Philadelphia VA PADRECC

Parkinson's Disease Research, Education & Clinical Center

Lewy Bodies and Dementia

John E. Duda, M.D.

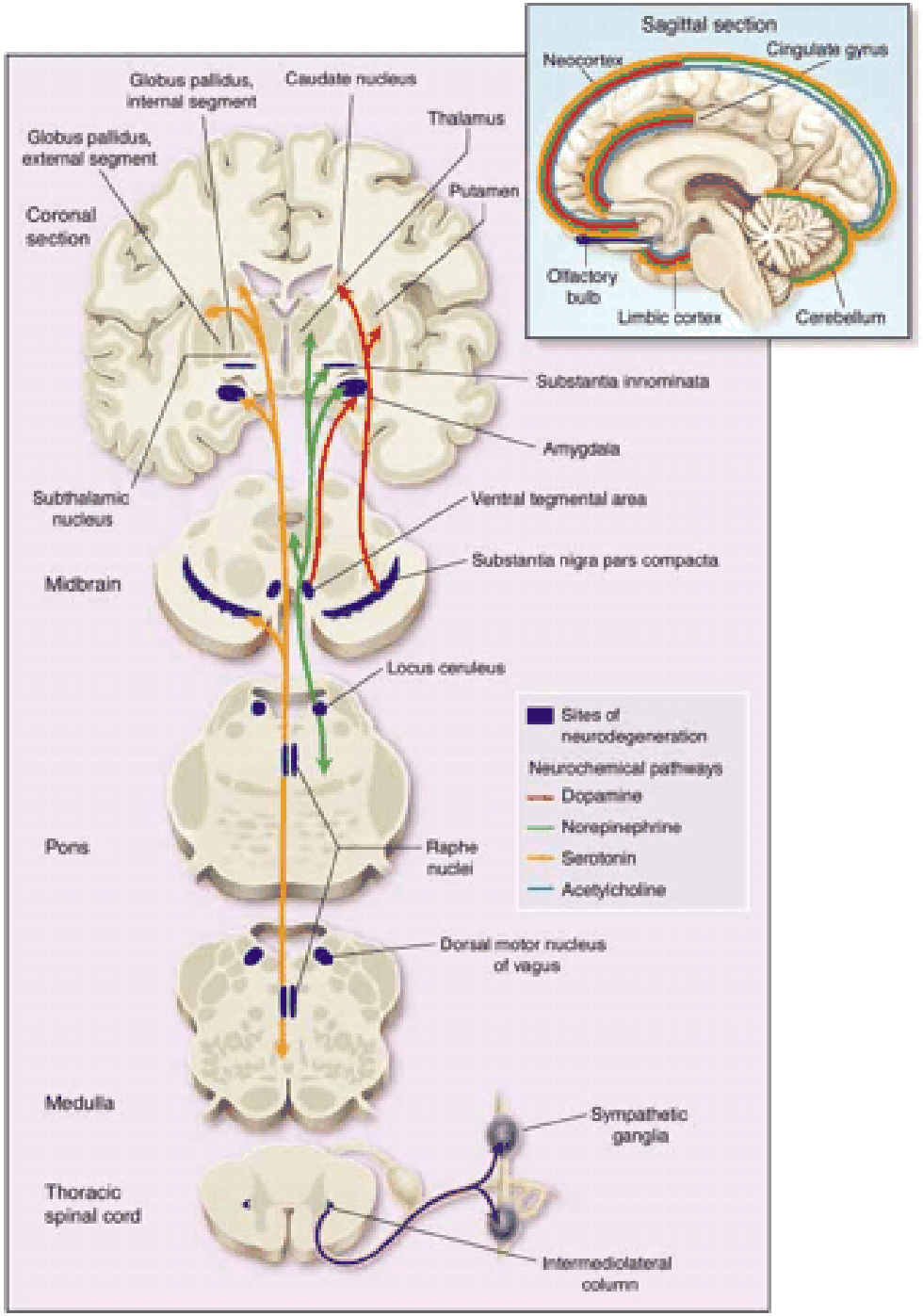
Director, Parkinson's Disease Research, Education and Clinical Center
Philadelphia VA Medical Center

Assistant Professor of Neurology
University of Pennsylvania School of Medicine
Philadelphia, Pennsylvania

Objectives

- **Understand the relationship between dementia with Lewy bodies and Parkinson's disease with dementia**
- **Learn recent changes in the diagnosis and management of PDD and DLB**
- **Understand the emerging role of neuroimaging in the diagnosis of PDD and DLB**

