Lewy Body Dementia

Monique Cherrier, Ph.D.
Research Assistant Professor
Department of Psychiatry and Behavioral Sciences U. of Washington School of Medicine
and
University of Washington Alzheimer's Disease Research Center and Veterans Administration
Mental Illness, Research, Education and Clinical Center

Co-Investigators and Technical Support

Debby Tsuang, M.D., M.Sc.
Eric Larson, M.D., MPH
Walter Kukull, Ph.D.
Lauren Bonner, M.D.
Elaine Peskind, M.D.
Murray A. Raskind, M.D.
Pamela McMillan, Ph.D.
Thomas Bird, M.D.
Gerard Schellenberg, Ph.D.
Thomas Montine, M.D., Ph.D.
Lee-Way Jin, M.D., Ph.D.
David Nochlin, M.D.

Mel Ball, M.D.
Jeffrey Kaye, M.D.
Jay Nutt, M.D.

Lynne Greenup
Matt Kraybill
Christina Walker
Lillian DiGiacomo
Charisma Eugenio

Marisa Johnson

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AN

ESSAY

ON THE

SHAKING PALSY.

BY

JAMES PARKINSON,
MEMBER OF THE ROYAL COLLEGE OF SURGEONS.

LONDON:
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1817.

AN

ESSAY

ON THE

SHAKING PALSY.

CHAPTER I.

DEFINITION—HISTORY—ILLUSTRATIVE CASES.

SHAKING PALSY. *(Paralysis Agitans.)*

Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forward, and to pass from a walking to a running pace: the senses and intellects being uninjured.

History of Parkinson's Disease

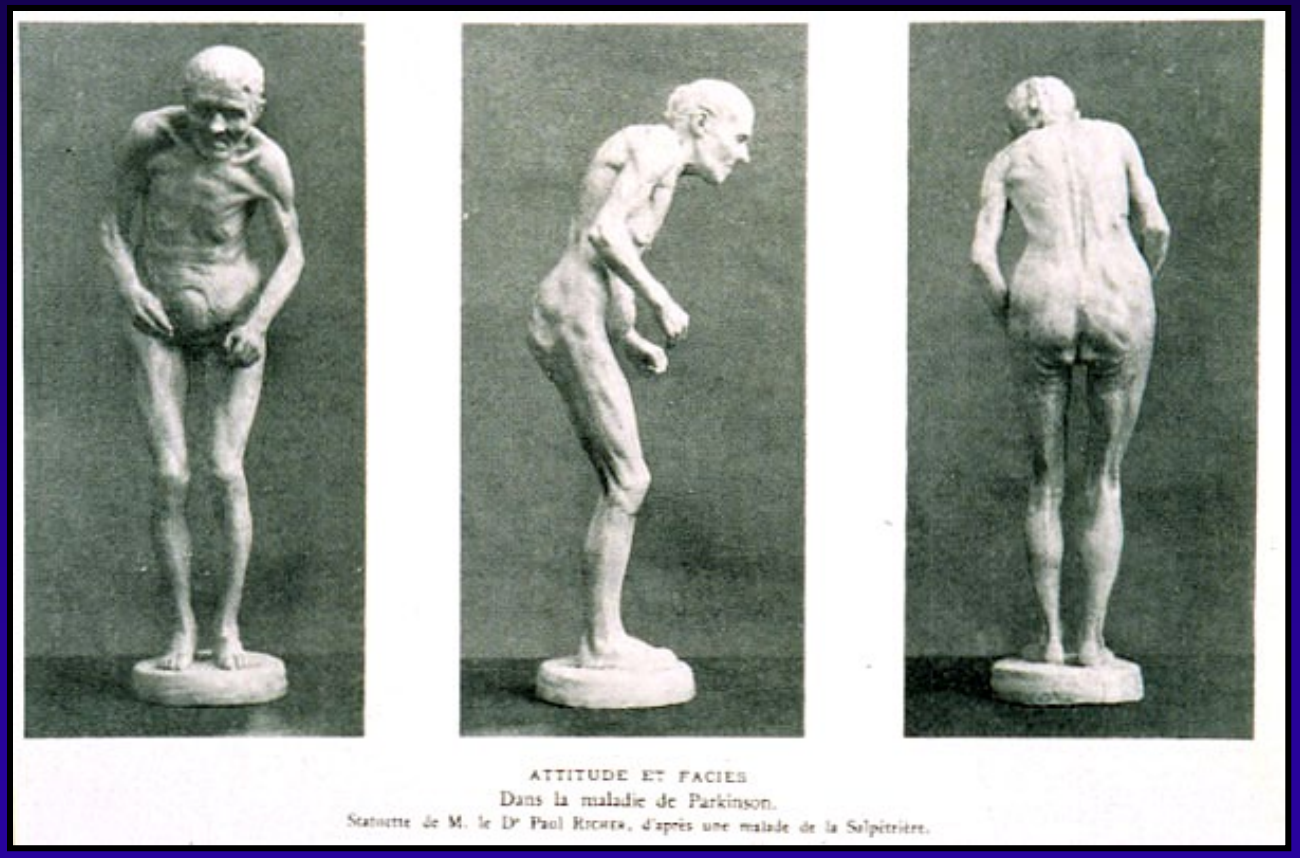
138-201	Galen describes resting tremor
1817	Initial description of disease by James Parkinson
1859/68	Trousseau describes intellectual decline
1861-95	Charcot and Brissaud emphasize rigidity, bradykinesia and "psychic troubles"

Clinical Symptoms in Parkinson's Disease

- Tremor (resting)
- Rigidity
- Bradykinesia
- Postural instability

Parkinson's Disease

Parkinson's Disease



ATTITUDE ET FACIES
Dans la maladie de Parkinson.
Statuette de M. le Dr Paul Richer, d'après une malade de la Salpêtrière.

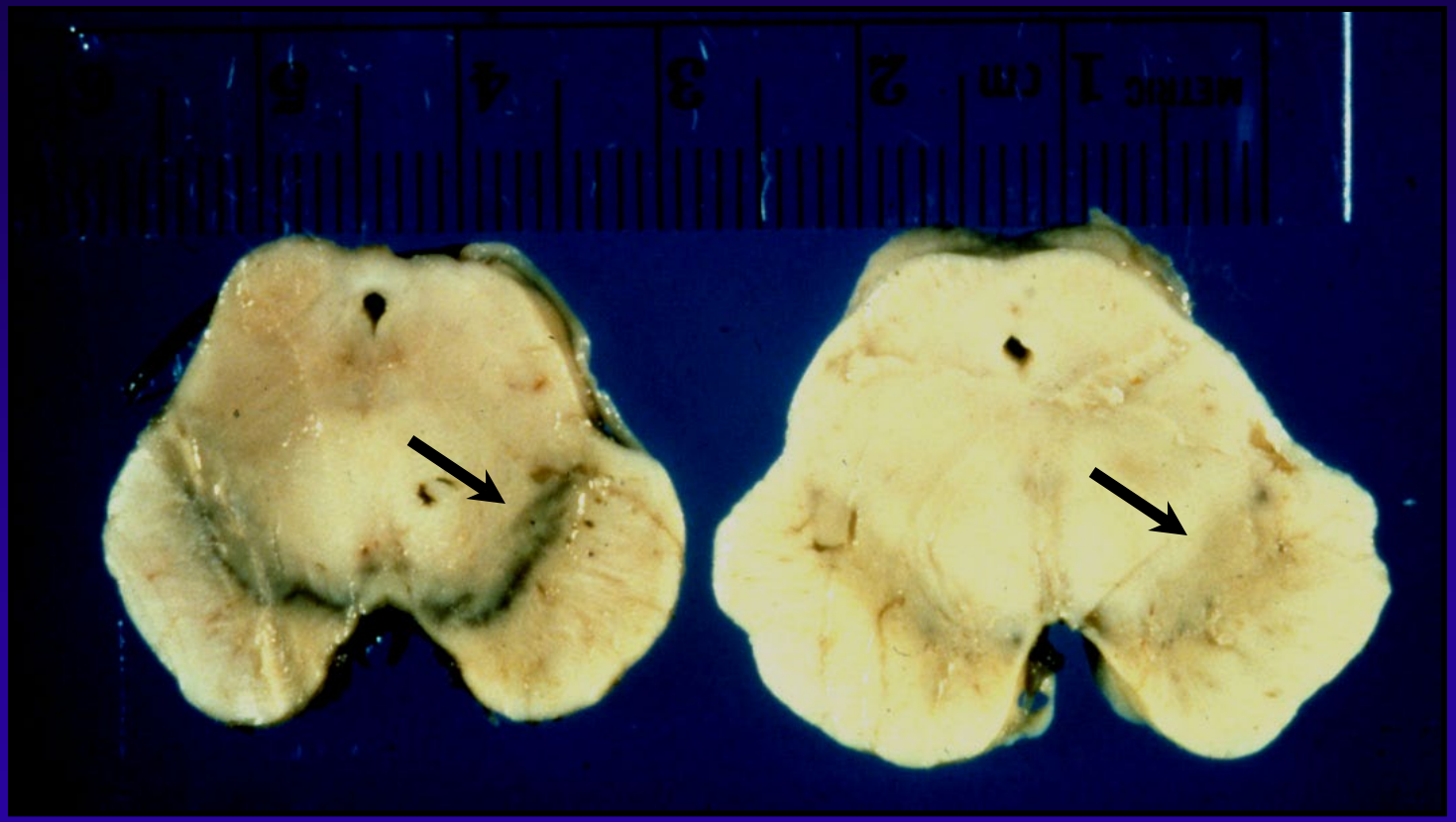
Pathology in Parkinson's Disease

- Clinical history of parkinsonism
- Neuronal loss and Lewy body inclusions in the substantia nigra, locus coeruleus, basal forebrain and cerebral cortex

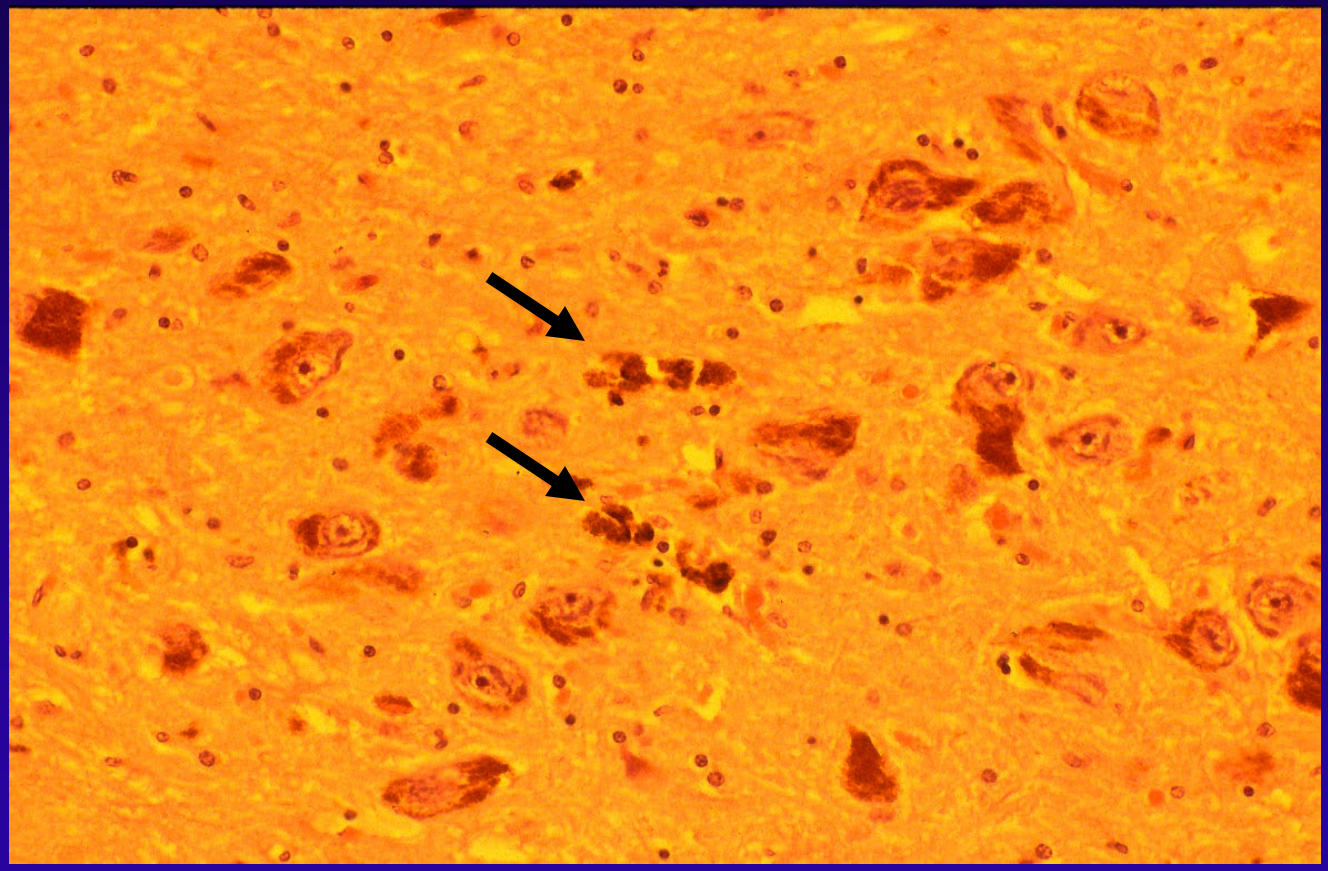
Lewy Body Inclusions

- Characteristic inclusions in substantia nigra neurons of patients with Parkinson's disease
- Immunoreactive for neurofilaments, ubiquitin and alpha-synuclein, but not tau (NFT are tau and ubiquitin positive)
- In substantia nigra it is cytoplasmic, round, eosinophilic with clear halo
- In cortex less distinct appearance, best visualized with alpha-synuclein immunohistochemistry

