Serious Mental Illness and Dementia

Larry Tune, MD, MAS

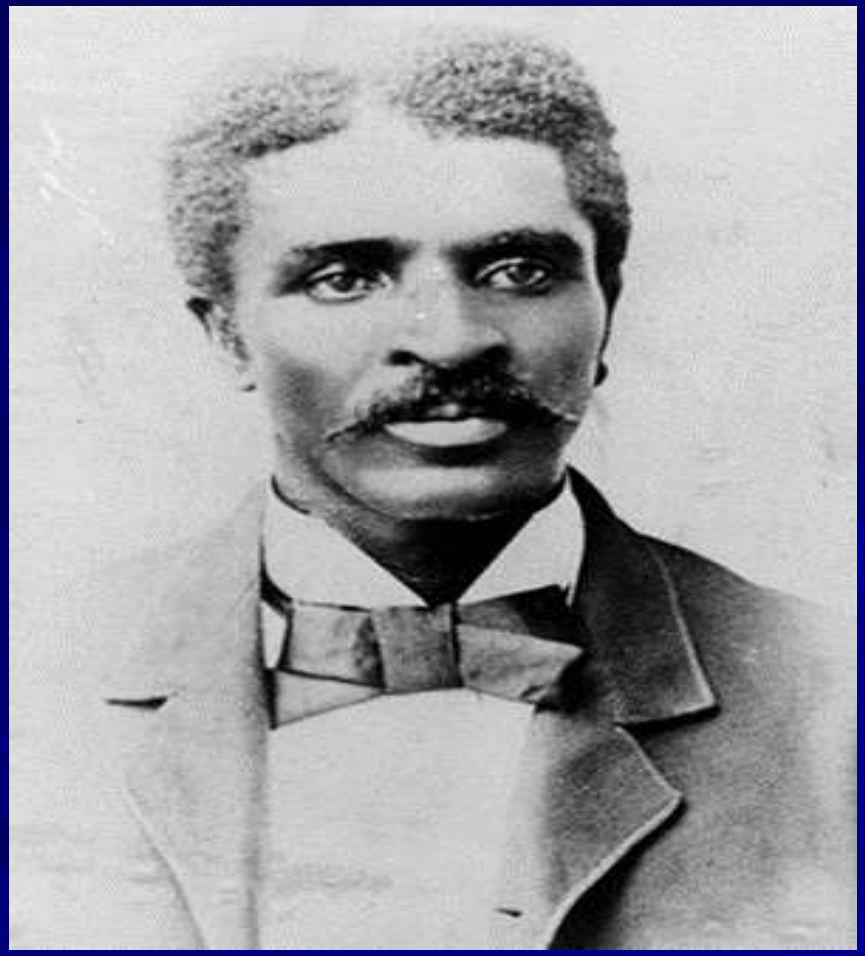
Professor, Psychiatry and Neurology

Emory University School of Medicine

Medical Director for Psychiatric Services-

Sparta H&R; Providence H&R; Chaplinwood H&R; The Fountainview Center

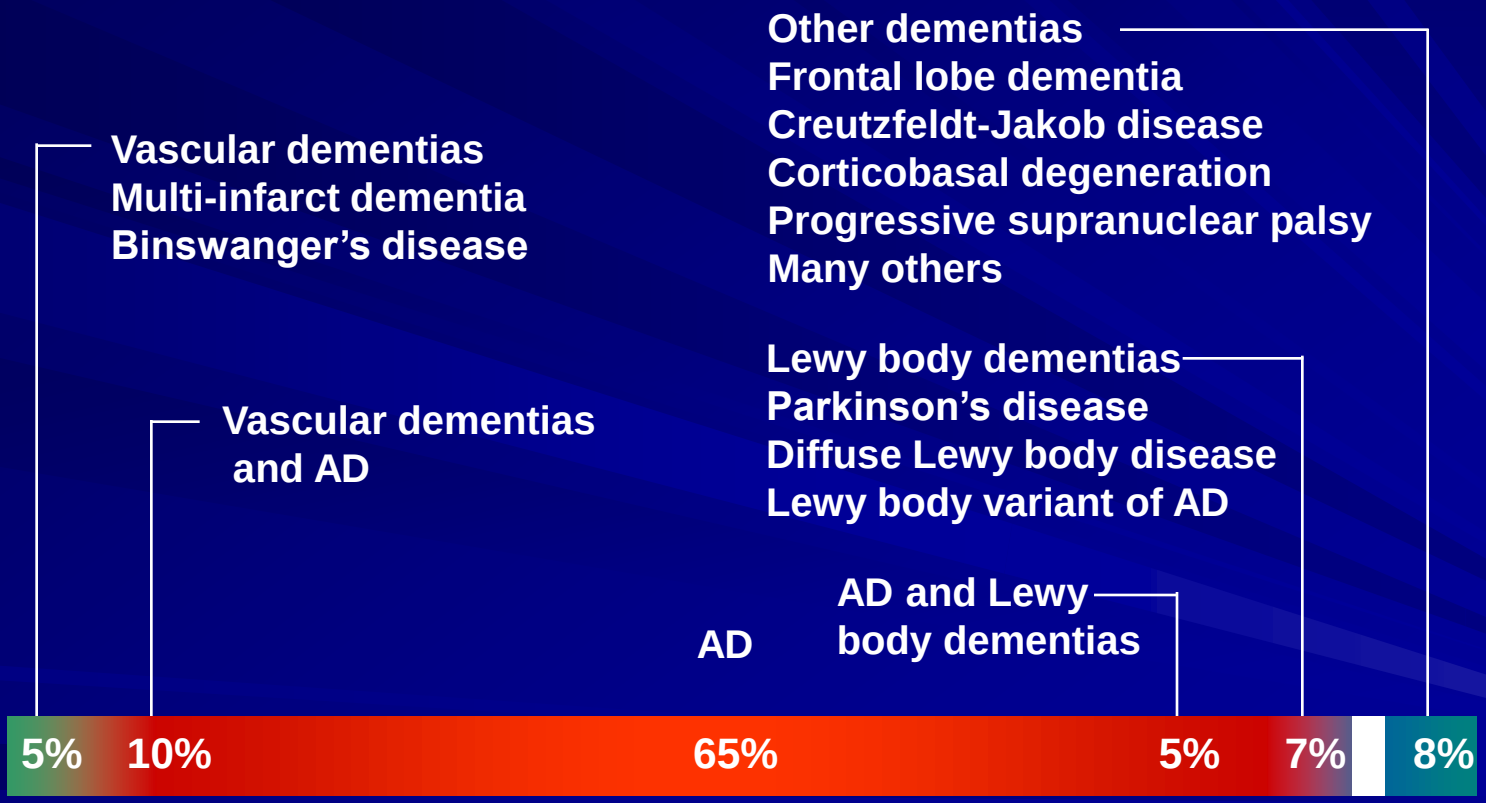
Perspective….



“ How far you go in life depends on your being tender with the young, compassionate with the aged, sympathetic with the striving, and tolerant of the weak and strong. Because someday in your life you will have been all of these.”

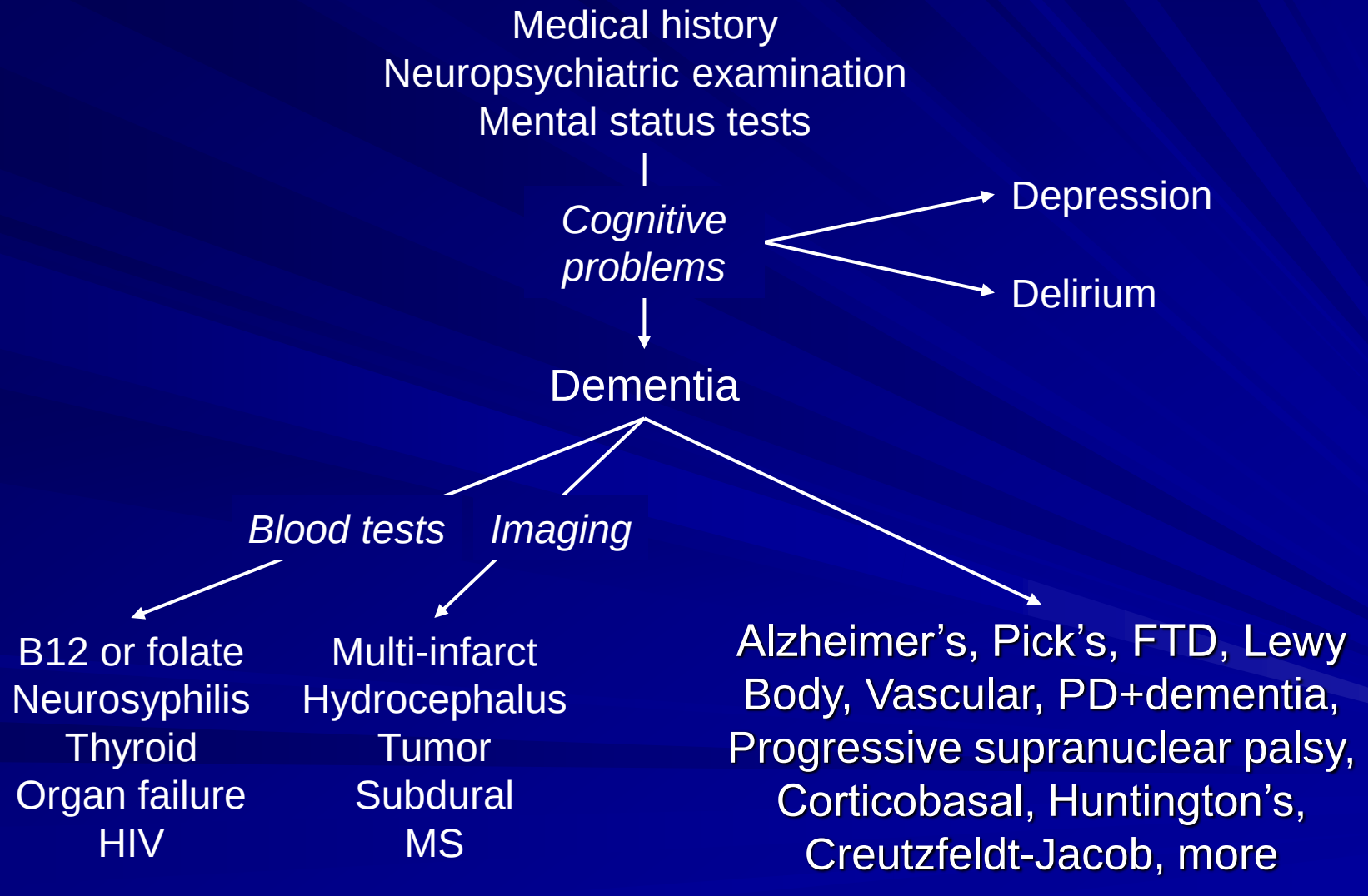
George Washington Carver

DIFFERENTIAL DIAGNOSIS OF DEMENTIA

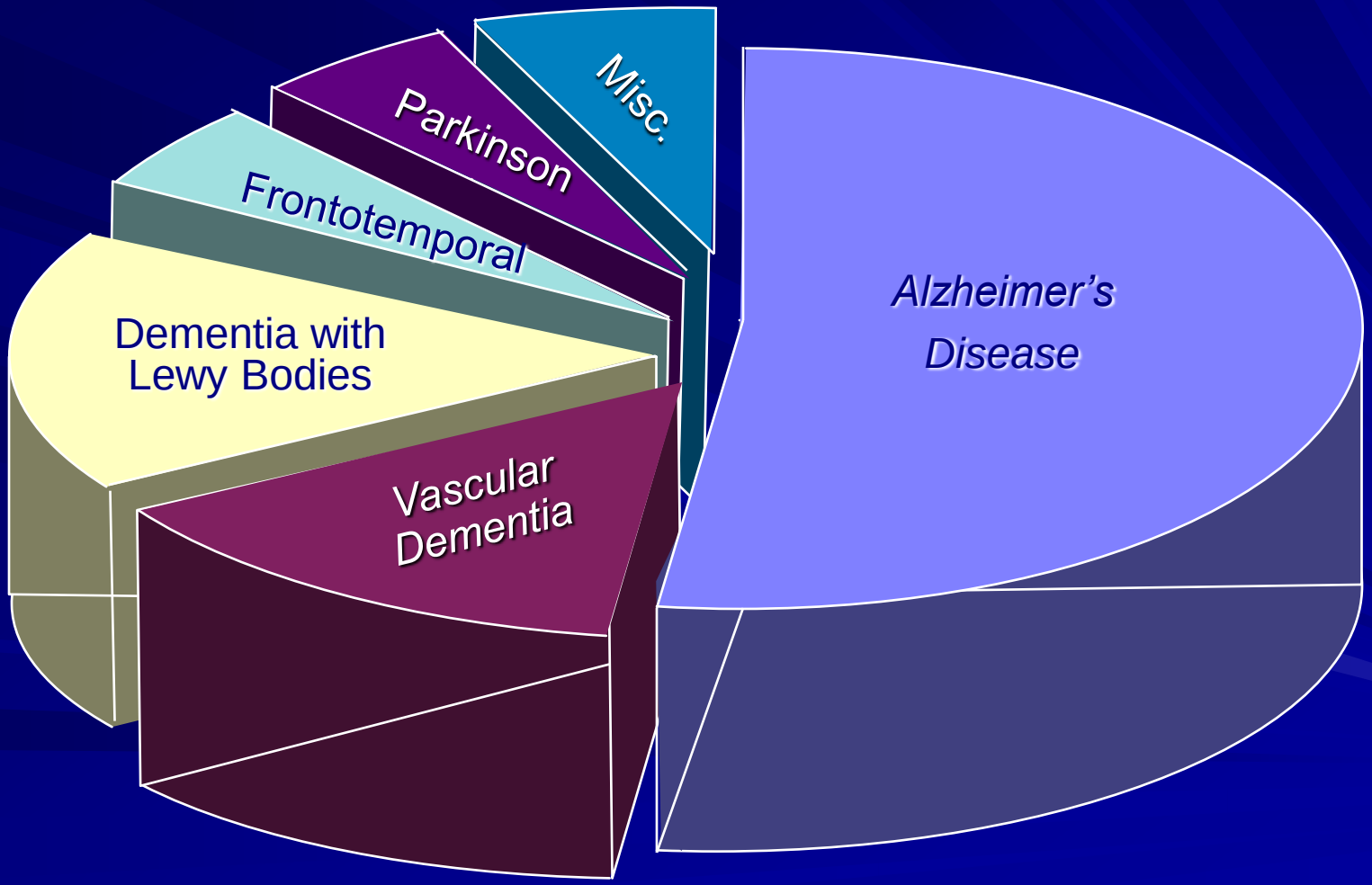


Small GW, et al. *JAMA*. 1997;278:1363-1371.
American Psychiatric Association. *Am J Psychiatry*. 1997;154(suppl):1-39.
Morris JC. *Clin Geriatr Med*. 1994;10:257-276.