Parkinson's Disease is not just a Dopaminergic Disease



Lang et al. NEJM 1998

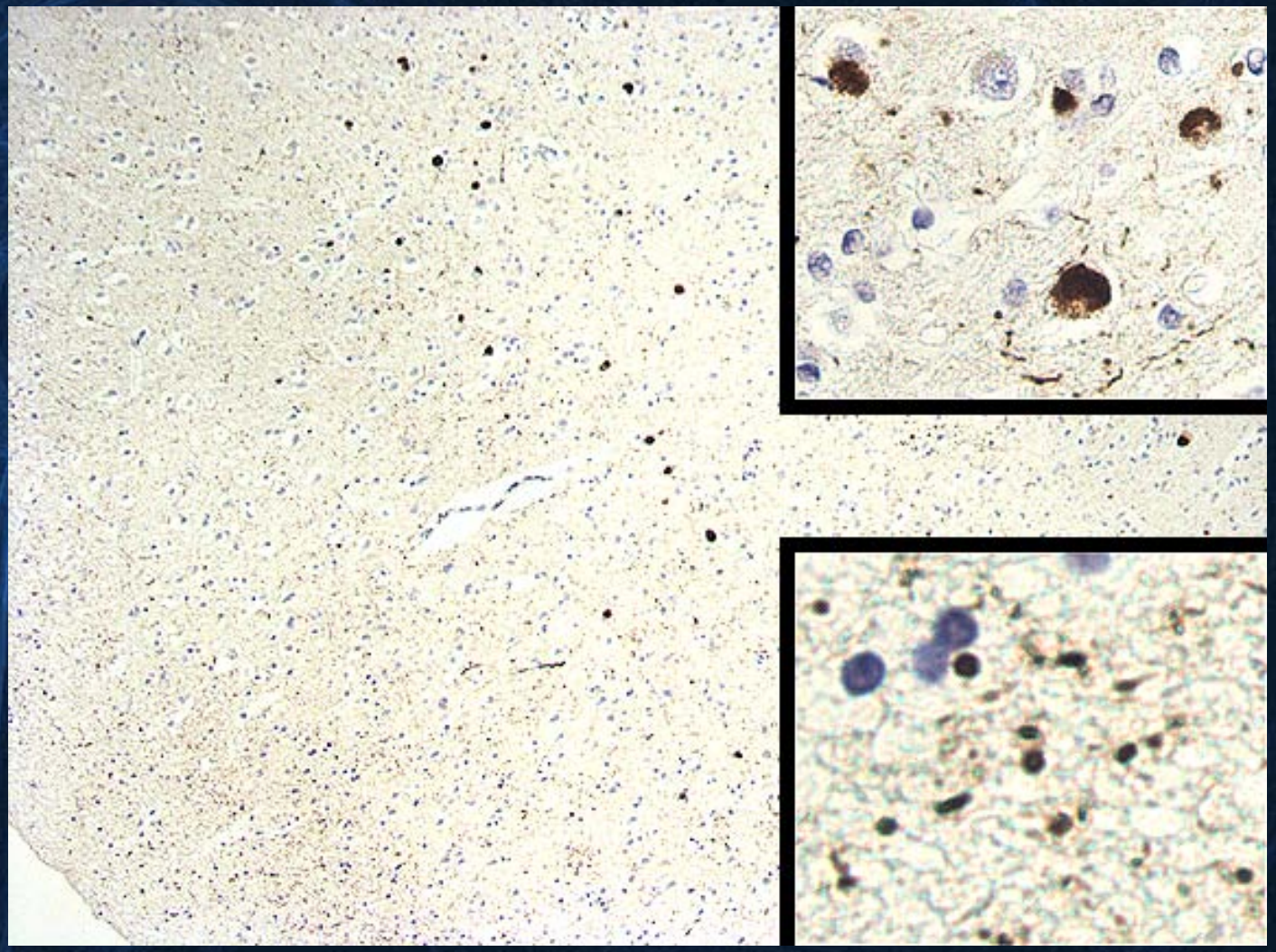
Diagnostic Criteria for PDD

- **Impairment in ≥2 core cognitive domains**
  - **Impaired attention, executive functions, visuospatial functions, and free recall memory which usually improves with cueing**
- **Presence of at least one behavioral symptom (apathy, depressed or anxious mood, hallucinations, delusions, excessive daytime sleepiness) supports diagnosis**
- **End result:**

- More sensitive (shift from focus on memory)
- Bring in line with existing criteria for DLB

Emre et al. *Movement Disorders* 2007;22:1689-1707.

Some patients with dementia will have Lewy bodies in many areas of the brain



What do we call it?

- **Nomenclature**
  - **Diffuse Lewy body disease**
  - **Cortical Lewy body disease**
  - **Senile dementia of Lewy body type**
  - **Lewy body variant of Alzheimer's disease**
  - **Parkinson's disease dementia**
  - **Dementia with Lewy bodies**
    - **Proposed by the First International Workshop of the Consortium on Dementia with Lewy bodies**
      - ***Neurology* (1996) 47:1113**

Dementia with Lewy Bodies
Consensus Criteria for the Clinical Diagnosis

- **Progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational function**
- **Core features (2→probable DLB; 1→possible DLB)**
  - **Fluctuating cognition**
  - **Recurrent visual hallucinations**
  - **Parkinsonism**
- **Features supportive of the diagnosis are**
  - **Repeated falls**
  - **Syncope**
  - **Transient loss of consciousness**
  - **Neuroleptic sensitivity**
  - **Systematized delusions**
  - **Hallucinations in other modalities**
- **Diagnosis is less likely in the presence of**
  - **cerebrovascular disease**
  - **Any physical illness or brain disorder sufficient to account for the clinical picture**

***Neurology* (1996) 47:1113**

Validation of ’96 Consensus Criteria

Reference	DLB cases/all cases	Diag. criteria	Sens.	Spec.	PPV	NPV	κ	Comments and recommendations
Mega et al.[31]	4 DLB/24 AD	Prob.	75	79	100	93	F = 0.25 H = 0.59	Retrospective; suggest 4 of 6 of H, C, R, B, N, Fl
		Poss.	NA	NA	NA	NA	P = 0.46	
Litvan et al.[9]	14 DLB/105 PD, PSP, MSA, CBD, AD	[a]	18	99	75	89	0.19–0.38	Retrospective; no formal criteria for DLB used; comparison mainly with movement disorder patients
Holmes et al.[26]	9 DLB/80 AD, VaD	Prob.	22	1.00	100	91	NA	Retrospective; no specific recs.; mixed pathology cases hardest to diagnose
		Poss	NA	NA	NA	NA		
Luis et al.[29]	35 DLB/56 AD	Prob.	57	90	91	56	F = 0.30 H = 0.91	Retrospective; suggest H, P, Fl, and rapid progression
		NA	NA	NA	NA	NA	P = 0.61	
Verghese et al.[32]	18 DLB/94 AD	Prob.	61	84	48	90	F = 0.57 H = 0.87	Retrospective; suggest 3 of 6 of P, Fl, H, N, D and F
		Poss.	89	28	23	91	P = 0.90	
Lopez et al.[28]	8/40		0	100	0	80		Retrospective; probable DLB not diagnosed once by team of 4 raters; no specific recs.
Hohl et al.[25]	5 DLB/10 AD	Prob.	100	8	83	100	NA	Consensus criteria applied retrospectively; clinician diagnosis without Consensus criteria had PPV of 50
		Poss.	100	0	NA	NA		
McKeith et al.[30]	29 DLB/50 AD, VaD	Prob.	83	95	96	80	NA	Prospective; false negatives associated with comorbid pathology
		Poss.	NA	NA	NA	NA		
Lopez et al.[27]	13 DLB/26 AD	Prob.	23	100	100	43		Prospective, met NINCDS-ADRDA criteria for AD, only 4 of them met DLB criteria
		Poss.	NA	NA	NA	NA		

“DLB 3” Diagnostic Criteria

- **Central feature (essential for a diagnosis of possible or probable DLB)**
  - **Dementia defined as progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational function**

- **Core features (two core features are sufficient for a diagnosis of probable DLB, one for possible DLB)**
  - **Fluctuating cognition with pronounced variations in attention and alertness**
  - **Recurrent visual hallucinations that are typically well formed and detailed**
  - **Spontaneous features of parkinsonism**

McKeith et al. Neurology 2005:65;1863-72

“DLB 3” Diagnostic Criteria (cont’d)

- **Suggestive features (If one or more of these is present in the presence of one or more core features, a diagnosis of probable DLB can be made. In the absence of any core features, one or more suggestive features is sufficient for possible DLB. Probable DLB should not be diagnosed on the basis of suggestive features alone.)**
  - **REM sleep behavior disorder**
  - **Severe neuroleptic sensitivity**
  - **Low dopamine transported uptake in basal ganglia demonstrated by SPECT or PET Imaging**

“DLB 3” Diagnostic Criteria (cont’d)