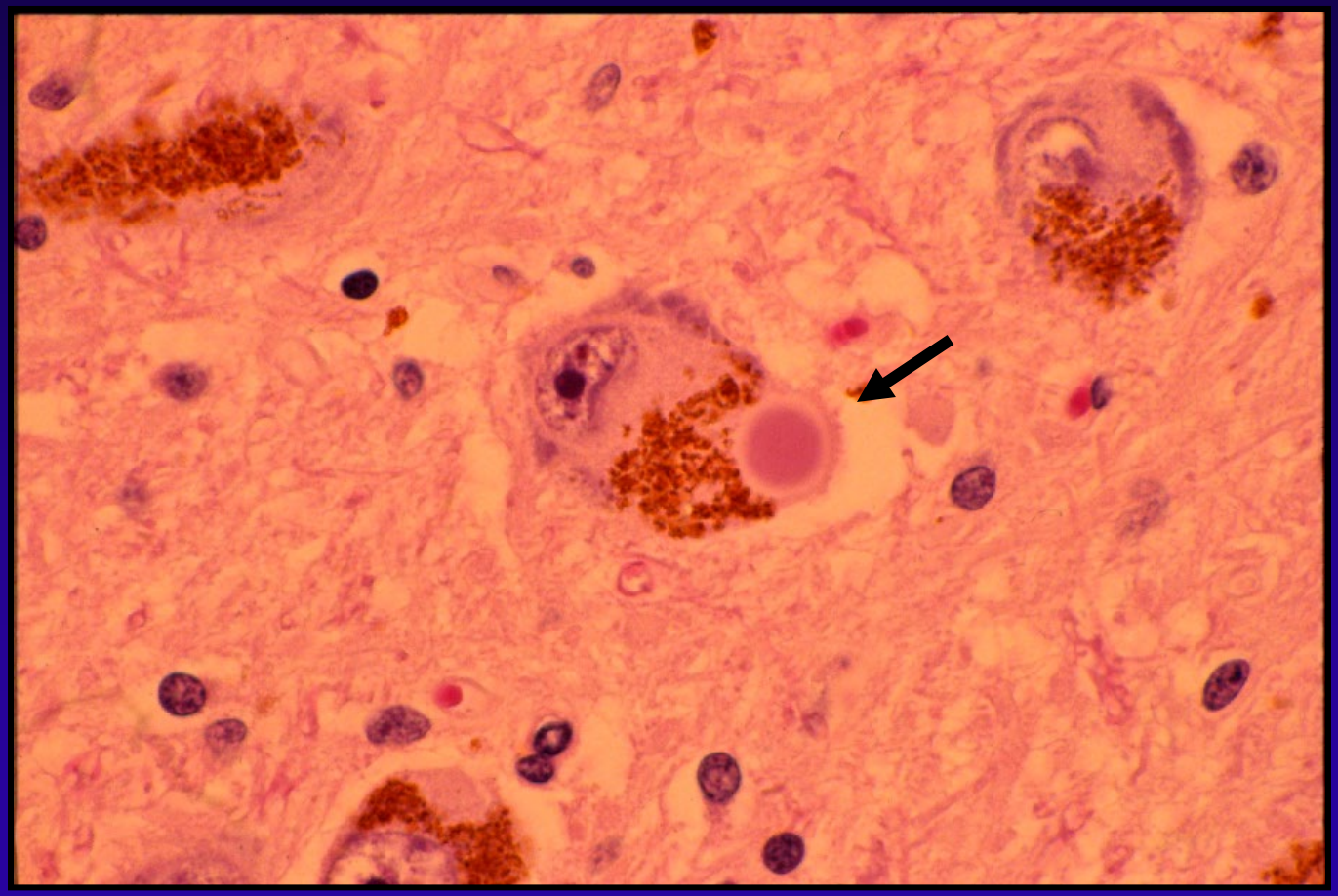
Pathology in Parkinson's Disease



Pathology in Parkinson's Disease



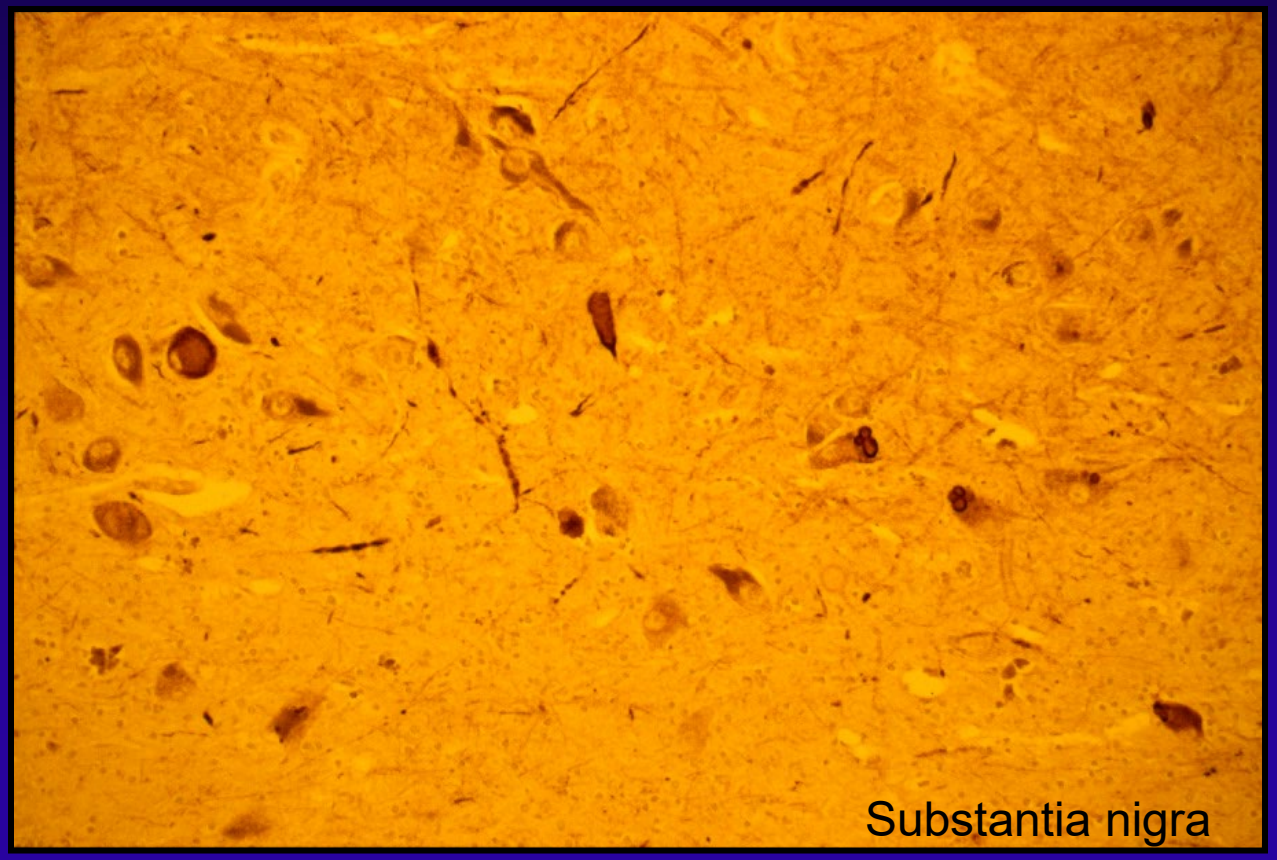
Pathology in Parkinson's Disease



Pathology in Parkinson's Disease: Improved Detection of LB Pathology

- Alpha-synuclein mutations in familial PD
- ASN immunoreactivity in all LBs
  - » classic brainstem LB
  - » cortical LB
  - » Lewy neurtites
- *Detection of a large number of amygdala LB in AD cases (up to 60 %) using ASN immunohistochemistry*

Pathology in Parkinson's Disease and Dementia with Lewy Bodies



Dementia and Lewy Bodies

Dementia in PD - Aarsland et al

- 8-year prospective study
- 224 PD vs. 3295 non-PD
- Dementia prevalence (DSM III-R)
  - » 4 year - 51.6% (vs. 18.5%)
  - » 8 year - 78.2%
- Risk factors
  - » hallucinations and akinetic dominant PDism

Aarsland et al, Arch Neurol 60:387-92, 2003

Neo- and Limbic Cortical Pathology in PD with dementia/DLB

- Hurtig et al (2000)
  - PD with and without dementia (n = 42)
  - assessment of cortical LBs, dystrophic neurites, amyloid plaques and neurofibrillary tangles
  - cortical LBs best correlate with clinical dementia
- Harding et al (2002)
  - DLB, PD with dementia, PD alone
  - LB counts in multiple cortical and limbic regions
  - overall LB density associated with dementia for PD
  - hallucinations associated with greater LB density in medial temporal lobe (amygdala and PHG)

The Clinical Diagnosis of Dementia with Lewy Bodies

History of Dementia with Lewy Bodies

1961	First report of cortical LB's in dementia (Okazaki et al)
1974	Start of clinical reports of parkinsonism in AD
1986	High frequency of LB in AD patients (Leverenz & Sumi)
1990	"Lewy body variant" proposed (Hansen et al)
1990	"Diffuse Lewy body disease" (Crystal et al)
1996	"Dementia with Lewy bodies" (Consortium on DLB)

Consensus Criteria for Dementia with Lewy Bodies

1. Progressive cognitive decline with loss of normal social and occupational function: loss of memory, attention, executive function skills, visuospatial ability
2. Two of the following:
    a. fluctuating cognition, attention, alertness
    b. visual hallucinations
    c. motor features of parkinsonism
3. Supportive features: falls, syncope, LOC, neuroleptic sensitivity, delusions, non-visual hallucinations

Consensus Criteria for Dementia with Lewy Bodies

"It is suggested that if dementia occurs within 12 months of the onset of extrapyramidal motor symptoms, the patient should be assigned a primary diagnosis of possible DLB … "

"If the clinical history of parkinsonism is longer than 12 months, PD with dementia … will usually be a more appropriate diagnostic label …"

Consensus Criteria for Dementia with Lewy Bodies

- Criteria good predictor of Lewy body pathology (with or without concomitant AD pathology) - *high positive predictive value*
- Criteria poor predictor of the absence of Lewy body pathology - *low negative predictive value*

Clinical Signs and Symptoms in DLB

- Early psychiatric symptoms
  - » Visual hallucinations, complex delusions
- Parkinsonism
  - » Early gait and posture/stance difficulties
  - » Tremor less frequent
  - » May never be clinically evident

Clinical Signs and Symptoms in DLB

- Cognition
  - » Short-term memory loss
  - » Greater insight
- Neuroleptic sensitivity

Clinical Signs and Symptoms in DLB

- Examination
  - » Gait evaluation (arm swing, posture, postural stability
  - » Frontal release signs (snout, glabellar, palmomental)
- Neuropsychological Assessment
  - » standard dementia w/u

Consensus Criteria for Dementia with Lewy Bodies

Pathology

- Essential for diagnosis of DLB
  - » Lewy bodies
- Associated but not essential
  - » Lewy-related neurites
  - » Plaques (all morphologic types)
  - » Neurofibrillary tangles
  - » Regional neuronal loss (substantia nigra, locus coeruleus, basal forebrain)
  - » Microvacuolation and synapse loss
  - » Neurochemical abnormalities and neurotransmitter deficits

Lewy Body Frequency in Alzheimer's Disease

1986 28% of AD (Leverenz and Sumi)

1987 55% of AD (Ditter and Mirra)

1995 21% in CERAD registry (Hulette et al)

1998 23% in community based series (Lim et al)

1996 Dementia with Lewy bodies, *largest pathological subgroup after pure AD* (Consortium on DLB)

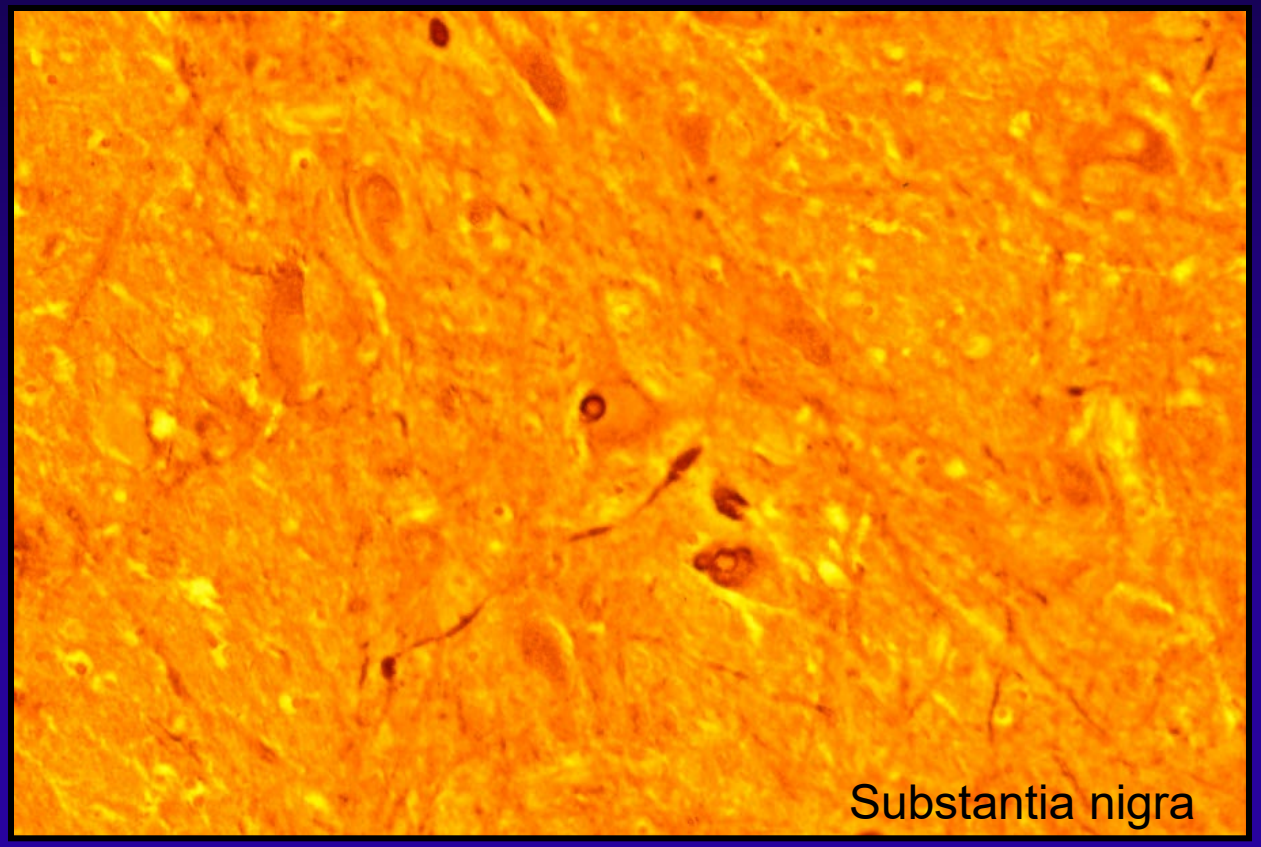
Lewy Body Frequency in Alzheimer's Disease

- 1998 to 2000
  - » Using ASN immunohistochemistry and amygdala sampling
  - » 63% PS-1/APP mutation AD
  - » 50% of Down syndrome
  - » 61% of "sporadic" AD
  - » 64% PS-2 mutation AD

