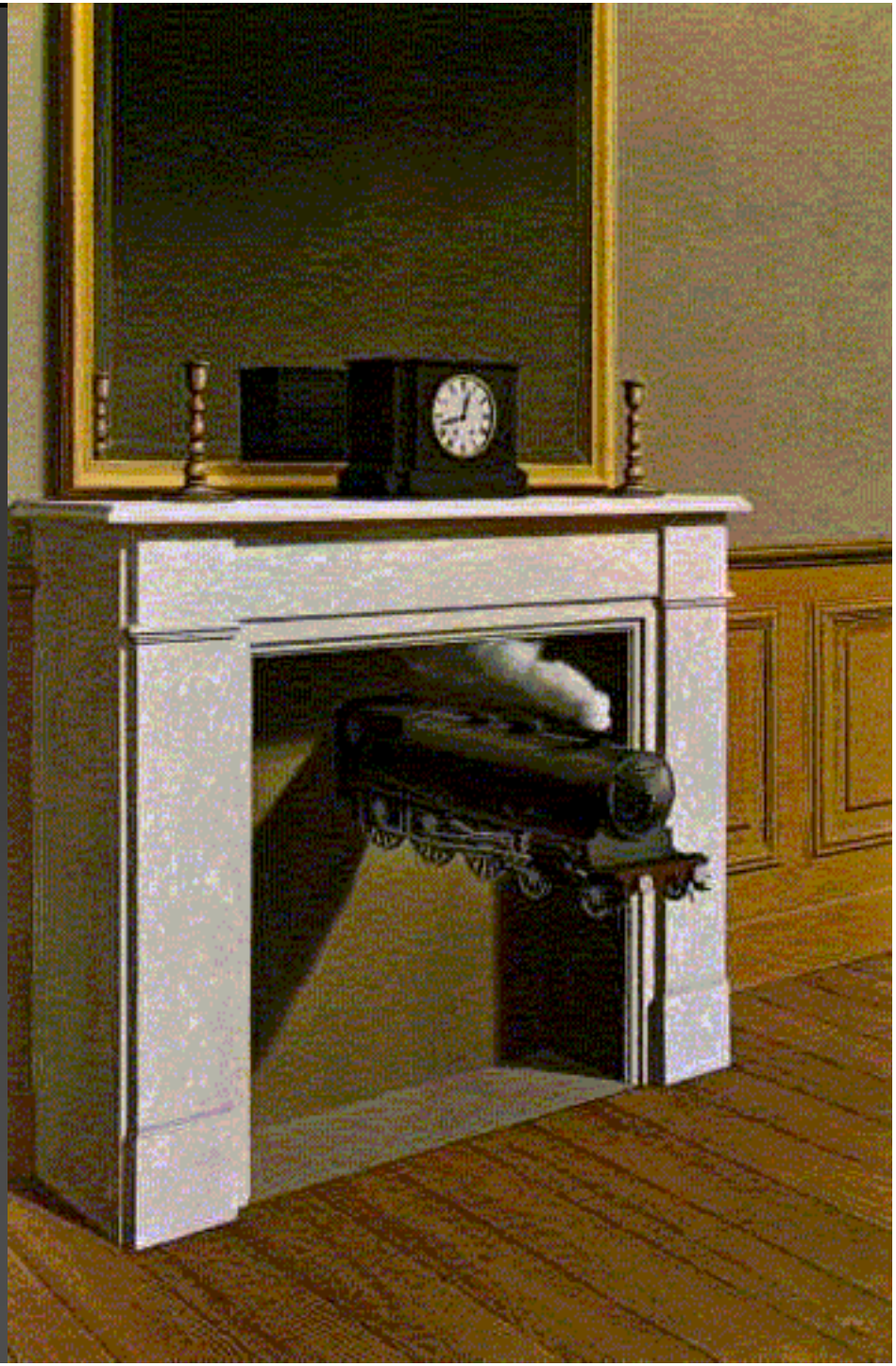
Table 4. Pharmacologic Treatment of Delirium.