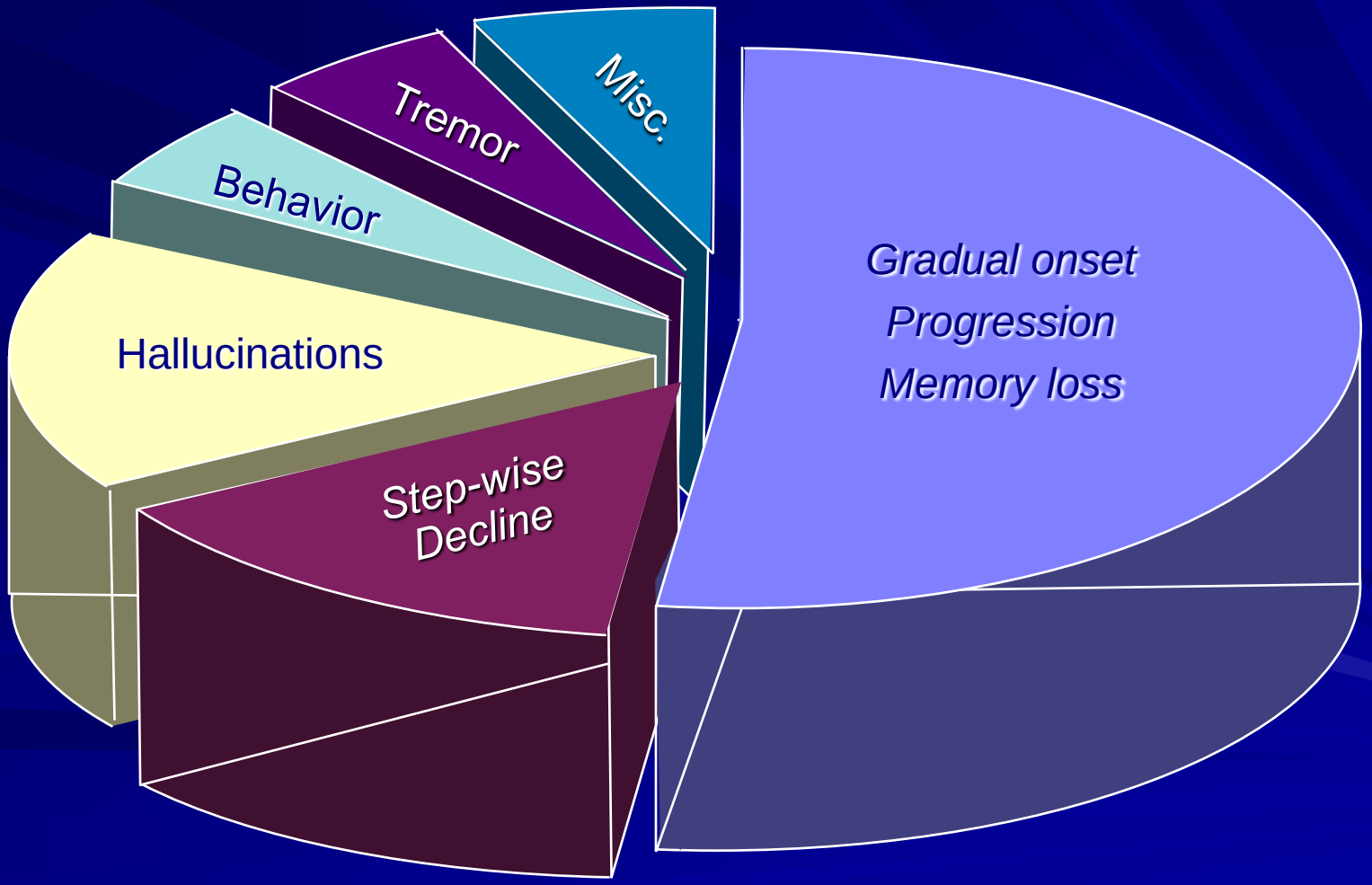
Assessment of Dementia



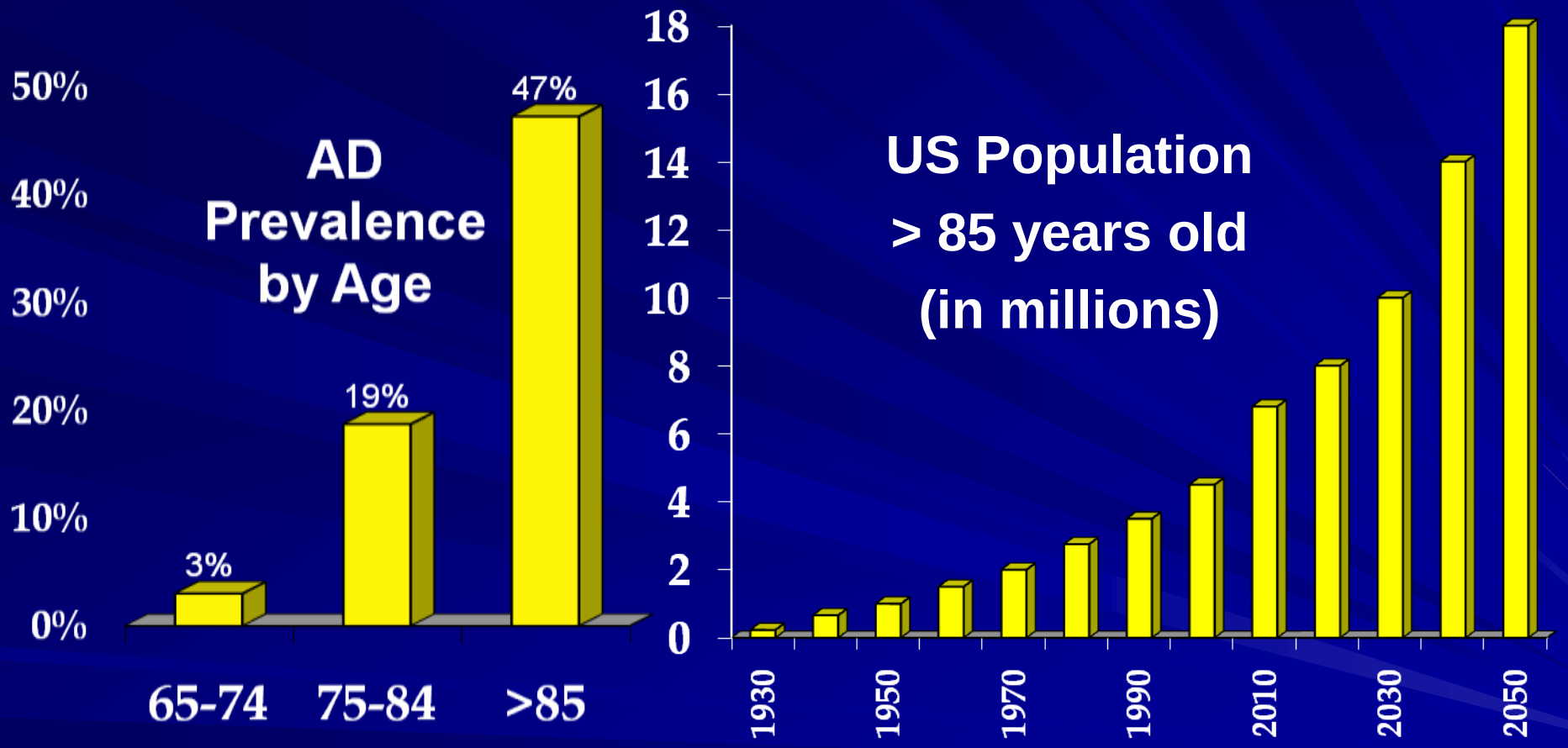
How do we know it's not Alzheimer's?



How do we know it's not Alzheimer's?

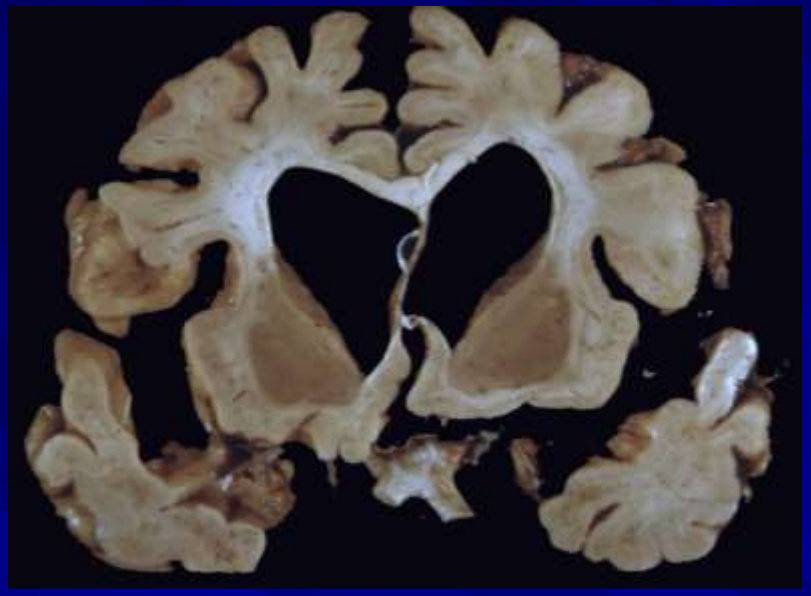


The Alzheimer's Disease Epidemic

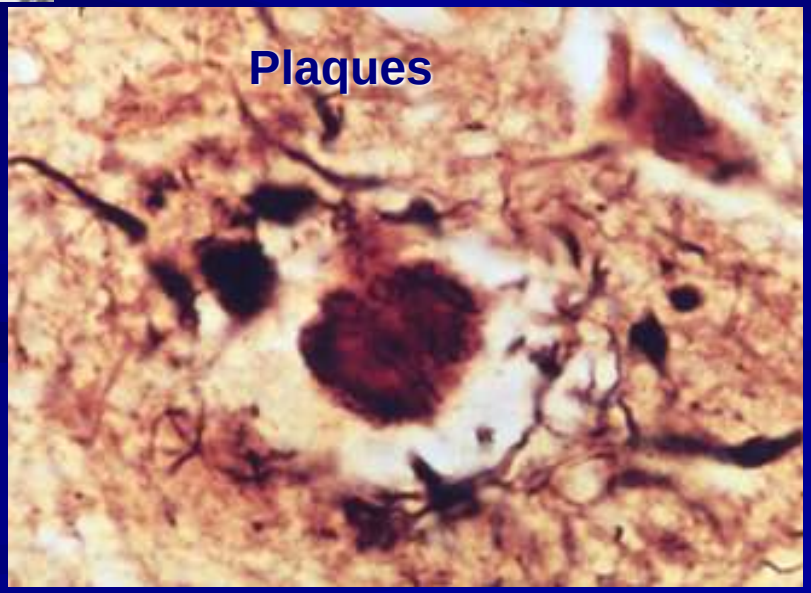


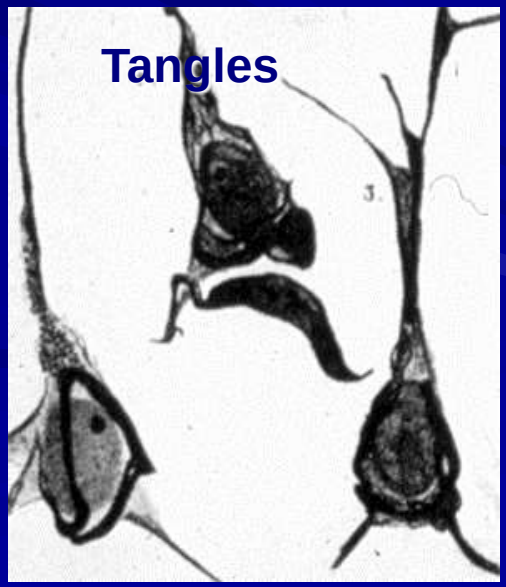
. . . ~ 5 million today . . . nearly 50% over age 85 have AD . . .
70 million baby boomers . . . ~$150 B annual costs today . . .