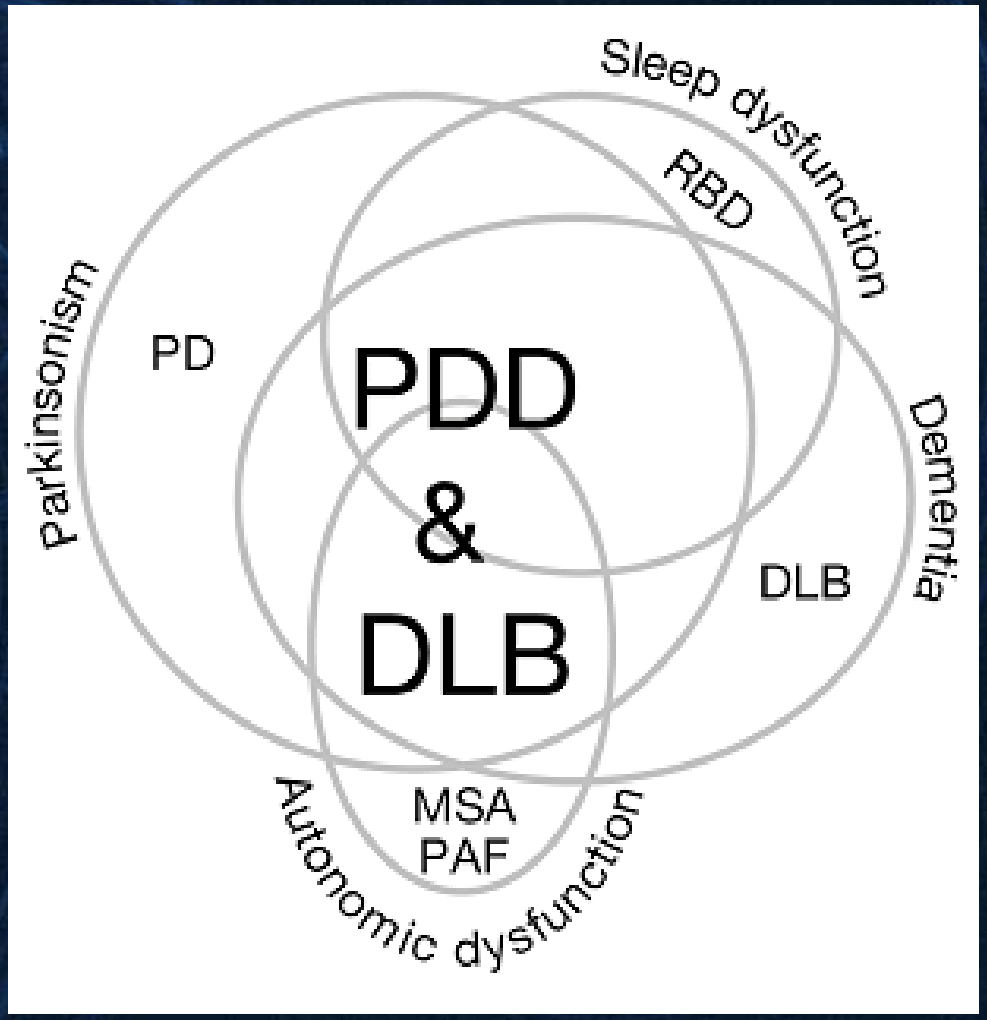
- **Supportive features (commonly present but not proven to have diagnostic specificity)**
  - Repeated falls and syncope
  - Transient, unexplained loss of consciousness
  - Severe autonomic dysfunction
  - Hallucinations in other modalities
  - Systematized delusions
  - Depression
  - Relative preservation of medial temporal lobe structures on CT/MRI scan
  - Generalized low uptake on SPECT/PET perfusion scan with reduced occipital activity
  - Abnormal (low uptake) MIBG myocardial scintigraphy
  - Prominent slow wave activity on EEG with temporal lobe transient sharp waves

Current Consensus Terms

Term	Abbreviation
Dementia with Lewy bodies	DLB
Parkinson's disease	PD
Parkinson's disease with dementia	PDD
Lewy body dementias (PDD and DLB)	LB dementias
Lewy body disease (PD, PDD and DLB)	LB disease

Lippa et al. Neurology 2007:68;812-819

The Spectrum of Lewy body diseases



Duda. Dement Geriatr Cogn Disord 2004:17(Suppl 1);3-14

Prevalence of LBD

- **DLB causes 10-15% of irreversible dementia**
- **25% of AD cases have parkinsonism and most of these cases have LBs at autopsy**
- **PD affects 1 in 100 persons over the age of 60, with a yearly incidence of dementia increasing with age to 13.7%/yr over the age of 70.**
- The combined sum of patients with parkinsonism and dementia may approach 2 million

Evaluation of LBD

- **History and physical examination**
- **Psychometric testing**
  - **verbal and non-verbal memory, attention, concentration, abstraction, visuospatial abilities and construction**
- **Neuroimaging**

Screening Instruments

MMSE: “Gold Standard”

- Cognitive domains assessed
  - Orientation (10 points)
  - Language (8 points)
  - Memory (6 points)
  - Attention (5 points)
  - Visuospatial (1 point)
- Maximum score = 30 points
- Age- and education-adjusted scores available

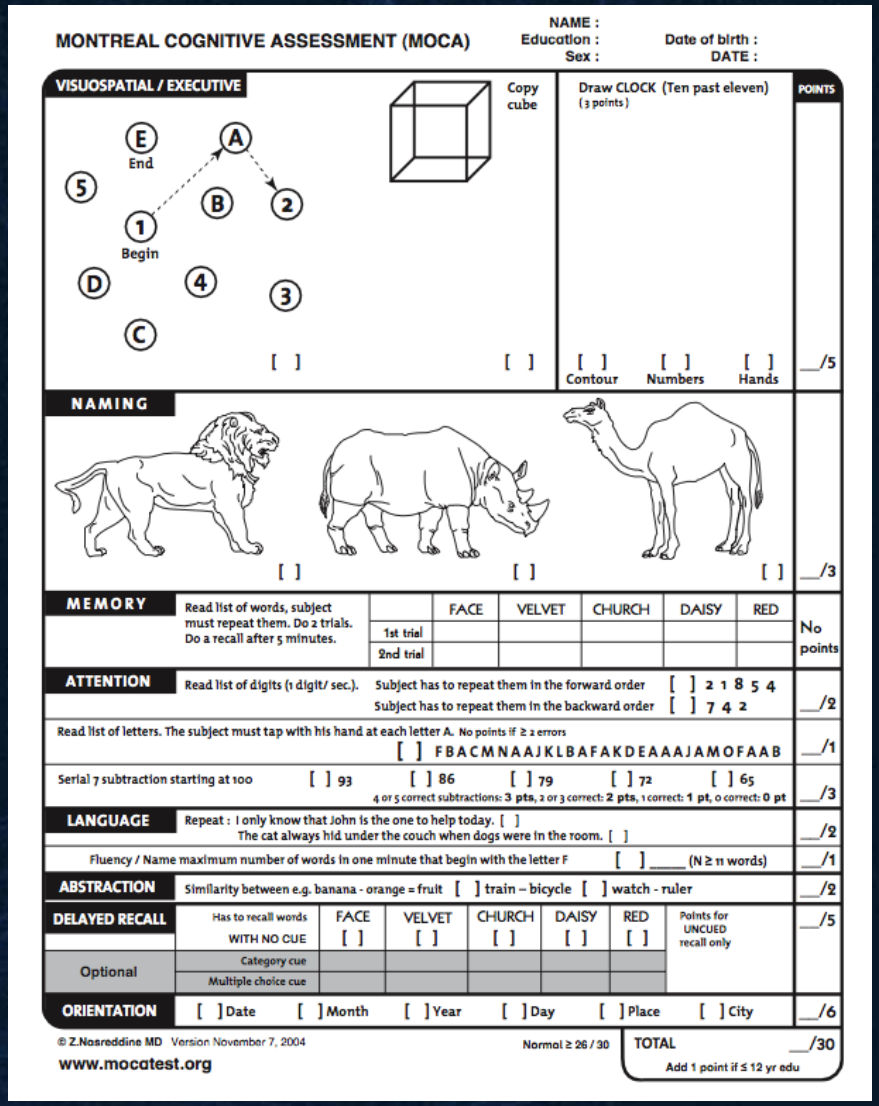
Question	Maximum Scores
Orientation What is the (year) (season) (date) (day) (month)? Where are we? (State) (County) (Town) (Hospital) (Floor)	One point for each correct answer, maximum of five. One point for each correct answer, maximum of five
Registration: Name three objects: One second to say each. Then ask the patient all three after you have said them	One point each correct answer, maximum of three
Attention and Calculation: Serial 7's: Subtracts 7 from 100 and keep doing it backward until five answers. Alternatively, spell "world" backward or name all the twelve months backward	One point for each correct answer, maximum of five.
Recalls: Ask for the three objects repeated above	One point for each correct answer, maximum three
Language: Name a pencil, and watch Repeat the followings: No if;s, and's or but's. Follow a 3-stage command: Take a paper in your right hand, fold it in half, and put it on the floor. **Read and Obey the following:** Close your eyes Write a sentence Copy the following design 	One point for each correct answer, maximum two One point One point each, maximum of three One point One point One point if copied all ten surfaces and ten angles.