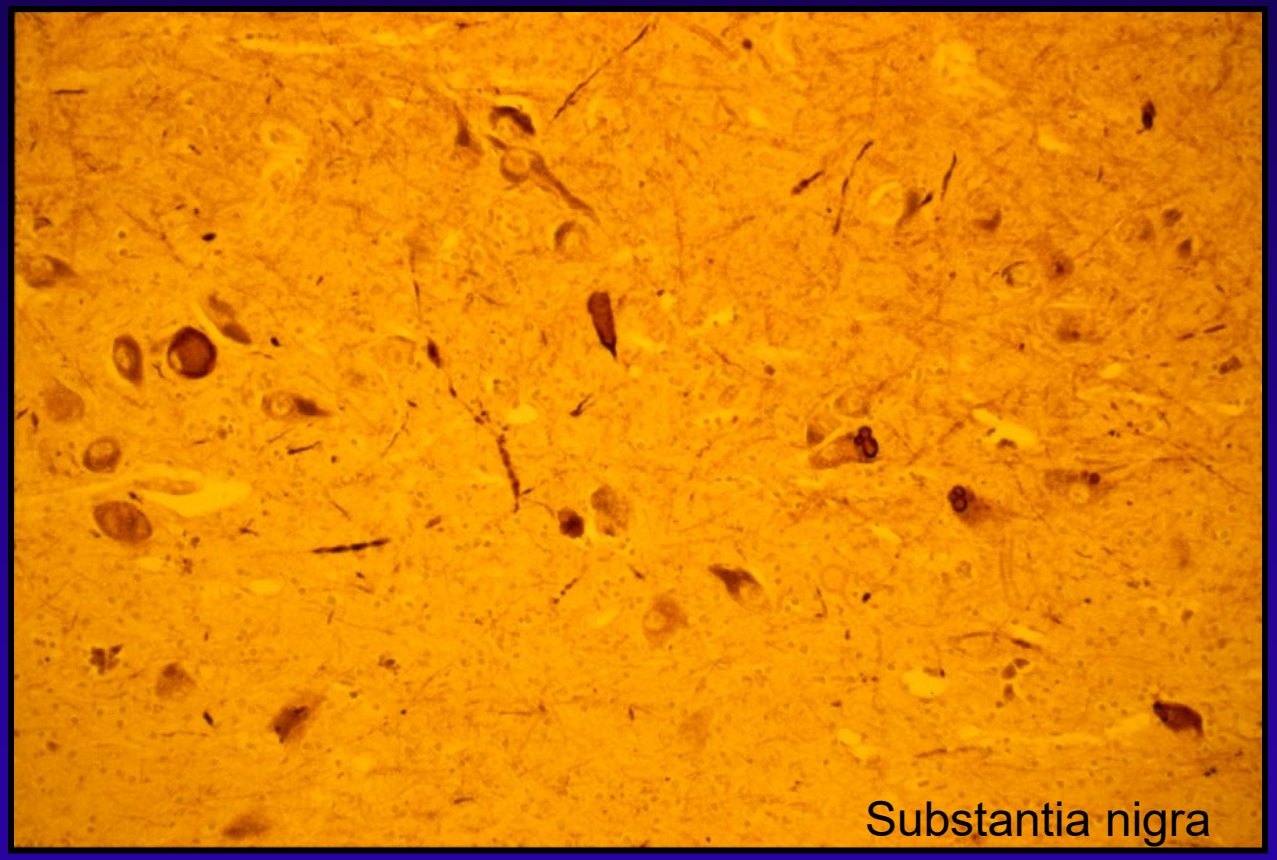
Pathology in Dementia with Lewy Bodies

- Neuronal loss and LB's in substantia nigra
- Cortical LB's and CA-2 ubiquitinated fibers
- Full AD pathology (SP/NFT), ~ 80%
- Restricted AD pathology (diffuse SP and restricted NFT distribution), ~ 20%