Pathology of Alzheimer's Disease



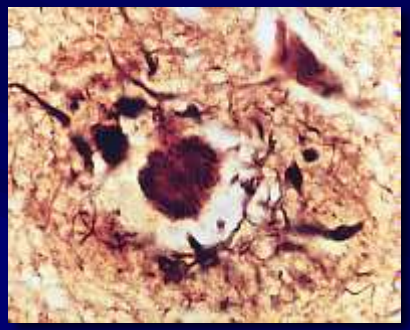
Brain Atrophy





The Amyloid Hypothesis

Neuritic Plaque

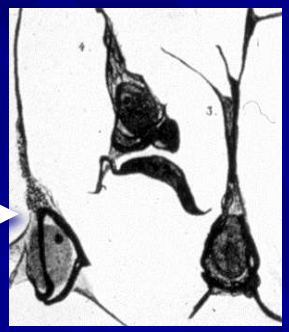


Amyloid Precursor Protein

γ-secretase

Presenilins

Neurofibrillary Tangles



Aβ42

ApoE

Aβ42

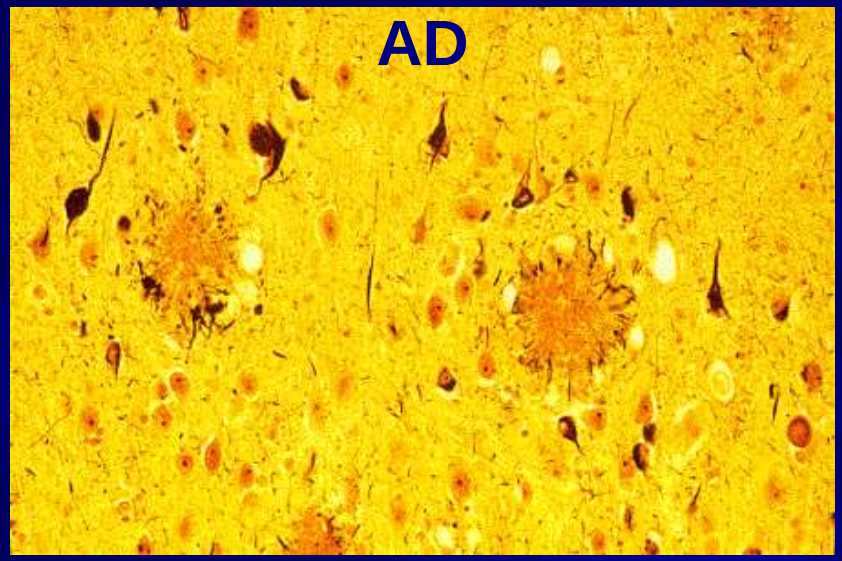
ApoJ

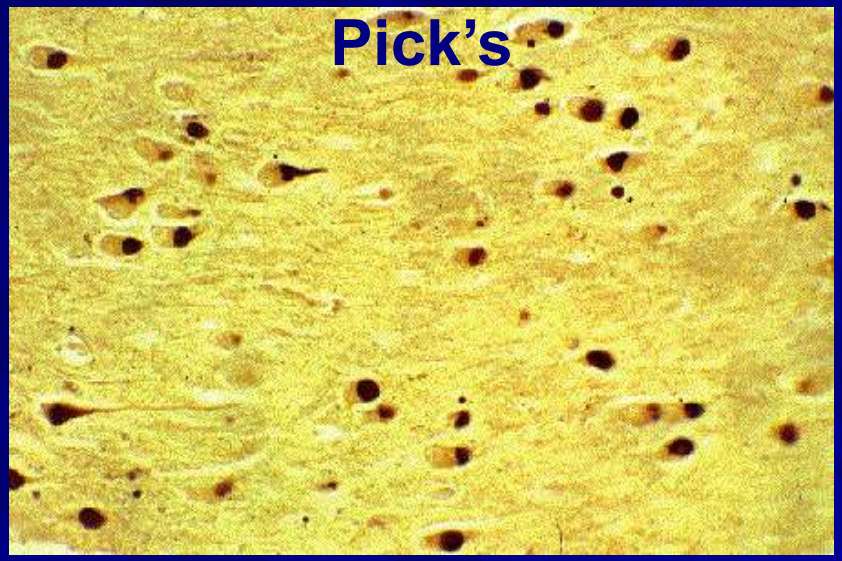
Aβ42

Amyloid Oligomers

Amyloid Clearance

Tauopathies

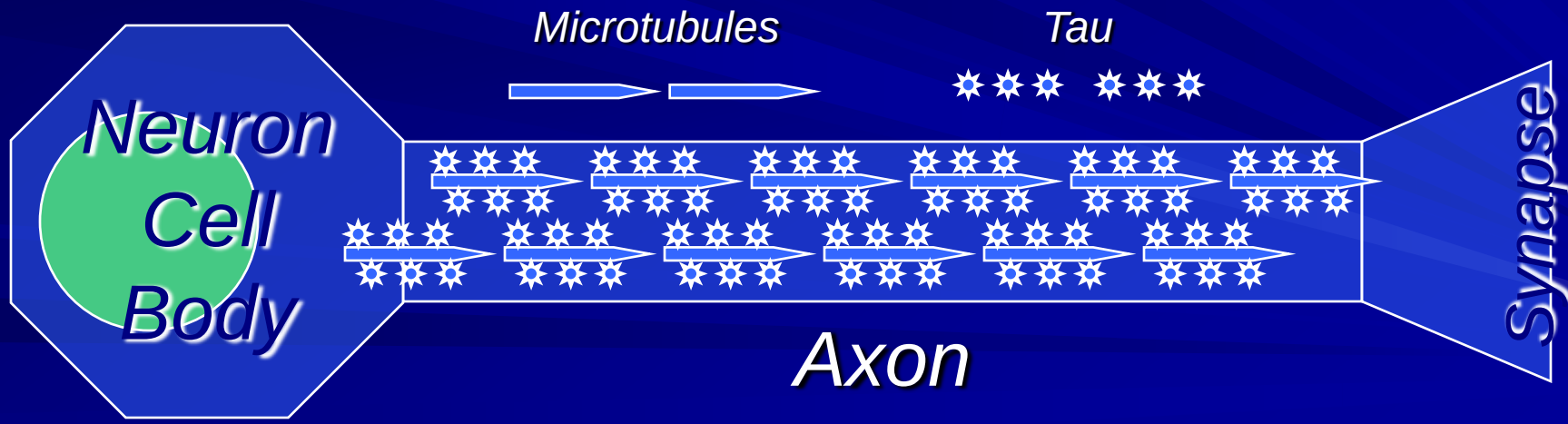




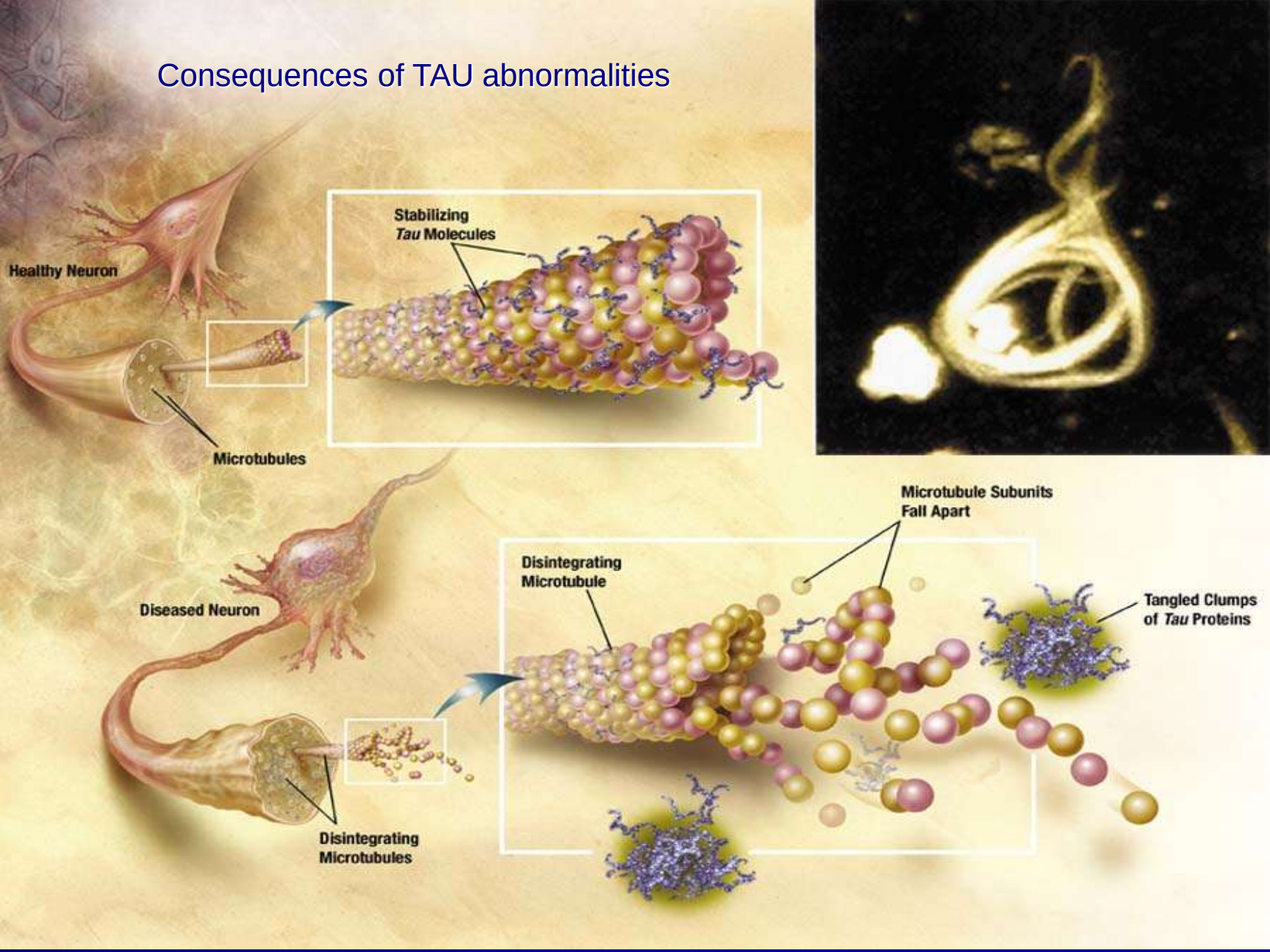
- Neurofibrillary tangles in AD composed of aggregated tau protein
- Pick bodies and other abnormal inclusions in FTD also composed of aggregated tau
- AD brains also contain deposits of amyloid in plaques

What is Tau?

- Neurons transport material to and from the cell body and synapse through axons along microtubule ‘tracks’
- Tau protein binds to microtubules, stabilizes the tracks, and helps them function normally

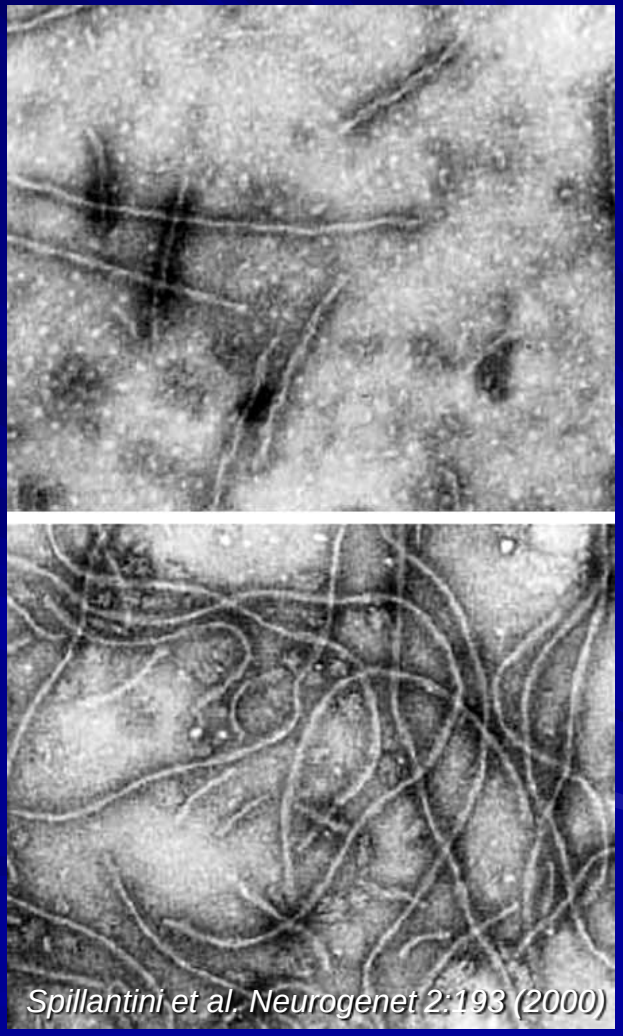


Consequences of TAU abnormalities



Disease Mechanisms in Tauopathies

- Tau proteins stick together in ‘aggregates’
- Insoluble Tau accumulates and damage neurons
- Microtubules may not function properly
- Axonal transport may be disrupted



Biomarkers of Brain Aging

- **Serum/Blood:**
  - APOE
  - presenilin/APP mutations
  - TREM2
- CSF:
  - AB-42
  - Phosphorylated tau
- Structural Imaging
  - CT, MRI
  - PET-Amyloid/tau
  - DTI
- Functional Imaging
  - FDG-PET, fMRI
- Other
  - Sniff test
  - Risk factors

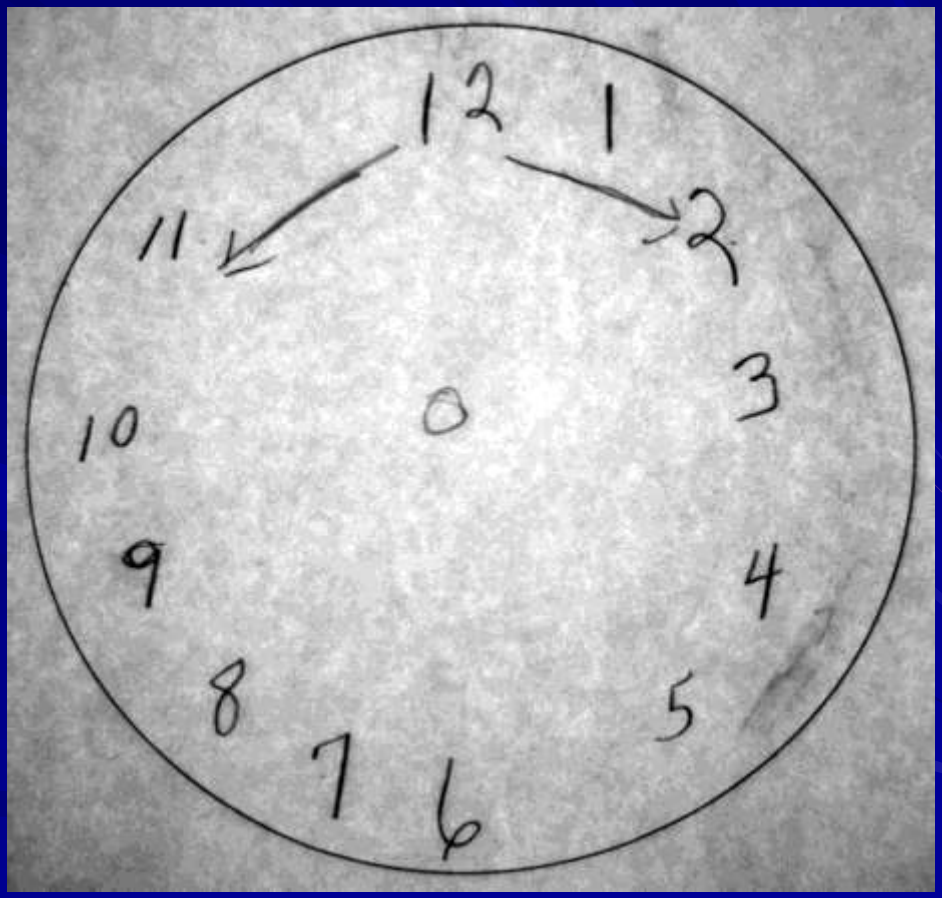
Poor recognition of early memory loss

- <10% of patients with mild dementia recognized by MD at the time of office visit
- 3.2% of MCI cases recognized
- Why???
  - Differences between normal age-associated memory lapses and clinically important MCI are subtle
  - Average length of office visit: 13-18 minutes
  - The most common screening test: 7-10 minutes

Callahan and Hendrie 1995; Valcour et al. 2000)

“Low-tech” approach to detect early symptoms of AD

- Requirements for widespread screening
  - Quick & easy
  - Cheap
  - Quick & easy!
- Mini-Cog (Borson et al. 2000)
  - Brief 3-item memory test
  - Clock drawing test
  - 3-5 min to perform
  - No special training



Draw A Clock Task

- Ask patient to draw a large circle (1 pt)
- Ask patient to place numbers on the face of the clock (1 pt)
- Ask patient to put hands on the clock to display ten minutes after eleven
  - One point for correct hand placement
  - One point for correct hand length

The Montreal Cognitive Assessment

- 30-question test
- Takes around 10 minutes to complete
- Published in 2005
- Assesses orientation, short-term memory, executive function, language abilities, and visuospatial ability
- Includes a clock drawing task and Trails B
- Scoring of the MoCA
  - Scores range from 0 to 30
  - 26 and higher generally considered normal
  - Normal controls had an average score of 27.4
  - 22.1 in people with mild cognitive impirment
  - 16.2 in people with Alzheimer's disease

SLUMS

- Saint Louis University Mental Status Examination
- Designed to be more sensitive to MCI than the MMSE
- 11 items
- Measures orientation, short-term memory, calculations, naming of animals, clock drawing, and recognition of geometric figures
- Scores range from 0 to 30
  - 27-30 considered normal
  - 21-26 suggests Mild Neurocognitive Disorder
  - 0-20 indicates dementia

SLUMS

- SLUMS and the MMSE compared in 705 male veterans 60 and older
- Both tools detected dementia
- Only the SLUMS recognized patients with MCI
- Took an average of seven minutes to administer
- Test is free

Folstein Mini-Mental State Exam

- Takes approximately 10 minutes to administer
- Examines areas including

Orientation (person, place, and time)

Attention (spelling “World” backwards or counting by 3’s)

Memory (recalling 3 items)

Language (naming two objects, following a command, writing and reading a sentence)

Visuomotor Functioning (copying a design)

Score ranges from 0-30 points

___

___

Neurodegenerative Disease: Complex Traits with Common Environmental and Genetic Factors

Genes

Alzheimer's Disease

Environment

Risk or Protective Factors

- Head trauma
- Depression
- Hypertension
- Cholesterol
- Homocysteine
- B12, folate
- Education
- Exercise
- Mediterranean Diet
- NSAIDS
- Statins
- Red Wine

Alzheimer's Disease Treatments

Symptomatic

- Cholinesterase inhibitors

  (Aricept, Razadyne, Exelon)
- Memantine (Namenda)

Failed

- NSAIDS
- Estrogen
- Statins
- Vitamin B Supplements
- Flurizan
- Gingko Biloba
- …..and many more

Neuroprotective?