Folstein MF et al. *J Psychiatr Res.* 1975;12:196-198. Crum RM et al. *JAMA.*1993;269:2386-2391.

Montreal Cognitive Assessment (MoCA)

- Assesses a broad range of cognitive domains
  - Attention/concentration (5 points)
  - Executive function (4 points)
  - Memory (5 points)
  - Language (6 points)
  - Visuospatial skills (4 points)
  - Orientation (6 points)
- Education adjusted
  - +1 point if ≤ 12 years
- Maximum possible score = 30 points
- **Total score <26 indicative of at least MCI**

Nasreddine et al. *Journal of the American Geriatrics Society* 2005;53:695-699.



MoCA Performance in PD Patients with Normal MMSE

- **100 PD patients administered MoCA and MMSE in counterbalanced fashion**
- **Patients with abnormal MMSE scores (bottom 25th percentile) were excluded**
  - **Mean MMSE =29**

52% of PD patients scored <26 on MoCA

Nazem et al. *Journal of the American Geriatrics Society* 2009;57:304-308.

PD Performance on MoCA Subscores by Impairment Status

MoCA Subscore	Mean (SD)		t (df) or Z score	P value
	Cognitively Impaired (N=52)	Cognitively Unimpaired (N=48)		
Visuospatial/Executive	**3.5 (1.0)**	**4.3 (0.8)**	**- 4.1[a]**	**<.001[b]**
Naming	**2.7 (0.5)**	**3.0 (0.2)**	**- 3.6[a]**	**<.001[b]**
Attention	**5.3 (1.0)**	**5.9 (0.4)**	**- 3.9[a]**	**<.001[b]**
Language	**1.5 (1.0)**	**2.7 (0.5)**	**- 5.9[a]**	**<.001[b]**
Abstraction	**1.4 (0.7)**	**1.7 (0.6)**	**- 2.1[a]**	**.04**
Delayed Recall	**1.8 (1.5)**	**3.8 (1.0)**	**- 6.2[a]**	**<.001[b]**
Orientation	**5.9 (0.3)**	**6.0 (0.1)**	**- 1.8[a]**	**.07**

[a] Mann-Whitney U test.

[b] Significant after Bonferroni correction for multiple comparisons.

Correlates of Cognitive Impairment

Variable	Univariate Analyses			Multivariate Analysis[a]		
	Odds Ratio	95% Confidence Interval for Odds Ratio	P value	Odds Ratio	95% Confidence Interval for Odds Ratio	P value
Age[b]	**1.75**	**1.36 – 2.25**	**<.001**	**1.60**	**1.24 – 2.07**	**<.001[c]**
Sex	**4.65**	**1.81 – 11.95**	**.001**	**3.77**	**1.21 – 11.73**	**.02**
Education	**0.87**	**0.77 – 0.98**	**.02**	**0.85**	**0.74 – 0.98**	**.03**
Hoehn & Yahr	**3.13**	**1.46 – 6.71**	**.003**	**2.58**	**1.03 – 6.50**	**.04**
UPDRS	**1.07**	**1.02 – 1.11**	**.006**	**-**	**-**	**-**
Marital Status	**1.78**	**0.68 – 4.63**	**.24**	**-**	**-**	**-**
Dopamine agonist use	**0.52**	**0.24 – 1.16**	**.11**	**-**	**-**	**-**
GDS Score	**0.96**	**0.86 – 1.06**	**.40**	**-**	**-**	**-**
Levodopa dosage[e]	**1.06**	**0.95 – 1.17**	**.31**	**-**	**-**	**-**
DBS	**0.80**	**0.29 – 2.16**	**.65**	**-**	**-**	**-**
Duration PD	**0.99**	**0.93 – 1.05**	**.76**	**-**	**-**	**-**

[a] Hoehn and Yahr stage included as measure of disease severity; [b] Odds ratio for age presented calculated for 5-year increments; [c] Significant after Bonferroni correction for multiple comparisons; [d] Odds ratio for levodopa dosage calculated for 100-mg increments.

Validation of MoCA and MMSE for Diagnosis of MCI or PDD

	MoCA												
Cut-off	17/18	18/19	19/20	20/21	21/22	22/23	23/24	24/25*	25/26	26/27	27/28	28/29	29/30
Sensitivity	18	18	20	28	35	45	48	70	80	90	93	100	100
Specificity	99	98	96	94	91	90	85	75	64	53	39	22	10
PPV	88	78	67	65	64	78	58	55	49	46	40	36	32
NPV	73	73	73	75	76	79	79	85	88	92	92	100	100
% correctly diagnosed	74	73	73	73	74	77	73	73	69	64	55	45	36
AUC (95% CI)	.79 (.72 – .87)												
	MMSE												
Cut-off								24/25	25/26	26/27	27/28	28/29*	29/30
Sensitivity								20	28	38	53	78	90
Specificity								99	96	88	83	63	38
PPV								89	73	58	57	48	39
NPV								74	75	76	80	87	90
% correctly diagnosed								75	75	73	73	67	54
AUC (95% CI)	.76 (.67 – .85)												

* = point of maximum combined sensitivity and specificity
Blue = optimal screening cut-off point
Red = optimal diagnostic cut-off point
PPV, positive predictive value; NPV, negative predictive value; AUC, area under curve; CI, confidence interval

Hoops et al. *Neurology,* Nov 2009; 73: 1738 - 1745.