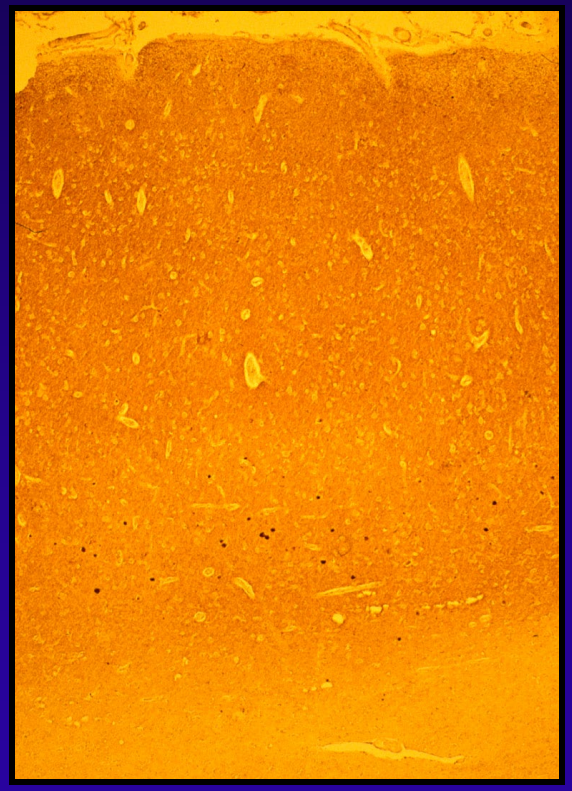
Pathology in Dementia with Lewy Bodies

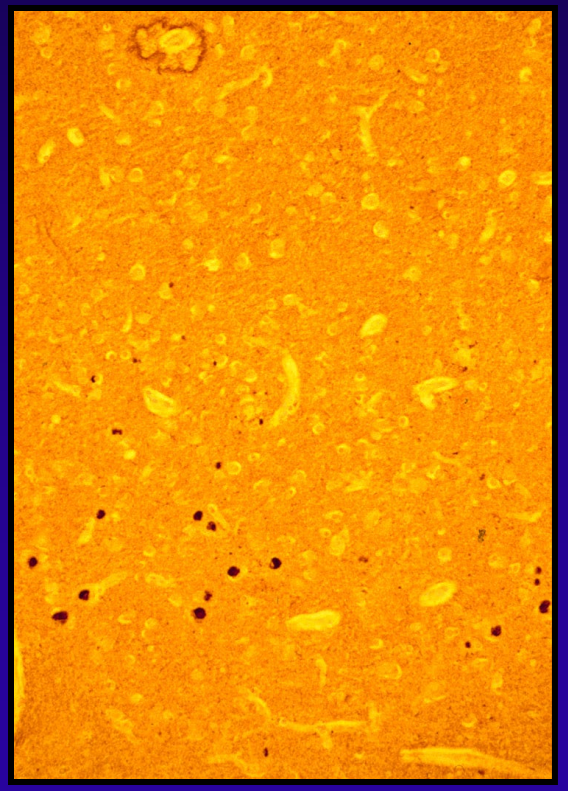


Pathology in Dementia with Lewy Bodies



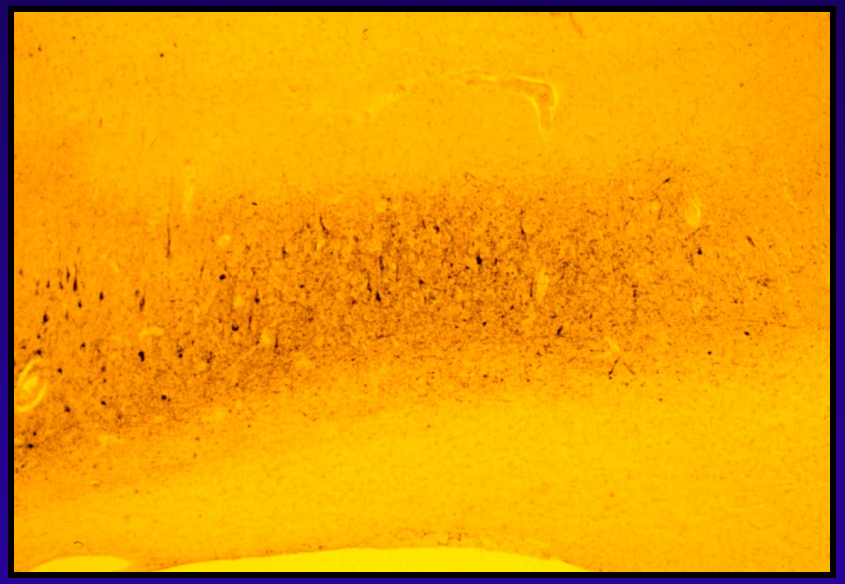
Pathology in Dementia with Lewy Bodies

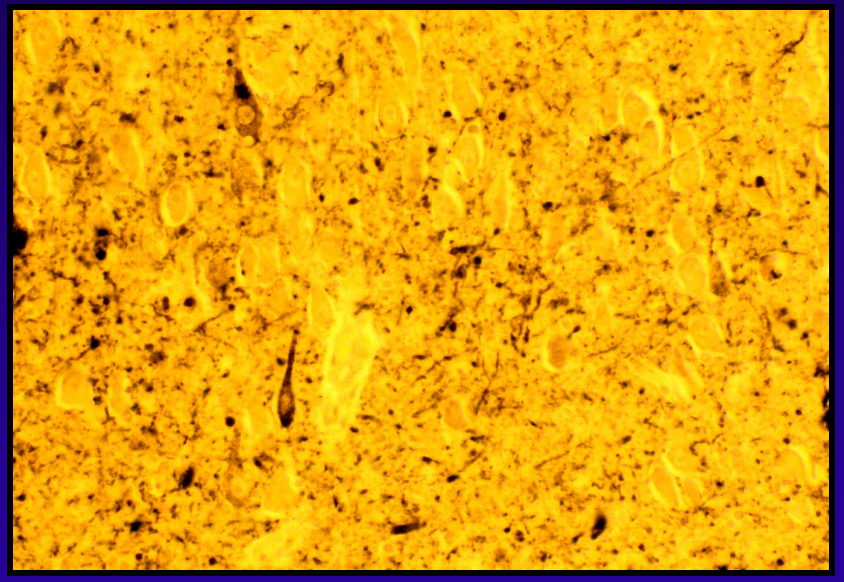




Cerebral Cortex

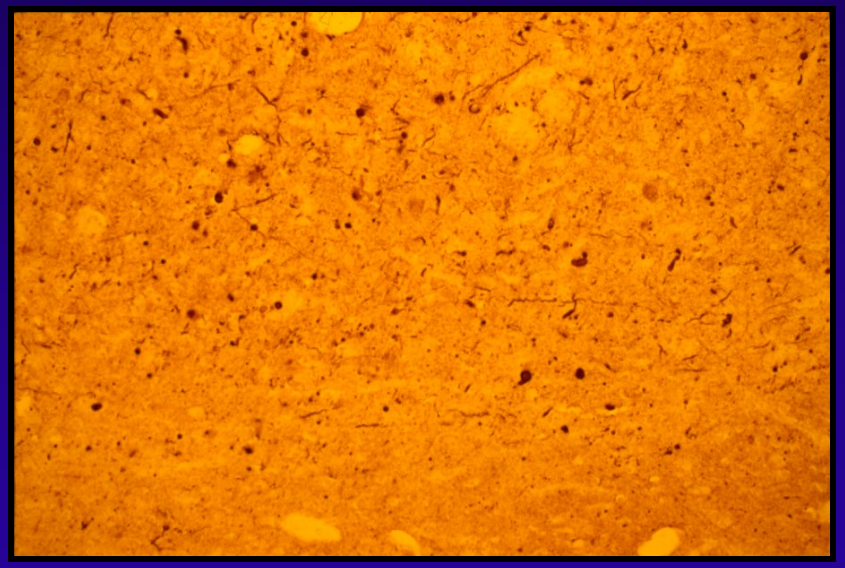
Pathology in Dementia with Lewy Bodies

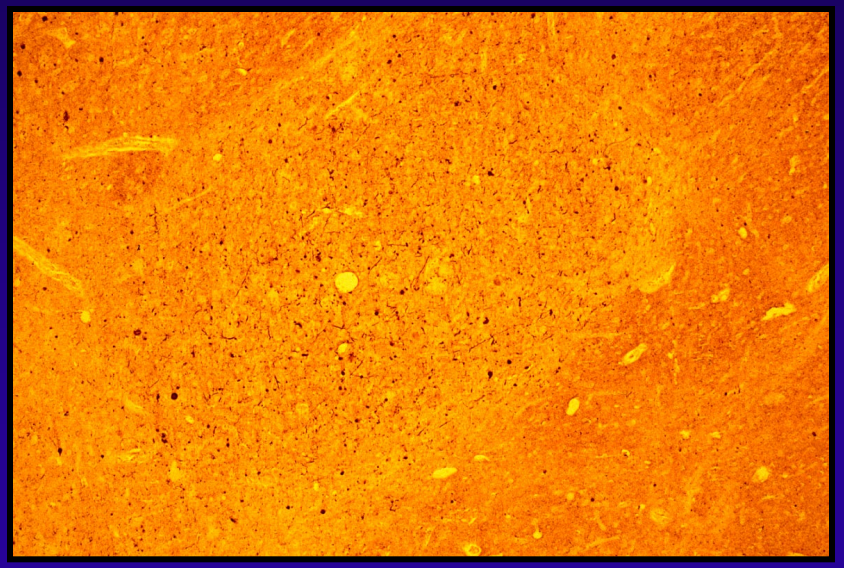




Hippocampal CA-2 Neurites

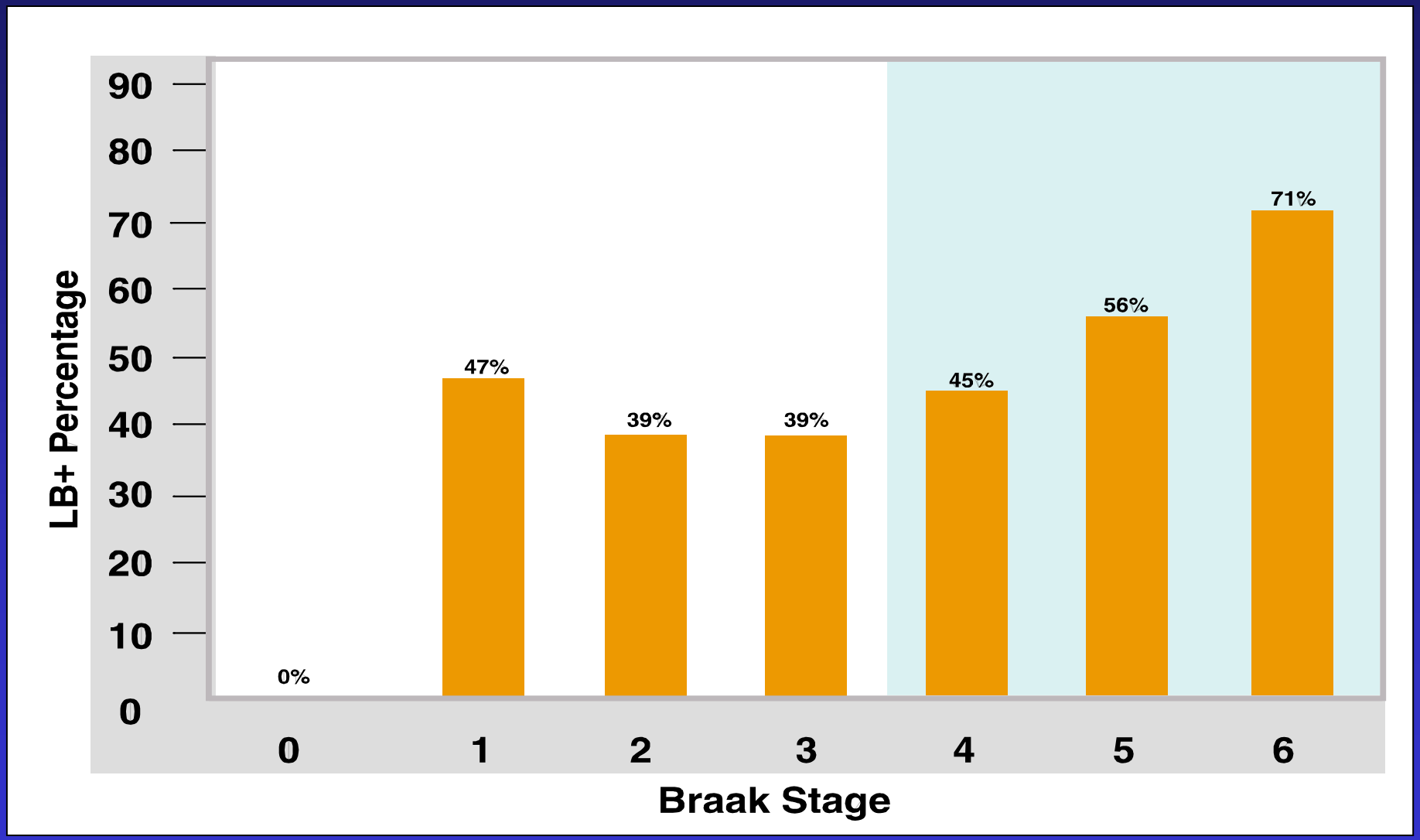
Pathology in Dementia with Lewy Bodies





Amygdala

LB Pathologic Change by Braak Stage



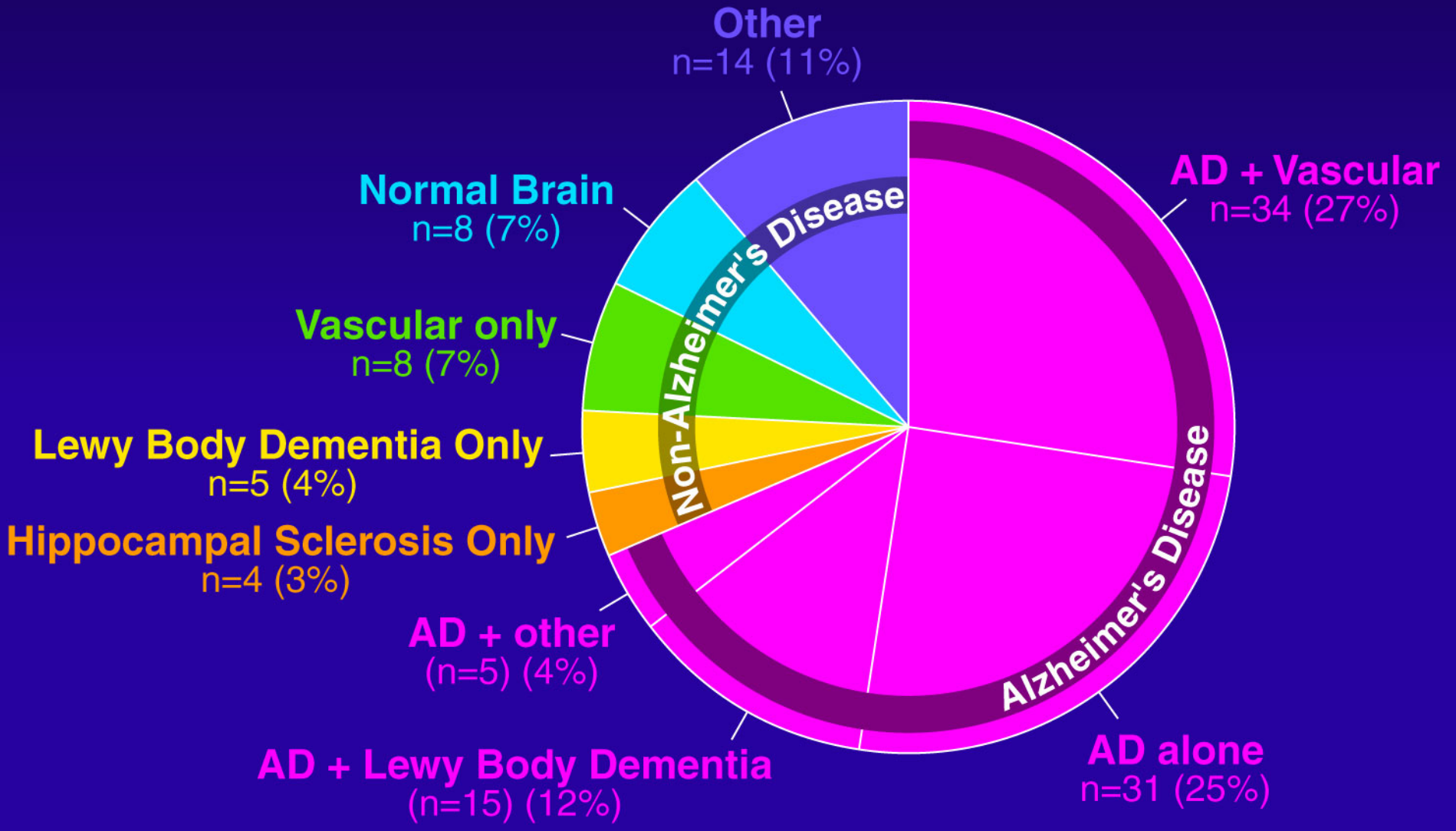
Lewy Body Pathology in a Community-Based Dementia Sample

- Frequency of LB in a broader “community based” population of dementia
- Neuropathology
- Epidemiologic, clinical, and genetic characterization

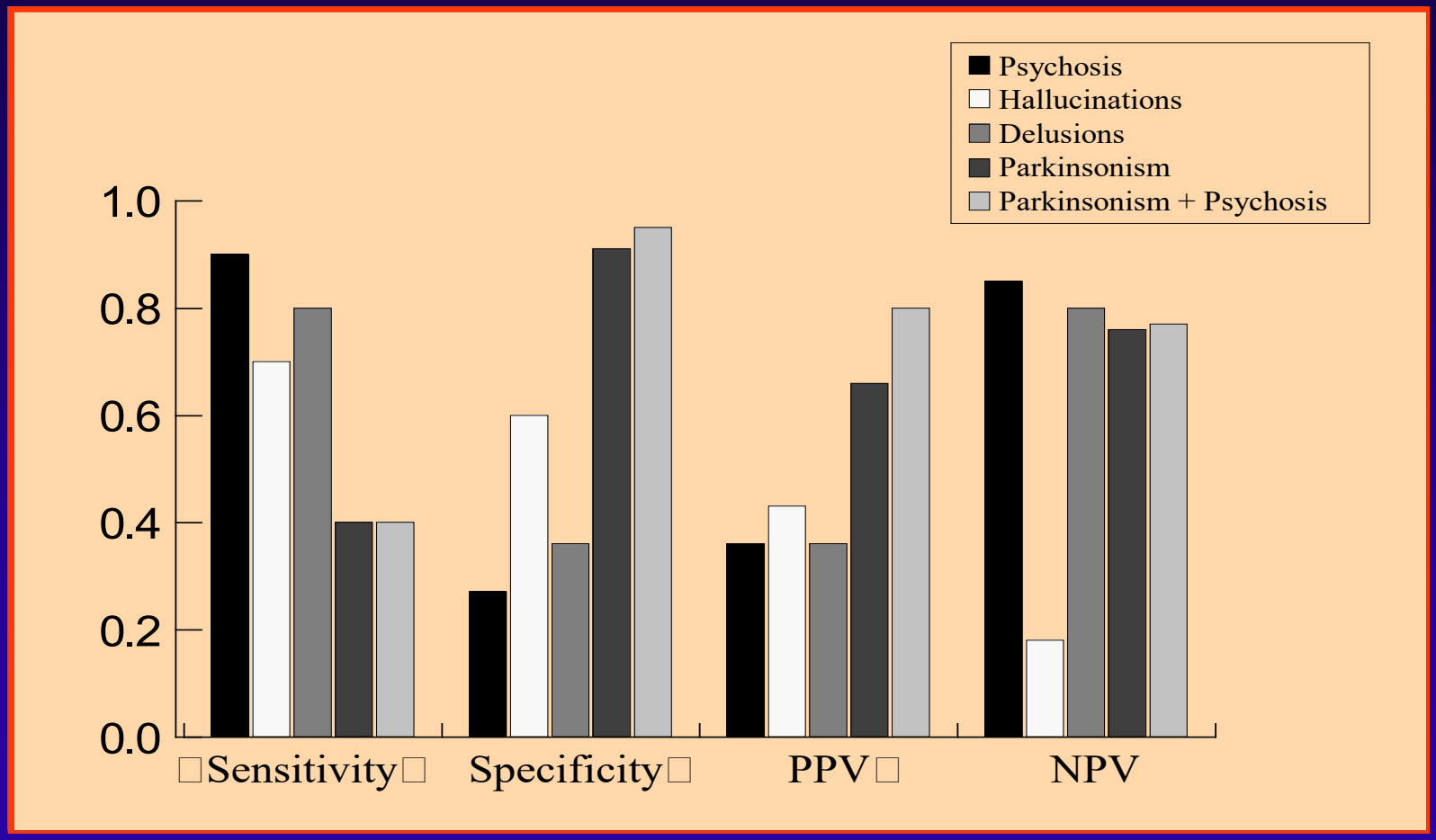
Methods: Subjects

- University of Washington Alzheimer's Disease Patient Registry (ADPR)
  - » Community-based registry of incident dementia
  - » 1,028 patients registered from 1987 to 1996, with 970 coming to evaluation
  - » 77% met NINCDS-ADRDA criteria for dementia, 58% with probable or possible AD
  - » ~ 300 autopsies to date

Neuropathological Diagnosis in 124 Community-based Incident Dementia Cases



Diagnostic Accuracy of DLB in a Community-Based Sample



Neuroimaging Studies

Glucose hypometabolism (PET)

- DLB< AD
  - Cerebellum
  - Occipital lobes, primary visual areas
- AD<DLB
  - Medial Temporal
  - Cingulate

Visuo-perceptual Impairment

- Well formed visual hallucinations and delusions
- Impairments in visuoperceptual tasks compared with AD
  - » Size discrimination (lines and figures)
  - » Form discrimination (four figures, choose disorted one)
  - » Overlapping figure discrimination (overlapping line drawings)
  - » Visual Counting (sheets with figures in two colors)

Mori et al. (2000)

Visuo-perceptual Impairment

- Impairments in visuoperceptual tasks compared with AD
  - » Figure –ground discrimination
  - » Fragmented letters
  - » Silhouette identification

Calderon et al. (2001)

Retrospective studies with autopsy-proven Lewy body disease

Visuospatial Functions							
Domain and Study	N			Matched on	Performance[a]		
	DLB	AD	HC		DLB<AD	DLB=AD	DLB>AD
Forstl et al. 1993[34]	8	8	0	Age, sex	-	CAMCOG (praxis)	-
Galasko et al. 1996[52]	13	13	0	Education, age, MMSE	Block Design (WAIS)	-	-
					Clock (copy)	Clock (free drawing)	-
					Cube (copy)	-	-
Salmon et al. 1996[51]	5[b]	5	0	MDRS total score	Construction (MDRS)	-	-
					Block Design (WAIS)	-	-
					Clock (copy)	Clock (free drawing)	-
Connor et al. 1998[96]	23	23	0	Age, education, MMSE or MDRS total score	-	Construction (MDRS)	-

Simard et al. (2000)

Retrospective studies with autopsy-proven Lewy body disease

Verbal Fluency and Language

Domain and Study	N			Matched on	Performance[a]		
	DLB	AD	HC		DLB<AD	DLB=AD	DLB>AD
Hansen et al. 1990[47]	9	9	0	IMC (Blessed Scale)	Lexical fluency	Semantic fluency	-
					-	Naming	-
Forstl et al. 1993[34]	8	8	0	Age, sex	-	CAMCOG (language)	-
Galasko et al. 1996[52]	13	13	0	Education, age, MMSE	Lexical fluency	Semantic fluency	-
Salmon et al. 1996[51]	5[b]	5	0	MDRS total score	-	-	Lexical and semantic fluency

Simard et al. (2000)

Retrospective studies with autopsy-proven Lewy body disease

Working Memory and Executive Functions

Domain and Study	N			Matched on	Performance[a]		
	DLB	AD	HC		DLB<AD	DLB=AD	DLB>AD
Hansen et al. 1990[47]	9	9	0	IMC (Blessed Scale)	Digit Span	-	-
					Similarities	-	-
					-	Arithmetic (WAIS)	-
Salmon et al. 1996[51]	5[b]	5	0	MDRS total score	-	Digit Span	-
					Trail Making A-B	-	-
Galasko et al. 1996[52]	13	13	0	Education, age, MMSE	Trail Making A	-	-
					Arithmetic (WAIS-R)	-	-
Connor et al. 1998[96]	23	23	0	Age, education, total MMSE or MDRS	Initiation/ Perseveration (MDRS)	Attention and Conceptualization (MDRS)	-

Simard et al. (2000)

Retrospective studies with autopsy-proven Lewy body disease

Memory							
Domain and Study	N			Matched on	Performance[a]		
	DLB	AD	HC		DLB<AD	DLB=AD	DLB>AD
Hansen et al. 1990[47]	9	9	0	IMC	-	BSRT (free & cued recall)	-
					-	Visual Reproduction (WMS)	-
					-	Vocabulary (WAIS)	-
Forstl et al. 1993[34]	8	8	0	Age, sex	-	CAMCOG (memory)	-
Galasko et al. 1996[52]	13	13	0	Education, age, MMSE	-	BSRT	-
					-	Visual Reproduction (WMS)	-
					-	Number Information Test	-
Salmon et al. 1996[51]	5[b]	5	0	MDRS total score	-	CVLT	-
Connor et al. 1998[96]	23	23	0	Age, education, MMSE or MDRS total score	-	-	MDRS-Memory subscale
Samuel et al. 1997[71]	17[b]	12	5	Duration of the disease, # months between last testing and death	-	IMC	-

Simard et al. (2000)

Studies with clinical criteria for Lewy body disease

Visual Attention: Spatial Working Memory							
Domain and Study	N			Matched on	Performance[a]		
	DLB	AD	HC		DLB<AD	DLB=AD	DLB>AD
Galloway et al. 1992[103]	7	10	16	Age, premorbid IQ, MMSE, CDR	Conditional pattern location, paired associative learning	Visual recognition	-
Sahgal et al. 1992[104]	7	10	16	Age, premorbid IQ, MMSE, CDR	Delayed matching to sample task	-	-
Sahgal et al. 1992[105]	7	10	16	Age, premorbid IQ, CDR	Visual search matching to sample	KOLT	-
Sahgal et al. 1992[106]	7	10	16	CDR, age	Spatial workng memory task	Corsi's test	-
Shimomura et al. 1998[56]	26	52	0	Age, sex, MMSE, education	Digit Symbol (WAIS)	-	-

Simard et al. (2000)