Class and Drug	Dose	Adverse Effects	Comments
Antipsychotic			
Haloperidol	0.5–1.0 mg twice daily orally, with additional doses every 4 hr as needed (peak effect, 4–6 hr) 0.5–1.0 mg intramuscularly; observe after 30–60 min and repeat if needed (peak effect, 20–40 min)	Extrapyramidal symptoms, especially if dose is >3 mg per day Prolonged corrected QT interval on electrocardiogram Avoid in patients with withdrawal syndrome, hepatic insufficiency, neuroleptic malignant syndrome	Usually agent of choice Effectiveness demonstrated in randomized, controlled trials[20,37] Avoid intravenous use because of short duration of action
Atypical antipsychotic			
Risperidone Olanzapine Quetiapine	0.5 mg twice daily 2.5–5.0 mg once daily 25 mg twice daily	Extrapyramidal effects equivalent to or slightly less than those with haloperidol Prolonged corrected QT interval on electrocardiogram	Tested only in small uncontrolled studies Associated with increased mortality rate among older patients with dementia
Benzodiazepine			
Lorazepam	0.5–1.0 mg orally, with additional doses every 4 hr as needed*	Paradoxical excitation, respiratory depression, oversedation	Second-line agent Associated with prolongation and worsening of delirium symptoms demonstrated in clinical trial[37] Reserve for use in patients undergoing sedative and alcohol withdrawal, ~~those with Parkinson's~~ disease, and those with neuroleptic malignant syndrome
Antidepressant			
Trazodone	25–150 mg orally at bedtime	Oversedation	Tested only in uncontrolled studies

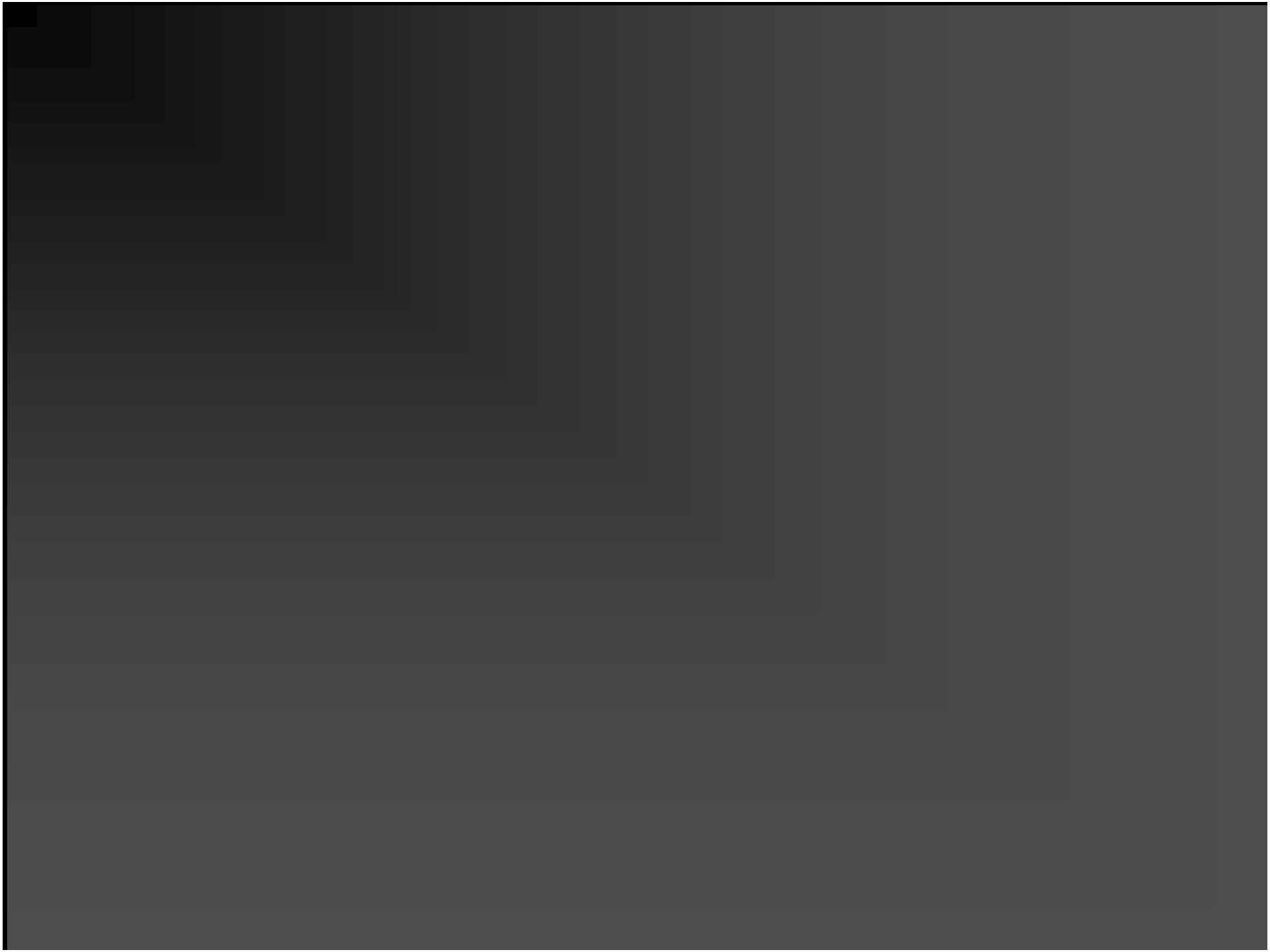
* Intravenous use of lorazepam should be reserved for emergencies.