LBD: Cognitive Fluctuation

- Most confusing aspect
- Spontaneous impairment of alertness and concentration
- May appear drowsy but awake, look “dazed”
- Vary from day to day or week to week
- Loss of consciousness has been described
- No EEG correlate
- Mayo Clinic Fluctuation Scale (Ferman, 2005)
  - Drowsy or lethargic during day
  - Sleeps for 2 or more hours during day
  - Thinking illogical, unclear, incoherent
  - Stares into space

LBD: Behavioral abnormalities

Visual hallucinations

- more prominent with poor eyesight
- well-formed
- early in the course of the illness

Delusions

- misidentification
- persecutory/paranoid
- phantom boarder
- abandonment

LBD: Behavioral abnormalities

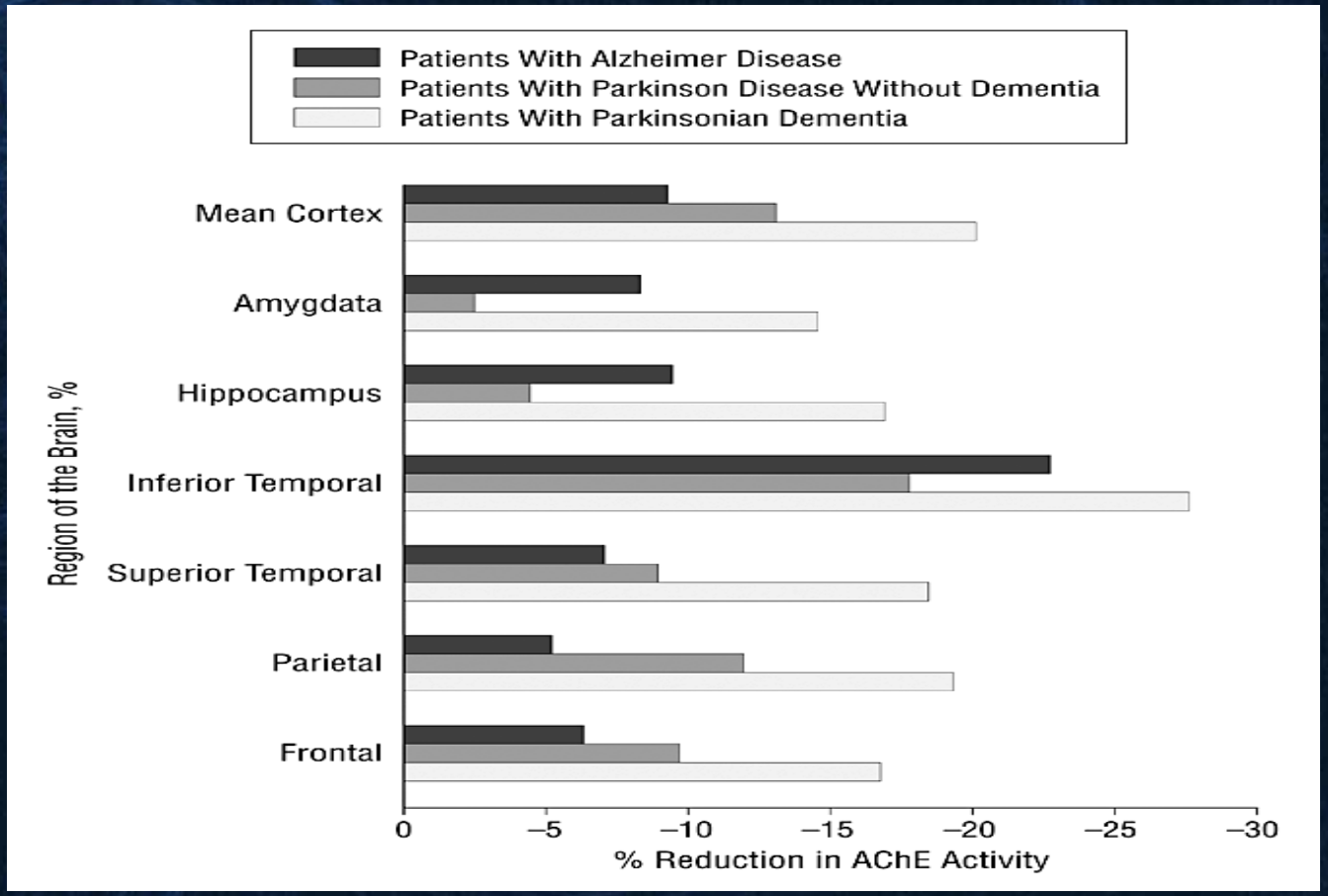
- Depression
- Anxiety
- Irritability
- Apathy/Amotivational states
- Aggression/violent behavior
- Nocturnal confusion/insomnia

REM Behavior Disorder

- **Act out violent (attacking, chasing) dreams during rapid eye movement (REM) sleep**
- **Shouting, kicking, punching**
- **When they wake up, they remember the dream**
- **Often hurt themselves or bed partners**
- **Usually responds to low-dose clonazepam (0.5-1mg qhs)**

So what do we do with these patients?

Cholinergic Function in PD, PDD, and AD



AChE = acetylcholinesterase activity

Bohnen et al. *Arch Neurol* 2003;60:1745-1748.

Cognitive disorder

- **Central Acting Cholinesterase Inhibitors**
  - **modest improvement in cognition**
  - **diminished hallucinations**
  - **improvement in behavior**
  - **may improve gait**
  - **improvement in attention**
  - **Rivastigmine only FDA-approved treatment for PDD**
- **Role of Memantine is unclear**

Movement Disorder

- **Becomes a balance between alleviating motor symptoms and worsening neuropsychiatric symptoms**
- **Management often optimal with carbidopa/levodopa monotherapy**
- **Dopamine agonists, COMT inhibitors, anti-cholinergics and MAO-B inhibitors often can worsen psychosis, hallucinations and delirium**

Psychotropics and Behavioral Disorders

- **No FDA-approved orally administered agents for behavioral disturbances in AD/dementia**

Agitation	Psychosis	Depression
• Atypical antipsychotics* • Mood stabilizers/anticonvulsants • Antidepressants, anxiolytics, etc	• Atypical antipsychotics*	• SSRIs • SSRNIs

*FDA Public Health Advisory (April 2005): Clinical trials of antipsychotic drugs to treat behavioral disorders in elderly patients with dementia have shown a higher death rate compared to placebo.
SSRIs = selective serotonin reuptake inhibitors; SSRNIs = selective serotonin and noradrenergic reuptake inhibitors.

Tariot PN. *J Am Geriatr Soc*. 2003;51(5 suppl Dementia):S305-S313.

Safety of Antipsychotics

- **FDA Public Health Advisory, April 2005:**
  - **Clinical trials of atypical antipsychotic drugs to treat behavioral disorders in dementia patients have shown a 1.6-1.7-fold higher death rate compared to placebo**
  - **Specific causes of death were primarily due to:**
    - **Heart-related events (eg, heart failure, sudden death)**
    - **Infections (mostly pneumonia)**
- **Wang PS, et al. *N Engl J Med*. December 2005**
  - **Conventional antipsychotics were associated with higher risk of death than atypical antipsychotics in elderly patients.**
  - **Risk is highest:**
    - **Soon after therapy is initiated**
    - **At high doses**

Schneider LS, et al. *JAMA*. 2005;294:1934-1943; Wang PS, et al. *N Engl J Med.* 2005;353:2335-2341; FDA Public Health Advisory. Available at: http://www.fda.gov/cder/drug/advisory/antipsychotics.htm. Accessed October 2007.