Studies with clinical criteria for Lewy body disease

Visual Attention and Memory; Executive Functions							
Domain and Study	N			Matched on	Performance*		
	DLB	AD	HC		DLB<AD	DLB=AD	DLB>AD
Walker et al. 1997[107]	17	17	0	CDR, MMSE, CAMCOG (global), duration of disease, age, education	-	CAMCOG:	CAMCOG:
					-	-	Delayed Recall
					-	Attention/ Calculation	-
					-	Orientation	-
					-	Remote Memory	-
					-	Current Information	-
					-	Verbal Fluency	-
					-	Abstract Reasoning	-
Sahgal et al. 1992[105]	7	10	16	Age, pre rbid , R		Vocabulary (WAIS-R)	-
						Comprehension (WAIS-R)	-
					-	Visual set shifting	-
Sahgal et al. 1992[105]	7	10	16	Age, premorbid IQ, CDR	Vocabulary (WAIS-R)	-	-
					Comprehension (WAIS-R)	-	-
					Visual set shifting	-	-
Gnanalingham et al. 1997[83]	16	25	22	CDR, MMSE, age, education	-	Digit Span	-
					-	Lexical and semantic fluency	-
					-	Motor sequencing	-
					-	Nelson Card Sorting	-
Shimomura et al. 1998[56]	26	52	0	Age, sex, MMSE, education	Picture Arrangement (WAIS)	-	-
					Raven Matrices		-
						-	Word Recall (ADAS)
						-	

Simard et al. (2000)

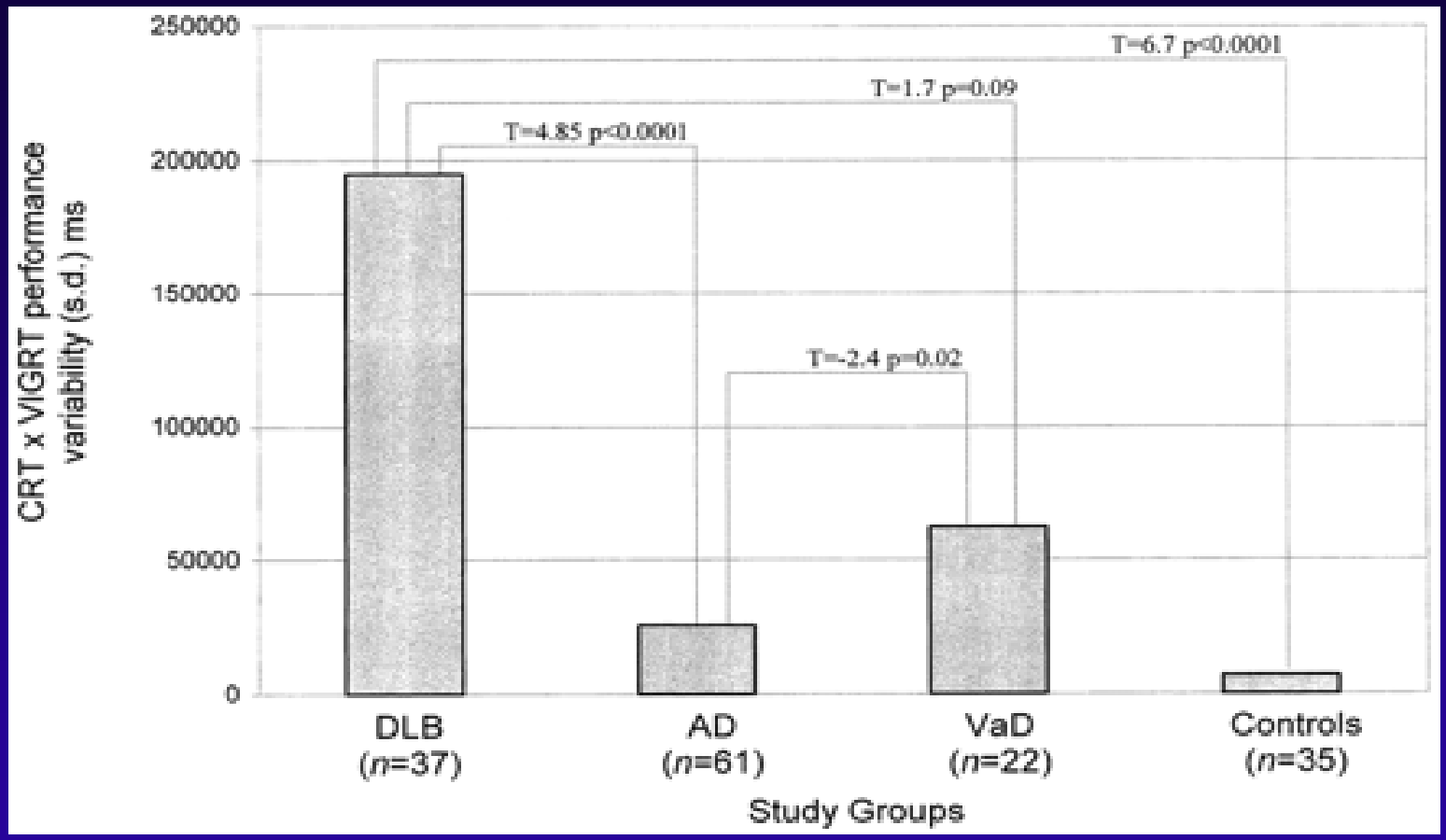
Studies with clinical criteria for Lewy body disease

Visual Praxis and Visual Perception

Domain and Study	N			Matched on	Performance[a]		
	DLB	AD	HC		DLB<AD	DLB=AD	DLB>AD
Sahgal et al. 1992[104]	7	10	16	Age, premorbid IQ, MMSE, CDR	-	Visual Perception/ simultaneous matching to sample task	-
Gnanalingham et al. 1996[108]	14	14	16	Age, sex. MMSE	Clock (copy)	-	-
Gnanalingham et al. 1997[83]	16	25	22	Age, education, MMSE, CDR	Clock (copy)	Clock (Free Drawing)	-
Walker et al. 1997[107]	17	17	0	CDR, MMSE, CAMCOG (global), duration of illness, age, education	CAMCOG: visuospatial praxis	CAMCOG: visual perception/ face and object recognition	-
Shimomura et al. 1998[56]	26	52	0	Age, MMSE, education	Object Assembly (WAIS)	-	-
					Block Design (WAIS)	-	-

Simard et al. (2000)

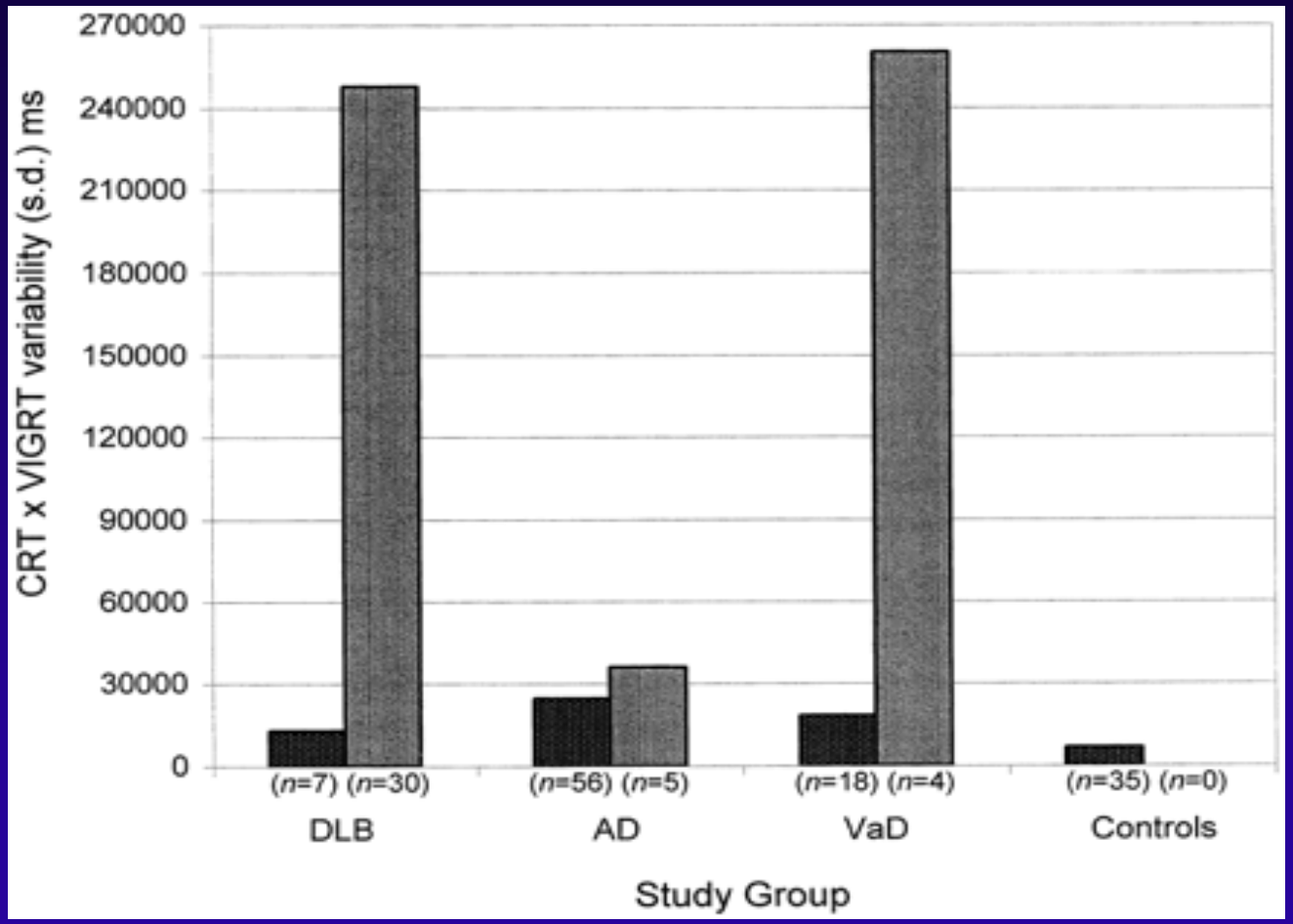
Variability in Reaction Time



Also demonstrated fluctuations in EEG

Walker et al., Neurology, 2000

Variability in Reaction Time & Behavioral Fluctuation



Walker et al., Neurology, 2000

PD vs DLB with Parkinsonism

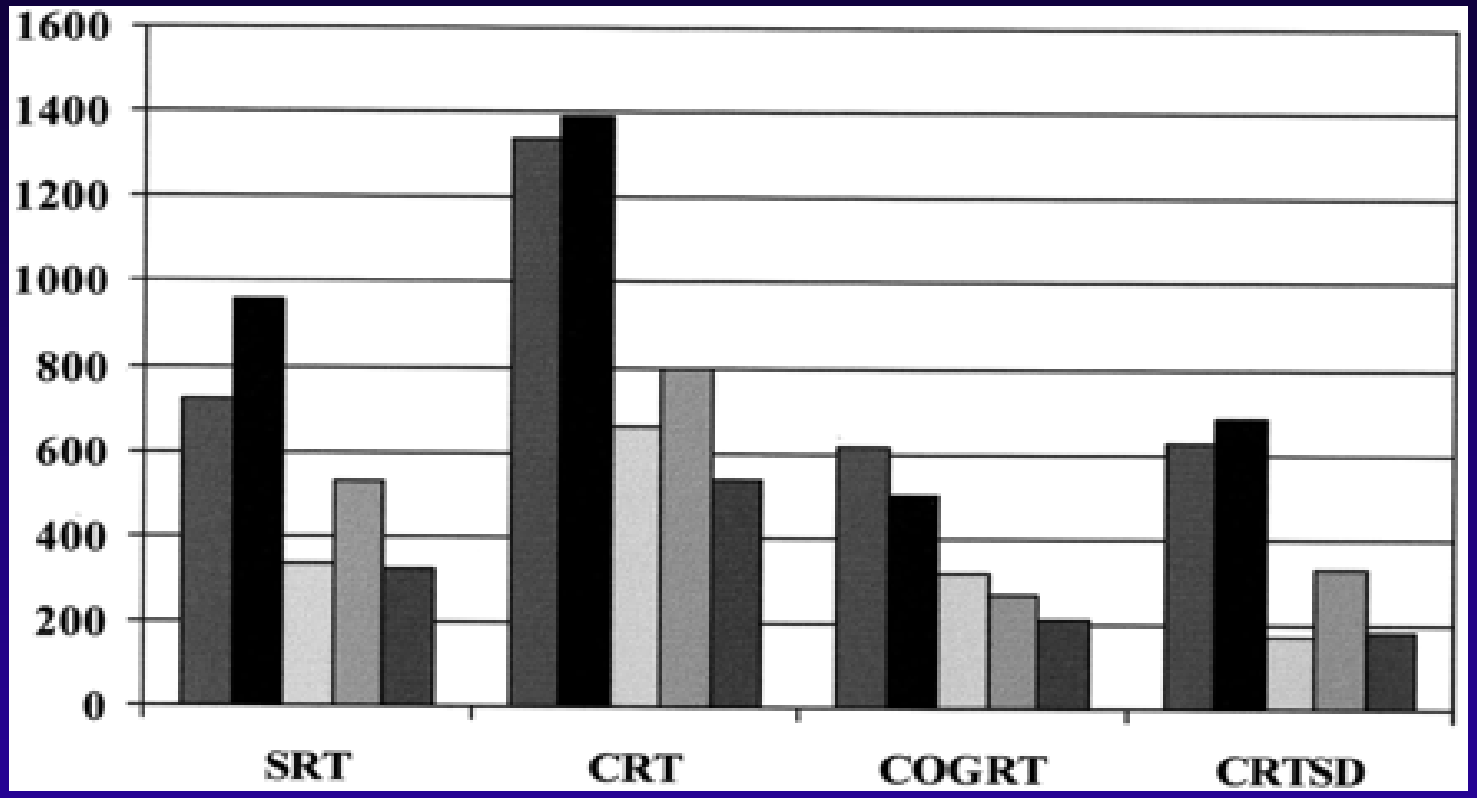
DLB-50

PDD-48

AD-80

PD-50

CON-50



Simple Reaction time

Choice Reaction time

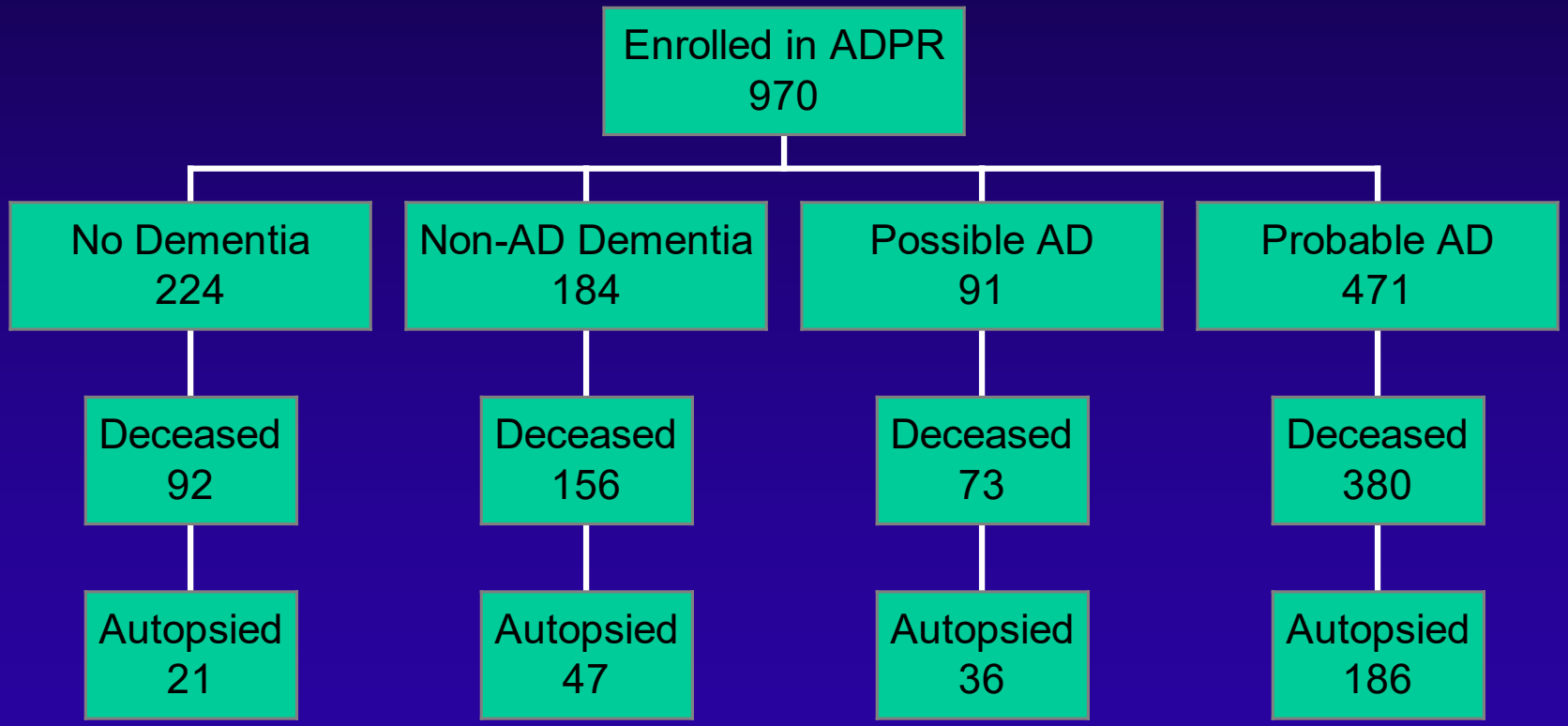
Cognitive Reaction time

Choice Reaction time Standard Deviation

Ballard et al., Neurology (2002)