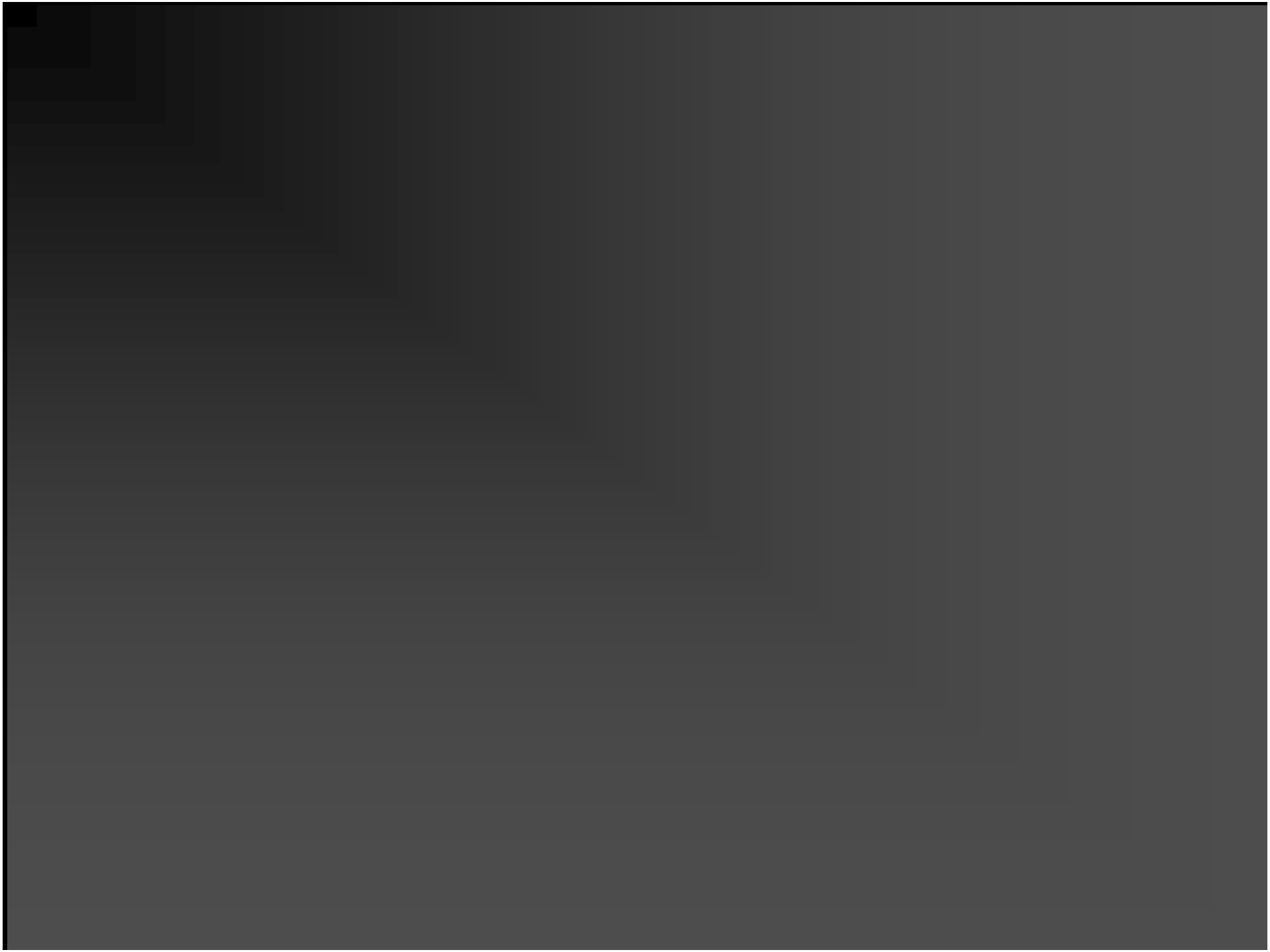
Statistically significant, clinical significance unclear

Inouye SK. N Engl J Med 2006;354:1157-1165.