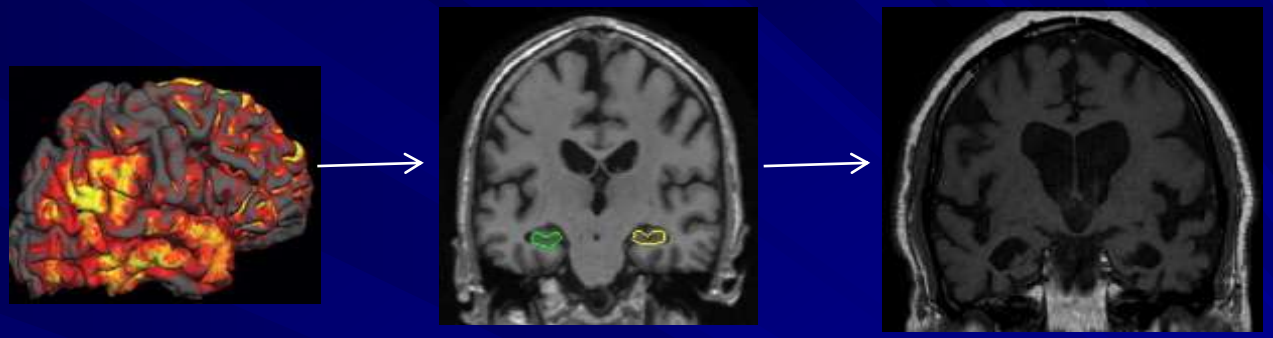
Importance of MCI Recognition

- ~10 - 15% annual conversion rate of MCI to dementia
- ~1-2% annual conversion rate in cognitively normal individuals
- Identification of MCI allows early intervention
- Identification of MCI necessary for research to develop better treatments and prevention of AD and other dementias

Biomarkers Change Long before the disease is detected

- Amyloid deposition begins 17 years before the disease is expressed
- Hippocampal Atrophy begins at least 4 years before the disease is expressed
  - Australian Imaging Biomarker and Lifestyle Study (villemagne, Lancet Neurology 2013:12:357-67.

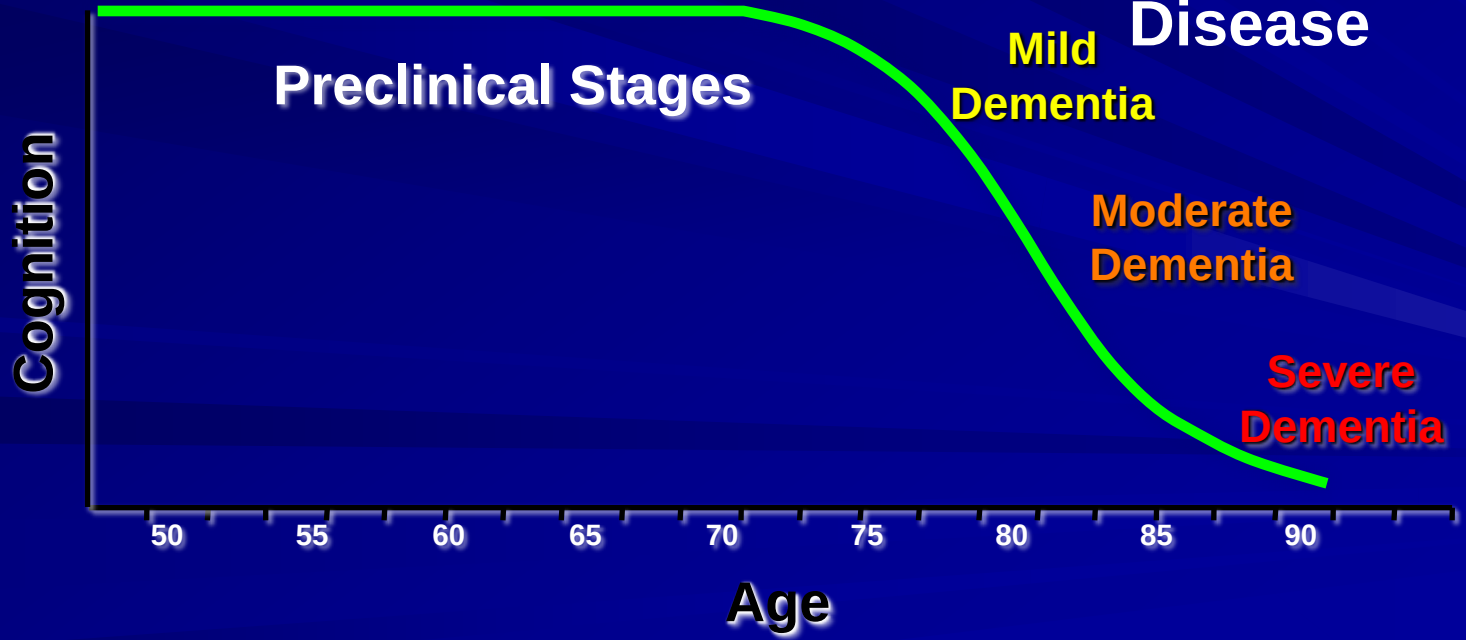
Early Detection and Prediction of AD: PET and MRI



"Healthy"

Mild Cognitive Impairment

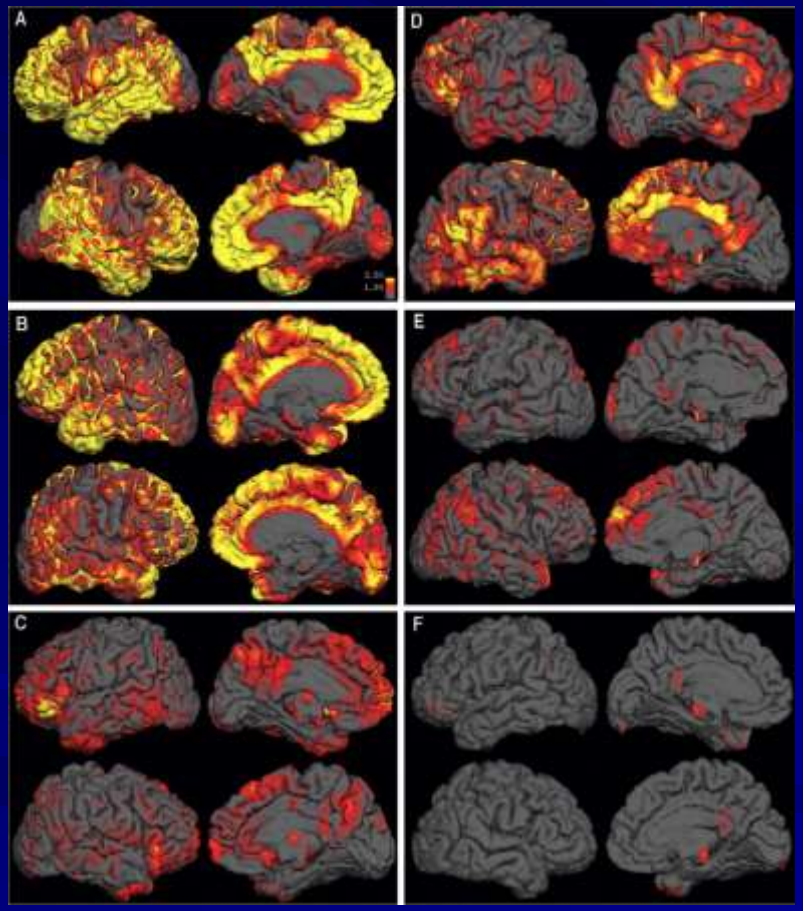
Alzheimer Disease

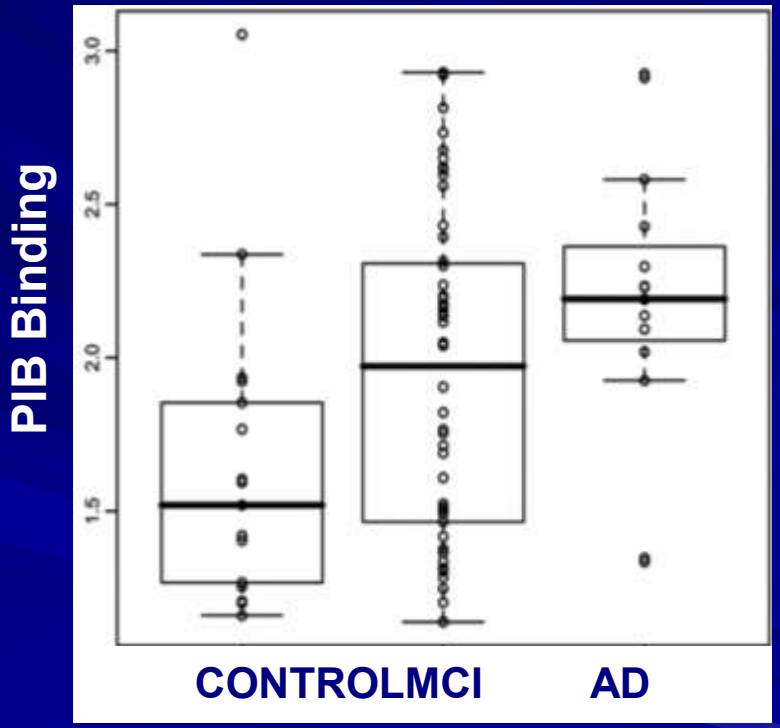


Early Detection and Prediction of AD: PET Imaging of Aß in the Alzheimer Disease Neuroimaging Initiative

Alzheimer Disease

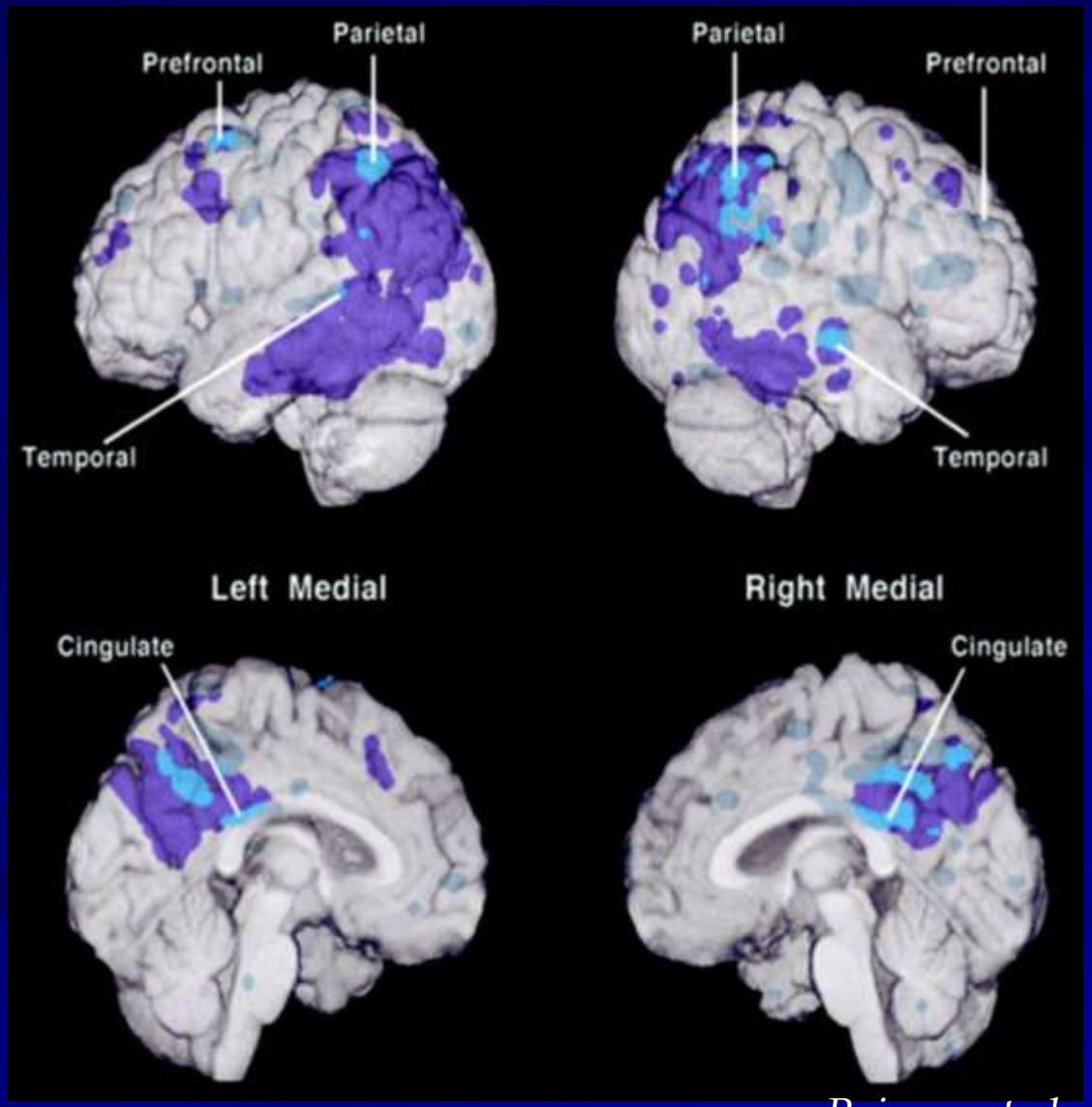
Control





Mormino et al., Brain, 2009

Preclinical Evidence of Alzheimer's Disease in Asymptomatic Individuals with ApoE4