Rank of Atypical Antipsychotics by relative risk of EPS effects

Clozapine < Quetiapine < Olanzapine = Ziprasidone

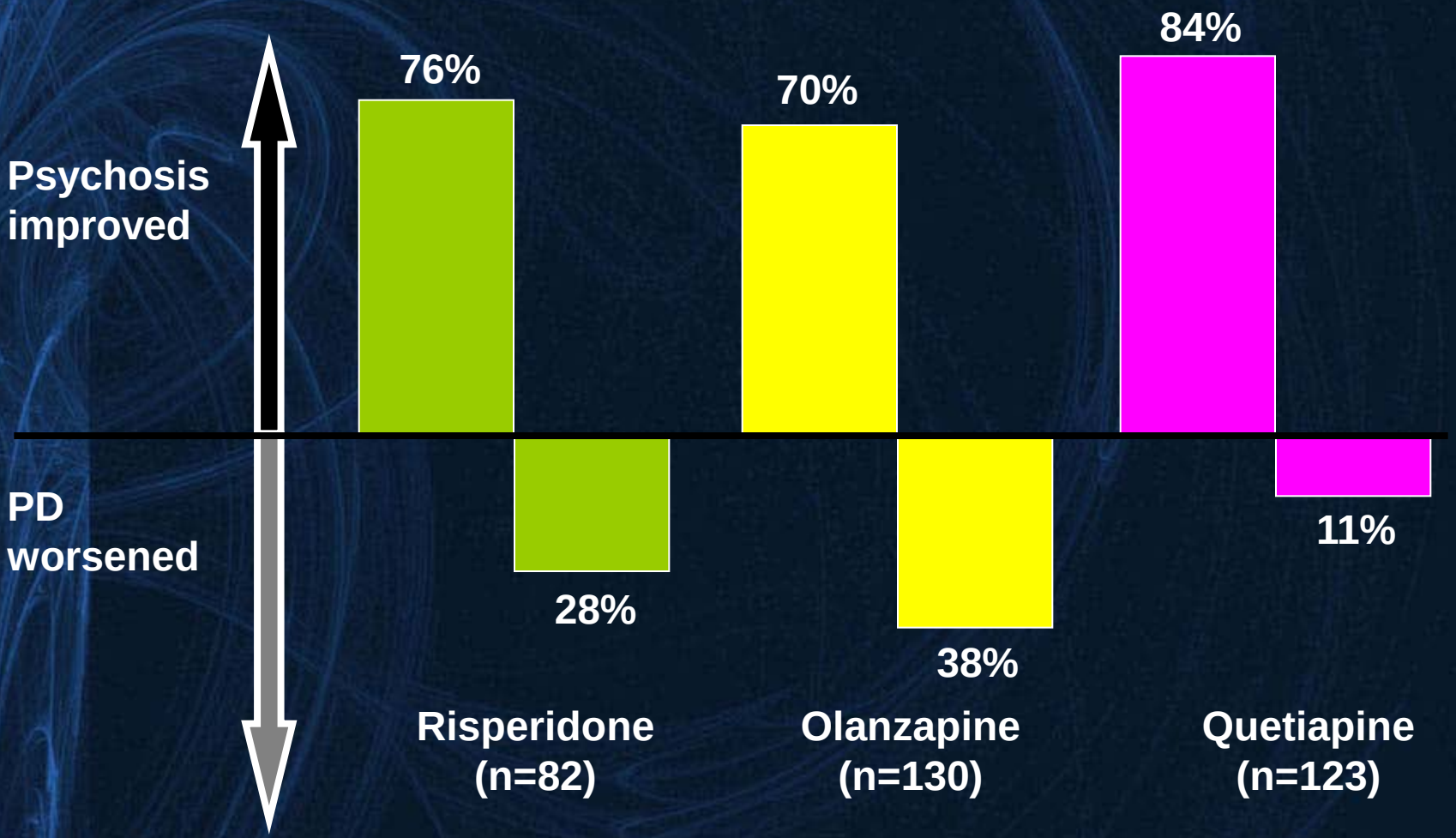
Risperidone (low dose)

Risperidone (high dose)

EPS effects: dystonia, EPS, akathesia, tardive

Ranking is inversely related to D_2 potency

Atypical Antipsychotics in Parkinson's Disease



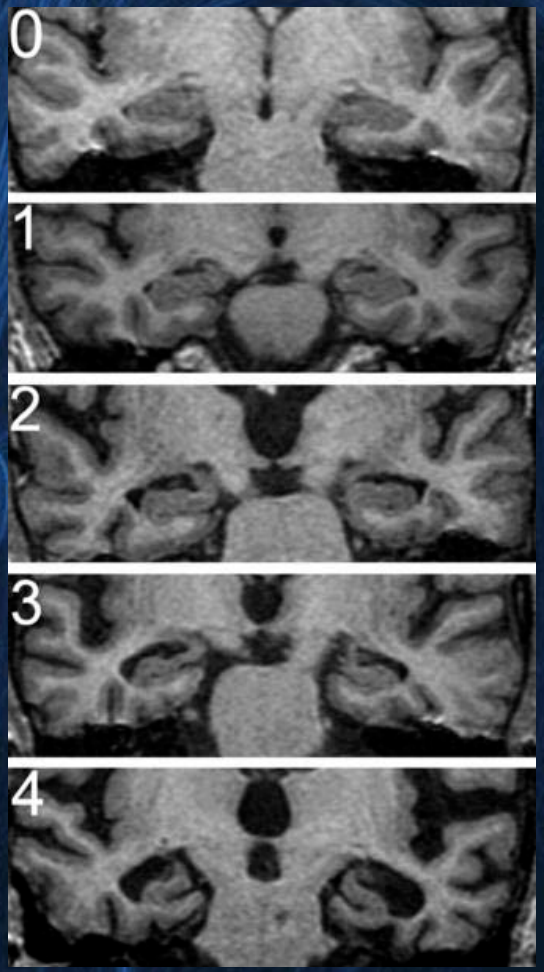
Adapted from Friedman & Factor 2000

Management of Psychosis

- **Quetiapine and clozapine have become first line agents**
- **LBD patients will often respond to doses MUCH lower than commonly used so ‘start low and go slow’**
- **Strenuously avoid typical neuroleptics to prevent neuroleptic sensitivity reactions (Aarsland et al. J Clin Psychiatry 2005:66:63-7)**

How imaging is beginning to play a role in the diagnosis and management of patients with PDD/DLB

Medial Temporal Lobe Atrophy in Neurodegenerative Diseases



Medial temporal lobe atrophy	Control	PD	PDD	DLB	AD
Right	1.46 ± 0.94*	1.88 ± 0.49	2.03 ± 0.66	2.36 ± 0.81	3.06 ± 0.81
Left	1.33 ± 0.93*	1.82 ± 0.64	1.87 ± 0.99	2.20 ± 0.76	3.06 ± 0.85

Values are means ± SD.

* Control < PD, PDD, DLB, AD, post-hoc Mann-Whitney *U* test.

PD = Parkinson disease; PDD = Parkinson disease dementia; DLB = dementia with Lewy bodies; AD = Alzheimer disease.

MTA includes hippocampus, subiculum, parahippocampal and dentate gyri.

Tam et al. *Neurology* 2005;64:861-865.