Magritte, *Time Transfixed*,
Oil on canvas, 1938



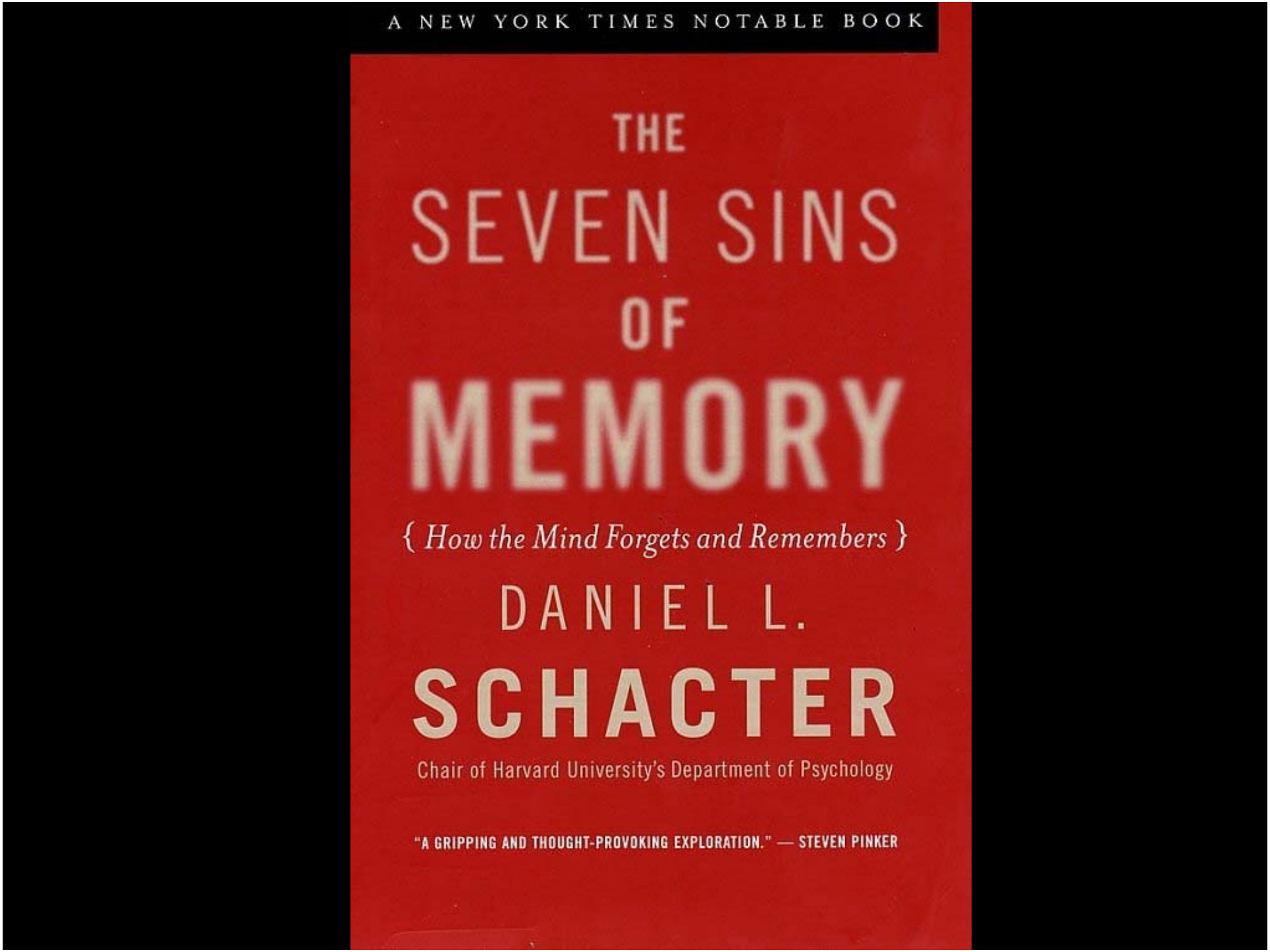


Extra slides (not covered)

Key Concepts of AD

- Depression is common & treatable
  - Depression may be an early sign (???)
- Parkinsonism can appear in advanced stages
- Cholinesterase inhibitors are first-line
  - May benefit even in late stages
- NMDA antagonists studied only in late stage dz

Normal Errors of Memory


A NEW YORK TIMES NOTABLE BOOK
THE
SEVEN SINS
OF
MEMORY
{ How the Mind Forgets and Remembers }
DANIEL L.
SCHACTER
Chair of Harvard University's Department of Psychology
"A GRIPPING AND THOUGHT-PROVOKING EXPLORATION." — STEVEN PINKER