)

Reiman et al., NEJM 334:752, 1996

Emerging Therapeutics in AD

- Anti-amyloid agents
  - Immunotherapy (vaccines, immunizations)(Phase II)
  - Secretase inhibitors and modulators (Phase III)
  - Fibrillization inhibitors (Phase III)
  - Statins (Phase IV)
- Neuroprotective compounds (examples)
  - Antioxidants (curcumin - proof of concept)
  - Nerve growth factor-like (Phase III)
  - NMDA receptor blockers
  - Tau-related agents
- Symptomatic agents
  - Transmitter-based (cholinergic and non-cholinergic)

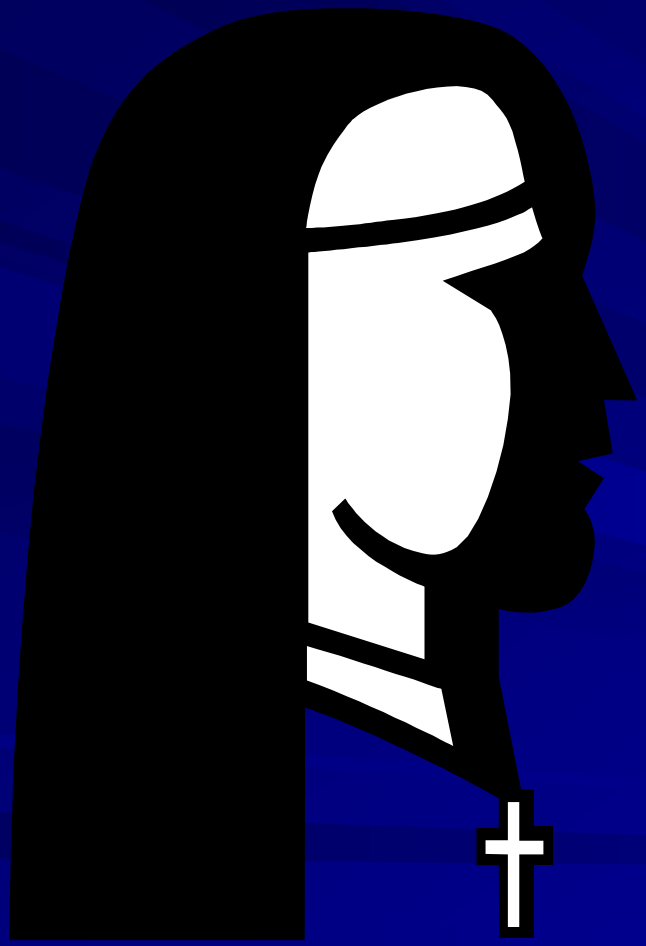
How do we improve cognitive reserve?

- Life exposures
  - Family Environment
  - Education
  - Occupation
  - Leisure
- Physical/vascular factors
  - Exercise
- Direct effect of life experiences
  - Stress
  - Work experiences

Educational Level

- Strong association with risk of any Dementia
  - Kungsholmen Project
    - 1810 ss over 75 yo
    - Subjects with <8 years education were 2.6 times more likely to get AD
  - Nurses Health Study
    - 19,319 nurses >70
    - The higher the attainment, the better the test performance
  - Nun Study

The Nun Study



- 700 School Sisters of Notre Dame are participating
- Current ages are from 75 to 106 years old
- Information is available from their early teen years to the time of death, including autopsy in those participants who have died

Exercise Protects the Brain

Effect of Physical Activity on Cognitive Function in Older Adults at Risk for Alzheimer Disease

A Randomized Trial

JAMA®
The Journal of the American Medical Association

Context Many observational studies have shown that physical activity reduces the risk of cognitive decline; however, evidence from randomized trials is lacking.

Objective To determine whether physical activity reduces the rate of cognitive decline among older adults at risk.

Design and Setting Randomized controlled trial of a 24-week physical activity intervention conducted between 2004 and 2007 in metropolitan Perth, Western Australia. Assessors of cognitive function were blinded to group membership.

Participants We recruited volunteers who reported memory problems but did not meet criteria for dementia. Three hundred eleven individuals aged 50 years or older were screened for eligibility, 89 were not eligible, and 52 refused to participate. A total of 170 participants were randomized and 138 participants completed the 18-month assessment.

Intervention Participants were randomly allocated to an education and usual care group or to a 24-week home-based program of physical activity.

Results In an intent-to-treat analysis, participants in the intervention group improved 0.26 points (95% confidence interval, –0.89 to 0.54) and those in the usual care group deteriorated 1.04 points (95% confidence interval, 0.32 to 1.82) on the ADAS-Cog at the end of the intervention. The absolute difference of the outcome measure between the intervention and control groups was –1.3 points (95% confidence interval, –2.38 to –0.22) at the end of the intervention. At 18 months, participants in the intervention group improved 0.73 points (95% confidence interval, –1.27 to 0.03) on the ADAS-Cog, and those in the usual care group improved 0.04 points (95% confidence interval, –0.46 to 0.88). Word list delayed recall and Clinical Dementia Rating sum of boxes improved modestly as well, whereas word list total immediate recall, digit symbol coding, verbal fluency, Beck depression score, and Medical Outcomes 36-Item Short-Form physical and mental component summaries did not change significantly.

Conclusions In this study of adults with subjective memory impairment, a 6-month program of physical activity provided a modest improvement in cognition over an 18-month follow-up period.

Lautenschlager et al., JAMA 2008

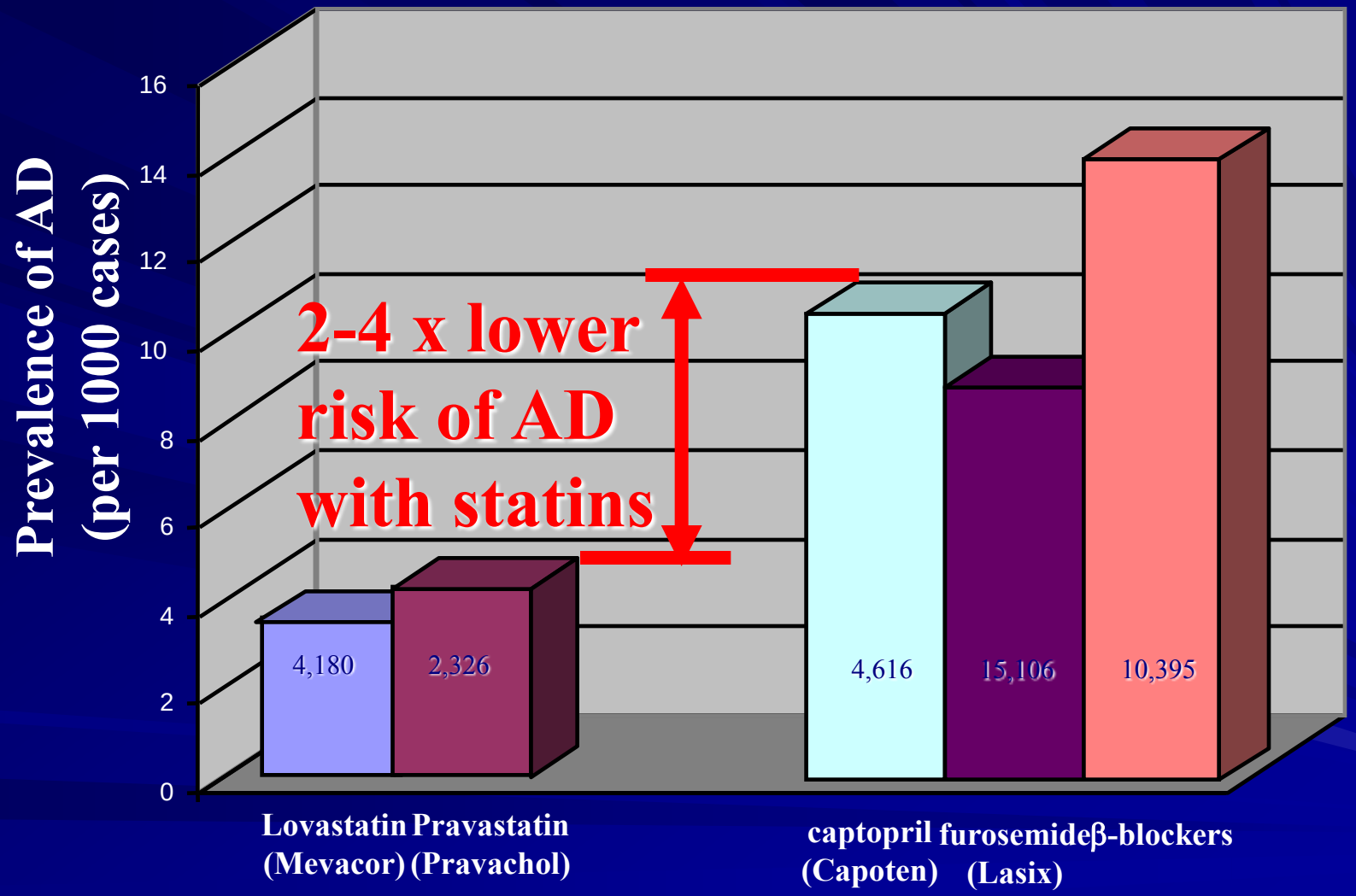
Physical Activity

- Colcombe, et al (1995):
  - Metaanalysis of 18 longitudinal studies of adults >55 yo
  - Greater activity associated with greater cognitive improvement
  - Combination exercise (aerobic+stretching)>aerobics alone
  - *Sessions less than 30 minutes did nothing*

Cognitive and Leisure Activity

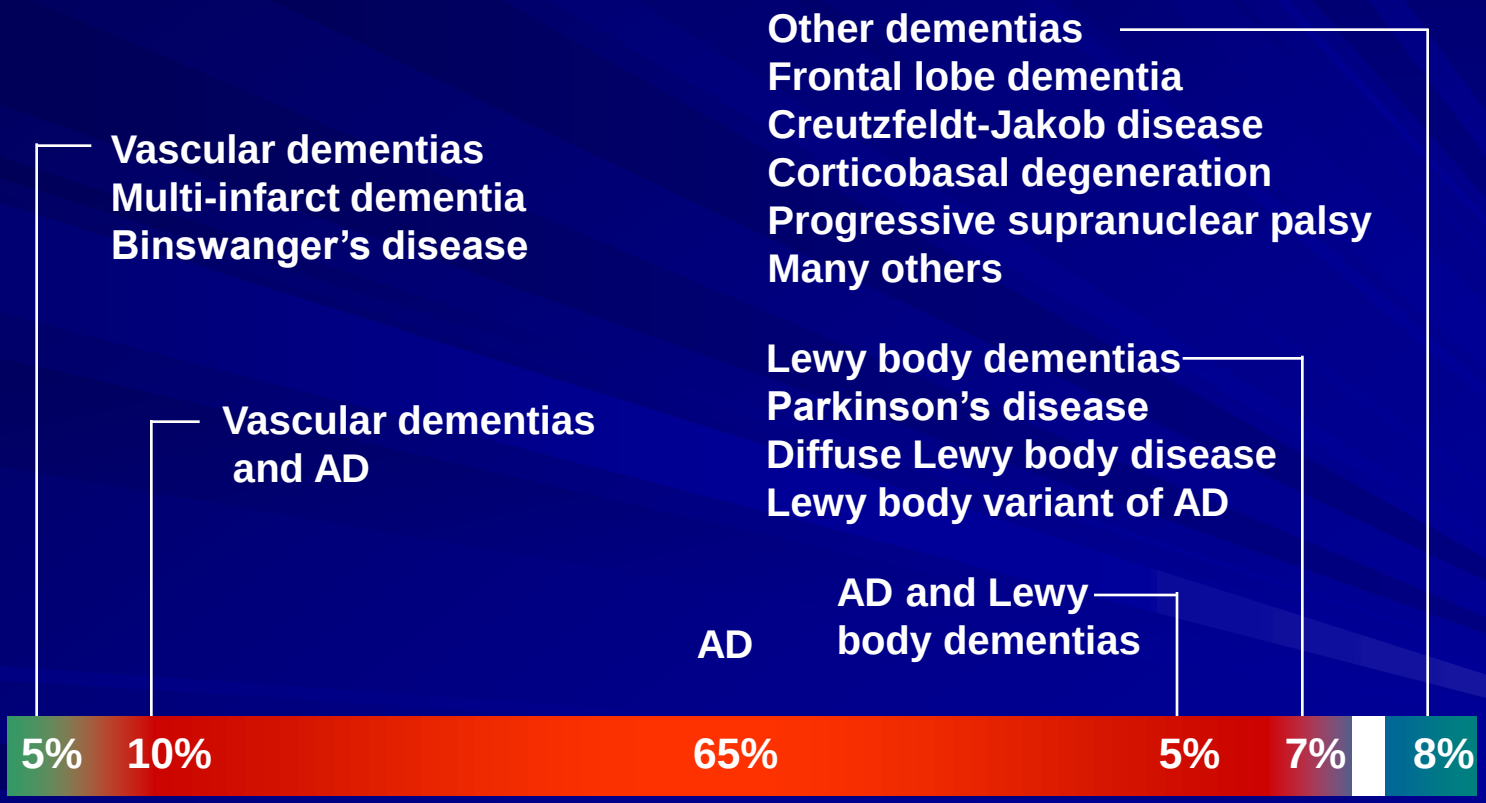
- Bronx Aging Study (1980-83)
  - 469 ss age 75-85
  - Activities associated with lower risk of dementia included…
    - Playing board games
    - Playing a musical instrument
    - Reading
    - *Dancing*

Cholesterol Lowering Drugs & Risk of AD



Wolozin et al., Arch Neurol 2000

DIFFERENTIAL DIAGNOSIS OF DEMENTIA



Small GW, et al. *JAMA*. 1997;278:1363-1371.
American Psychiatric Association. *Am J Psychiatry*. 1997;154(suppl):1-39.
Morris JC. *Clin Geriatr Med*. 1994;10:257-276.

Focus on…

Frontotemporal Dementia

Lewy Body Dementia

Frontotemporal dementia..