University of Washington Alzheimer's Disease Patient Registry (ADPR)

Figure 1. Enrollment Process



Cherrier et al., Neurobiology of Aging, 2002; Kraybill et al., SNS CD-ROM Abstracts, 2003

Neuropsychological Characteristics of a Community Dwelling Cohort

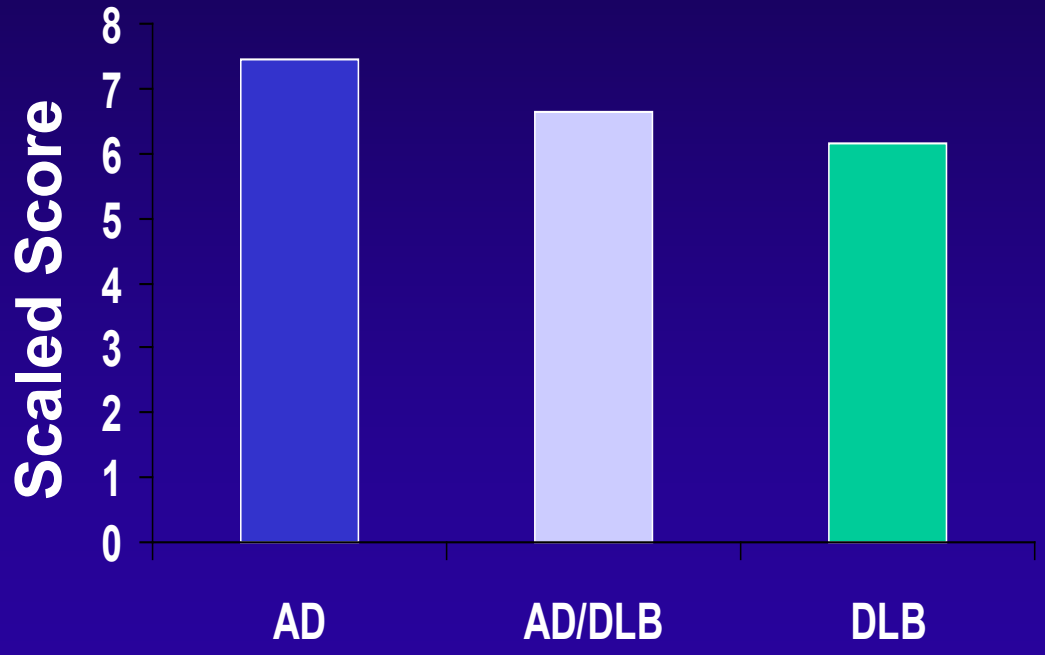
	AD Mean (SD)	AD/DLB Mean (SD)	DLB Mean (SD)	Total Mean (SD)
Age at Intake	79.82 (7.1)	77.49 (5.9)	80.88 (6.4)	79.17 (7.0)
Education [1]	2.36 (0.8)	2.21 (0.7)	2.18 (0.9)	2.26 (0.8)
Intake MMSE	19.51 (6.4)	19.11 (5.6)	19.47 (7.0)	19.99 (5.9)
Intake DRS	114.45 (17.1)	110.67 (19.5)	112.43 (17.4)	113.11 (18.0)
Braak Staging	4.77 (0.6)	4.93 (0.6)	2.21 (0.8)	3.82 (1.5)
N	61	75	34	228

1. Education: 1= Less than High School; 2 = High School or equivalent; 3 = Greater than High School

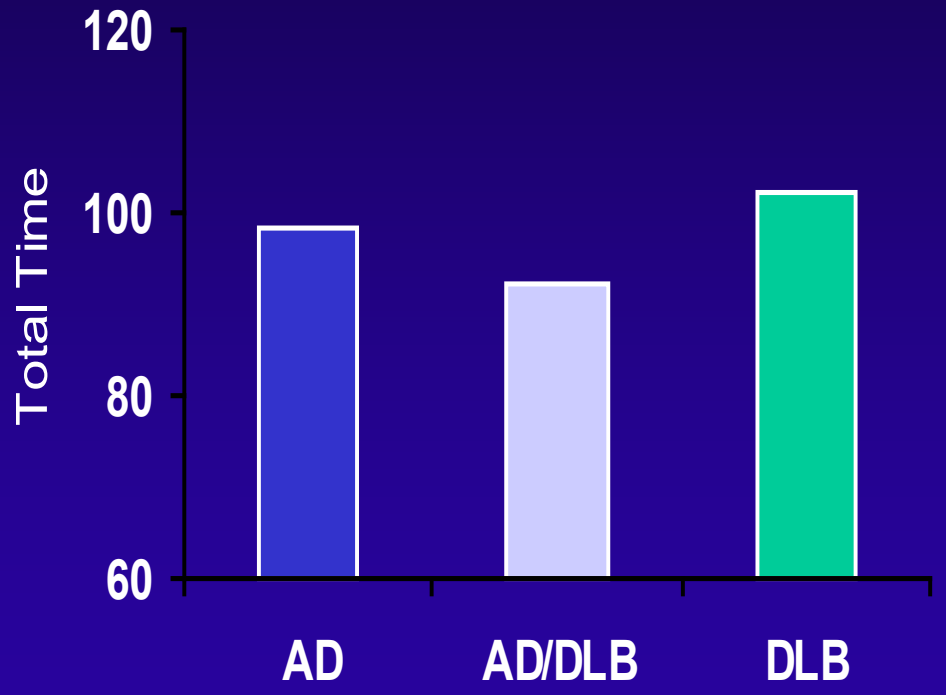
Cherrier et al., Neurobiology of Aging, 2002; Kraybill et al., SNS CD-ROM Abstracts, 2003