Normal Memory Errors

- Omissions
  - Transience
  - Absent-mindedness
  - Blocking
- Commission
  - Misattribution
  - Suggestibility
  - Bias
  - Persistence

Normal Memory Errors

- Omissions: common patient complaints
  - Transience: normal loss of detailed memory over time
    - Recall problem
    - Ebbinghaus, 1885
  - Absent-mindedness: attentional disruption
    - Encoding problem
  - Blocking: inability to access known information
    - Retrieval problem

Parkinson's Plus Syndromes

- Multiple System Atrophy (MSA; Shy-Drager)
  - DOMAINS
    - Apraxia, amnesia, anomia
  - TEMPO
    - Gradual but rapidly progressive
  - ASSOCIATED FINDINGS
    - Orthostasis & urinary incontinence
    - Parkinsonism
    - Cerebellar dysfunction (ataxic dysarthhtria, limb ataxia, sustained gaze-evoked nystagmus)
    - Corticospinal dysfunction
  - CONTEXT
    - Otherwise healthy
- (OPCA/SND: Probably pathologic diagnoses, subset of MSA.)

Multiple System Atrophy: Features*

I. Autonomic dysfunction

   Orthostatic hypotension, urinary dysfunction

II. Parkinsonism

III. Cerebellar dysfunction

IV. Corticospinal tract dysfunction

* simplified

J Neurol Sci 1999;163:94-98

Multiple System Atrophy: Diagnosis

- Possible MSA*
  - Features from 3 categories of I-IV
- Probable MSA
  - Autonomic failure or urinary dysfunction AND
  - DOPA-unresponsive parkinsonism OR cerebellar dysfunction
- Definite MSA
  - Pathologic confirmation

* simplified

J Neurol Sci 1999;163:94-98

Research in AD

- AD begins earlier in Latinos than Anglos (*Arch Neurol* 2005;62:774)
- Survival in AD depends on age at dx (*Arch Neurol* 2005;62:779)
- Atypical antipsychotics *may* increase risk of MI & stroke (*Am J Ger Psych* 2006;14:191)
- CSF levels of tau and Aβ-42 may predict conversion from MCI to AD (*Lancet Neurol* 2006;5:228)
- Impaired odor detection may predict AD (*Ann Neurol* 2005;58:155)
- Immune tx with myelin oligodendroglial glycoprotein reduced Aβ-42 deposits in mice (*J Clin Invest* 2005;115:2423)

More on Clinical Features of Delirium

- Global cognitive impairment
  - Implies ***not*** focal, such as aphasia, apraxia, or spatial neglect
    - Though memory, language, praxis, and spatial reasoning commonly affected….why?
  - Reduced clarity of awareness of environment
  - Disorganized thinking, rambling flow of ideas

- Attentional dyscontrol
  - Attentional systems profoundly affected (why?)
  - Difficulty focusing, sustaining, & shifting attention
  - Difficulty maintaining thread of conversation

Treating Delirium

- Diligent search for underlying causes
  - Infection (pneumonia, bladder, sepsis)
  - GI: bowel obstruction, perforated ulcer or diverticulum, hyperammonemia, pancreatitis
  - Pulmonary: PE, hypoxemia, pleural effusion
  - CV: MI, CHF, hyper-/hypotension, dehydration
  - Renal: electrolytes, uremia, ARF
  - Skin: decubiti (infection)
  - Sensory deprivation: glasses, hearing aids
  - Neurologic: stroke, meningitis, encephalitis, occult seizure
  - Iatrogenic: drugs, polypharmacy, narcotics, untreated pain
  - Substance use/withdrawal: ETOH, benzos, narcotics

Pathogenesis of delirium

- Not well understood
- Implicates multi-nodal, polysynaptic pathways
- Imaging & electrophysiology supports widespread neocortical dysfunction

- ***May be the only presenting symptom of life-threatening illness (MI, infection, impending respiratory failure).***
  - ***Do your very best workup ever.***

Pathogenesis of delirium

- Likely multifactorial
  - Evidence of cholinergic dysfunction*
  - Possible role of dopamine & other neurotransmitters†
  - Cytokines, TNF-α, and interferon may contribute‡
  - Chronic stress → hypercortisolemia → hippocampal serotonin£

**Han et al, Arch Int Med 2001;161:1099-1105; Roche Am J Med Sci 2003;325-20-30*
† Cole Am J Geriatr Psychiatry 2004;12:7-21
‡ Broadhurst & Wilson, Br J Psychiatry 2001;179:288-289.
£ Meijer & de Kloet Crit Rev Neurobiol 1998;12:1-20