Structural MRI

- **Study of PD patients including those with normal cognition and MCI diagnosis**

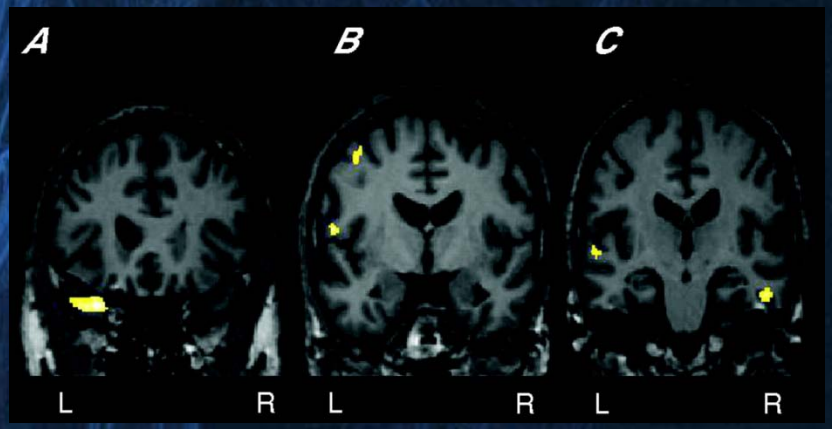


Table 3 Anatomical location of areas of reduced grey matter in patients with Parkinson's disease with mild cognitive impairment compared with no cognitive impairment

Cluster size	Voxel level	Anatomical location	x	y	z	T score
420	L	Superior temporal	–30	21	–28	5.31
103	L	Precentral gyrus	–58	–5	11	4.75
75	R	Inferior temporal	55	–20	–21	4.49
79	L	Superior temporal	–62	–22	3	4.27
107	L	Precentral gyrus	–42	–5	56	4.08
	L	Middle frontal	–39	3	58	3.74

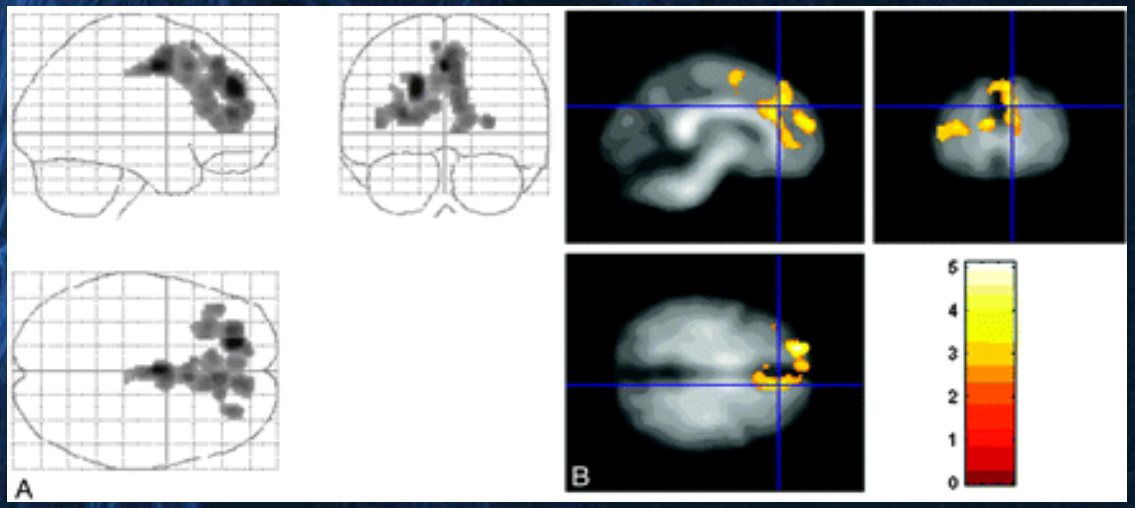
L, left; R, right.

The coordinates x, y and z refer to the anatomical location, indicating standard stereotactic space as defined by Talairach and Tournoux.[42] Only clusters >200 mm^3 are included. In this table, all reported voxels are p uncorrected <0.001.

Significant changes with MCI are found in the (A) left superior temporal gyrus, (B) left frontal lobe (precentral gyrus), and (C) right temporal lobe (inferior temporal gyrus) and left temporal lobe (superior temporal gyrus).

Beyer et al. *J Neurol Neurosurg Psychiatry* 2007;78:254-259.

Diffusion Tensor Imaging (DTI) - Fractional Anisotropy (FA)

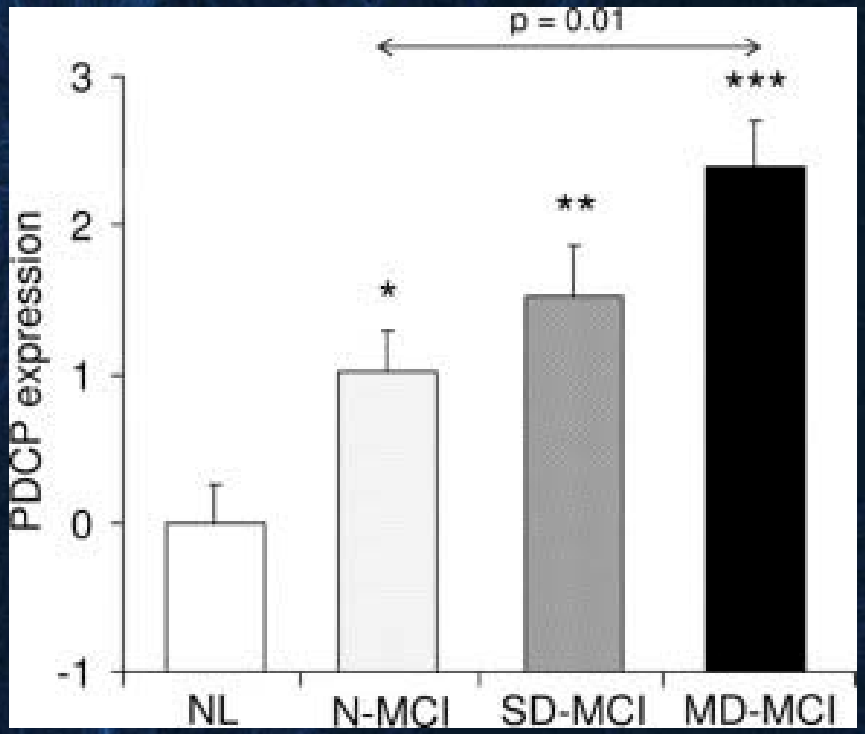


- 12 non-demented PD patients (mean MMSE=28) and 13 controls
- Significant decrease in FA values in PD patients bilaterally in the medial frontal cortex, the right superior longitudinal fasciculus, and left corpus callosum.

Kendi et al. *Am J Neuroradiol* 2008;29:501-505.