Attention

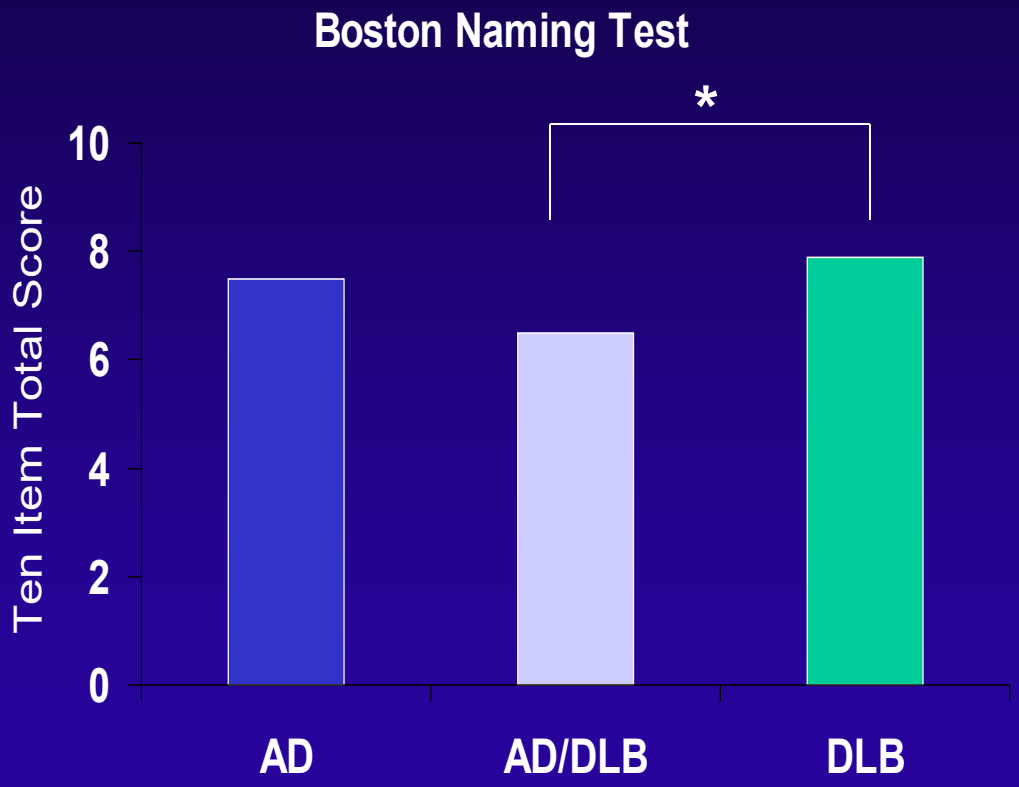
Wais-R Digit Span

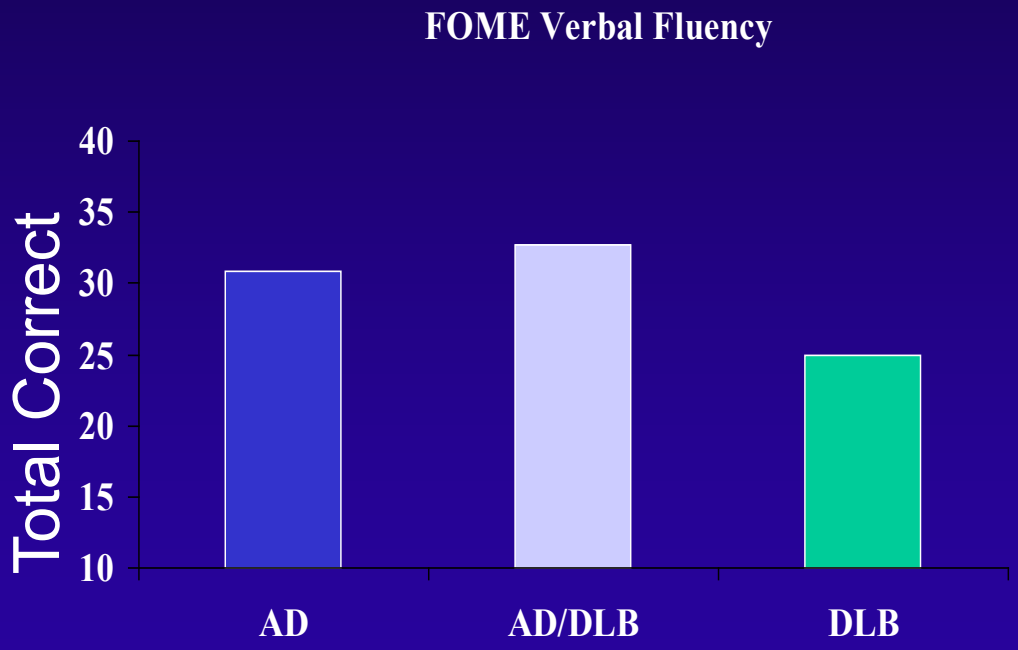


Trail making Test Part A



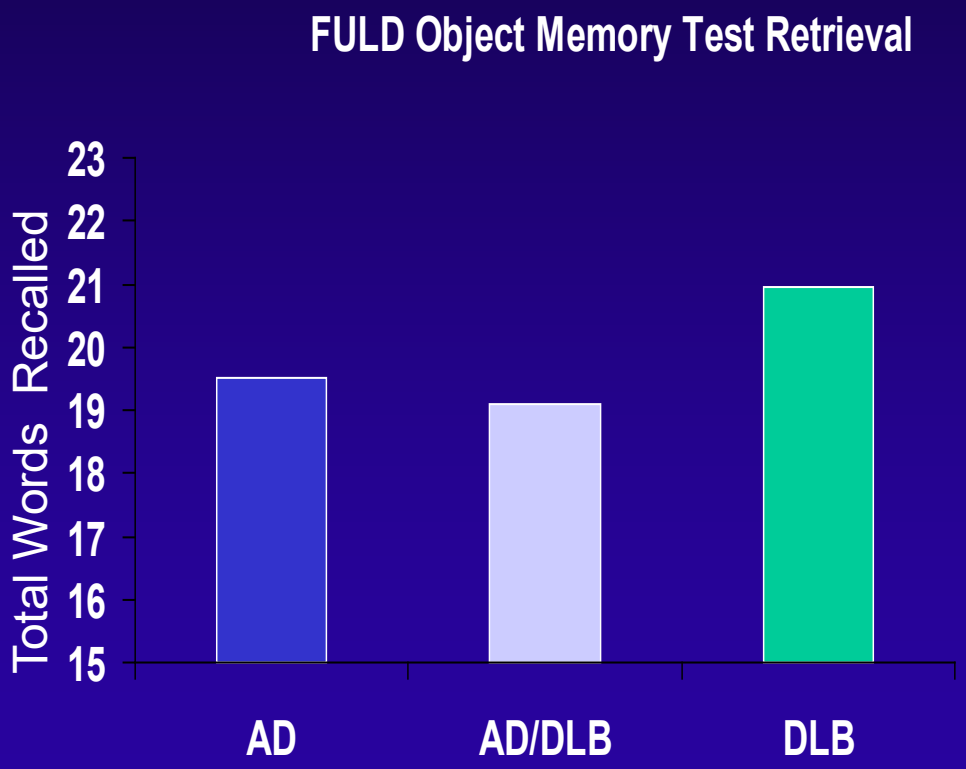
Language/ Fluency

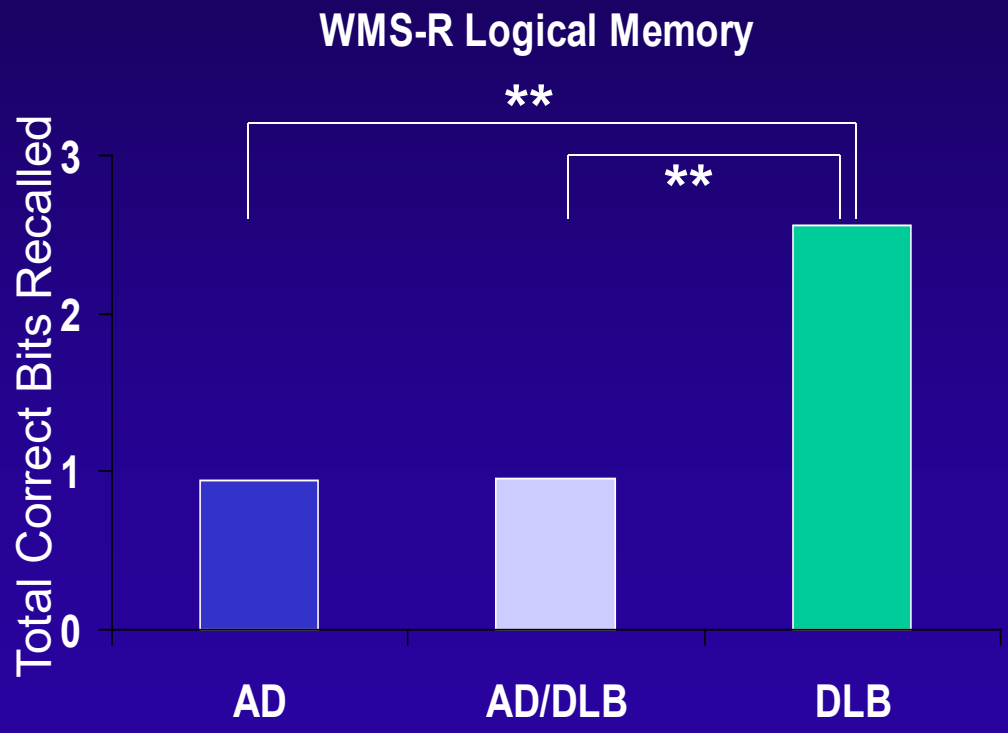




*p<.05

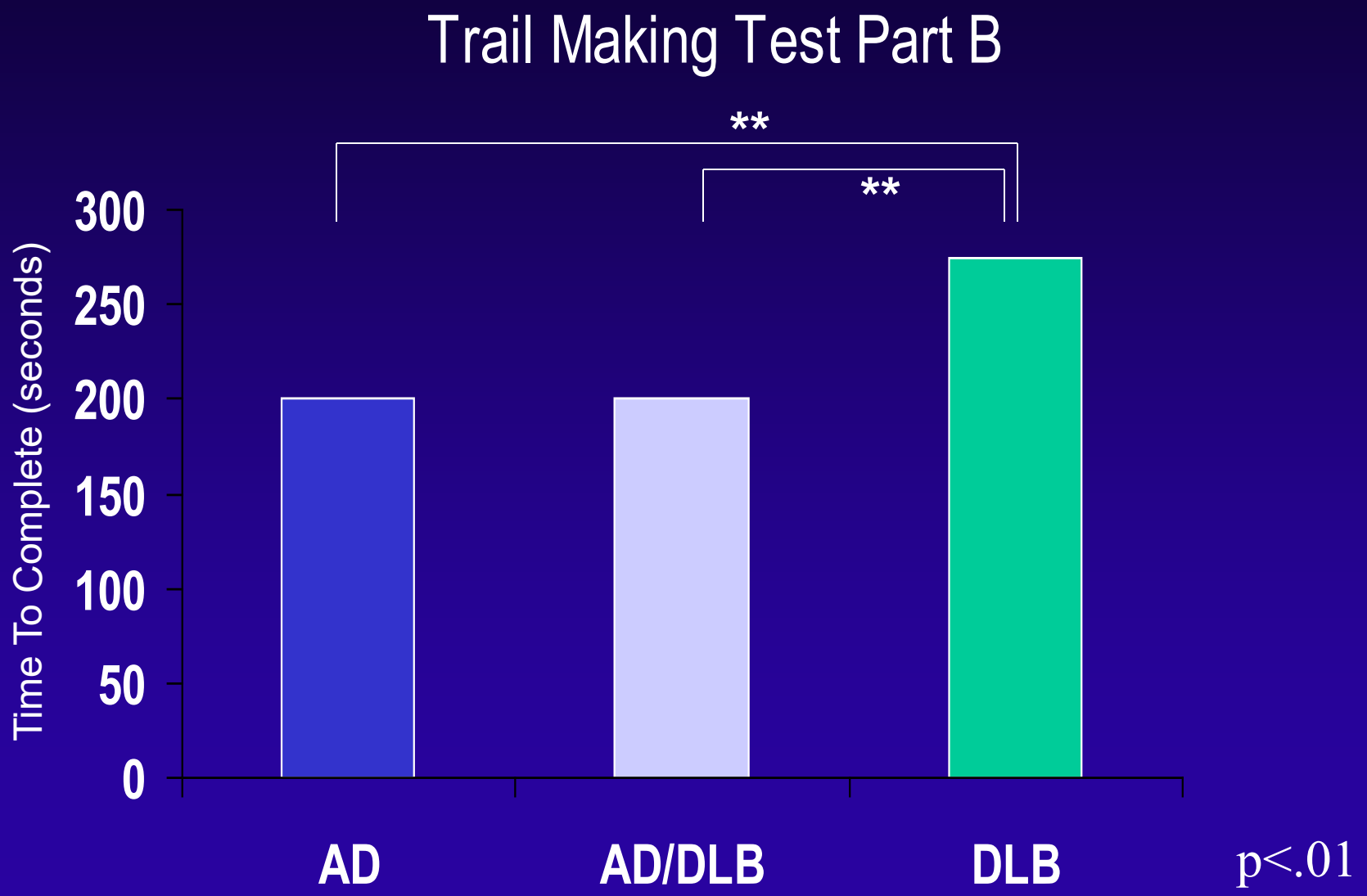
Verbal Memory





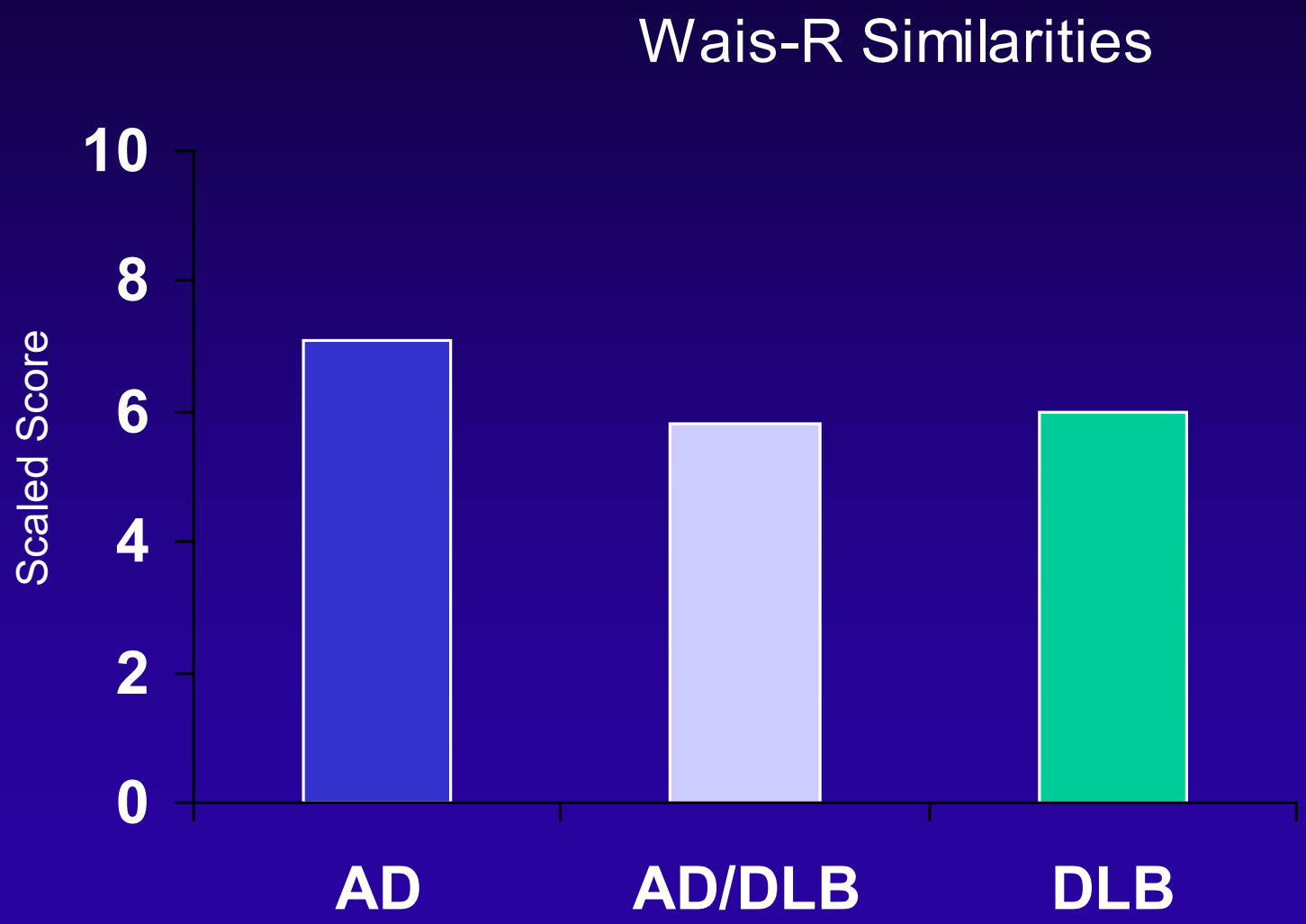
p<.01

Divided Attention/ Visual Scanning



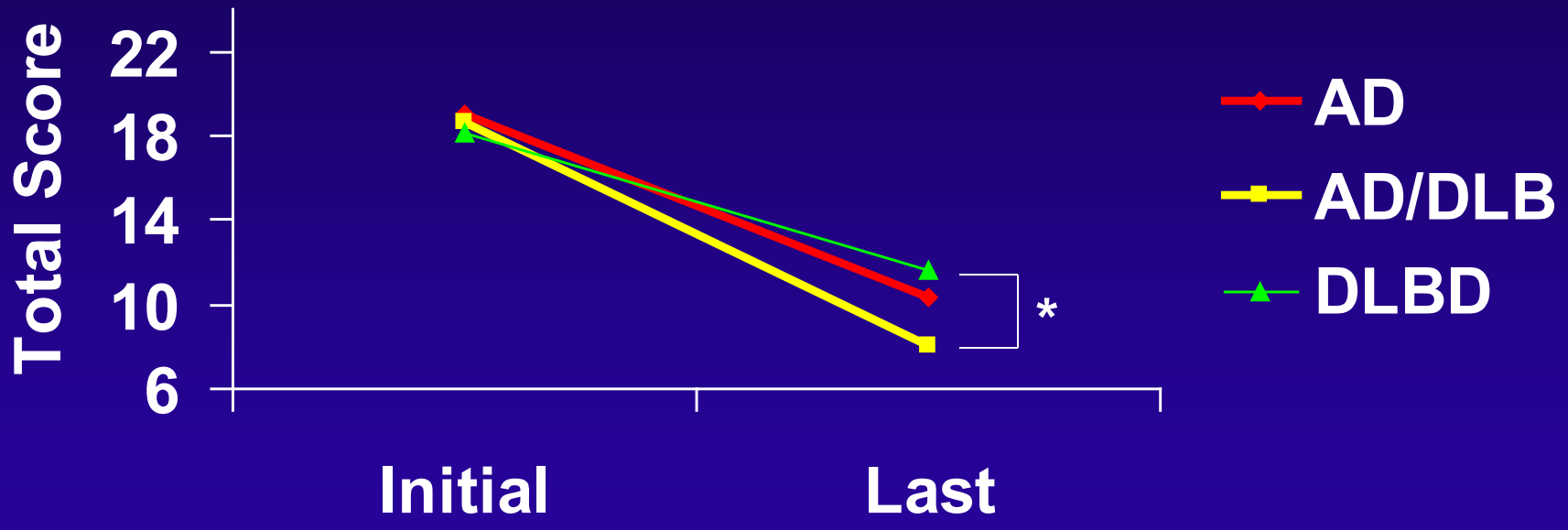
p<.01

Executive Functions: Verbal Abstraction



Rate of Progression

MMSE



*p<.05

Longitudinal Studies

- Miller et al. (1991) AD-EPS 67% faster decline – MMSE
- Chui et al. (1994) hallucinations, agitation, EPS – significantly predicted cog. Decline
- Ballard et al. (1996) DLB faster decline on CAMCOG than AD & VaD
- Olichney et al. (1998) DLB faster decline on MMSE than AD

Cholinergic Enhancement Strategies

- Analogous to dopaminergic enhancement strategies for Parkinson's disease
- Cholinesterase inhibitor therapy
  - » inhibits AChE (BuChE-tacrine/rivastigmine), degradative enzyme for acetylcholine
  - » results in increase of acetylcholine available to postsynaptic neurons
  - » increases cholinergic neurotransmission

Is There a Cholinergic Deficit in DLB ?