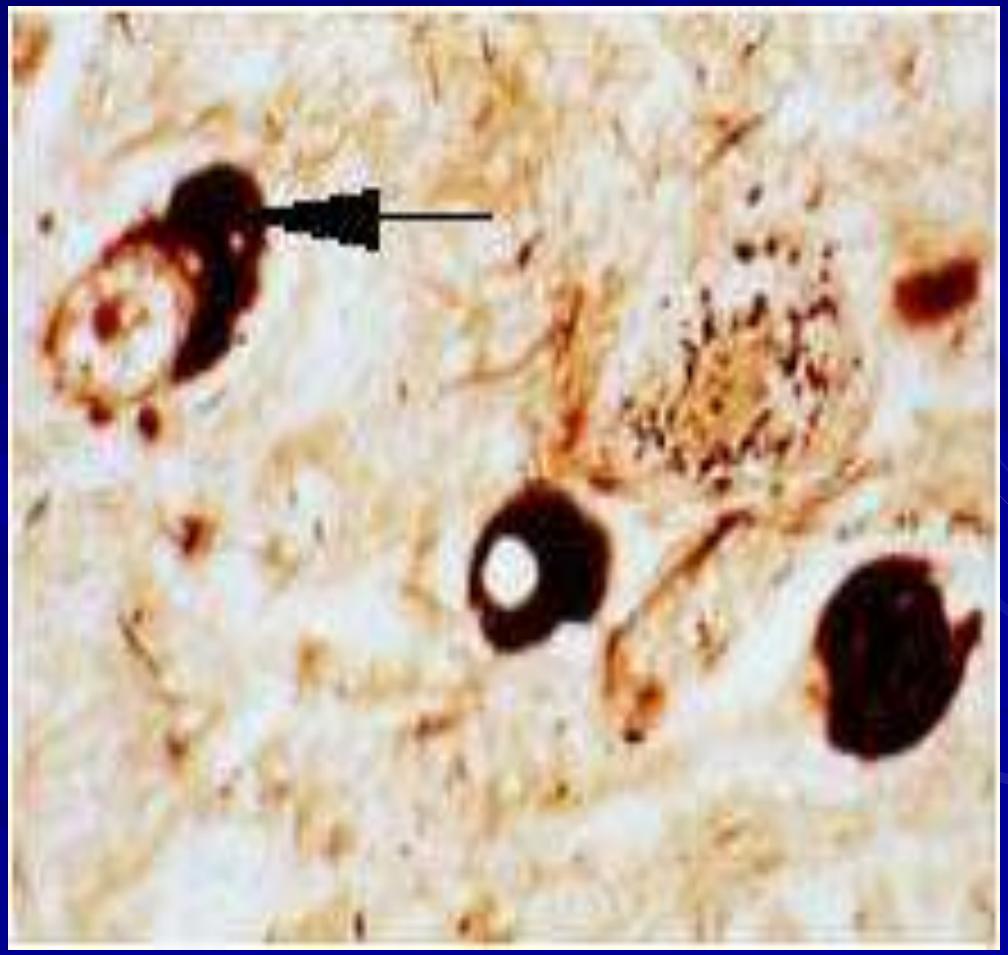
- Prevalence==~10% of presenile dementias
- Onset 6-7th decade
- E4 allele overrepresented

Frontotemporal Dementia

- Associated with degeneration of frontal, temporal lobes
- Syndromes include…
  - Progressive subcortical gliosis
  - Non AD frontal lobe dementia
  - Primary progressive aphasia (Mesulam syndrome)
  - Semantic dementia
  - Pick's Disease

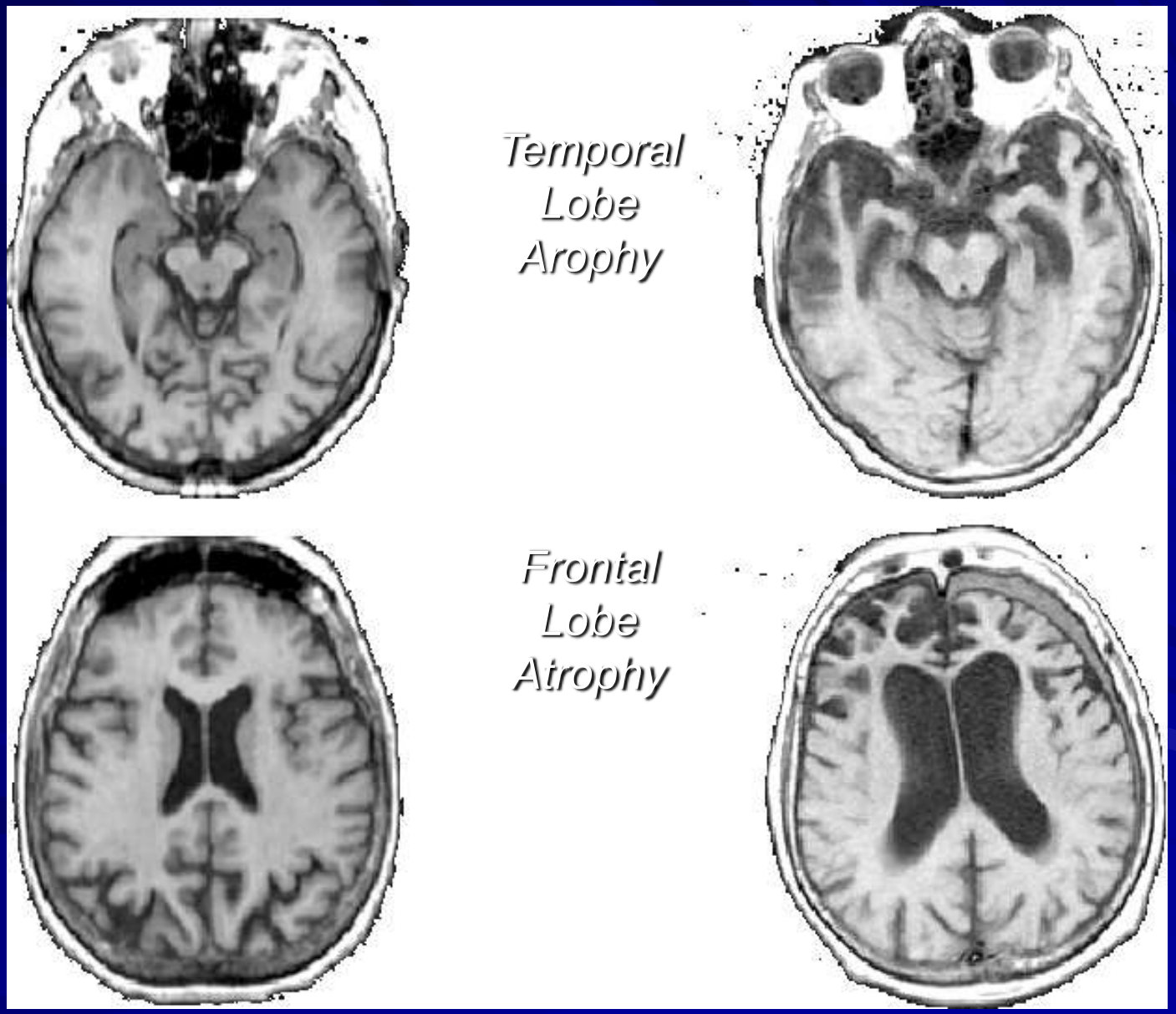
Pick's Disease and FTD- Are they the same thing?

- First clinical description by Arnold Pick in 1892
- Pathology described by Alzheimer in 1911
  - Pick bodies
  - Composed of Tau
- Classic cases of Pick's disease are rare
- Similar clinical features to other types of FTD



Control

FTD



Frontotemporal Dementia

- Distinctive core features
  - Decline in social interpersonal conduct
  - Impaired regulation of personal conduct
  - Emotional blunting
  - Loss of insight
  - Severe language disturbance
  - No severe memory loss
  - No spatial disorientation
- Supportive features
  - Decline in personal hygiene
  - Mental rigidity
  - Distractibility
  - Hyperorality & dietary changes
  - Stereotyped behavior
  - Utilization behavior
  - Earlier onset

Neary et al. (1998) Neurology 51:1546

Clinical Features

- Personality changes usually precede GROSS dementia by several years
- Sometimes withdrawn and apathetic
- Sometime disinhibited, loss of judgement
  - 50% commit an antisocial act that can lead to arrest

FTD-clinical features

- Kluver-Bucy Syndrome:
  - In animals, removal of anterior temoporal lobes, bilateral amygdala
    - Hyperorality
    - Placidity
    - Sensory agnosia
    - Lose social behaviors
- Loss of serotonin!

FTD- cognitive features

- Economical language decline is usually the first feature
  - Verbal stereotypies
  - Word list generation impairments
  - Semantic anomia
  - Visuospatial skills relatively preserved
- EEG:
  - Frontal sowing, or normal

Distinguishing FTD from AD

- Many FTD patients may meet clinical criteria for Alzheimer's disease
- Severe focal atrophy may not be detectable early
- Core features of FTD can occur in AD
  - Personality changes
  - Behavioral problems
  - Language difficulties
- Clinical features most effective in distinguishing FTD from AD
  - Social conduct disorders
  - Hyperorality
  - Akinesia
  - Lack of severe amnesia
  - Lack of visual perceptual deficit

Rosen et al. (2002) Neurology 58:1608

Distinguishing FTD from SMI

FTD

- Personality changes
- Behavioral problems
- Language difficulties

- **SMI**
  - Hyperorality
  - Akinesia
  - Lack of severe amnesia
  - Lack of visual perceptual deficit

Treatment of FTD

- No specific treatment
- Neurochemical changes not well defined
  - Possible reduction in frontal-temporal serotonin
  - No established benefit of cholinesterase inhibitors for cognitive symptoms
- Limited effectiveness of drugs against specific target symptoms
- Symptomatic drug therapy
  - SSRI antidepressants
    - Mood disturbances
    - Compulsions
    - Hyperorality
  - Antiepileptics
    - Carbamazepine; Valproate
    - Agitation and aggression
  - Atypical neuroleptics
    - Agitation and aggression

Treatment of FTD

- Behavioral approaches
  - Susceptible to environment
    - Control environmental triggers for problem behaviors
  - Poor executive function
    - Provide structure
  - Limited judgment & insight
    - Early cessation of driving
    - Limit financial dealings
    - Possible job changes
- Education-support
  - Potential for severe difficulty at early stages
  - Socially inappropriate behaviors
  - Loss of emotional responsiveness
  - Severe communication problems
  - Risk of agitation and aggression
    - Often younger patients

Lewy Body Dementia

- First described in 1960's
  - Okasaki, et al 1961
- # 2 cause of dementia
  - Accounts for at least 10% of post-mortem samples
  - 15% community-based dementias in London
  - 36% US ADC referrals

Dementia with Lewy Bodies (DLB)

- Core features of DLB
  - Fluctuations
    - Periods of severe confusion of unresponsiveness
  - Hallucinations
    - Complex, vivid visual hallucinations
  - Parkinson's-like symptoms
    - Initially may be mild
    - Tremor less frequent
- Supportive features
  - Frequent falls
  - Syncope or transient loss of consciousness
  - Neuroleptic sensitivity
  - Systematized delusions
  - Non-visual hallucinations

McKeith et al. (1996) Neurology 47:1113

DLB: Presentation

- Delirium
  - Fluctuating confusion
  - Attentional deficits
  - Intermittent lloss of consciousness
- Psychiatric symptoms
  - Visual hallucinations
    - Persistent, complex
- Parkinsonian symptoms
  - May precede dementia
  - Rigid, akinetic parkinsonism
  - Frequent falls

Memory complaints are first in 60-70%

Faster rate of decline than AD

death in 5-8 years

Minimal response to l-dopa

DLB: International Consensus Criteria

- Core symptoms:
  - Fluctuating confusion
  - Visual hallucinations
  - Spontaneous parkinsonism
- Two needed for probable DLB,
- 1 needed for possible DLB

- Specificity>0.8
- Sensitivity~.22-0.8
- Attention, visuospatial skills more impaired than AD
- Recent memory may be well preserved early

Other Symptoms…

- Sleep disturbance:
  - REM sleep behavior disorder is common
- Depression
  - 33-50%
  - *No data on treatment for depression*

DLB Similarities to AD and PD

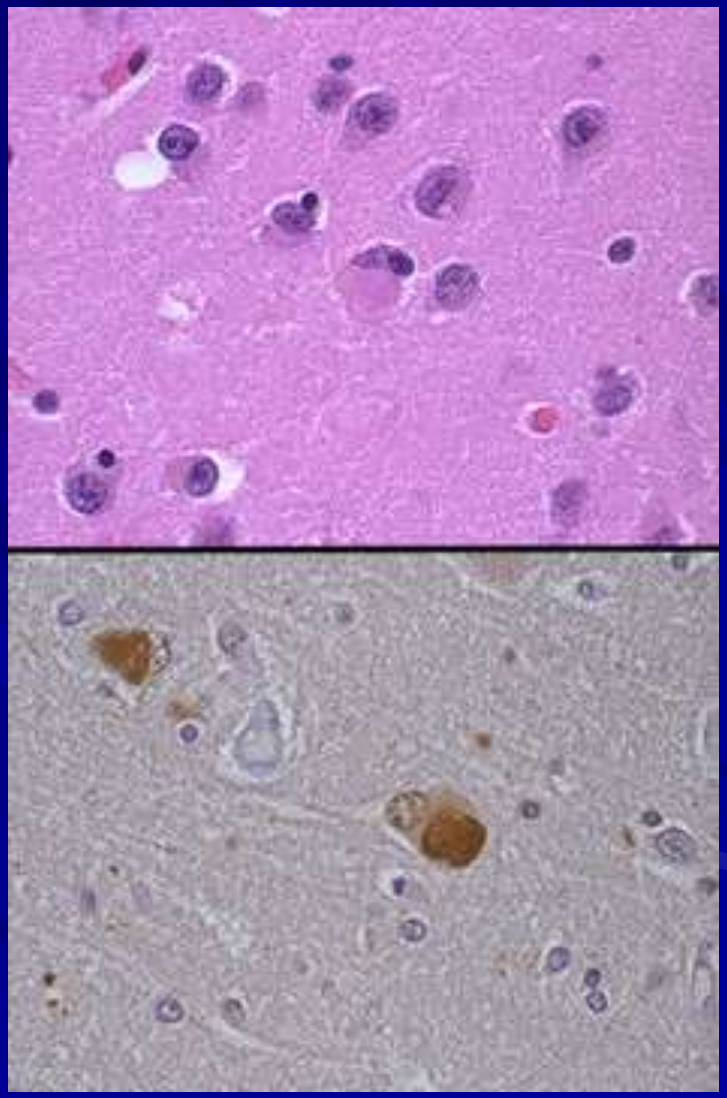
- Cognitive symptoms similar to AD
  - Prominent memory loss
  - Executive dysfunction
  - Visuospatial impairments
  - Language impairments
- Some atypical features
  - Prominent attentional problems
- Motor symptoms similar to PD
  - Bradykinesia
  - Postural instability
  - Rigidity
- Some atypical features
  - Symmentric
  - Less frequent tremor
  - Less responsive to dopaminergic therapy

What are Lewy bodies?