Spatial Covariance Pattern

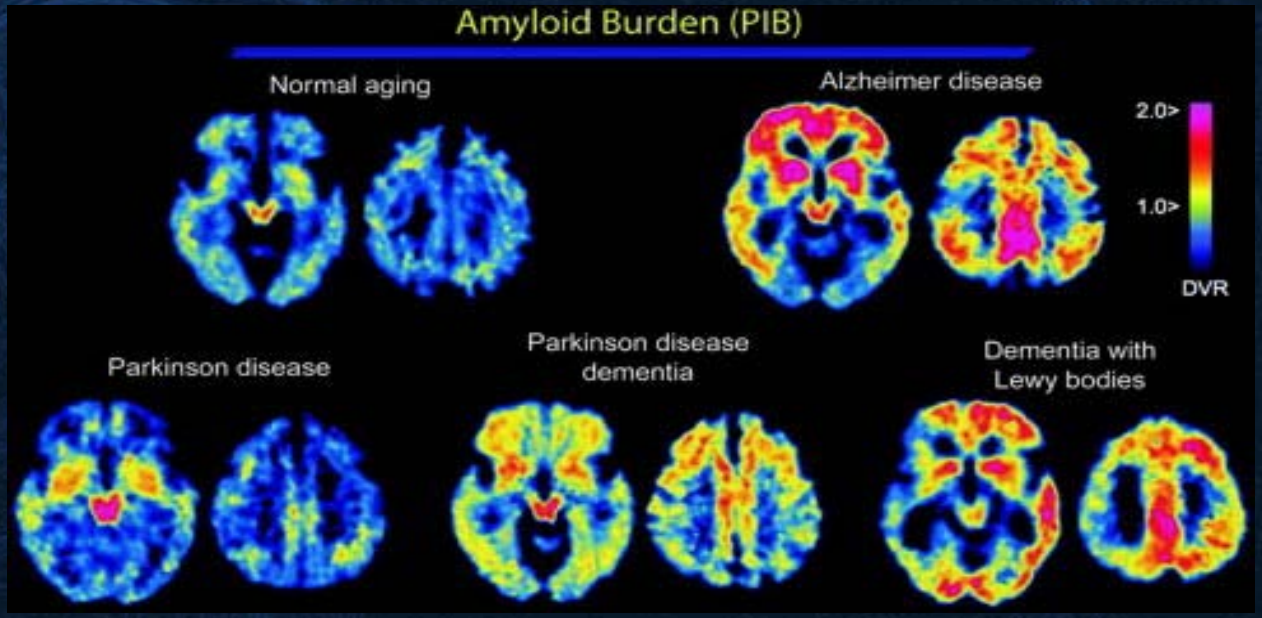
- **Cognition-related spatial covariance pattern (PDCP) using FDG-PET**



Parkinson disease-related cognitive pattern expression in multiple domain mild cognitive impairment (MD-MCI), single domain MCI (SD-MCI), without mild cognitive impairment (N-MCI), and age-matched controls.

Huang et al. *Neurology* 2008;70:1470-1477.

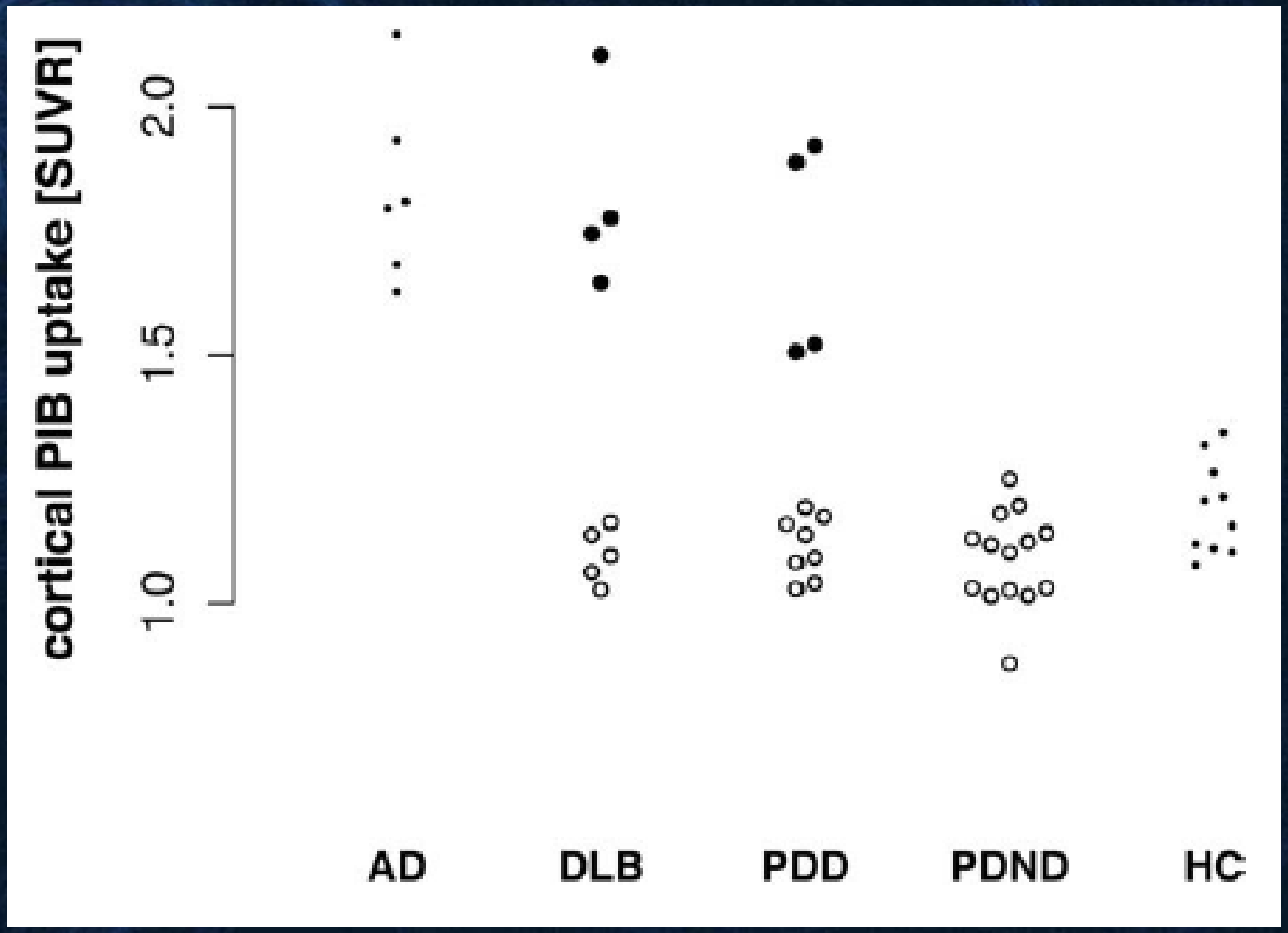
Imaging Amyloid Deposition in PD



PiB images from a 75-year-old normal control, a 79-year-old patient with AD (MMSE score 25), a 65-year-old patient with PD (MMSE score 27), a 69-year-old patient with PDD (MMSE score 25), and a 71-year-old patient with DLB (MMSE score 8). Note that Pittsburgh Compound B (PiB) retention is qualitatively increased in AD, PDD, and DLB compared with NC and PD

Gompers et al. *Neurology* 2008;71:903-910.

PiB Uptake Distinguishes PDD and DLB Subgroups



Maetzler et al. Neurobiol Dis 2009:34;107-112

Conclusions

- **PDD and DLB are similar disorders that may lie upon a spectrum of Lewy body diseases**
- **Diagnostic screening of PD patients may be improved with the MoCA**
- **Management requires a balance between alleviating motor and cognitive symptoms**
- **Novel imaging techniques may soon play important roles in diagnosis and management**