- Samuel et al (JNEN 1997)
  - » 30% reduction of ChAT in AD
  - » 75% reduction of ChAT in DLB
- Tiraboschi et al (Arch Psychiat 2002)
  - » ChAT preserved in mild AD
  - » ChAT significantly lower in early DLB

Cholinesterase Inhibitors: Treatment of DLB

- Multiple positive open-label trials (tacrine, donepezil, rivastimine)
- McKeith et al (Lancet 2000)
  - » Double-blinded, 120 patients
  - » Rivastigmine up to 12 mg/d
  - » Focus on behavioral symptoms using NPI

Cholinesterase Inhibitors: Treatment of DLB

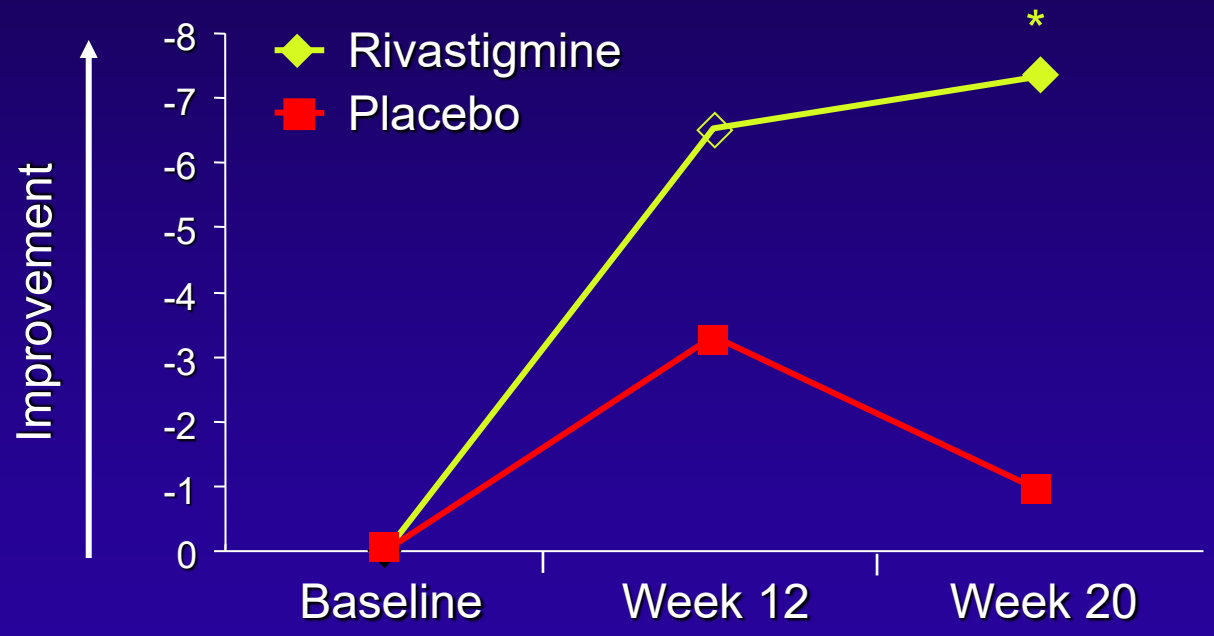
- McKeith et al (Lancet 2000)
  - NPI
    - Positive - apathy, indifference, anxiety, delusions, hallucinations and aberrant motor behavior
    - No change - depression, agitation/aggression, irritability, sleep

Cholinesterase Inhibitors: Treatment of DLB

- McKeith et al (Lancet 2000)
  - MMSE trend positive ($p = 0.07$)
  - Individual cognitive data all “significantly favoured rivastigmine.” and “...will be described more fully elsewhere.”

Rivastigmine International Lewy Body Dementia Trial: Behavioural Changes (NPI)

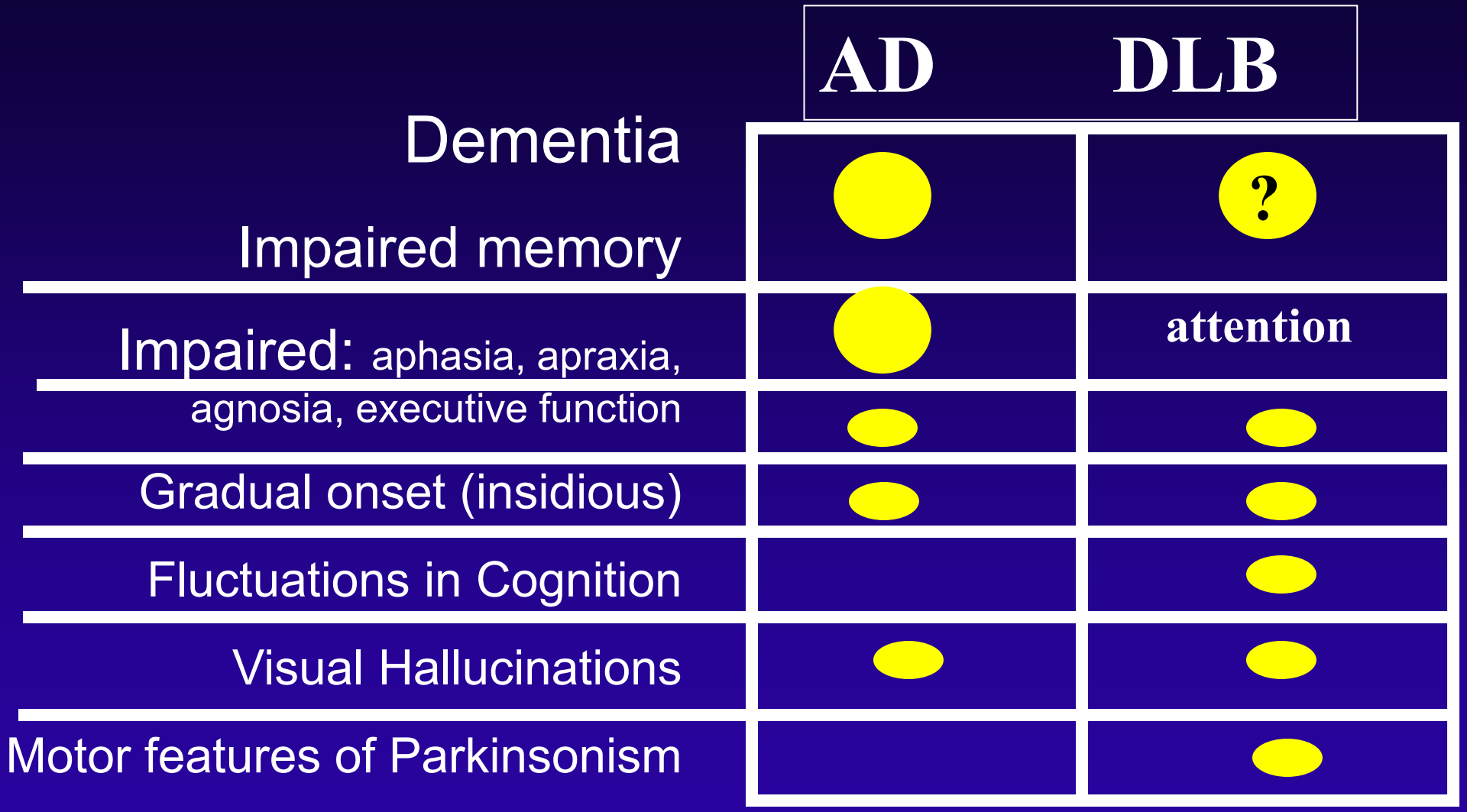
NPI 10-item Score–Mean Change from Baseline (OC)



**P*<0.01 vs placebo (ANOVA/ANCOVA)

McKeith IG, et al. American Academy of Neurology 52nd Annual Meeting. April 29-May 6, 2000. San Diego, California.

Diagnostic Criteria:AD vs DLB



DSM-IV and DLB Consensus Criteria

Summary

- What is Dementia with Lewy bodies ?
  - » Variant of Alzheimer's disease
  - » Variant of Parkinson's disease
  - » Clinical syndrome with unique clinical presentation and management issues
  - » Common pathology in dementia (30 to 60%)
  - » Additional study needed to fully characterize this "second-leading" cause of dementia

Prevalence and Incidence

- Third most common cause of cortical dementia following AD and Lewy Body Disease
- Approximately 20-25 percent of FTLD patients can be characterized as having Pick's disease
- True prevalence may be unknown due to the frequent misdiagnosis
  - » In a retrospective study, Mendez et al. (1993) found that of 21 post mortem confirmed Pick's cases, 18 were diagnosed with AD during life

Incidence

- Netherlands case finding study found 74 cases of FTD in the 15 million country population (clinical history, behavioral checklists, neurology examination and neuroimaging)

Approximate incidence per age range:

30-40 years 1.2 cases

41-50 years 3.4 cases

51-60 years 10.7 cases

61-70 years 28 cases

Nosology

- Frontotemporal Dementia (FTD) diagnostic characterization initially proposed by the Lund and Manchester Groups (Brun, 1994)
- Frontal lobe degeneration of the non-Alzheimer type (FLD) proposed by Brun (1987) and Gustafson (1987)
- Pick's disease (PiD) first described by Arnold Pick (1892) and generally refers to a clinical diagnosis of FTD with subsequent autopsy confirmation of the presence of Pick bodies
- Pick complex (PC) is a term that has been suggested can encompass all the related entities both clinically and pathologically (Kertesz, 1994)

Clinical Characteristics

- Age of onset
  - » mean of 57 years
  - » range 37 to 73
- Males and females equally affected
- Average disease duration 8-11 years
- 42-50% of patients with Pick's disease have a first degree relative with FTD

Diagnostic Clinical Profile
Frontotemporal Lobar Degeneration-FTLD

I. Core Features

A. Insidious Onset

B. Early decline in social interpersonal conduct

C. Early impairment in regulation of personal conduct

D. Early emotional blunting

E. Early loss of insight

Neary et al. (1998)

Diagnostic Clinical Profile Frontotemporal Lobar Degeneration

II. Supportive Diagnostic Features

A. Behavioral Disorder

- 1. Decline in personal hygiene and grooming
- 2. Mental rigidity and inflexibility
- 3. Distractibility and impersistence
- 4. Hyperorality and dietary changes
- 5. Perseverative and stereotyped behavior
- 6. Utilization behavior

Neary et al. (1998)

Diagnostic Clinical Profile
Frontotemporal Lobar Degeneration

II. Supportive Diagnostic Features

B. Speech and Language changes

- 1. Altered speech output
  - Aspontaneity and economy of speech
  - Press of speech
- 3. Stereotypy of speech
- 4. Echoalalia
- 5. Perseveration
- 6. Mutism

Neary et al. (1998)

Diagnostic Clinical Profile
Frontotemporal Lobar Degeneration

II. Supportive Diagnostic Features

C. Physical Signs

- 1. Primitive reflexes
- 3. Incontinence
- 4. Akinesia, rigidity, and tremor
- 5. Low and labile pressure
- 6. Mutism
- Onset before age 65
- Bulbar palsy, muscular weakness and wasting, fasiculations (MND) Neary et al. (1998)

Diagnostic Clinical Profile
Frontotemporal Lobar Degeneration

II. Supportive Diagnostic Features

D. Investigations

- 1. Neuropsychology: significant impairment on frontal lobe tests in the absence of severe amnesia, aphasia, or perceptual disorder
- 2. Electroencephalography: normal EEG
- 3. Brain imaging (structural and functional): predominant frontal/and or temporal abnormality

Neary et al. (1998)

Diagnostic Clinical Profile
FTLD: Progressive Non-fluent Aphasia

I. Core Features

A. Insidious onset and gradual progression

B. Non-fluent spontaneous speech with at least one of the following:

- agrammatism
- phonemic paraphasias
- anomia

Neary et al. (1998)

Diagnostic Clinical Profile
FTLD: Progressive Non-fluent Aphasia

II. Supportive Diagnostic Features

A. Speech and Language

- 1. stuttering and oral apraxia
- 2. impaired repetition
- 3. alexia, agraphia
- 4. early preservation of word meaning
- 5. late mutism

Neary et al. (1998)

Diagnostic Clinical Profile:
FTLD: Progressive Non-fluent Aphasia

II. Supportive Diagnostic Features

B. Behavior

- 1. Early preservation of social skills
- 2. Late behavioral changes similar to FTD

C. Physical Signs: late contralateral primitive reflexes, akinesia, rigidity and tremor

Neary et al. (1998)

Diagnostic Clinical Profile:
FTLD: Progressive Non-fluent Aphasia

II. Supportive Diagnostic Features

D. Investigations

- 1. Neuropsychology: nonfluent aphasia in the absence of severe amnesia or perceptuospatial disorder
- 2. EEG normal or minor assymetric slowing
- 3. Brain imaging (structural and/or functional): assymetric abnormality predominantly affecting dominant (usually left) hemisphere

Neary et al. (1998)

Diagnostic Clinical Profile
FTLD: Semantic Dementia

I. Core Features

A. Insidious onset and gradual progression

B. Language disorder characterized by:

- progressive, fluent, empty spontaneous speech
- loss of word meaning, manifest by impaired naming and comprehension

C. Perceptual disorder characterized by:

- prosopagnosia: impaired recognition of faces
- associative agnosia: impaired object identity

Neary et al. (1998)

Diagnostic Clinical Profile
FTLD: Semantic Dementia

I. Core Diagnostic Features

C. Preserved perceptual matching and drawing reproduction

D. Preserved single word repetition

E. Preserved ability to read aloud and write to dictation orthographically regular words

Neary et al. (1998)

Diagnostic Clinical Profile:
FTLD: Semantic Dementia

II. Supportive Diagnostic Features

A. Speech and language: press of speech, idiosyncratic word usage, absence of phonemic paraphasias, surface dyslexia and dysgraphia perserved calculation

B. Behavior:loss of sympathy and empathy, narrowed preoccupations, parsimony

C. Physical Signs: absent or late primitive reflexes, akinesia, rigidity, and tremor

Neary et al. (1998)

Diagnostic Clinical Profile:
FTLD: Semantic Dementia

II. Supportive Diagnostic Features

D. Investigations

- Neuropsychology: profound semantic loss, failure of word comprehension and naming and object recognition

  Preserved phonology and syntax, and elementary perceptual processing, spatial skills, and day to day memorizing

- Brain imaging (structural and/or functional): predominant anterior temporal abnormality

Neary et al. (1998)

FTLD Neuropsychological Findings:

Attention:

simple essentially intact
- e.g. digit span

sustained attention poor
- (serial 7s)

Language:

confrontation naming usually intact e.g., BNT

conversational speech characterized by economy

Memory:

intact early, recognition better than recall

visual better than verbal

poor and/or lack of strategies can affect scores or inattention

e.g., WMSIII LM or VR

Visuospatial:

well preserved even into the late stages

e.g., Rey-O, WMSIII Block Design, Copying

Executive Functions:

impairments in abstraction, cognitive flexibility, set shifting, divided attention, poor organization, lack of initiation

e.g. Stroop Test, Wisconsin Card Sorting Test, Verbal Fluency,Trailmaking Test Part B

Comparative Neuropsychological Studies:

Extended mental status exam:

- FTD perform better than AD and VaD on digit span and constructional tasks (Cherrier et al., 1997; Mendez et al., 1996)

Neuropsychological Battery:

- AD and FTD are not significantly different examining absolute scores
- relative profile examination
  - FTD poorer on executive function and best at memory and visuoconstructional skills
  - AD poorest on memory, language, and visuoconstructional tasks and best at tests of executive functioning

Genetics

Frontotemporal Dementia with Parkinsonism linked to chromosome 17 (FTDP-17)

- a family with a progressive FTD like dementia and Parkinson like motor features (bradykinesia, rigidity and postural instability without resting tremor) was found to have a genetic linkage on chromosome 17q21-22 (Lynch et al, 1994) (Foster et al., 1997; Spillantini et al., 1998)
- Other families have also been identified with additional features of dysphasia (HDDD) (Lendon et al., 1988)

Genetics

Tau was suggested as a candidate gene

- Located within the 17q21-22 region
- Several additional families have been identified with a variety of mutations within the tau gene (Poorkaj et al., 1998)

Seattle study examining three families with a mutation in exon 10 of the tau gene with phenotypic similarities and differences (Bird et al., 1999)

- Autopsy diagnoses included Parkinsons disease, Picks disease, Neurofibrillary tangle disease

Neuropsychological Results for Seattle Study- Three Families

	D family	F family	G family
MMSE	**9/30**	**21/30**	**26/30**
Orientation	-	+	+
Simple Attention	-	-	-
Construction	+	+	+
Language	-	-	-
Memory	+/-	+/-	+/-
Executive Fxn	-	-	-
Calculations	-	-mild	•

+ Intact - Impaired +/- Mixed • Not Assessed Bird et al., 1999