- Composed of multiple proteins
  - Cytoskeletal proteins
  - Protein degrading enzymes
  - Alpha-synuclein aggregates
- Mutations in alpha-synuclein responsible for rare cases of genetic PD
  - Normal function is unknown
  - Protein aggregation promoted by mutations

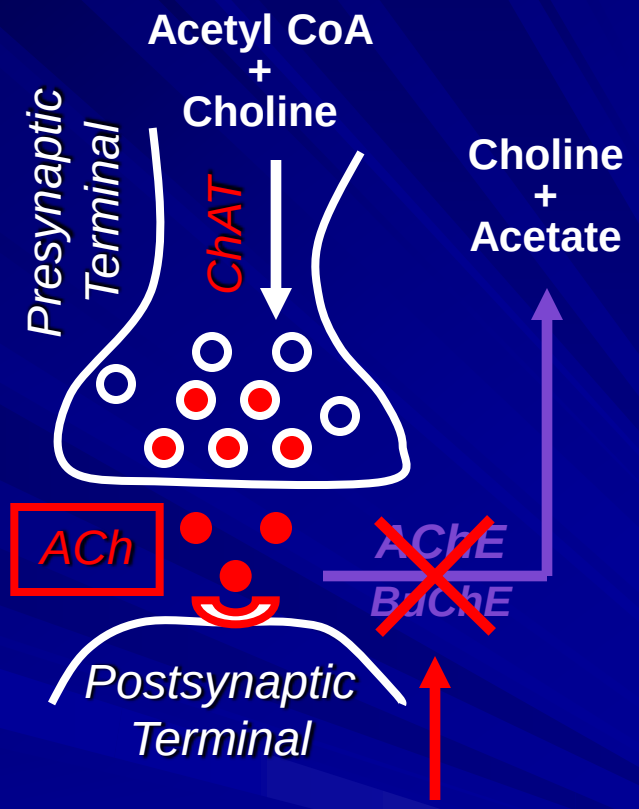
Neuropathology in DLB

- Distribution of Lewy bodies
  - Brainstem Lewy bodies
  - Degeneration of nigra
  - Dopamine deficiency
  - Diffuse cortical Lewy bodies
- Alzheimer's-like pathology
  - Pathological overlap with AD
  - AD cases with Lewy bodies
- Combined neurochemical deficiencies
  - Acetylcholine
  - Dopamine



Treatment of DLB

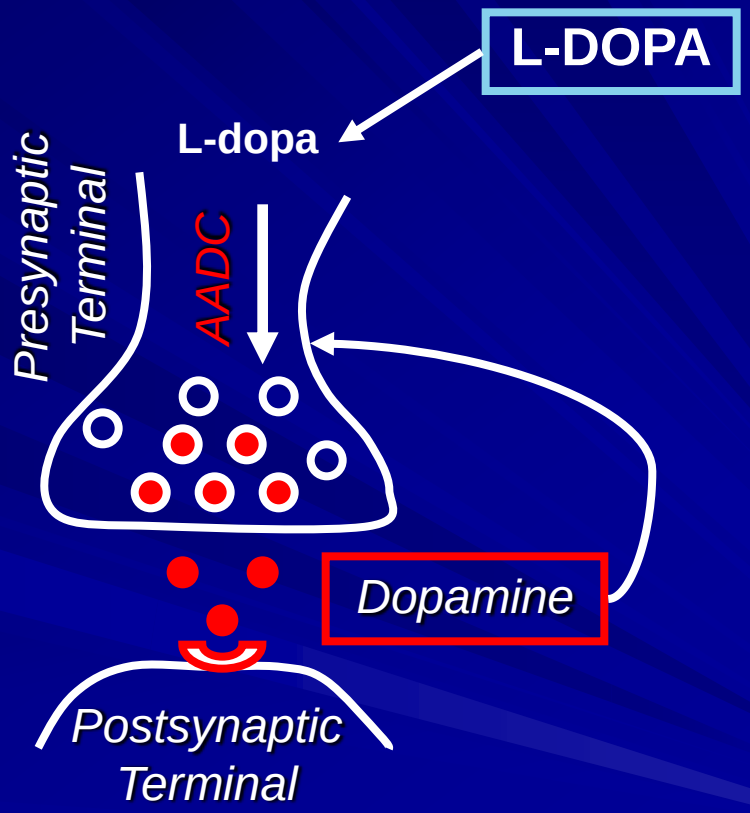
- Cholinergic deficits
  - Loss of acetylcholine producing cells
  - Severe deficit
  - Possibly best responders to cholinesterase inhibitors
- Dopaminergic deficits
  - Loss of dopamine-producing cells
  - Variable response to dopamine replacement therapy



Tacrine (Cognex)
Donepezil (Aricept)
Rivastigmine (Exelon)
Galantamine (Reminyl)

Treatment of DLB

- Cholinergic deficits
  - Loss of acetylcholine producing cells
  - Severe deficit
  - Possibly best responders to cholinesterase inhibitors
- Dopaminergic deficits
  - Loss of dopamine-producing cells
  - Variable response to dopamine replacement therapy



Treatment:AchE Inhibitors

- Limited, open label trials show reductions in
  - Hallucinations
  - Delusions
  - Apathy

Schizophrenia in late life

- One year prevalence over age 65 is 0.6%
- 12% of schizophrenics were over 50 years old in 2004
  - Will double by 2024
- Economic costs associated with functional impairment are among the highest in late life
  - Cognition is the strongest predictor of function
  - 80% are in the community

Positive symptoms

Schizophrenia

- Delusions
  - Fixed, false, idiosyncratic
  - Not mood congruent
- Hallucinations
  - Most are auditory…can be visual/smell/taste/touch
- Disorganization
  - Speech or thought
- Catatonia

Compared to Dementia

- Delusions often ‘reality based’
- Visual hallucinations more common
- Responds to lower doses of antipsychotics..usually
- Disorganized later in disease

Longitudinal study of of hallucinations in NYC

- 104 subjects followed 12-116 months
- 35% lived independently or with family
- Cross sectional results: 36 % had hallucinations
  - 32% auditory
  - 13% visual9% olfactory

Auditory Hallucinations in NYC

- 73% clear
- 55% every day
- 56% were pleasant
- 61% good
- 58% command
- 56% obeys commands

Type and Identity of voices…

- Type:
  - 34% evaluative
  - 34% directive
  - 32% Mundane
- Identity:
  - 23% God
  - 3% Devil
  - 15% Relatives

Negative symptoms

- Social withdrawal (Autism)
- Difficulty with emotions(affect)
- Poor self care(ambivalence)
- Anhedonia (Affect)

Paranoid subtype

- Delusions of persecution, sometimes grandiose
- Attention difficulties
- Normal Intellect
- Behavioral problems include..
  - Anger
  - Withdrawal
  - anxiety

Cognition in Schizophrenia

- Cognition declines after at least 2 years followup among institutionalized individuals
- After age 65, MMSE declines by 1 point per year
- Community dwelling schizophrenics show stability in cognitive measures compared to age matched controls.
  - Also, no decline in social functioning

Cognitive impairments in…

- Schizophrenia-impairments in:
  - Working memory
  - Long term memory
  - Attention
  - *Processing speed*
  - Executive function
- Dementia-impairments
  - Amnesia-recent memory
  - Aphasia-language
  - Apraxia
  - Agnosia

So… how does SMI interact with dementia

- Badly
- Often, in facilities one diagnosis is neglected
  - Its usually Serious Mental Illness
- Dementia often makes psychotic symptoms less vivid, sometimes more ‘reality based’
- Dementia mitigates the expression of schizophrenia, not the opposite
- In SNF’s, regulatory pressures often result in undermedicating
  - Mandatory attempts at dose reduction

Tyrant in the house?

"Thorazine" can control the agitated, belligerent senile

and help the patient to live a composed and useful life.

When "Thorazine" is administered to the agitated senile, there is a marked decrease in his error-making confusion of hostility, irritability, abusiveness, incessant talking and "day-and-night" pacing or restlessness.

On "Thorazine" therapy, the patient often begins more regular eating and sleeping habits and improves in his personal hygiene. As the patient becomes more tractable and cooperative, he is able to live a composed and useful life.

THORAZINE®

one of the fundamental drugs in medicine

Smith Kline & French Laboratories, Philadelphia

for prompt control of

senile agitation

THORAZINE®

"Thorazine" can control the agitated, belligerent senile and help the patient to live a composed and useful life.

Smith Kline & French Laboratories

Overview of RCT Evidence for Drugs

- Pain medications
- Anticonvulsants
- Antidepressants
- Benzodiazepines
- Cholinesterase inhibitors
- Memantine
- Antipsychotics

Pain Medications

• Empiric pain management protocol in nursing home residents with agitation
– Placebo-controlled 8 week RCT, n=352
• Step 1: acetaminophen (68%)
• Step 2: oral morphine (2%)
• Step 3: buprenorphine patch (23%)
• Step 4: pregabalin (7%)
– Agitated symptoms improved at 8 weeks with
treatment vs. placebo, and worsened in 4 week
washout

Husebo et al, *BMJ. 2011;343:d4065*

Antidepressants

- **SSRIs**

– 5 studies vs. placebo
– 3 studies vs. typical antipsychotics
– Possible small benefits on agitated symptoms

Other Antidepressants

– Trazodone
- **2 studies = haloperidol, small N**
- **1 study = placebo**

Seitz et al, Cochrane Reviews 2011;2;CD008191

Anticonvulsants

Divalproex

– 4 studies = placebo, poorly tolerated
– Cognitive decline and hippocampal damage?

Carbamazepine

– Mixed evidence
– Concerns of poor tolerability, drug interactions

Lonergan and Luxenberg, Cochrane Reviews 2009;3;CD003945
Tariot et al, Arch Gen Psychiatry 2011;68(8):853-61
Fleisher et al, Neurology 2011;77(13):1263-71
Sink et al, J Am Med Assoc 2005;293(5):596-608
Konovalov et al, Int Psychogeriatr 2008;20(2):293-308.

Benzodiazepines/anxiolytics

Oxazepam, alprazolam, diphenhydramine, buspirone

– 3 studies = haloperidol
– No placebo controlled studies

trial design problems, cognitive impairment issues with most of these drugs

• Not recommended for scheduled use

Meeks and Jeste, Current Psychiatry 2008;7(6):50-65

Antipsychotic Choice

• Evidence supports modest symptom improvements with
– **Haloperidol *(Haldol®)****
– **Olanzapine *(Zyprexa®)***
– **Quetiapine *(Seroquel®)***
• **less supportive evidence**
– **Risperidone *(Risperdal®)****
– **Aripiprazole *(Abilify®)***
• Research does not support use of other
antipsychotics in dementia
*available as less expensive generic

Evidence for the Use of Antipsychotics for Behavioral Disturbances

Modest efficacy in RCTs with some drugs

- **Risperidone for psychosis**
- **Aripiprazole and Risperidone for neuropsychiatric symptoms**

Benefits less in those without psychosis, in nursing homes, and with severe cognitive impairment

- **Haloperidol similar efficacy to atypicals**
- **4 negative placebo controlled trials with quetiapine**

Jeste et al, Neuropsychopharmacology 2008;33:957-70.
Maglione et al. Off-label use of atypical antipsychotics: an update. www.effectivehealthcare.ahrq.gov/report/final.cfm.
Gentile, Psychopharmacology 2010;212:119-129.

Evidence for the Use of Antipsychotics for Behavioral Disturbances

CATIE-AD

– Time to discontinuation was primary outcome
• Olanzapine, Quetiapine, Risperidone no better than placebo
– Time to discontinuation due to lack of efficacy favored Olanzapine and Risperidone
– Time to discontinuation due to adverse effects favored placebo
Schneider et al, N Engl J Med 2006;355(15):1525-38.

AHRQ Summary of Efficacy: Atypical Antipsychotics

Aripiprazole Olanzapine Quetiapine Risperidone

Dementia-Overall ++ + + ++
Dementia-Psychosis + +/- +/- ++
Dementia-Agitation + ++ +/- ++

Legend:
++ = Moderate or high evidence of efficacy
+ = Low or very low evidence of efficacy
+/- = Mixed results

http://www.effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-andreports

Potentially appropriate antipsychotic treatment targets

- **Hallucinations**

- **Delusions (note: memory problems are often mistaken for delusions, e.g. thinks people are stealing lost items…or are they?)**

- **Aggressive behavior (especially physical)**

Appropriate antipsychotic treatment targets

- If the symptom presents a danger to the patient or others

- Or, causes the patient to experience
  - Inconsolable or persistent distress
  - Significant decline in function
  - Substantial difficulty receiving needed care

Inappropriate antipsychotic treatment targets

•

.Wandering
• Unsociability
• Poor self-care
• Restlessness
• Impaired memory
• Inattention or indifference to surroundings

• Verbal expressions or behaviors that do not represent a danger to the resident or others
• Nervousness
• Uncooperativeness
• Fidgeting
• Mild anxiety

Parkinson's Disease / Lewy Body Dementia

– Tolerate antipsychotics poorly
– Reduce antiparkinson med doses for psychosis
– Cholinesterase inhibitors may reduce hallucinations
– Memantine may produce global improvements

Frontotemporal Dementia

– Preliminary data for trazodone and stimulants
– Mixed data on paroxetine
• May worsen cognition

Weintraub and Hurtig, 2007;164:1491-8. Huey et al, J Clin Psychiatry 2008;69(12):1981-2. Deakin et al, Psychopharmacology 2003;10:10. Moretti et al, Eur Neurol 2003;49:13-9.

We can learn from antipsychotic RCT's

- Rule out/ treat concomitant medical illness
- Simplify medications
- Give attention to subjects
- 'Passively educate' staff

Antipsychotic discontinuation studies

The few placebo-controlled studies of antipsychotic discontinuation show mixed results and some recent studies showed little difference on drug versus placebo

The largest study that discontinued AD patients from different antipsychotics showed greater worsening on placebo by 12 months in patients with greater baseline psychopathology

Ballard C et al, Plos Med 5(4): e76, 2008

Pilot Study of haloperidol discontinuation in AD

44 AD patients with psychosis or agitation
received open haloperidol treatment for 20 weeks

- 22 responders were randomized, double-blind, to continue haloperidol or switch to placebo for 24 weeks
- 40% relapsed on haloperidol, 80% relapsed on placebo

Devanand DP et al, Int J Geriatr Psychiatry 26:937-943, 2011

Antipsychotic Discontinuation in Alzheimer's Disease: ADAD trial

Identification of target symptoms in AD patients with psychosis or agitation/aggression

- Initial systematic open treatment with risperidone
- Responders at 16 weeks were randomized
- Two clinically relevant time-points (16 and 32 weeks after randomization) for discontinuation

ADAD trial: Key Inclusion/Exclusion criteria

- Age 50-95 years
- Probable AD
- MMSE 5-26 outpatients, 2-26 nursing home patients
- Excluded stroke, TIA, uncontrolled atrial fibrilllation
- Presence of either psychosis (NPI ≥ 4 on delusions or hallucinations) or behavioral dyscontrol (NPI ≥ 4 on agitation/aggression)

Phase A open label risperidone treatment

Reduction in NPI core (t=17.2, p < .0001), target symptoms (t=22.4, p < .0001)

- Average 0.7 point increase in EPS (Simpson-Angus Scale, t=2.64, p=0.009), no change in AIMS
- Somatic symptoms improved (TESS, t=6.1, p < .0001)
- MMSE decreased half a point on average (t=2.7, p=0.007) and ADAS-cog did not change

Relapse in first 16 weeks after randomization

Last observation carried forward for all subjects except:
(1)Death was counted as relapse;
(2)Patients counted as relapsed if they were at imminent risk of relapse before dropout based on review of records by a psychiatrist independent of the study (n=2 on placebo and n=1 on risperidone)

Time to relapse and risk of relapse favored risperidone over placebo

Relapse rates
60% (24/40) relapsed on placebo, 32.9% (23/70) relapsed on Risperidone (Chisq=7.40, p=0.004)

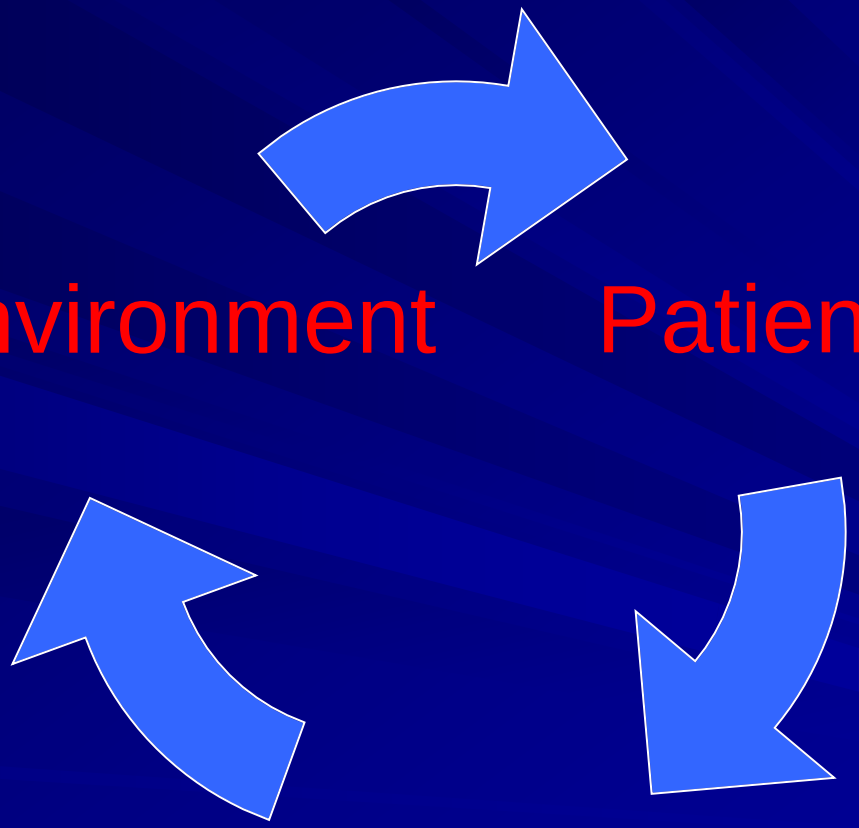
Relapse in final 16 weeks after randomization

Both time to relapse and risk of relapse favored risperidone over Placebo

Relapse rates
48% (13/27) relapsed on placebo
15% (2/13) relapsed on risperidone
Chisq=4.33, p=0.017

Non-antipsychotic Management of Difficult Behaviors in dementia and chronic severe mental illness

For every patient we should assess…



What we really need is an effective…

Behavioral Management Team

"I lift, you grab. ... Was that concept just a little too complex, Carl?"

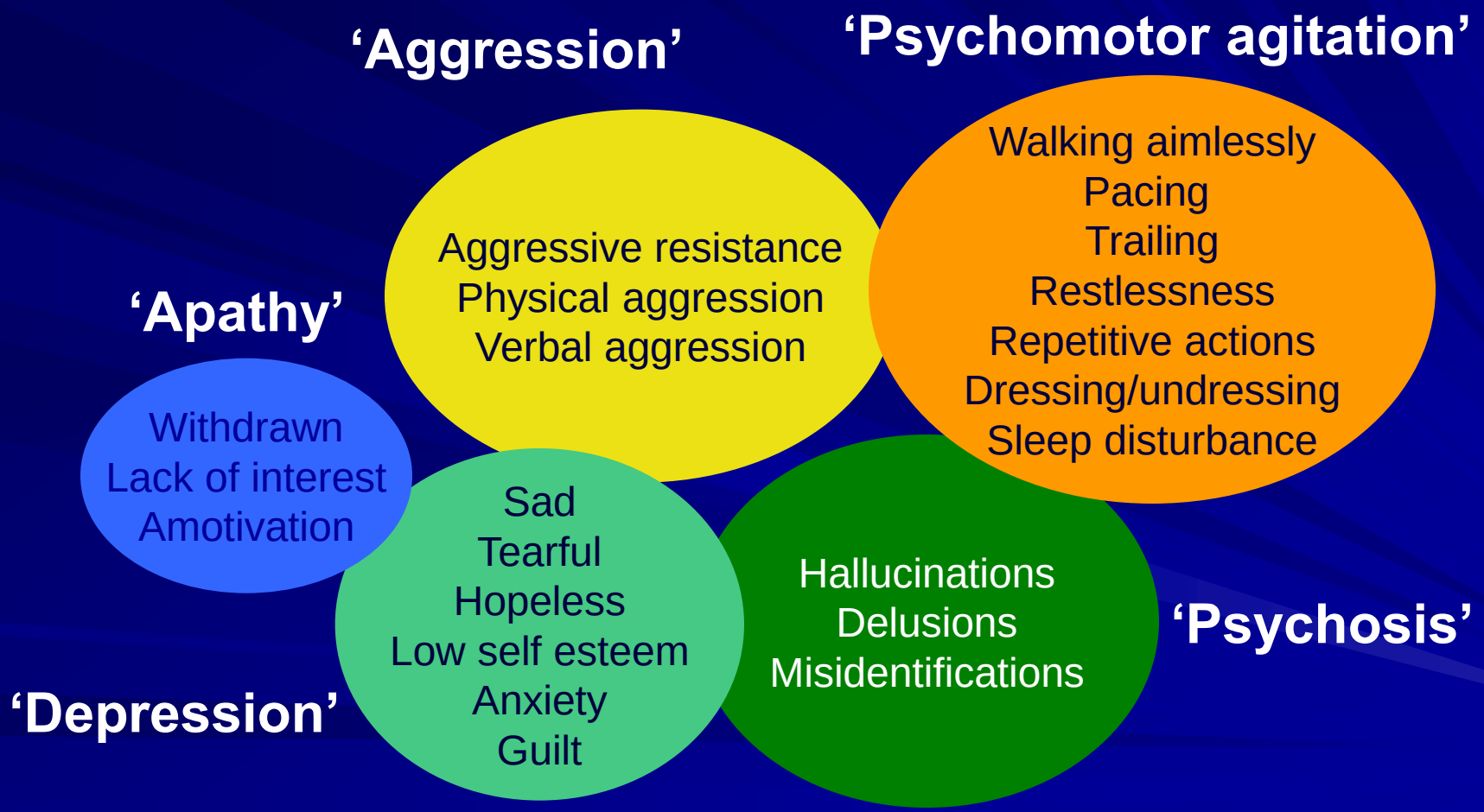
Approach to Agitation, Psychosis in the elderly

- Medical issues --**delirium** should be first concern
  - Treatable cause of psychosis
  - Important cause of morbidity, mortality
- Prior psychiatric diagnosis associated with psychosis
  - Depression, Dementia complicated by delusions
- Psychosocial influences
  - Premorbid personality, inappropriate environment

Caregiver Education in the Nursing Home

- Intervention
  - *Ongoing education is critical…it will have to go beyond the minimal requirements*
- Patient Response
  - Improved social interactions
  - Decreased agitation during care
  - Improved function (social)
- Caregiver Response
  - Improved interactive behaviors
  - Change in caregiver burden

BPSD Clusters



Adapted from McShane R. Int Psychogeriatr 2000

Psychosis/Delusions in Dementia

- Delusional thought content (eg, paranoia) is common (studies suggest 34% to 50% incidence)
- Common delusions, many of which are written off
  - Marital infidelity
  - Patients, staff are trying to hurt me
  - Staff, family members are impersonators
  - People are stealing my things
  - My house is not my home
  - Strangers living in my home
  - Misidentification of people
  - People on TV are real

Sources: Deutsch et al. *Am J Psychiatry.* 1991;148:1159-1163./Drevets. *Biol Psychiatry*. 1989;25:39-48.

At the heart of all behavioral interventions are simple concepts

- Take the entire context into account
- Simplify Everything, break it down
- Realize that management is often counter-intuitive
- Realize the patient is lost

Nonpharmacologic Management of Behavioral Disturbances

- Distraction
- Tolerance
- Speak slowly, low pitched voice
- 1-step commands
- Exercise
- Assure adequate lighting
- Music..the right kind
- Time orientation
- Routine
- Slow pace

Before Intervening…

- Review, treat medical, psychiatric conditions
- Possible causes…Delirium!
  - UTI
  - Medications
  - Delirium, dehydration, infection,
  - Pain
  - “simple” adjustment to change
- Identify Target symptoms
- Evaluate context

Interpersonal Interventions

- Repetition
- Redirection
  - Distraction
- Reassurance

  The mindset of most demented patients is to be ***lost.***
- Group activities

Environmental Modifications 1

- Provide visual cues
- Reasonable level of stimulation
- Assess Mirrors, TV, overhead paging
- Assure proper lighting
- Locks, alarm systems

Environmental correlates of agitation

- 53 special care units
- 3723 observations of patient behaviors
- Factors associated with agitation
  - Low light
  - Low “home likeness”
  - Low cleanliness
  - Low staff treatment quality

Environment is independent of staff, treatment issues

Sloan, 1998

Environmental Modification 2

- Wandering paths
- Visual barriers
  - Doorknobs
  - Window panels in doors
  - Door screens
  - Tape patterns on floors
- Routine activities routinely

Wanderers

- The activity is the treatment
- Need safe wandering space
- Appropriate level of stimulation
  - Adequate staff-patient interactions
  - Reduce extraneous noise
- Environment adjustments to reduce elopements

Intervening with severe disruptive vocalizers

- At 2 months follow-up, 50-66% were better
- Helpful interventions (6 month follow-up):
  - Food, drink, tobacco 11.7%
  - Verbal interaction 11.1%
  - Family visit 8.3%
  - Comfort measures 7.8%
  - Companionship 6.7%

All medications combined accounted for 10.6% helpful interventions

Sloane, 1999

The Daughterectomy

- She’s on a mom induced guilt trip
- She’s after something
- She just cant slip out..
- Must have the long goodbye

Physical Aggression

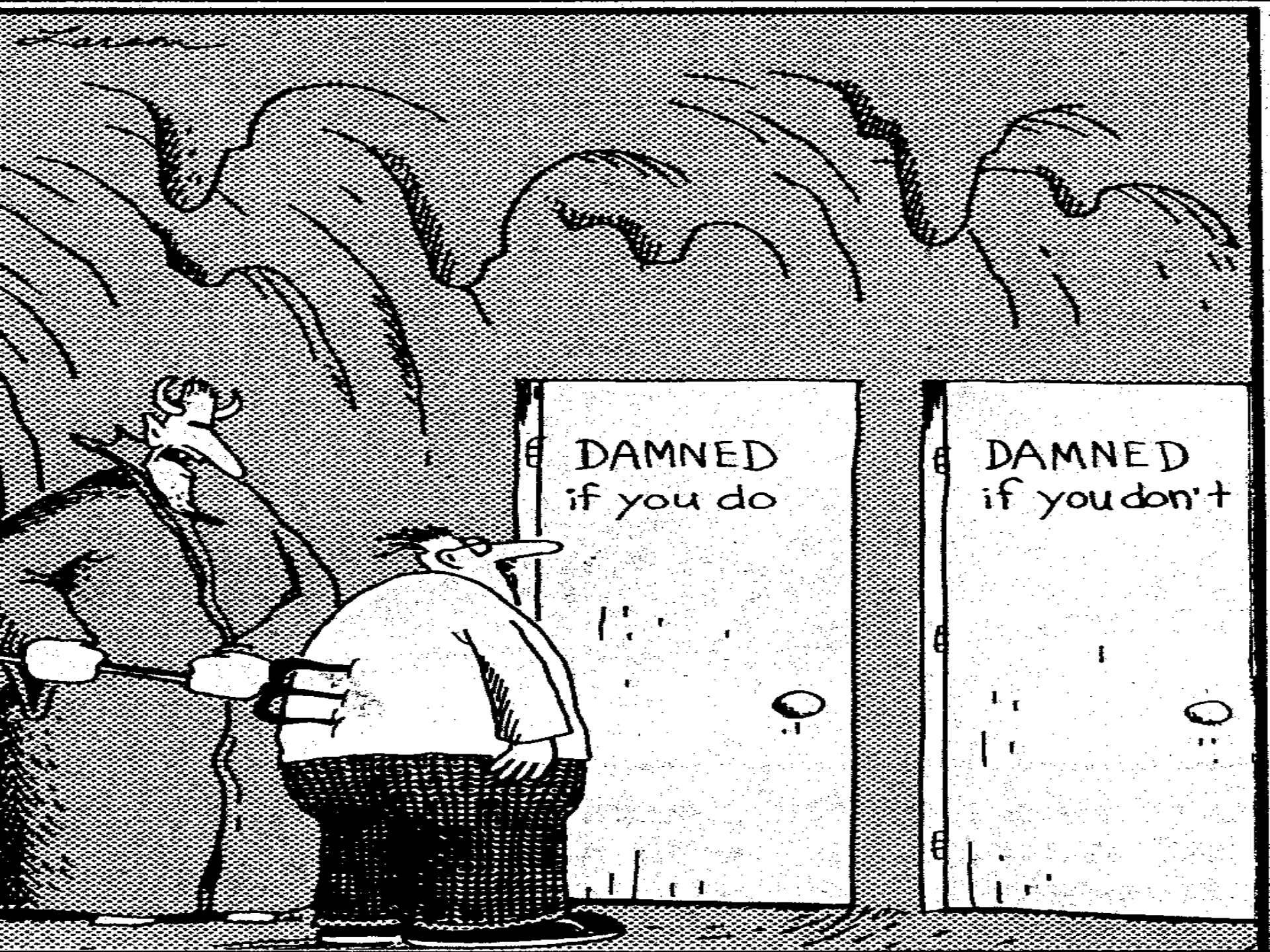
- Identify triggers
- Staff feedback
  - In basic ADL's
- Redirect, reassure
- Control affect
- Staff training

Personal Care Tasks

- Divide tasks into small steps
- Demonstrate the task
- Have patience
- Reassure, provide positive feedback

Summary: Behavioral Interventions

- Identify target behaviors
- Involve patient, caregiver, and environment
- Accommodate
- Be creative


DAMNED
if you do
DAMNED
if you don't